REPORT OF PESTICIDES PEER REVIEW TC 190

PROPYZAMIDE – MRL Art.10 Evaluating Member State: SE/DK

2. Mammalian toxicity

Date: 28 November 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by EMS DK	Danish Environmental Protection Agency (DK) - DK
National Expert nominated by EMS SE	Swedish Food Agency - SE
National Expert nominated by AT	Austrian Agency for Food and Health Safety (AGES) – AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS LT	The State Plant Service under the Ministry of Agriculture - LT
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS SK	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK

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[1] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/independence-policy-2024.pdf
[2] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/decision-ed-on-competing-interest-management-2024.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 1.1 Experts to discuss the toxicological profile of metabolites RH-24848, RH-25891, RH-26521, RH-26059, RH-25337, RH-26702 and RH-24644.	RH-24644 Genotoxicity hazard identified?: No (Based on experimental data) Reference values of parent applied?: Open (An analysis of the repeated dose toxicity studies (28-day studies, including TGR studies) available for parent and metabolite RH-24644 is missing.) RH-25891 Genotoxicity hazard identified?: No (Based on silico analysis (QSAR, grouping and read-across from RH-24644).) Reference values of parent applied?: Open (Same conclusions as for RH-2644.) **An analysis of the repeated dose toxicity studies (28-day studies, including TGR studies) available for parent and metabolite RH-24644 is needed to conclude on whether reference values of the parent should apply or whether specific reference values should be set. A data requirement is proposed.**

Subject	Conclusions Pesticides Peer Review Meeting
	RH-25337 Genotoxicity hazard identified?: No (Based on in vitro experimental data, not including the mammalian gene mutation assay.) Reference values of parent applied?: Yes (As a worst case, health-based guidance values of parent can be used, considering that there are no indications that the metabolites are of higher toxicity than the parent, including grouping approach where there is experimental data with RH-25337 and RH-26702.) RH-26702 Genotoxicity hazard identified?: No (Based on experimental data, not including the mammalian gene mutation assay.) Reference values of parent applied?: Yes (As a worst case, health-based guidance values of parent can be used, considering that there are no indications that the metabolites are of higher toxicity than the parent, including grouping approach where there is experimental data with RH-25337 and RH-26702.) RH-24848, RH-26521, RH-26059: Genotoxicity hazard identified?: No (Based on silico analysis (QSAR, grouping and read-across from RH-25337 and RH-26702).) Reference values of parent applied?: Yes (Based on silico analysis (QSAR, grouping and read-across from RH-25337 and RH-26702).)

REPORT OF PESTICIDES PEER REVIEW TC 190

CLOFENTEZINE – Art 12 MRL review | Evaluating Member State: NL

2. Mammalian toxicity

Date: 28 November 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by EMS NL	Ctgb - NL
National Expert nominated by AT	Austrian Agency for Food and Health Safety (AGES) – AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency (DK) - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS LT	The State Plant Service under the Ministry of Agriculture - LT
National Expert nominated by MS SE	Swedish Food Agency - SE
National Expert nominated by MS SK	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	**Conclusions Pesticides Peer Review Meeting**
Experts' consultation 1.1 Experts to discuss new toxicological data avaialable on 2-chlorobenzonitrile available under article 12 review of clofentezine.	2-chlorobenzonitrile Genotoxicity, hazard identified: No (Based on experimental data, not including the in vitro MN test but the new in vivo MN test provided under article 12 MRL review). General toxicity, reference values of parent applied: Open (No further assessment / data provided under article 12 MRL review).

REPORT OF PESTICIDES PEER REVIEW

TC 189 and TC 190

CYMOXANIL – AIR IV

Rapporteur Member State: LT

2. Mammalian toxicity

Date: 28 November 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS LT	State Plant Service under the Ministry of Agriculture - LT
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS LT	The State Plant Service under the Ministry of Agriculture - LT
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS SK	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK
Observer	Swiss Federal Office for the Environment - CH
Observers	Federal Food Safety and Veterinary Office (FSVO) - CH

Status	Name of institution/attendee
Observer	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK
Observers	Public Health Authority of the Slovak Republic - SK

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.15 MSs experts to discuss the ED assessment of the active substance cymoxanil in an experts' meeting.	With regard to T modality, the dataset was considered complete, and a pattern of T-mediated adversity was not identified for cymoxanil. Regarding EAS-modalities, no EAS-mediated adversity was observed. However, EAS-mediated parameters were not sufficiently investigated (i.e. lack of OECD TG 416, version from 2001, or OECD TG 443) ruling out the possibility to exclude other potential EAS-mediated adverse effects. The EAS-related endocrine activity: - E-mediated activity is considered sufficiently investigated in the presence of a negative ER-ToxCast model. - A-modality is considered negative based on a WoE including negative AR-ToxCast model and negative valid Hershberger. - In the absence of valid studies, the ED potential of cymoxanil regarding the S-modality cannot be concluded (data gap and issue not finalised). **Open point**: The RMS to update the RAR reflecting the meeting discussions.
Expert consultation TOX proposed by EFSA MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for	Regarding the co-formulants contained in the formulation supported for the representative uses 'Cymoxanil 45 WG' based on the currently available information, sufficient toxicological data were available for most components. However, for some components, toxicological data is insufficient (including on genotoxicity, short- and long-term toxicity/carcinogenicity) and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation.

Subject	Conclusions Pesticides Peer Review Meeting
representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	**Open point**: The RMS to revise the RAR Vol.4 in line with the discussion and to provide an overview of the genotoxicity, repeated dose toxicity and carcinogenicity data of some co-formulants based on the available data to substantiate the RMS conclusion.
Experts' consultation TOX proposed by EFSA MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation supported for the representative uses 'Rival Duo' based on the currently available information, sufficient toxicological data were available for most components. However, for some components, toxicological data is insufficient (including on genotoxicity, short- and long-term toxicity/carcinogenicity) and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. **Open point**: The RMS to revise the RAR Vol.4 in line with the discussion and to provide an overview of the genotoxicity of a co-formulant based on the available data to substantiate the RMS conclusion. For completeness, the composition of co-formulant mixtures should be reported in a separate RAR Vol.4 ('not for applicants').

REPORT OF PESTICIDES PEER REVIEW TC 189

PIRIMIPHOS-METHYL – AIR III

Rapporteur Member State: FR

2. Mammalian toxicity

Date: 25 November 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Expert nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS LT	State Plant Service under the Ministry of Agriculture - LT
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS SK	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK
Observer	Swiss Federal Office for the Environment - CH
Observer	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK
Observers	Public Health Authority of the Slovak Republic - SK

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.15 The **ED assessment** of pirimiphos-methyl should be discussed in an expert consultation in line with the ECHA/EFSA guidance and the eligibility to waive further testing to be agreed in a dedicated MSs meeting.	With regard to **T-modality**, the data set was considered complete, and a pattern of T-mediated adversity was not identified for pirimiphos-methyl. The new data available (ToxCast and literature studies) did not challenge the previous conclusion (ED criteria not met, Scenario 1a). For the **EAS-modalities**, EAS-mediated parameters were not sufficiently investigated. The available data do not show a pattern of EAS mediated adversity, however there is some equivocal evidence of endocrine activity for the EAS modalities based on ToxCast and some literature data. However, based on the toxicological profile of the test substance (a potent AChE inhibitor), it is considered unlikely that EAS-mediated adversity may be observed at doses not showing inhibition. Therefore, there would be no added value to perform additional tests for this substance and a waiver for the conduction of additional level 5 study is acceptable. It is concluded ED criteria are unlikely to be met for the EAS-modalities.

REPORT OF PESTICIDES PEER REVIEW TC 189

BIFENAZATE – confirmatory data

Rapporteur Member State: SE

2. Mammalian toxicity

Date: 25 November 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency (KEMI) - SE
National Experts nominated by MS AT	Austrian Agency for Food and Health Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS NL	Ctgb - NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the appropriateness of the studies and their contextualisation in a weight-of-the-evidence (WoE) analysis of the potential interaction of bifenazate with the EAS-mediated ED parameters. See EFSA Technical Report, Appendix A, point 2(5).	**T-modality** In the EFSA Technical report (June 2025) on the public consultation of the revised RAR it was confirmed that bifenazate does not meet the criteria for identification as endocrine disruptor for humans for the T-modality. **EAS-modalities** EAS-mediated parameters have been sufficiently investigated, and a pattern of EAS-mediated adversity was not observed in the available dataset of studies. Scenario 1a of the ECHA/EFSA ED Guidance (2018) is applicable and the ED criteria for the EAS-modalities are considered not met. As regards the rat metabolite D9569 (4,4'-biphenol) a thorough investigation of its ED properties cannot be performed on the available dataset, but its endocrine potential cannot be excluded. Nonetheless, the ED potential of the metabolite 4,4'-biphenol is unlikely to be expressed in studies on bifenazate as the toxicity of bifenazate would be a limiting factor. **Open points:** RMS to update the RAR reflecting the discussion of the meeting, in particular: 1. RMS to update the RAR providing further information on the HCD and its limited use for the interpretation of VO and BPS in the 2-generation study. 2. RMS to update the RAR correcting the spelling mistake regarding the day of VO for 97% of the animals at mid dose

Subject	Conclusions Pesticides Peer Review Meeting
	3. RMS to correct the top dose level of the 2-generation study as reported in the ED discussion on the metabolite D9569RMS to reflect in a revised RAR the outcome of the discussion in the experts consultation meeting.

REPORT OF PESTICIDES PEER REVIEW TC 189

THIACLOPRID – Art.43 mandate

Rapporteur Member State: N/A

2. Mammalian toxicity

Date: 25 November 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by MS AT	Austrian Agency for Food and Health Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS NL	Ctgb - NL
National Experts nominated by MS SE	Swedish Chemicals Agency (KEMI) - SE

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the ED assessment for thiacloprid for the EATS-modalities for HH. In particular: - To perform a data check and assessment of the information on the endocrine-disrupting properties of thiacloprid for humans that had been submitted as part of the renewal process, so that major data gaps, if any, are identified. - To discuss and agree on the completeness of the dataset. - In case of data gaps, identify the additional toxicological test(s) needed to conclude on the endocrine- disrupting properties for human health considering the criteria set under point 3.6.5 of Annex II to Regulation (EC) No 1107/2009 as amended by Commission Regulation 2018/605, that should be	**T-modality** - Based on a complete dataset in line with ED ECHA/EFSA guidance (2018), T-mediated adversity is confirmed (mainly in the 2-year rat study: follicular cell hypertrophy, hyperplasia in both sexes, and follicular cel adenomas in males only). - ED criteria are considered met (Scenario 1a). **EAS-modalities** - Based on a complete dataset in line with ED ECHA/EFSA guidance (2018), EAS-mediated adversity is confirmed (uterine glandular hyperplasia and adenocarcinomas in the 2-year study in rats, increased incidence of ovarian luteomas in the carcinogenicity study in mice) supported by effects on EAS – sensitive parameters (dystocia/stillborn in the 2 gen study in rats). - EAS mediated activity is not sufficiently investigated (i.e., A and S); however, indications of hormonal perturbation are noted in vivo involving estrogen and progesterone levels and estrogen/progesterone balance. - ED criteria are considered met (Scenario 2b). As regards TRVs, the current ADI and ARfD are covering the identified endocrine disrupting properties of the substance and are considered sufficiently protective for consumers. **Open point for EFSA**: to revise the EAS-mediated MoA in the report and include the still birth effects as sensitive to but not diagnostic of ED.

Subject	Conclusions Pesticides Peer Review Meeting
requested via a call for data open to all stakeholders. See mandate received from the European Commission on 26 May 2025.	

REPORT OF PESTICIDES PEER REVIEW TC 183

MECOPROP-P – MRL Art.10 Evaluating Member State: IE

2. Mammalian toxicity

Date: 26 September 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by EMS IE	Pesticide Registration Division, Dept. of Agriculture, Food & the Marine Laboratories - IE
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR)- DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Expert nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 MSs experts to discuss the toxicological profile (genotoxicity and general toxicity) of the metabolite hydroxymethyl-mecoprop-P (HMCPP) in an experts' meeting.	Metabolite: HMCPP Genotoxicity hazard identified?: No (Based on experimental data,i.e. negative Ames test and a negative in vivo MN test, with evidence of BM exposure (decrease PCE/NCE ratio).) Reference values of parent applied?: Yes (As a worst-case, since there are indications of lower toxicity than parent based on a 28-day study.)
Experts' consultation 2.2 MSs experts to discuss the toxicological profile (genotoxicity and general toxicity) of the metabolite carboxy-mecoprop-P (CCPP) in an experts' meeting.	Metabolite: CCPP Genotoxicity hazard identified?: No (Based on experimental data,i.e. negative Ames test and a negative in vitro MN test.) Reference values of parent applied?: Yes (Structural changes compared to parent not expected to increase toxicity.)
Experts' consultation 2.3 MSs experts to discuss the toxicological profile (genotoxicity and general toxicity) of the metabolite 4-glucosyl-MPP in an experts' meeting.	Metabolite: 4-Glucosyl MPP Genotoxicity hazard identified?: Open (No concern for gene mutation; however potential concern for chromosome aberration based on in silico analysis. An in vitro MN test is not available.) Reference values of parent applied?: Open (Genotoxicity open. In silico analysis supporting read-across for general toxicity not fully reliable (partially based on the conjugate and not on the aglycon).)

REPORT OF PESTICIDES PEER REVIEW

TC 182 and TC183

FLONICAMID – AIR IV

Rapporteur Member State: FI

2. Mammalian toxicity

Date: 26 September 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES)
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL

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Discussion points/Outcome

2. Mammalian toxicity

Please note that information part of this report may have been masked by EFSA in accordance with Article 63 of Regulation (EC) No 1107/2009 as well as EFSA's Practical Arrangements concerning confidentiality in accordance with Articles 7 and 16 of Regulation (EC) No 1107/2009, or EFSA's Practical Arrangements concerning transparency and confidentiality as a consequence of confidentiality requests submitted by the applicant on application dossiers for pesticides active substances or Maximum Residue Levels, respectively. Please note that information disclosed in this report is without prejudice to pre-existing intellectual property rights and data exclusivity clauses set out in Union law, and particularly in Article 62 of Regulation (EC) No 1107/2009.

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	**Conclusions Pesticides Peer Review Meeting**
Experts' consultation 2.1 Experts to confirm in a Peer Review Expert Meeting the oral absorption value for flonicamid.	The oral absorption of flonicamid is larger than 80%, but a calculation for an exact value is not included in the RAR. **Open point:** RMS to perform calculations for oral absorption of flonicamid and to provide a single value for oral absorption with rationale throughout a revised RAR.
Experts' consultation 2.2 Experts to discuss in a Peer Review Expert Meeting the comparative in vitro metabolism studies of flonicamid.	Based on an acceptable comparative in vitro metabolism study with plated primary hepatocytes, no unique human metabolites (UHM) nor disproportionate human metabolites (DHM) were identified for flonicamid.
Experts' consultation 2.3 Experts to discuss in a Peer Review Expert Meeting the genotoxicity of flonicamid.	Based on the available information, flonicamid is unlikely to be genotoxic.
Experts' consultation 2.4 Experts to discuss in a Peer Review Expert Meeting the critical effects of Flonicamid in long-term rodent studies and the human relevance of	The **NOAEL for rat systemic toxicity** is 200 ppm (7.32 mg/kg bw per day) in males based on reduced body weight and nephropathy at 1000 ppm, and 1000 ppm (44.1 mg/kg bw per day) in females based on reduced body weight gain, mild anemia, hepatic hypertrophy, hepatic dysfunction, renal tubular vacuolation, chronic nephropathy and accelerated age-related eye and muscle lesions at 5000 ppm.

Subject	Conclusions Pesticides Peer Review Meeting
all the observed neoplastic and non-neoplastic changes including mechanistic considerations.	The NOAELs for rat carcinogenicity are the highest doses tested, i.e. ≥1000 ppm (36.5 mg/kg bw per day) in males and ≥ 5000 ppm (219 mg/kg bw per day) in females. The **NOAEL for mouse carcinogenicity and systemic toxicity** is 80 ppm (corresponding to 10 mg/kg bw per day in males and 11.8 mg/kg bw per day in females) based on the elevated incidence of pulmonary adenoma in males and hyperplasia in both sexes at 250 ppm.
Experts' consultation 2.5 Experts to discuss in a Peer Review Expert Meeting the adequacy of the dose selection in the Rat 2-generation reproductive toxicity and the relative parental, offspring and reproductive NOAELs.	In the **Rat 2-generation reproductive toxicity study** • **Parental NOAEL** is 300 ppm (equivalent to 18.3 / 28.2 mg/kg bw per day) based on reduced ovary/adrenal weights and renal tubular vacuolation at 1800 ppm in parental females, and reduced 17β-estradiol concentration in F1 females. The thyroid weight was slightly increased in parental males and degenerative renal tubular lesions were observed at 1800 ppm in both parental and F1 males. • **Offspring NOAEL:** 300 ppm (equivalent to 30.5 mg/kg bw per day) based on delayed vaginal opening and reduced uterus weights (abs. and relative 19% decrease) in F1 female progeny only. • **Reproduction NOAEL: ≥**1800 ppm (equivalent to 109.1 and 163.8 mg/kg bw per day in males and females, respectively), based on the absence of effects at these dose levels. **Open point:** RMS to update the RAR based on the agreements reached during the PRM.
Experts' consultation 2.6 Experts to discuss in a Peer Review Expert Meeting the developmental toxicity studies carried out in rats and rabbits, the relevance of the findings for humans and to agree on the maternal and developmental NOAELs of the studies.	In the **developmental toxicity studies:** **Rat Maternal NOAEL** is 100 mg/kg bw per day based on liver and kidney effects at 500 mg/kg bw per day **Rat Developmental NOAEL** is 100 mg/kg bw per day based on increased incidence of skeletal variations, namely extra cervical ribs at 500 mg/kg bw per day. **Rabbit Maternal NOAEL is** 7.5 mg/kg bw per day based reduced weight gain and food consumption at 25 mg/kg bw per day. **Rabbit Developmental NOAEL** is ≥25 mg/kg bw per day based on the absence of developmental toxicity at the highest dose employed.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.7 Experts to discuss in a Peer Review Expert Meeting the ED assessment of flonicamid including the completeness of the dataset.	**T-modality** T-mediated parameters have been sufficiently investigated and a pattern of T-mediated adversity was not observed in the available dataset of studies. Scenario 1a of the ECHA/EFSA Guidance (ECHA/EFSA, 2018) is applicable and the **ED criteria for the T-modality are considered not met**. **EAS-modalities** EAS-mediated parameters have been sufficiently investigated, and a pattern of EAS-mediated adversity was not observed in the available dataset of studies. Scenario 1a of the ECHA/EFSA Guidance (ECHA/EFSA, 2018) is applicable and the **ED criteria for the EAS-modalities are considered not met**. **Open point:** RMS to report the outcome of the discussions in the revised RAR. **Open point**: RMS to correct the % of variation of ovarian weight and uterine weight in comparison with controls in the RAR Volume 3. **Open point**: RMS to check whether information on the (lack of) proper randomisation is supported.
Experts' consultation 2.8 Experts to discuss in a Peer Review Expert Meeting the genotoxicity and general toxicity of flonicamid metabolites based on the available information, and the setting of reference values if required, including TFNA, TFNA-AM, OH-TFNA-AM, TFNG, TFNG-AM, TFA, and N-oxide of TFNA-AM.	**Metabolite: TFNA** Genotoxicity hazard identified?: No (Based on an in vitro test battery, including gene mutation in mammalian cells.) Reference values of parent applied?: Yes (As a worst-case scenario, based on not adverse effects observed at the highest dose tested level in a 90-day rat study (high dose higher than 90-day NOAEL parent).) Groundwater relevance, other hazard identified?: Not triggered **Metabolite: TFNA-OH** Genotoxicity hazard identified?: No (Not triggered as residue; assessment triggered as groundwater: Based on an in vitro test battery, including gene mutation in mammalian cells.) Reference values of parent applied?: Not triggered (Assessment not triggered as groundwater or as residues: The experts discussed and agreed that as a worst-case scenario, based on higher NOAEL of TFNA-OH in a 90-day rat study than NOAEL of parent in 90-day rat study). Groundwater relevance, other hazard identified?: No **Metabolite: TFNA-AM**

Subject	Conclusions Pesticides Peer Review Meeting
	Genotoxicity hazard identified?: No (Based on an in vitro test battery, including gene mutation in mammalian cells. In addition, it is a major rat metabolite.) Reference values of parent applied?: Yes (Major rat metabolite, covered parent.) Groundwater relevance, other hazard identified?: Not triggered (Metabolite is considered responsible for the pesticide activity.) **Metabolite: OH-TFNA-AM** Genotoxicity hazard identified?: No (Based on read-across to TFNA-AM and TFNA-OH (structural similarities and organic functional groups)) Reference values of parent applied?: Yes (Same conclusions as for TFNA-AM and TFNA-OH (based on read-across).) Groundwater relevance, other hazard identified?: Not triggered **Metabolite: TFNG** Genotoxicity hazard identified?: No (Based on an in vitro test battery, including gene mutation in mammalian cells.) Reference values of parent applied?: Yes (As a worst-case scenario, based on not adverse effects observed at the highest dose tested level in a 90-day rat study (high dose higher than 90-day NOAEL parent).) Groundwater relevance, other hazard identified?: Not triggered **Metabolite: TFNG-AM** Genotoxicity hazard identified?: No (Based on an in vitro test battery, including gene mutation in mammalian cells.) Reference values of parent applied?: Open (Read-across to TFNG not accepted (not sufficiently robust).) Groundwater relevance, other hazard identified?: Not triggered **Metabolite: TFA** Genotoxicity hazard identified?: No (Reference to flurtamone and flufenacet peer review. EFSA statement on TFA reference values and ECHA RAC opinion ongoing.) Reference values of parent applied?: No (Reference to flurtamone and flufenacet peer review. EFSA statement on TFA reference values and ECHA RAC opinion ongoing.) Groundwater relevance, other hazard identified?: Reference to flurtamone and flufenacet peer review. EFSA statement on TFA reference values and ECHA RAC opinion ongoing **Metabolite: N-oxide of TFNA-AM**

Subject	Conclusions Pesticides Peer Review Meeting
	Genotoxicity hazard identified?: No (Based on an in vitro test battery, including gene mutation in mammalian cells.) Reference values of parent applied?: Not triggered Groundwater relevance, other hazard identified?: Not triggered
Experts' consultation 2.9 Experts to discuss in a Peer Review Expert Meeting the toxicological reference values of flonicamid, including consideration of the oral absorption.	The **ADI** of flonicamid is 0.073 mg/kg bw per day based on the NOAEL of 7.32 mg/kg bw per day from the 2-year rat study, applying a standard UF of 100. The **ARfD** of flonicamid is 0.075 mg/kg bw based on the NOAEL of 7.5 mg/kg bw per day from the developmental toxicity study in rabbits, applying a standard UF of 100. The **AOEL** of flonicamid is 0.073 mg/kg bw per day based on the NOAEL of 7.32 mg/kg bw per day from the 2-year rat study, supported by the NOAEL of 8 mg/kg bw per day of the 90-day and 1-year dog studies, applying a standard UF of 100. There is no need for correcting the value for oral absorption, as oral absorption is higher than 80%. The **AAOEL** of flonicamid is 0.075 mg/kg bw based on the NOAEL of 7.5 mg/kg bw per day from the developmental toxicity study in rabbits, applying a standard uncertainty factor of 100. There is no need for correcting the value for oral absorption, as oral absorption is higher than 80%. These values are proposed to replace the current HBGVs of flonicamid, i.e. ADI, ARfD and AOEL: 0.025 mg/kg bw per day, AAOEL: not set.
Experts' consultation 2.10 Experts to discuss the dermal absorption data and additional information provided for the formulation **IKI-220 100 OD** and its dilution(s).	The agreed dermal absorption values for flonicamid in the formulation **IKI-220 100 OD** are 3.4% for concentrate (100 g/L) and 29% for dilution (0.0832 g/L).
Experts' consultation 2.11 Experts to discuss the NDE for the formulation IKI-220 100 OD.	Non-dietary exposure estimates, based on the EFSA GD 2022, for the representative uses of the formulation **IKI-220 100 OD**, are below the (A)AOEL for operator, worker, resident and bystander without the application of risk mitigation measures.
Experts' consultation 2.12	Based on the *in vitro* study in human skin the dermal absorption values for flonicamid in the **IKI-220 500 WG**

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the dermal absorption data, additional data provided and the applicability of the triple-pack approach for the formulation IKI-220 500 WG and its dilution(s).	formulation are 0.10% and 23.88% for the concentrate (500 g a.s./L) and dilution (0.05 g a.s./L). Based on the *in vitro* study in rat skin, the dermal absorption values are 11.68% and 37.89% for the concentrate (500 g a.s./L) and dilution (0.05 g a.s./L). Based on the *in vivo* study with rats, the dermal absorption values are 10.45% for the concentrate (500 g a.s./L) and 26% for the dilution (0.05 g a.s./L). Based on the agreed triple pack approach, the final dermal absorption values for flonicamid in IKI-220 500 WG are 0.1% for the concentrate and 16.4% for the dilution (0.05 g a.s./L). **Open point**: RMS to include the revised calculations of the dermal absorption values by use of the triple pack approach, considering the agreements reached during the peer review meeting for the different in vitro and in vivo studies.
Experts' consultation 2.13 Experts to discuss the NDE for the formulation IKI-220 500 WG.	Approaches for non-dietary exposure estimates for the representative uses of the formulation IKI-220 500 WG were discussed and agreed. Regarding the indoor use on high vegetables (0.08 kg a.s./ha), reported only for MRL Application, non-dietary exposure estimates will not be needed if it is not part of the representative uses. **Open point:** RMS to provide revised non-dietary exposure estimates using the EFSA model 2022 (online calculator) for the formulation **IKI-220 500 WG** taking into account the agreed approaches and toxicological endpoints (AOEL, AAOEL and dermal absorption values).
Experts' consultation 0.1 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the	Regarding the co-formulants contained in the formulation used for representative uses (IKI-220 100 OD), sufficient toxicological data were available for all components, but six: for 5 of them a data gap was set for all endpoints (genotoxicity, repeated dose toxicity and carcinogenicity) in the absence of sufficient information, for the remaining one, a data gap was set for genotoxicity and carcinogenicity. **Open point:** The RMS should amend/integrate the RAR with the information provided during the meeting in a revised version. The RMS should also remove all data gaps for ED assessment of co-formulants/ components.

Subject	Conclusions Pesticides Peer Review Meeting
toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation used for representative uses (IKI-220 500 WG), sufficient toxicological data were available for all components, but six: for four a data gap was set for all endpoints (genotoxicity, repeated dose toxicity and carcinogenicity) in the absence of sufficient information. For another co-formulant/component, a data gap was set for both repeated dose toxicity and carcinogenicity, while for the sixth one a data gap was set only for carcinogenicity. **Open point:** The RMS should amend/integrate the RAR with the information provided during the meeting in a revised version. The RMS should also remove all data gaps for ED assessment of co-formulants/ components.

REPORT OF PESTICIDES PEER REVIEW TC 184

BACILLUS VELEZENSIS FZB42 - NAS 1107 Rapporteur Member State: NL

6. Microorganisms - Mammalian toxicity

Date: 25 September 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS NL	Ctgb - NL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS SE	Swedish Chemichals Agency (KEMI) -SE
National Expert nominated by MS SI	Agricultural institute of Slovenia - SI
National Expert nominated by MS SI	National Institute of Public Health - SI
External expert	Nicolas Radomski
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Ministry of Health - ES

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the experts at the beginning of this meeting.

[1] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/independence-policy-2024.pdf
[2] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/decision-ed-on-competing-interest-management-2024.pdf

Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	**Conclusions Pesticides Peer Review Meeting**
Experts' consultation 6.1 Discuss the secondary metabolites of potential relevance for human health, with focus on: 1) the strategy used for screening the genome to identify secondary metabolites potentially produced by *B. velezensis* FZB42 and the outcome of the analysis, i.e. a full list of the substances potentially produced 2) whether the list of potentially produced substances is adequate based on the available literature search (i.e. fengycin, iturin, surfactin, bacillibactin, bacilysin, bacillaene, difficidin, macrolactin, amylocyclicin and plantazolicin) or should be extended. 3) conclusion on the (potential) relevance of the secondary	Given that **subtilisin**, a respiratory sensitiser, can be produced by members of the *Bacillus subtilis* species complex, including *Bacillus velezensis*, analytical data should be provided to demonstrate that its levels are below the threshold for classification and labelling (**data gap**). Due to the lack of information on the level of subtilisin in the technical material, specific risk mitigation measures should be adopted beyond generic warning used for micro-organisms, such as personal protective equipment for the relevant exposed populations (operators and workers). Based on sufficiently reliable literature searches and whole genome sequencing (WGS) analysis, no other secondary metabolites of toxicological concern that may be produced by *Bacillus velezensis* strain FZB42 have been identified. **Open point**: RMS to clearly differentiate secondary metabolites from enzymes (both of potential concern) in a revised RAR.

Subject	Conclusions Pesticides Peer Review Meeting
metabolites for human health.	
Experts' consultation 6.2 Discuss the acute toxicity/pathogenicity studies in rats with FZB42, including the adequacy of the applied protocols and the results, with focus on the clearance.	The acute toxicity/pathogenicity of *Bacillus velezensis* FZB42 was sufficiently investigated in rats. Based on the available information it can be concluded that *B. velezensis* FZB42 has low infectivity and toxicity/pathogenicity potential.
Experts' consultation 6.3 Discuss the genotoxicity of surfactin C and of other secondary metabolites.	Based on the available dataset no genotoxicity concern is identified for surfactin C.
Experts' consultation 0.1 (tox) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	With regard to the formulation for the representative uses 'AmyProtec® 42', sufficient toxicological data were available for all components. The available information, including information from the existing uses other than plant protection products, under regulated EU frameworks, did not highlight any concern. **Open point**: RMS to align the revised RAR with the meeting notes.

REPORT OF PESTICIDES PEER REVIEW TC 183

FLUAZINAM – AIR IV after ED clock stop

Rapporteur Member State: AT

2. Mammalian toxicity

Date: 26 September 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Expert nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS NL	Ctgb - NL

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the experts at the beginning of this meeting.

[1] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/independence-policy-2024.pdf
[2] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/decision-ed-on-competing-interest-management-2024.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.13 Experts to discuss the reliability assessment and the analysis of the **developmental neurotoxicity study** (CA 5.7.1/05, CA 5.7.1/06). This should also consider, but not be limited to, the new evaluations ([redacted] 2023 and CA 5.7.1/07) on some developmental neurotoxicity endpoints, i.e., brain weight and auditory startle. The statistical analysis and its **impact on the setting of the NOAELs** should be also discussed during the experts' meeting.	The developmental neurotoxicity (DNT) study (CA 5.7.1/05, CA 5.7.1/06) is regarded as reliable. Based on the re-evaluation of some developmental neurotoxicity endpoints, i.e., brain weight and auditory startle, the following study NOAELs were agreed upon. • **NOAEL (offspring, neurotoxicity):** fluazinam is a developmental neurotoxicant and the NOAEL (offspring, neurotoxicity) is 10 mg/kg bw per day based on changes in the auditory startle response, reduced brain weight at post-natal day (PND) 21 in males and reduced brain width in males at PND 21 and 66. • **NOAEL (offspring, systemic):** 10 mg/kg bw per day based on lower body weight and body weight gains, a small number of offspring that showed dark and/or distended abdomens and delayed balano-preputial separation at the LOAEL of 50 mg/kg bw per day. • **NOAEL (maternal, systemic):** 10 mg/kg bw per day based on reduced body weight gain during gestation and food consumption during lactation. It is nevertheless highlighted that there is not a clear pattern of adversity in dams. Overall, the Health Based Guidance Values of fluazinam are not impacted. The new **auditory startle reflex test** (ASR) is considered supplementary (reliable with restrictions) and negative. The results of the **milk transfer study** do not impact the DNT study; however, they should have been considered for the dose selection in the new supplementary ASR test.

Subject	Conclusions Pesticides Peer Review Meeting
	Open point RMS to revise the RAR in line with the peer review meeting discussion.
Experts' consultation 2.14 Experts to discuss the outcome of the **Milk transfer study in lactating rat dams** (CA 5.6.1/05) and its implications on the outcomes of the DNT study (CA 5.7.1/05, CA 5.7.1/06), Reproduction toxicity Study (CA 5.6.1/03, CA 5.6.1/04) and Comparative Thyroid Assay (CA 5.8.3/18).	Milk transfer is overall negligible. The implication of the milk transfer study on the outcome of the DNT study, the ASR Test Reproduction toxicity Study and the Comparative Thyroid Assay are discussed under Experts' consultation 2.13 and Experts' consultation 2.12, respectively.
Experts' consultation 2.15 Experts to discuss the adequacy of the doses selected and the outcome of the **Reproduction toxicity study** (CA 5.6.1/03, CA 5.6.1/04) and its **implications on the toxicological endpoints and human health risk assessment** in an experts' meeting.	The doses tested in the **new Reproduction toxicity study** (CA 5.6.1/03, CA 5.6.1/04) in rats – P generation study were considered sufficient for setting the study NOAELs and LOAELs. **Parental NOAEL**=100 ppm (corresponding to 5.82 mg/kg bw per day in males and 6.92 mg/kg bw per day in females), based on increased liver weight in males accompanied by an increased incidence of centrilobular hepatocellular hypertrophy, and increased thyroid weight accompanied by increased follicular cell height in females at 500 ppm. **Reproductive NOAEL**= 500 ppm (highest dose tested, corresponding to 28.8 mg/kg bw per day in males and 34 mg/kg bw per day in females, respectively). **Offspring NOAEL**=100 ppm (corresponding to 5.82 mg/kg bw per day in males and 6.92 mg/kg bw per day in females), based on increased ano-genital distance in females, increased liver weight (PND 26) as well as decreased thymus (PND 26) and thyroid weight (PND 4). Furthermore, histopathological changes (i.e. increased follicular height) were observed at PND 26 at the top dose level. The NOAELs of this study have no impact on the Health Based Guidance Values of fluazinam.
Experts' consultation 2.16	The doses selected for the **CTA** study are considered too low due to the dietary route of administration and the low oral

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the adequacy of the doses selected and the outcome of the **Comparative Thyroid Assay** (**CTA**) (CA 5.8.3/18) and its **implications on the toxicological endpoints and human health risk assessment** in an experts' meeting.	absorption of fluazinam. Furthermore, the top dose did not cause adverse liver findings. The **maternal NOAEL is 100 ppm** (corresponding to 6.44 mg/kg bw per day) based on statistically significant increased average grade for thyroid follicular cell height at 500 ppm. The **foetal NOAEL is 100 ppm** (corresponding to 6.44 mg/kg bw per day) based on the decreased absolute and relative thyroid weight at the highest dose tested. The results of the CTA study have no impact on the Health Based Guidance Values (HBGVs) of fluazinam which are confirmed as follows: **ADI: 0.01 mg/kg bw per day** based on the NOAEL of 1.12 mg/kg per day (males) and 1.16 mg/kg bw per day (females) from the 2-year mouse study, as supported by the NOAEL of 1 mg/kg bw per day from the 52-week dog study, applying an UF of 100. **AOEL: 0.004 mg/kg bw per day** based on the NOAEL of 1 mg/kg bw per day from the 52-week dog study, as supported by the rabbit developmental study, applying an UF of 100 and correcting for oral absorption (35%). **ARfD: 0.07 mg/kg bw** based on the NOAEL of 7 mg/kg bw per day from the second developmental toxicity study in rabbit, applying an UF of 100. **(A)AOEL: 0.025 mg/kg bw** based on the NOAEL of 7 mg/kg bw per day from the second developmental toxicity study in rabbit, applying an UF of 100 and correcting for oral absorption (35%). **Open point** (for non-dietary exposure: this was not an Expert consultation point, still this OP applies after AOEL and AAOEL re-confirmation): RMS should revise non-dietary exposure estimates using the EFSA calculator (2014 or 2022), including both application rates (e.g. for IKF-1216 500 SC: 200 and 150 g a.s./ha) when presented for the same use. Different re-entry activities for the workers could be included if the exposure estimates are above the AOEL (e.g. inspection activities) with the online calculator, and DFR and DT50 values (agreed during the TC 48 in April 2021) should be used as refinement for workers, residents and bystanders.

Subject	Conclusions Pesticides Peer Review Meeting
New experts' consultation point proposed by EFSA for completeness (EC 01): MS experts to discuss whether the available information is sufficient to characterise the **full toxicological profile** of the formulation **'MCW 465 500 SC'** for representative use(s) with respect to the **acute, genotoxicity, short- and long-term toxicity**. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation used for representative uses (**MCW 465 500 SC**), sufficient toxicological data were available for all components, but [redacted]: for [redacted] of them a data gap for all endpoints (genotoxicity, repeated dose toxicity and carcinogenicity) was set in the absence of sufficient information. For the remaining [redacted], a data gap for genotoxicity was set. **Open point** The RMS should amend/integrate the RAR with the information provided during the meeting, including the updated harmonised classification of [redacted], in a revised version.
New experts' consultation point proposed by EFSA for completeness: (EC 02): MS experts to discuss whether the available information is sufficient to characterise the **full toxicological profile** of the formulation '**TIFC 500 SC'** for representative use(s) with respect to the **acute, genotoxicity, short- and long-term toxicity**. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation used for representative uses (**TIFC 500 SC**), sufficient toxicological data were available for all components, but [redacted] for which a data gap for all endpoints (genotoxicity, repeated dose toxicity and carcinogenicity) was identified in the absence of sufficient information. **Open point** The RMS should amend/integrate the RAR with the information provided during the meeting.
New experts' consultation point proposed by EFSA for completeness (EC 03):	Regarding the co-formulants contained in the formulation used for representative uses (**IKF-1216 500 SC**), sufficient toxicological data were available for all components, but [redacted]: for [redacted] a data gap for all endpoints (genotoxicity, repeated dose toxicity and carcinogenicity) was set in the absence of

Subject	Conclusions Pesticides Peer Review Meeting
MS experts to discuss whether the available information is sufficient to characterise the **full toxicological profile** of the formulation **'IKF-1216 500 SC'** for representative use(s) with respect to the **acute, genotoxicity, short- and long-term toxicity**. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	sufficient information. For the [redacted], a data gap for genotoxicity was set. **Open point** The RMS should amend/integrate the RAR with the information provided during the meeting in a revised version.

REPORT OF PESTICIDES PEER REVIEW

TC 182 and TC183

FENPYROXIMATE – AIR IV after ED clock stop Rapporteur Member State: AT

2. Mammalian toxicity

Date: 26 September 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL

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[1] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/independence-policy-2024.pdf
[2] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/decision-ed-on-competing-interest-management-2024.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	**Conclusions Pesticides Peer Review Meeting**
Experts' consultation 2.13 MSs experts to discuss the ED assessment of fenpyroximate for the EATS modalities in an experts' meeting.	**T-modality** T-mediated parameters have been sufficiently investigated and a pattern of T-mediated adversity was not observed in the available dataset of studies. Scenario 1a of the ECHA/EFSA Guidance (ECHA/EFSA, 2018) is applicable and the **ED criteria for the T-modality are considered not met**. **EAS-modalities** EAS-mediated parameters were not sufficiently investigated; however, no EAS-mediated adversity was observed in the available dataset of studies. The endocrine activity was sufficiently investigated (i.e., the following level 2 and 3 studies: ToxCast ER AUC model, OECD TG 456, OPPTS 890.1200, OECD TG 458 and OECD TG 441 were available) and negative. Therefore, the **ED criteria for humans for the EAS-modalities are not met**, and scenario 2a(ii) of the ECHA/EFSA ED Guidance (2018) is applicable. **Open point** RMS to report the outcome of the discussions in the revised RAR.
Experts' consultation 1 added by EFSA: MS experts to discuss whether the available information is sufficient to characterise the full **toxicological profile** of the	Sufficient toxicological data were available for all components contained in the formulation for representative uses 'NNI-850 SC', but [redacted] (present [redacted] in the final formulation). For these components the available toxicological information did not sufficiently address genotoxicity, repeated dose toxicity and carcinogenicity and that they might be considered for further assessment (data gap). The collected information, including information from the existing uses other than plant

Subject	Conclusions Pesticides Peer Review Meeting
formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	protection products, under regulated EU frameworks, did not highlight any concern. **Open point** RMS to report the outcome of the discussions in the revised RAR.
Experts' consultation 2 added by EFSA: Re-discussion of the toxicological reference values (TRVs) (follow-up of TC 60 (September 2021). EFSA note: Fenpyroximate is a **mitochondrial complex I inhibitor** and the experts' consultation has been included by EFSA to follow up the discussion about the selection of uncertainty factors (Ufs) for deriving TRVs values. This is to take into consideration the approach followed in similar cases, e.g., metyltetraprole, for possible alignment.	Fenpyroximate is a mitochondrial complex I inhibitor. There is neither information on the mitochondrial respiration inhibitory potency of this active substance nor on its actual brain concentrations after in vivo exposure in relation to inhibitory potency of the substance. As agreed in the previous Peer Review Experts' Teleconference 60 (September 2021), all experts and EFSA reconfirmed that a mechanistic understanding in the context of the existing Adverse Outcome Pathway (AOP) No. 3[3] i.e., Inhibition of the mitochondrial complex I of nigro-striatal neurons leads to parkinsonian motor deficits, is needed. A data gap was unanimously reconfirmed for conducting an AOP-informed IATA based on AOP No.3 i.e., for assessing the possible relation of fenpyroximate exposure to the Molecular Initiating Event (MIE) of binding and inhibition of mitochondrial complex I further leading to Parkinsonian adverse outcome, with the inclusion of appropriate ADME data for IVIVE suitable for Physiological-Based Kinetic (PBK) modelling. In light of the early status of the complex I inhibitors Mode of Action (MoA) research, the arbitrary choice of a potential Uncertainty Factor (UF), and the lack of a specific data requirement in Regulation (EU) No. 283/2013, EFSA expressed reservations about including an additional UF in the derivation of an AOEL and ADI for fenpyroximate to account for this uncertainty. Conversely, all the MS experts including the RMS agreed to keep both the data gap and the extra UF of 2 for the ADI and AOEL derivation to account for uncertainties due to the acknowledged MoA of this substance, as proposed in the Peer Review Experts' TC 60.

[3] Leist, M., & Schildknecht, S. AOP 3: Inhibition of the mitochondrial complex I of nigro-striatal neurons leads to parkinsonian motor deficits. Available at the following link: https://aopwiki.org/aopwiki/snapshot/html_file/3-2017-10-12T14:34:19+00:00.html

Subject	Conclusions Pesticides Peer Review Meeting
	Therefore, the **ADI is 0.005 mg/kg bw per day** based on the 2-year rat study NOAEL of 0.97 mg/kg per day and applying an additional UF of 2 to the standard UF of 100 considering the uncertainty due to the acknowledged MoA of this substance. The **AOEL is 0.004 mg/kg bw per day** based on the 90-d rat oral toxicity study NOAEL of 1.3 mg/kg bw per day and applying an additional UF of 2 to the standard UF of 100 considering the uncertainty due to the acknowledged MoA of this substance. Correction for 60% oral absorption was applied. **Open point** RMS to provide revised non-dietary exposure estimates.

REPORT OF PESTICIDES PEER REVIEW TC 184

TRICHODERMA HARZIANUM T78– NAS 1107 Rapporteur Member State: NL

6. Microorganisms - Mammalian toxicity

Date: 25 September 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS NL	Ctgb - NL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS SE	Swedish Chemicals Agendy (KEMI) - SE
National Expert nominated by MS SI	National Institue of Public Health - SI
External expert	Nicolas Radomski
Observer	Austrian Agency for Health and Food Safety (AGES) - AT

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Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Subject	**Conclusions Pesticides Peer Review Meeting**
Experts' consultation 6.1 Experts to discuss the outcome of the available toxicity studies with *T. harzianum* T78, including additional tabulated results for the clearance of the microorganism in the acute intratracheal and intraperitoneal studies.	*T. harzianum* strain T78 has no potential for toxicity, infectivity or pathogenicity based on the available studies in rats.
Experts' consultation 6.2 Experts to discuss the available evidence regarding the toxicological profile of emodin and its production by *Trichoderma harzianum* T78 in the technical material and for the representative use in order to conclude if it's a metabolite of concern or not.	Based on genomic analyses, *Trichoderma harzianum* strain T78 has no genetic potential of producing emodin. Moreover, emodin was not found during the analytical evaluation of the technical material.
Experts' consultation 6.3 Experts to discuss the available evidence	Based on genomic analysis and literature searches, **peptaibols** were identified as secondary metabolites potentially produced by *T.harzianum* strain T78, however they are considered of no toxicological relevance.

Subject	Conclusions Pesticides Peer Review Meeting
regarding the toxicological profile of secondary metabolites identified in the literature, as well as regarding their production by Trichoderma harzianum T78 in the technical material and for the representative use in order to conclude if metabolites of concern identified or not. It should also be considered if [redacted] has to be concluded as relevant impurity.	[redacted] was identified as a relevant impurity and has to be included in the specification, due to its toxic properties (harmonized classification H315; Causes skin irritation; H318: Causes serious eye damage; H372: Causes damage to lungs through prolonged or repeated inhalative exposure). The RMS disagreed and considered that [redacted] is a primary metabolite common to many microorganisms. In the case of the assessed technical product, it is considered not of concern because its level is below the level triggering classification.

REPORT OF PESTICIDES PEER REVIEW TC 183

FLUROCHLORIDONE – AIR IV

Rapporteur Member State: AT

2. Mammalian toxicity

Date: 26 September 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Expert nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	**Conclusions Pesticides Peer Review Meeting**
Expert consultation 2.13 Member State experts to discuss non-dietary exposure estimates in the context of negligible exposure as presented in Vol. 3 B.6 CP – AG-F8-250 CS (version Feb.2025, revised RAR after 2nd ED clock-stop).	The experts agreed on the outcome of the negligible exposure assessment performed by the RMS, following the draft "EU Commission guidance on negligible exposure", May 2015. For the formulation AG-F8-250-CS, negligible exposure could not be demonstrated for residential children and bystanders (both children and adults). For the formulation AG-F8-250-EC, negligible exposure could not be demonstrated for bystander children. **Open point**: RMS to revise the RAR including as a 1st tier approach on negligible exposure, considerations on the RMMs to be applied to reach exposure estimates < 10% of the (A)AOEL, for both formulations.

REPORT OF PESTICIDES PEER REVIEW TC 184

TRICHODERMA ASPERELLUM T34 – AIR V Rapporteur Member State: SE

6. Microorganisms - Mammalian toxicity

Date: 25 September 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agendy (KEMI) - SE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS SI	National Institue of Public Health - SI
External expert	Nicolas Radomski
Observer	Austrian Agency for Health and Food Safety (AGES) - AT

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Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	**Conclusions Pesticides Peer Review Meeting**
Expert consultation 6.1 Experts to discuss the infectivity/pathogenicity potential of *T. asperellum* T34 (all administration routes), taking into account the results of the acute studies as well as the biological properties (growth temperature, (lack of) relationship to known pathogens, others as relevant).	The potential for infectivity/pathogenicity of *T. asperellum* strain T34 is considered to be sufficiently investigated and concluded to be low, based on the biological properties of this microorganism, and on the provided acute toxicity, pathogenicity and infectivity studies in rats.
Expert consultation 6.2 Experts to discuss the secondary metabolites potentially produced by *T. asperellum* T34 of potential toxicological concern.	The available information is not sufficient to exclude the production of metabolites of potential toxicological concern by *T. asperellum* strain T34 and their presence in the MPCA/MPCP. Among these metabolites, the concentration of the genotoxic metabolite emodin should be kept below 0.1% in the MPCP. Consequently, the risk assessment for consumers, operators and workers exposed to metabolites in the product or after application cannot be concluded (**data gap**).
Expert consultation 0.7 Experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation **T34 Biocontrol** for representative use(s) with	With regard to the formulation **T34 Biocontrol** for the representative uses, sufficient toxicological data were available for all components. Based on the available information, including information from the existing uses other than plant protection products, under regulated EU frameworks, no concern was identified.

Subject	Conclusions Pesticides Peer Review Meeting
respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	
Expert consultation 0.8 Experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation **Xilon** for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	As the product **Xilon GR** has been discontinued and is thus no longer part of the renewal application for *T. asperellum* strain T34, no further discussion took place.

REPORT OF PESTICIDES PEER REVIEW TC 184

CANDIDA OLEOPHILA STRAIN O – AIR V

Rapporteur Member State: SI

6. Microorganisms - Mammalian toxicity

Date: 25 September 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Expert nominated by RMS SI	Agricultural institute of Slovenia - SI
National Expert nominated by RMS SI	National Institute of Public Health - SI
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS NL	Ctgb - NL
National Experts nominated by MS SE	Swedish Chemichals Agency (KEMI) -SE
External expert	Nicolas Radomski
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Ministry of Health - ES

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Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Subject	**Conclusions Pesticides Peer Review Meeting**
Experts' consultation 6.1 Experts to discuss the **toxins/metabolites** (potentially) produced by *C. oleophila*, either related to the mode of action (MoA) or secondary metabolites and their potential relevance for human and animal safety.	Based on sufficiently reliable literature review and whole genome sequences analysis, no secondary metabolites of toxicological concern are identified for *Candida oleophila* strain O. The primary metabolites glucanases are further discussed in Experts' consultation point 6.2.
Experts' consultation 6.2 Experts to discuss the **sensitisation properties** of MPCA and MPCP.	Literature data indicate a possible concern for allergenicity for β-1,3-glucanases. Since it cannot be excluded that β-1,3-glucanases could be produced by *Candida oleophila* strain O during/after post-harvest indoor treatment of pome fruit (representative use), specific risk mitigation measures should be implemented, such as personal protective equipment for the operators (and workers); not only the risk mitigation measures related to the generic warning sentence used for micro-organisms.
Experts' consultation 0.2 (tox) MS experts to discuss whether the available information is sufficient to characterise the full **toxicological profile** of the formulation for	[redacted] used in the manufacturing of the formulated product Nexy Biomass. **Open point**: RMS to update the DAR in line with the meeting discussion.

Subject	Conclusions Pesticides Peer Review Meeting
representative uses with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	

REPORT OF PESTICIDES PEER REVIEW TC 176

MELALEUCA ALTERNIFOLIA, ESSENTIAL OIL (TEA TREE OIL) – AIR IV

Rapporteur Member State: PL

2. Mammalian toxicity

Date: 19 June 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	European Commission - SANTE
National Expert nominated by RMS PL	Eko-Futura Sp. z o.o. - PL
National Expert nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS EL	Benaki Phytopathological Institute (BPI) - EL
National Expert nominated by MS SK	National reference laboratory for pesticides - SK
Hearing expert	Mohammad Chaudhry - UK
Hearing expert	Corrado Galli - IT

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.3 Follow-up discussion on the two generation reproductive toxicity study in Wistar rats – NOAEL setting and implications for health-based guidance values. Experts to discuss the following NOAELs • Reproductive, parental and offspring toxicity NOAELs in the newly submitted 2-generation study in rat KCA 5.6.1/01. • maternal and developmental toxicity NOAELs in the developmental toxicity study in rats and in rabbits, studies KCA 5.6.2/01 and	Tea Tree Oil (TTO) is currently listed in the CosIng[3] database with multiple functions (antioxidant, skin conditioning, antimicrobial, and perfuming activities) and it is used in a variety of skin and hair care products as well as oral care formulations. The Scientific Committee on Consumer Safety (SCCS) received a mandate from Commission to carry out a safety assessment on this ingredient. In this context, in February 2025, EFSA was approached by the SCCS secretariat for clarification on the NOAEL (reproductive) selection discussed in previous TC 131 (March 2024). A preliminary SCCS Scientific Opinion, open for comments with deadline 18 August 2025, is available[4]. An SCCS rapporteur, attending the Peer Review Meeting as hearing expert, presented information from the assessment of the SCCS. The SCCS considers that a NOAEL of 25 mg/kg bw per day could be derived for fertility and reproductive toxicity from the 2-generation toxicity study. The previously selected NOAEL (reproductive) i.e., 10 mg/kg bw per day based on the effects on sperm parameters (decreased number of sperms per cauda and decreased number of sperms per gram cauda) observed in F1 generation at the dose of 25 mg/kg bw per day, has been deemed still appropriate by the majority of MSs experts, excluding the RMS. The MSs experts also considered that no change, compared to what previously agreed in TC 131, in HBGV is needed.

[3] Available at this link https://ec.europa.eu/growth/tools-databases/cosing/user-manual
[4] SCCS (Scientific Committee on Consumer Safety), Scientific Opinion on Tea Tree Oil (CAS/EC No. 68647-73-4 /285-377-1) used in cosmetic products, preliminary version of 28 May 2025, SCCS/1681/2. Available at this link: https://health.ec.europa.eu/publications/sccs-scientific-opinion-tea-tree-oil-casec-no-68647-73-4-285-377-1_en; last accessed by EFSA in June 2025.

Subject	Conclusions Pesticides Peer Review Meeting
5.6.2/02 (newly submitted), respectively. Moreover, the skeletal findings observed at 30 mg/kg bw per day in the rat developmental toxicity study KCA 5.6.2/01 to be discussed by the experts.	**Post-meeting note (July 2025)**: After internal discussion on the proposal presented by SCCS, EFSA agreed that the reproductive NOAEL should be set at 25 mg/kg bw per day based on: - statistically significant decreased male and female fertility indices associated with decreased sperm motility (-12%), increased percentage of abnormal sperm counts (+486%) and decreased number of sperms per cauda epididymis (-32%) and number of sperm per gram cauda epididymis (-19%) observed at the top dose of 50 mg/kg by per day in P generation. - statistically significant decreased (confirmed by Dunnett's, Bonferroni and Scheffé correction; $p < 0.001$) number of sperm of cauda epididymis (-19%) and number of sperm per gram of cauda epididymis (-18%) associated with a statistically significant decreased sperm motility (-16%) in F1 generation at 38 mg/kg bw per day. The following consideration were taken into account by EFSA while revising the NOAEL (reproductive): - **Statistical significance**. For Group 4 - F1, statistical significance versus the control group ($p<0.01$) is reached for both number of sperms per cauda epididymis and number of sperms per gram of cauda epididymis applying Dunnett's correction, Bonferroni correction or Scheffé correction. Whereas, in Group 3, removing the outlier, the statistical significance, $p < 0.05$ but not $p<0.01$, is reached only applying Dunnett's correction. - **Dose-response**. The endpoint number of sperm per gram of cauda epididymis lack the dose-response relationship when the outlier in Group 3 is removed from the analysis (0%, 10%, 8%, 18% at 0, 10, 25, 38 mg/kg bw per day, respectively). - **Biological plausibility**. At the dose level of 25 mg/kg bw per day, mid-dose level, other sperm parameters are not affected in P and in F1 generation; however, it should be noted that in the F1 generation sperm morphology was assessed only in control and Group 4 (high-dose group). It has to be noted that in the dataset of studies available for TTO, effects on sperm, testis and epididymis are also observed in different species (i.e., rat and dog) and in studies of different duration starting from the dose level of 60 mg/kg bw per day (LOAEL) with a NOAEL of 30 mg/kg bw per day, corroborating the selection of the NOAEL (reproductive) from the 2-generation toxicity study at 25 mg/kg bw per day. Moreover, EFSA noted that the dose-spacing between Group 3 and 4 (25 and 38 mg/kg bw per day) is not ideal as the doses are too close to ensure a proper understanding of the dose-response relationship.

Subject	Conclusions Pesticides Peer Review Meeting
	The ADI and AOEL was based on the NOAEL (reproductive) of 10 mg/kg bw per day. Therefore, on the basis of the above-mentioned considerations, the TRVs are modified as follows: 1. ADI: 0.125 mg/kg bw per day (NOAEL 25 mg/kg bw per day) and standard UF of 100 and extra UF of 2 (subchronic to chronic toxicity). 2. AOEL: 0.125 mg/kg bw per day (NOAEL 25 mg/kg bw per day) and standard UF of 100 and extra UF of 2 (to account for lack of TK data to derive the oral absorption value). **Open point** The RMS to update the RAR in line with the conclusion of the Pesticide Peer Review Meeting TC 176 including a revision of the risk assessment for TTO.

REPORT OF PESTICIDES PEER REVIEW TC 177

BEAUVERIA BASSIANA R444 – NAS 1107 Rapporteur Member State: DK

6. Microorganisms - Mammalian toxicity

Date: 20 June 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Expert nominated by RMS DK	Danish Environmental Protection Agency – DK
National Experts nominated by MS AT	AGES – Austrian Agency for Health and Food Safety – AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment – DE
National Expert nominated by MS IT	ICPS - Centro Internazionale per gli Antiparassitari e la Prevenzione Sanitaria - IT
National Expert nominated by MS NL	CTGB - Dutch Board for the Authorisation of Plant Protection Products and Biocides – NL
National Expert nominated by MS SE	Swedish Chemicals Agency – SE
Observer	AGES – Austrian Agency for Health and Food Safety – AT
Observer	Ministry of health of Spain - ES

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[1] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/independence-policy-2024.pdf
[2] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/decision-ed-on-competing-interest-management-2024.pdf

Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 1) To discuss the strategy followed by the applicant for the identification of secondary metabolites of potential toxicological relevance for *Beauveria bassiana* strain R444; 2) To agree on the secondary metabolites of potential toxicological relevance and on the need to analytically evaluate them in the technical substance.	The strategy to identify secondary metabolites of potential toxicological concern combines literature searches and genomic analyses, and overall it is considered adequate. No secondary metabolites of potential toxicological concern were identified for discussion, but beauvericin. This metabolite has no genotoxic potential; its general toxicity profile cannot be concluded on the basis of the available information to allow for a quantitative risk assessment. Considering the measured low levels in the product and (based on MS experts' view) the expected low levels after application, it was considered of no concern. EFSA disagreed, since the general toxicity profile cannot be concluded on the basis of the available information, and insufficient data were available on the residue behaviour (in situ production after application) to finalise the risk assessment. **Open point** RMS to revise the DAR to integrate the comments discussed in the meeting.
Experts' consultation 1.1 (mammalian toxicity section) Pending the outcome of the request for additional information on the status of [redacted] and [redacted] in the MPCA as	Regarding the co-formulants contained in the formulation supported for the representative uses ('Bb-Protec'), based on the currently available information, sufficient toxicological data were available all components and it is possible to conclude that they do not impact on the toxicity/classification and safety of the proposed formulation.

Subject	Conclusions Pesticides Peer Review Meeting
manufactured, MS experts to discuss whether the available information is sufficient to characterize the full toxicological profile of the formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	

REPORT OF PESTICIDES PEER REVIEW TC 177

METARHIZIUM BRUNNEUM CB15-III Rapporteur Member State: DE

6. Micro-organisms - Mammalian toxicity

Date: 20 June 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS DE	German Federal Institute for Risk Assessment – DE
National Experts nominated by MS AT	AGES – Austrian Agency for Health and Food Safety – AT
National Expert nominated by MS DK	Danish Environmental Protection Agency – DK
National Expert nominated by MS IT	ICPS - Centro Internazionale per gli Antiparassitari e la Prevenzione Sanitaria - IT
National Expert nominated by MS NL	CTGB - Dutch Board for the Authorisation of Plant Protection Products and Biocides – NL
National Expert nominated by MS SE	Swedish Chemicals Agency – SE
Observer	AGES – Austrian Agency for Health and Food Safety – AT
Observer	Ministry of health of Spain - ES

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Discussion points/Outcome

6. Micro-organisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 Member State experts to discuss secondary metabolites potentially produced by the species *M. brunneum* in an experts' meeting.	The strategy to identify secondary metabolites of potential toxicological concern, combining literature searches and genomic analyses, is considered adequate with some limitations (incomplete whole genome sequence (WGS) analysis and literature search for some metabolites). Few metabolites were analysed in the product and no data on in situ production are available. Based on MS experts' view, except for a few metabolites (data gap), no concern is identified for most metabolites based on expected low levels after application. EFSA disagreed since, for some metabolites, the general toxicity profile cannot be concluded on the basis of the available information, and insufficient data were available on the residue behaviour (in situ production after application) to finalise the risk assessment.
Experts' consultation 2.2 Member State experts to discuss the genotoxic potential of *M. brunneum* strain CB15-III and its secondary metabolites in an experts' meeting.	As validated methods for genotoxicity testing of living microorganisms are not available, genotoxicity testing should only focus on secondary metabolites. The newly identified metabolites NG-391 and elymoclavine have been identified as potentially genotoxic compounds and this should be further investigated (data gap).
Experts' consultation 1.1 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the	Regarding the co-formulants contained in the formulation supported for the representative uses ('ATTRACAP'), based on the currently available information, sufficient toxicological data were available for all components and it is possible to conclude that they do not impact on the toxicity/classification and safety of the proposed formulation.

Subject	Conclusions Pesticides Peer Review Meeting
formulation for representative uses with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	**Open point:** RMS to provide an updated DAR, Vol. 4 with the information available and presented during the meeting.

REPORT OF PESTICIDES PEER REVIEW TC 177

TRICHODERMA ATROVIRIDE 77B – NAS 1107 Rapporteur Member State: NL

6. Microorganisms - Mammalian toxicity

Date: 20 June 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Expert nominated by RMS NL	CTGB - Dutch Board for the Authorisation of Plant Protection Products and Biocides – NL
National Experts nominated by MS AT	AGES – Austrian Agency for Health and Food Safety – AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment – DE
National Expert nominated by MS DK	Danish Environmental Protection Agency – DK
National Expert nominated by MS IT	ICPS - Centro Internazionale per gli Antiparassitari e la Prevenzione Sanitaria - IT
National Expert nominated by MS SE	Swedish Chemicals Agency – SE
Observer	AGES – Austrian Agency for Health and Food Safety – AT
Observer	Ministry of health of Spain - ES

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the experts at the beginning of this meeting.

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[2] https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/decision-ed-on-competing-interest-management-2024.pdf

Discussion points/Outcome

6. Micro-organisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 Member State Experts to discuss in an experts' meeting the evidence related to the possible production of emodin and/or exotoxins and/or other secondary metabolites by *Trichoderma atroviride* strain 77B and related possible toxicity issues (e.g. genotoxic effects of emodin).	The strategy to identify secondary metabolites of potential toxicological concern showed limitations (literature search indicated metabolites of potential toxicological concern, but no molecular or batch analysis). Based on MS experts' view, no metabolite of concern is identified based on expected low levels after application. EFSA disagreed e.g. for emodin since it is genotoxic and carcinogenic, and therefore, insufficient data were available on the residue behaviour (in situ production after application) to demonstrate that the human exposure to this metabolite is not significant.
Experts' consultation 6.2 Member State Experts to discuss the pathogenic potential of *Trichoderma atroviride* 77B in an experts' meeting.	Even in the absence of a reliable growth temperature study (submitted after the end of the clock stop), the available data do not show any concern regarding pathogenicity/infectivity of *Trichoderma atroviride* 77B.
Experts' consultation 1.2 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the	Regarding the co-formulants contained in the formulation supported for the representative uses ('BT-77'), based on the currently available information, insufficient toxicological data were available for all components and it is not possible to conclude that they do not impact on the toxicity/classification and safety of the proposed formulation.

Subject	Conclusions Pesticides Peer Review Meeting
formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity, and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	

REPORT OF PESTICIDES PEER REVIEW

TC 175 and TC 176

CLODINAFOP – AIR III, mandated for ED re-assessment

Rapporteur Member State: EL

2. Mammalian toxicity

Date: 19 June 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS EL	Benaki Phytopathological Institute (BPI) - EL
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency - DK
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS NL	Ctgb - NL
National Expert nominated by MS SK	National reference laboratory for pesticides - SK
Observer	Swiss Federal Office for the Environment - CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.9 identified after ED clock stop: MS experts to discuss the NOAEL values of the new studies provided for ED and their **implications on the toxicological endpoints** and human health.	**New 2-generation study in the rat**. • **NOAEL reproductive toxicity**: only LOAEL identified at 75 ppm, equivalent to 4.7/5.7 mg/kg bw per day for M/F based on statistically significant and dose related decreases in spermatid counts in testis and absolute epididymis weights. • **NOAEL parental toxicity**: 75 ppm, equivalent to 4.7/5.7 mg/kg bw per day for M/F based on increased liver weight accompanied by histopathological findings in males and slight but statistically significant decrease in body weight gain in females at 250 ppm (equivalent to 15.9/19.5 mg/kg bw per day for M/F, F0 premating) . • **NOAEL offspring**: 250 ppm equivalent to 18.8/20.8 mg/kg bw per day (F0 gestation/lactation). The LOAEL offspring is considered to be 750 ppm equivalent to 57.0/62.1 mg/kg bw per day (F0 gestation/lactation) based on the statistically significant decreases in body weight in pups towards the end of lactation and in organ weight differences in high dose pups. **New Oral Dietary CTA in CD (Sprague Dawley) IGS Rats.** • **Maternal NOAEL:** 200 ppm (equivalent to 30.23 mg/kg bw per day) based on liver and thyroid toxicity at 500 ppm (75.94 mg/kg bw per day). • **Offspring NOAEL:** 75 ppm (equivalent to 11.91 mg/kg bw per day), based on liver effects at 200 ppm (equivalent to 30.23 mg/kg bw per day).

Subject	Conclusions Pesticides Peer Review Meeting
	Neither the NOAELs from the new 2-generation study nor the NOAELs from the new CTA study have any impact on the health-based guidance values set for clodinafop in 2020 (EFSA Journal 2020;18(6):6151), that remain valid: **ADI**: 0.0003 mg/kg bw per day based on the NOAEL of 0.03 mg/kg bw per day from a rat 2-year study and an uncertainty factor (UF) of 100. **ARfD:** 0.05 mg/kg bw based on the NOAEL of 5 mg/kg bw per day from a rat developmental toxicity study, supported by a previous 2-generation reproductive study, and an UF of 100. **AOEL:** 0.0064 mg/kg bw per day from a NOAEL of 0.92 mg/kg bw per day from a rat 90-day study, and an UF of 143 (to also account for 70% oral absorption). **AAOEL:** 0.035 mg/kg bw from a NOAEL of 5 mg/kg bw per day from a rat developmental toxicity study, supported by a previous 2-generation reproductive toxicity study, and an UF of 143 (to also account for 70% oral absorption). **Open point** RMS to update the rationale and the offspring NOAEL of the new CTA study in a revised RAR.
Experts' consultation 2.10 MSs to discuss in a dedicated meeting the **ED assessment** of clodinafop, the appropriateness of the studies and their contextualisation in a weight-of-the-evidence (WOE) analysis. Furthermore, the proposed MoAs for the **T- and EAS-modalities** should be discussed.	**T-modality** T-mediated parameters have been sufficiently investigated and a pattern of T-mediated adversity was not observed in the available dataset of studies. Scenario 1a of the ECHA/EFSA Guidance (ECHA/EFSA, 2018) is applicable and the **ED criteria for the T-modality are considered not met**. **EAS-modalities** EAS-mediated parameters have been sufficiently investigated and a pattern of EAS-mediated adversity was not observed in the available dataset of studies. Scenario 1a of the ECHA/EFSA Guidance (ECHA/EFSA, 2018) is applicable and the **ED criteria for the EAS-modalities are considered not met**. **Open point** RMS to report the outcome of the discussions in the revised RAR. **Open points** • RMS to include the standard deviation in the THs/TSH data from the CTA in a revised RAR. • RMS to include the considerations on the available in vitro T4-UGT study in a revised RAR.

Subject	Conclusions Pesticides Peer Review Meeting
	• RMS to add standard deviation in relevant parameters in the new 2-generation reproductive study (OECD TG 416, 2001) in a revised RAR. • RMS to further substantiate the rationale applied to consider the lack of a clear pattern of EAS-mediated adversity in a revised RAR.

REPORT OF PESTICIDES PEER REVIEW TC 175

FLUAZINAM – AIR IV after ED clock stop

Rapporteur Member State: AT

2. Mammalian toxicity

Date: 17 June 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS BE	Federal Public Service Health, Food Chain Safety, Environment - BE
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Expert nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS EL	Benaki Phytopathological Institute (BPI) - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL
National Experts nominated by MS NO	Norwegian Food Safety Authority - NO
Observer	Norwegian Food Safety Authority - NO

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.12 Experts to discuss the assessment of the **ED properties** for fluazinam (human health). The lines of evidence for **EAS and T modalities** (endocrine mediated activity and adversity) should be presented in line with the ECHA/EFSA ED Guidance.	**T-modality** A pattern of T-mediated adversity was not observed in a sufficiently investigated dataset. **Scenario 1a** of the ECHA/EFSA Guidance (ECHA/EFSA, 2018) is applicable and the **ED criteria for T-modality are not met**. **EAS-modalities** EAS-mediated adversity was not sufficiently investigated; however, a pattern of EAS-mediated adversity was not observed in the available dataset of studies. The endocrine mediated activity was sufficiently investigated (ToxCast ER pathway model, OECD TGs 458, 441, 456 and Aromatase inhibition assay) and no EAS-mediated endocrine activity was observed. Therefore, **Scenario 2a(ii)** of the ECHA/EFSA Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for the **EAS-modalities are considered not met**. **Open point** RMS to revise the RAR in accordance with the outcome of the peer review meeting discussion.

REPORT OF PESTICIDES PEER REVIEW TC 175

PENCONAZOLE – AIR IV

Rapporteur Member State: NO

2. Mammalian toxicity

Date: 17 June 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS NO	Norwegian Food Safety Authority - NO
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS BE	Federal Public Service Health, Food Chain Safety, Environment - BE
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Expert nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS EL	Benaki Phytopathological Institute (BPI) - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL
Observer	Norwegian Food Safety Authority - NO

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.8 Experts to discuss whether T-modality is sufficiently investigated, and on which studies should be considered necessary.	T-mediated parameters have been sufficiently investigated and a pattern of T-mediated adversity was not observed in the available dataset of studies. **Scenario 1a** of the ECHA/EFSA Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for the T-modality are considered not met. **Open point** The RMS to report the outcome of the discussions in the revised RAR.
Experts' consultation 2.9 Experts to conclude on the EATS modalities.	The EAS-adversity is considered not sufficiently investigated; moreover, some positive predictions of androgen antagonist activity and androgen receptor binding (COMPARA) and effects (inhibition) on steroidogenesis activity are observed in vitro. **Scenario 2a(i)** of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and further data should be generated before a firm conclusion can be drawn on E, A and S modalities: - an OECD TG 443 study with cohort 1B and mating of cohort 1b to produce a second generation should be provided to address the data requirement. - An aromatase inhibition test (OPPTS 890.1200) should also be conducted in support to the MoA analysis. It is acknowledged that the applicant is conducting an OECD TG 416 study, although it is unclear whether it is carried out according to the EFSA recommendations (EFSA, 2020). Two different scenarios are identified: • in case the new OECD TG 416 study is considered adequate (i.e., according to EFSA 2020: includes anogenital distance of each F1 and F2 pups, presence and number of nipples/areolae in all male F1 and F2 pups, histopathological assessment of the mammary gland in P0 and F1 adult males and females, sperm parameters

Subject	Conclusions Pesticides Peer Review Meeting
	regardless if they have also been tested in the 90-days), the dataset would be considered as sufficient for the assessment of the EAS-mediated adversity. • In case the new OECD TG 416 study is considered as not adequate (i.e., not according to EFSA 2020, see above), and EAS-mediated adversity is not observed, an OECD TG 443 study with cohort 1B and mating of cohort 1b to produce a second generation should be provided to address the data requirement. References EFSA (European Food Safety Authority), 2020. Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology. EFSA supporting publication 2020:EN-1837. 26 pp. doi:10.2903/sp.efsa.2020.EN-1837 **Open points** - The RMS to check and revise the ToxCast information according to the latest information available on CompTox in the revised RAR. - The RMS to revise the interpretation of the OECD TG 456 according to the latest interpretative matrix reported in the latest version of the guidance (2023). - The RMS to reflect the outcome of the discussion in the revised RAR.

REPORT OF PESTICIDES PEER REVIEW TC 172

FATTY ACIDS - CAPRIC ACID – AIR IV

Rapporteur Member State: EL

2. Mammalian toxicity

Date: 22 May 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS EL	Benaki Phytopathological Institute - EL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS BE	Federal Public Service Health, Food Chain Safety and Environment - BE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish EPA - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS PT	Division of Management and Authorization of Plant Protection Products – PT
National Experts nominated by MS SE	Swedish Chemicals Agency - SE
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observers	Federal Public Service Health, Food Chain Safety and Environment - BE
Observers	Norwegian Food Safety Authority (Mattilsynet) - NO
Observer	Swedish Chemicals Agency - SE

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

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[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.1 MS experts to discuss in a Peer Review Meeting the ED properties of capric acid and the waiver proposed by the RMS.	A waiver of the ED assessment of capric acid for the EATS-modalities has been agreed based on the overall weight-of-evidence. Conduction of additional mammalian toxicity studies is not considered necessary based on lack of toxicological concern in all available studies on surrogate substances and due to the knowledge on its toxicological properties, in line with EFSA/ECHA guidance. **Open point** RMS to reflect the outcome of the discussion in a revised RAR.

REPORT OF PESTICIDES PEER REVIEW TC 172

FATTY ACIDS - CAPRYLIC ACID – AIR IV Rapporteur Member State: EL

2. Mammalian toxicity

Date: 22 May 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS EL	Benaki Phytopathological Institute - EL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS BE	Federal Public Service Health, Food Chain Safety and Environment - BE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish EPA - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS PT	Division of Management and Authorization of Plant Protection Products – PT
National Experts nominated by MS SE	Swedish Chemicals Agency - SE
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observers	Federal Public Service Health, Food Chain Safety and Environment - BE
Observers	Norwegian Food Safety Authority (Mattilsynet) - NO
Observer	Swedish Chemicals Agency - SE

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.1 MS experts to discuss the ED potential of caprylic acid on the basis of the available data and the waiver proposed by the RMS.	A waiver of the ED assessment of caprylic acid for the EATS-modalities has been agreed based on the overall weight-of-evidence. Conduction of additional mammalian toxicity studies is not considered necessary based on lack of toxicological concern in all available studies on surrogate substances and due to the knowledge on its toxicological properties, in line with EFSA/ECHA guidance. **Open point** RMS to reflect the outcome of the discussion in a revised RAR.

REPORT OF PESTICIDES PEER REVIEW TC 172

FATTY ACIDS – POTASSIUM SALTS (FATTY ACIDS FROM HYDROLYSED VEGETABLE OILS) – AIR IV
Rapporteur Member State: EL

2. Mammalian toxicity

Date: 22 May 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS EL	Benaki Phytopathological Institute - EL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS BE	Federal Public Service Health, Food Chain Safety and Environment - BE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish EPA - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS PT	Division of Management and Authorization of Plant Protection Products – PT
National Experts nominated by MS SE	Swedish Chemicals Agency - SE
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observers	Federal Public Service Health, Food Chain Safety and Environment - BE
Observers	Norwegian Food Safety Authority (Mattilsynet) - NO
Observer	Swedish Chemicals Agency - SE

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 The experts to discuss the **ED assessment** including the proposed study waivers.	A waiver of the ED assessment of fatty acids from hydrolysed vegetable oils for the EATS-modalities has been agreed based on the overall weight-of-evidence. Conduction of additional mammalian toxicity studies is not considered necessary based on lack of toxicological concern in all available studies on surrogate substances and due to the knowledge on its (lack of) toxicological properties, in line with the EFSA/ECHA ED guidance. **Open point** RMS to reflect the outcome of the discussion in a revised RAR.

REPORT OF PESTICIDES PEER REVIEW TC 171

PENCONAZOLE – AIR IV

Rapporteur Member State: NO

2. Mammalian toxicity

Date: 16 May 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Expert nominated by RMS NO	Norwegian Food Safety Authority - NO
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS BE	Federal Public Service Health, Food Chain Safety, Environment - BE
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS ES	Ministry of Health - ES
National Expert nominated by MS SE	Swedish Chemicals Agency (KEMI) - SE
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	National Institute of Public Health - CZ
Observers	Norwegian Food Safety Authority - NO
Observer	Swedish Chemicals Agency (KEMI) - SE
Observer	Federal Food Safety and Veterinary Office FSVO - CH

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 Experts to discuss whether the information on comparative metabolism of penconazole is adequate and sufficient to evaluate the metabolic profile in relevant toxicological species and in human, and to determine the relevance of toxicological animal data.	The provided in vitro comparative metabolism (IVCM) study with penconazole is mainly in line with the EFSA PPR Panel recommendations (EFSA, 2021) and considered sufficiently informative with regards to comparative metabolism in human and rat microsomes. No unique or disproportionate human metabolites were identified as compared to rat under the tested conditions. Since liver fractions from the animal species used in pivotal toxicological studies used to derive the health-based guidance values (dog and rabbit) were not tested, in line with Commission Regulation EU No. 283/2013 an IVCM study including rabbit and dog liver fractions is needed (**data gap**).
Experts' consultation 2.2 Experts to discuss and conclude on the photosafety (phototoxicity and photomutagenicity) of penconazole on the basis of the available information	The provided phototoxicity study with penconazole and, more in general, the phototoxicity assessment of penconazole show uncertainties (unclear UV absorption range of penconazole, phototoxicity in the UVB range not properly tested). No conclusions can be derived, and in line with Commission Regulation EU No 283/2013 requirement, a **data gap** is set for phototoxicity and photomutagenicity assessment of penconazole.
Experts' consultation 2.3 Experts to discuss liver findings in short term toxicity studies (e.g. rediscuss whether the	The short-term oral toxicity of penconazole was investigated in rats, mice and dogs. In all the three species, the liver was the main target organ of toxicity and concurred to identify the LOAELs and set the NOAELs. The lowest short-term NOAEL is 3 mg/kg body weight per day, based on the available 90-day/1 year study in the dog. Liver toxicity is known for triazoles and

Subject	Conclusions Pesticides Peer Review Meeting
observed cases with fibrosis in dogs should be considered as isolated cases and to expand also on other liver findings described as isolated throughout the provided short term studies in toxicological species).	ECHA RAC recently (2023) proposed STOT RE 2 classification for penconazole due to liver toxicity in the dog. Specific studies were discussed with regards the adversity of liver findings: - in a 90-day study in mice liver effects were considered adverse at 85 mg/kg bw per day (LOAEL in males) since consisting of both histopathological effects (hepatocellular hypertrophy) and increased organ weight (relative to body weight). The NOAEL has been set at 52 mg/kg bw per day (male mice). - in the short-term dog study, adverse liver effects were observed at ≥17 mg/kg bw per day and included increased organ weight (absolute and relative-to body weight), histopathological findings (inflammation with fibrosis, and hepatocyte cytoplasmic vacuolation and necrosis at top dose) and clinical chemistry changes. The NOAEL is set at 3 mg/kg bw per day (based on body weight gain changes and liver toxicity at 17 mg/kg bw per day). **New open point** RMS update the RAR taking into account the conclusions on liver toxicity and NOAEL of the discussed studies. RMS to quote the newest version of the ECHA RAC opinion (November 2023) in a revised RAR.
Experts' consultation 2.4 Experts to discuss if the reliability of the proposed in vitro and in vivo genotoxicity studies (e.g. in vitro chromosomal aberration assay (CHO) and in vivo micronucleus test in mouse and if these can be used to conclude on the genotoxic potential of penconazole.	A total of 8 genotoxicity studies with penconazole were provided and assessed (7 *in vitro* studies, of which three newly provided in this renewal dossier; and 1 *in vivo* micronucleus study in mouse). Based on a weight-of-evidence, penconazole is considered unlikely to be genotoxic taking into account the reliable and acceptable *in vitro* tests (negative) together with the available *in vivo* micronucleus test (negative, with limitations). The genotoxicity of penconazole was discussed by ECHA RAC (2023), based on the same data set discussed in the peer review. ECHA RAC concluded that for penconazole no classification is warranted for germ cell mutagenicity based on inconclusive data. EFSA will consult ECHA to clarify whether the 3 newly provided studies have been fully taken into account in the 2023 ECHA RAC assessment, and the discussion will be reopened.

Subject	Conclusions Pesticides Peer Review Meeting
	New open point RMS to introduce the 3 new genotoxicity studies (currently in Vol. 4 of the draft RAR) in Vol. 3, making sure to mask the confidential information on impurities (e.g., number, content, identity).
Experts' consultation 2.5 Experts to discuss the limitations/adequacy of the submitted rodent long term/carcinogenicity studies and whether these are sufficient to exclude a carcinogenic potential of penconazole.	Three long-term studies were provided (1 in rats and 2 in mice). Although uncertainties are noted (higher dose levels should have been tested), these studies are considered sufficient to explore the long-term toxicity and carcinogenicity of penconazole, and no further in vivo studies are needed. This conclusion is in line with ECHA RAC (2023). Some mechanistic information was provided on metabolic induction by penconazole in rats and mice, however, a comparative evaluation of penconazole with other triazoles has not been provided. A new literature search and supporting information from a thorough review of the literature available on liver toxicity/carcinogenicity by triazoles should be performed (**data gap**).
Experts' consultation 2.6 Experts to discuss the DNT assessment of penconazole, taking into account the information on neurotoxicity for triazole class fungicides on the basis of the available scientific information.	Based on the available information, no (developmental) neurotoxicity is expected for penconazole considering that there are no indications of neurotoxic effects for the chemical class to which it belongs (triazoles) and that no neurotoxic effects have been observed in the available dataset (see also experts' consultation 2.7)
Experts' consultation 2.7 Experts to discuss the neurotoxicity assessment of penconazole, taking into account the information on neurotoxicity for triazole class fungicides, on the basis of the available scientific information.	Based on the available information there is no evidence for an association between triazole pesticides exposure and neurotoxicity, or Parkinson's disease. Some literature studies support that just a few triazoles substances can cause specific neurotoxicity effects. Regarding penconazole, based on the assessment of the Body of Evidence for the active substance, no effects have been observed that would provide sufficient evidence on its potential of causing neurotoxicity.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.8 Experts to discuss whether T-modality is sufficiently investigated, and on which studies should be considered necessary.	This point will be discussed in the June/July 2025 round of peer review meetings.
Experts' consultation 2.9 Experts to conclude on the EATS modalities.	This point will be discussed in the June/July 2025 round of peer review meetings.
Experts' consultation 2.10 Experts to discuss the genotoxicity assessment of the metabolite CGA142856.	**CGA 142856 (Triazole acetic acid, TAA)** No genotoxicity hazard was identified (available data do not raise concern for genotoxicity. However, aneugenicity was not properly addressed - **data gap**). TAA has specific toxicological reference values: ADI and ARfD of 1 mg/kg bw per day based on NOAELs of 100 mg/kg bw per day from reproductive toxicity study in rats and developmental studies in rabbits. The setting of reference values might need to be reconsidered once data gap has been fulfilled. The groundwater relevance of this metabolite remains open since, no re-assessment of the available data has been done by the applicant or by the RMS. An assessment of available data is needed (see **new open point** below). **CGA71019 ([1,2,4] triazole, TRZ)** This metabolite has been recently assessed in the EU (EFSA, 2018). There are no indications that previous conclusions should be reconsidered, however, no re-assessment of the available data has been done by the applicant or by the RMS. An assessment of available data is needed (see **new open point** below). **CGA131013** **(triazole alanine, TA)** This metabolite has been recently assessed in the EU (EFSA, 2018). There are no indications that previous conclusions should be reconsidered, however no re-assessment of the

Subject	Conclusions Pesticides Peer Review Meeting
	available data has been done by the applicant or by the RMS. An assessment of available data is needed (see **new open point** below). **CGA205369** **(triazole lactic acid, TLA)** This metabolite has been recently assessed in the EU (EFSA, 2018). There are no indications that previous conclusions should be reconsidered, however, no re-assessment of the available data has been done by the applicant or by the RMS. An assessment of available data is needed (see **new open point** below). **New open point:** For CGA 142856 (Triazole Acetic Acid, TAA), CGA71019 ([1,2,4] triazole, TRZ), CGA131013 (triazole alanine, TA), and CGA205369 (triazole lactic acid, TLA): RMS to check the available data and provide a list of endpoints; RMS to revise the RAR accordingly.
Experts' consultation 2.11 Experts to conclude the toxicological assessment of the metabolites CGA127841, CGA132465, CGA177279, CGA177281 and CGA179944	**CGA132465** Genotoxicity hazard identified? NO (Based on a negative in vitro test battery including a mammalian gene mutation assay.) Reference values of parent applied? YES (Read-across to parent, based on commonalities of effects observed in short-term toxicity studies (28-day study with the metabolite). **CGA127841** Genotoxicity hazard identified? NO(Major rat metabolite; covered by parent.) Reference values of parent applied?: YES (Major rat metabolite; covered by parent.) **CGA190503** Genotoxicity hazard identified?: NO (Based on read-across to parent and to a major rat metabolite, CGA132465.) Reference values of parent applied?: Open (Read-across to parent and to a major rat metabolite, CGA132465; plausible, more robust read across is proposed to substantiate the case.)

Subject	Conclusions Pesticides Peer Review Meeting
	CGA179944 Genotoxicity hazard identified?: NO (Based on a negative in vitro test battery including a mammalian gene mutation assay. The same genotoxicity data package is available under tetraconazole.) Reference values of parent applied?: YES (Based on comparable NOAEL in rat developmental toxicity study to parental developmental toxicity study and the higher NOAEL in the rabbit developmental toxicity study compared to the parent). Groundwater relevance; other hazards identified?: YES, Based on a concern for developmental toxicity in available developmental toxicity studies, similarly to parent, the metabolite is considered a relevant groundwater metabolite. **CGA177279** Genotoxicity hazard identified?: NO (Major rat metabolite; covered by parent.) Reference values of parent applied?: Yes (Major rat metabolite; covered by parent.) **CGA189659** Genotoxicity hazard identified?: NO (Read-across to CGA179944 supported. Same conclusions for genotoxicity applies.) Reference values of parent applied?: Not triggered (/) **CGA205373** Triazolylglycolic acid Genotoxicity hazard identified?: Open (No data; no assessment) Reference values of parent applied?: Not triggered (/)
Experts' consultation 2.12 Experts to conclude on toxicological endpoints.	**ADI = 0.015 mg/kg bw/day** Based on the NOAEL of the short-term oral toxicity study in dogs (3 mg/kg bw per day) and 200X UF (100X standard UF and additional 2X to account for the extrapolation from subchronic to chronic). **ARfD = 0.5 mg/kg bw**

Subject	Conclusions Pesticides Peer Review Meeting
	Based on the NOAEL of the developmental toxicity study in rabbits (50 mg/kg bw per day) and 100X UF (standard). **AOEL = 0.03 mg/kg bw/day** Based on the NOAEL from the short-term study in dogs (3 mg/kg bw per day) and 100X UF (standard), with no additional correction factor for oral absorption. **AAOEL = 0.5 mg/kg bw** Based on the NOAEL of the developmental toxicity study in the rabbit (50 mg/kg bw per day) and 100X UF (standard).
Experts' consultation 2.13 Experts to agree on final dermal absorption values to use for product exposure and risk assessment.	The agreed dermal absorption values for penconazole formulated in A6209G are 0.51% for the undiluted product (100 g/L) and 23% for all tested dilutions (concentrations 0.026-0.3 g/L).
Experts' consultation 2.14 Experts to discuss the two DFR studies for grapevines and pome fruits.	Based on the DFR study on grapevines, the experts agreed on a representative initial DFR value (0DAA1) of 1.42 µg/cm²/kg a.s./ha and on a DT_{50} value of 2.7 days, suitable for Central and Northern EU zones (not for Southern EU zones). Based on the DFR study on pome fruits, the experts agreed on a representative initial DFR value (0DAA1) of 1.73 µg/cm²/kg a.s./ha and on a DT_{50} value of 5.5 days for uses on pome fruits in all EU zones. **New open point** RMS to check the field recoveries in both DFR studies and correct the raw data if field recoveries were below 95%. If corrections are done for low field recoveries, RMS should also check the derived DFR0 and DT_{50} values for both pome fruit and grape vine studies. RMS to provide revised non-dietary exposure estimates with the agreed toxicological endpoints (AOEL, AAOEL, dermal absorption values) and DFR/DT_{50} values (firstly with default values acc. to EFSA GD 2022, secondly with refined values and zonal applicability as agreed). RMS to consider also that a margin of exposure of 2 (max 50% of (A)AOEL) should be

Subject	Conclusions Pesticides Peer Review Meeting
	considered in the final step of the assessment to take into account the possible shift in isomer ratio (from the less toxic to the most toxic isomer) after application (for workers and residents).
Experts' consultation (new) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation supported for the representative uses (A6209G), based on the currently available information, sufficient toxicological data are available for most components. However, for [redacted] co-formulant (and its components) toxicological data is insufficient (including genotoxicity, short and long term toxicity/ carcinogenicity) and it is not possible to conclude whether it impacts on the toxicity/classification and safety of the proposed formulation. **Open point**: the RMS to revise the RAR Vol.4 in line with the discussion held during the peer review meeting.

REPORT OF PESTICIDES PEER REVIEW

TC 171 and TC 172

CLETHODIM – AIR IV

Rapporteur Member State: SE

2. Mammalian toxicity

Date: 22 May 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency (KEMI) - SE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS BE	Federal Public Service Health, Food Chain Safety, Environment - BE
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish EPA - DK
National Experts nominated by MS EL	Benaki Phytopathological Institute - EL
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	Ctbg - NL
National Expert nominated by MS PT	Division of Management and Authorization of Plant Protection Products - PT
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observers	Federal Public Service Health, Food Chain Safety, Environment - BE

Status	Name of institution/attendee
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH
Observer	National Institute of Public Health - CZ
Observers	Norwegian Food Safety Authority - NO
Observer	Swedish Chemicals Agency (KEMI) - SE

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the results (including assessment of unique and disproportionate human metabolites) and the reliability of the comparative in vitro metabolism study (Vol. 3, B.6.1.2/01).	The in vitro comparative metabolism study is considered reliable with restrictions. M5 is considered a human unique metabolite in vitro. **Open point**: RMS to include data on metabolite formation for all time points from the study report into a revised RAR (Tables 22, 23 and 24 from the study report) and to update the assessment and conclusions of the study in the revised RAR as agreed in the Experts' Meeting.
Experts' consultation 2.2 Experts to discuss the ADME study (B.6.1.1/01), including the newly provided data on different isomers and related determination of major rat metabolites, the toxicokinetic parameters, and the residue definition of body fluids and tissues (human biomonitoring).	The ADME study is considered acceptable with restrictions; toxicokinetic parameters were not determined but lack of that information does not impact the overall toxicological evaluation of clethodim. Oral absorption of clethodim is 88-93%. The major rat metabolites for clethodim are clethodim sulfoxide and S-methyl sulfoxide. The residue definition for body fluids and tissues is clethodim, clethodim sulfoxide and S-methyl sulfoxide. **Open point**: The RMS is kindly requested to update the RAR based on the agreements reached by the experts.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.3 Experts to discuss short-term toxicity potential of clethodim, including NOAEL setting and the reliability of the available studies.	5-week pilot feeding study in rats: The study is considered acceptable with limitations. The NOAEL is 200 ppm (corresponding to 12.5 mg/kg bw per day) based on increased relative liver weight and increased incidence in liver hypertrophy in males. Rat 90-day study: The study is considered acceptable with limitations. The NOAEL is 500 ppm (corresponding to 25 mg/kg bw per day) based on reduced body weight gain (≥10%), increased relative liver weight in males only (12%) and histopathological changes in the liver (hypertrophy). Literature study: 90-day rat study: The study is considered as supportive information, and no NOAEL can be derived. Mouse 28-day study: The study is considered acceptable with limitations. The NOAEL is 1500 ppm (corresponding to 179 mg/kg bw per day) based on increased relative liver weight and histopathological changes in the liver (centrilobular hypertrophy). Dog 90-day study: The study is considered acceptable. The NOAEL is 75 mg/kg bw per day (equal to 62 mg/kg bw per day after correction for purity for test substance) based on increased liver weight (absolute and relative), changes in biochemical parameters indicating liver toxicity (mainly increased alkaline phosphatase, cholesterol, globulins and decreased albumin/globulin ratio) and histopathological changes in the liver (increased severity of centrilobular vesicles/vacuoles). Dog 1-year study: The study is considered acceptable. The NOAEL is 1 mg/kg bw per day (equal to 0.83 mg/kg bw per day after correction for purity for test substance) based

Subject	Conclusions Pesticides Peer Review Meeting
	on increased liver weights and histopathological changes in the sternal bone marrow (hyperplasia). **Open point**: RMS to update the evaluation and NOAEL setting of the studies in a revised RAR as agreed in Experts' meeting and to provide specific information on the effects at the LOAEL.
Experts' consultation 2.4 Experts to discuss the genotoxicity potential of clethodim, including the reliability of the genotoxicity studies reported in Vol. 3, B.6.4.1/01, Vol. 3CA B.6.4.1/02, B.6.4.1/06, B.6.4.2/01 and the newly submitted mouse lymphoma assay.	<u>1st microbial reverse mutation assay (B.6.4.1/01):</u> The study is considered acceptable and reliable. Clethodim did not induce gene mutations. <u>2nd microbial reverse mutation assay (B.6.4.1/02):</u> The study is considered supplementary. Clethodim did not induce gene mutations. <u>In vitro Chromosome Aberration test (B.6.4.1/06):</u> The study is considered supplementary. The outcome of the study is equivocal in the absence of metabolic activation. <u>Mammalian Cell Gene Mutation Test (in vitro mouse lymphoma; B.6.4.1/08):</u> The study is considered acceptable. Clethodim did not induce gene mutations. <u>Mammalian in vivo chromosome aberration test (B.6.4.2/01):</u> The study is considered supplementary. Clethodim did not induce chromosome aberrations. <u>Overall conclusion genotoxicity:</u> Based on acceptable and reliable studies in vitro, clethodim is considered unlikely to be genotoxic. The available in vivo chromosome aberration study, although supplementary, did not show any concern for chromosome aberration. **Open point**: RMS to update the RAR with the conclusions reached during the Experts' Meeting on the genotoxicity studies for clethodim.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.5 Experts to discuss the systemic and carcinogenic NOAELS in both rat and mouse long term and carcinogenicity studies.	Chronic Oral Oncogenicity Study in Mice: The NOAEL for systemic toxicity is 24 mg/kg bw per day based on liver effects (increased relative liver weight and histopathological changes, i.e. hepatocellular hypertrophy, increased pigment in females and bile duct hyperplasia in males) and histopathological changes in the lung (foci of amphophilic alveolar macrophages). The NOAEL for carcinogenic effects is 238 mg/kg bw per day (highest dose level tested). Chronic toxicity/carcinogenicity study in rats: The NOAEL for systemic toxicity is 16 mg/kg bw per day based on liver effects (increased organ weight and histopathological changes, i.e., hepatocellular and centrilobular hypertrophy associated with increased number of binucleated cells) and decreased body weight gain. The NOAEL for carcinogenic effects is 86 mg/kg bw per day (highest dose level tested). **Open point**: RMS to provide information in an updated RAR on the dose conversion from ppm to mg/kg bw per day for the chronic/oncogenicity studies, including information on possible correction for purity of the test item. RMS to provide information on the adverse findings at the LOAELs (systemic toxicity) as agreed by the experts.
Experts' Consultation 2.6 Experts to discuss the generational studies for clethodim in rats, including palatability and dose levels for pilot study (B.6.6.1/01), and the NOAELs and the dose levels for the 2-generation rat study (B.6.6.1/02).	2-generation reproductive toxicity study in rats (B.6.6.1/01; dose range finding study): Considering that analysis of the diets is available, there is no need to use default values for converting chemical substance concentrations in feed. There is no clear evidence that palatability would be responsible for the reduced food consumption. 2-generation reproductive toxicity study in rats: The NOAEL for parental toxicity is 500 ppm (corresponding to 32.2 mg/kg bw per day) based on reduced body weights in both generations at 2500 ppm covering also reduced absolute prostate and seminal vesicles weights of unclear relevance in F1 adults.

Subject	Conclusions Pesticides Peer Review Meeting
	The NOAEL for offspring toxicity is 2500 ppm (corresponding to 163 mg/kg bw per day, the highest tested dose). The NOAEL for reproductive toxicity is 2500 ppm (corresponding to 163 mg/kg bw per day, the highest tested dose). **Open point**: RMS to provide information in an updated RAR on the dose conversion from ppm to mg/kg bw per day for the generational studies, including information on possible correction for purity of the test item. RMS to update NOAEL for offspring toxicity in an updated RAR as agreed by the experts.
Experts' consultation 2.7 Experts to discuss the developmental toxicity studies of clethodim.	<u>Developmental toxicity study in the rat:</u> The NOAEL for maternal toxicity is 100 mg/kg bw per day (equal to 83.3 mg/kg bw per day after correction for purity of test substance) based on clinical signs and reduced bodyweight gain. The NOAEL for developmental toxicity is 100 mg/kg bw per day (equal to 83.3 mg/kg bw per day after correction for purity of test substance) based on decreased foetal weight and incresased incidence of skeletal variations. <u>Developmental toxicity study in the rabbit:</u> The NOAEL for maternal toxicity is 25 mg/kg bw per day (20.8 mg/kg bw/day, after correction for purity of test substance) based on decreased bodyweight gain and clinical signs. The NOAEL for developmental toxicity is 100 mg/kg bw per day (83.3 mg/kg bw per day, after correction for purity of test substance) based on increased incidences of misaligned sutures (fontanelle), nasal irregular ossification, and angulation of the hyoid alae.
Experts' consultation 2.8 Experts to discuss the neurotoxicity studies of clethodim, including the study that has been used by Health Canada for setting the ARfD (if available).	<u>90-day neurotoxicity study in rats:</u> The NOAEL for systemic toxicity is 1500 ppm (corresponding to 94 mg/kg bw per day) based on reduced bodyweight and bodyweight gain. The NOAEL for neurotoxicity is 5000 ppm (corresponding to 331 mg/kg bw per day), the higest tested dose.

Subject	Conclusions Pesticides Peer Review Meeting
	The study used by Health Canada for setting of the ARfD was not provided for the current assessment of clethodim.
Experts' consultation 2.9 Experts to discuss the ED properties of clethodim.	**T-modality** A pattern of T-mediated adversity was not observed in a sufficiently investigated dataset. **Scenario 1a** of the ECHA/EFSA Guidance (2018) is applicable and the ED criteria for EAS-modality are not met for clethodim. **EAS-modalities** EAS-mediated activity has been sufficiently investigated (OECD TG 440, OECD TG 441, OECD TG 456, Aromatase assays were available) and no EAS-mediated endocrine activity has been observed. Although the EAS-mediated parameters have not been sufficiently investigated, there is no sufficient evidence of a pattern of EAS-mediated adversity in the available dataset of studies. **Scenario 2a(ii)** of the ECHA/EFSA Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for the EAS-modalities are not met for clethodim. **Open point:** The RMS to revise the RAR in line with the Peer Review Meeting discussion.
Experts' consultation 2.10 Experts to discuss the (geno)toxicological profile of clethodim's metabolites, including its comparison to the toxicological profile of the parent and setting of specific toxicological reference values when applicable. Subject to change, the following residue metabolites are to be discussed: - Clethodim sulfoxide (RE-45924): genotoxicity and general toxicity.	**Clethodim sulfoxide** Code: RE-45924 Genotoxicity hazard identified?: No (Major rat, covered by parent. As a groundwater a test battery is required.) Reference values of parent applied?: Yes (Major rat, covered by parent) Groundwater relevance; other hazards identified?: No (Parent not classified as Carcinogenic or Reproductive toxicant.) **Clethodim sulfoxide glucoside** Code: RE-45924 glucoside Genotoxicity hazard identified?: No (Covered by its aglycon, clethodim sulfoxide.) Reference values of parent applied?: Yes (Covered by its aglycon, clethodim sulfoxide.)

Subject	Conclusions Pesticides Peer Review Meeting
- Clethodim sulfoxide glucoside (RE-45924 glucoside): genotoxicity and general toxicity. - Clethodim 5-hydroxy sulfoxide (RE-51229): genotoxicity. - Clethodim sulfone (RE-47253): genotoxicity and general toxicity. - Clethodim sulfone glucoside (RE-47253 glucoside): genotoxicity and general toxicity. - Clethodim 5-hydroxy sulfone (RE-51228): genotoxicity. - Clethodim imine sulfoxide (RE-47718; M21R): genotoxicity. - Clethodim imine sulfone (RE-47719; M23R, M24R): genotoxicity. - 3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid (DME sulfone acid; M18R, M19R): genotoxicity and general toxicity. - Hydroxy clethodim imine sulfone glucoside (M20R(a)): genotoxicity. - Clethodim imine sulfone glucoside (M20R(b)): genotoxicity. - 3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid (DME sulfoxide acid; M16R, M17R): genotoxicity and general toxicity. - Hydroxy 3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid (M14R,	**Clethodim 5-hydroxy sulfoxide** Code: RE-51229 Genotoxicity hazard identified?: No (Read-across to clethodim sulfoxide.) Reference values of parent applied?: Not triggered. **Clethodim sulfone** Code: RE-47253 Genotoxicity hazard identified?: Open (An in vivo follow up would be needed for the positive Ames and MLA studies. In addition, the stability and the potential degradation products of concern should be further investigated.) Reference values of parent applied?: Open (Qualitatively different than parent). Specific reference values once genotoxicity is clarified. ADI of 0.004 mg/kg bw per day in the 28-day rat study based on a NOAEL of 4.1 mg/kg bw per day based on decrease bwg (15%) at 39.9 mg/kg bw per day (it was noted that haematological findings (below 10%) were considered not adverse) using a standard UF of 100 plus extra UF of 10 for extrapolation of short-term to chronic and lack of reproductive toxicity studies. Groundwater relevance; other hazards identified?: No (Parent not classified as Carcinogenic or Reproductive toxicant. **Clethodim sulfone glucoside** Code: RE-47253 glucoside Genotoxicity hazard identified?: Open (Covered by its aglycon, clethodim sulfone. Same conclusion applies.) Reference values of parent applied?: Open (Covered by its aglycon, clethodim sulfone. Same conclusion applies.) **Clethodim 5-hydroxy sulfone** Code: RE-51228 Genotoxicity hazard identified?: Open (Gene mutation: negative. Available in vitro CA test supplementary and lack of an in vitro MN test. Inconclusive for both clastogenicity and aneugenicity.)

Subject	Conclusions Pesticides Peer Review Meeting
M15R): genotoxicity and general toxicity. - 3-Chloroallyl alcohol glucoside (M14A, M15A): genotoxicity and general toxicity. - 3-Chloroallyl alcohol (3-CAA): genotoxicity and general toxicity. - 2-(Glutamylcysteinyl)-3-chloropropanol (M19A): genotoxicity. - Clethodim oxazole sulfoxide (RE-47796): genotoxicity and general toxicity. - Clethodim oxazole sulfone (RE-47797; M4): genotoxicity. - S-methyl sulfoxide (RE-47507): genotoxicity and general toxicity. - Clethodim oxazole: genotoxicity and general toxicity. - Deoxy-M17R: genotoxicity. - Hydroxy pentanoic acid glucoside (RT26): genotoxicity and general toxicity.	Reference values of parent applied?: Open (Lower toxicity than the parent. Once genotoxixicity is clarified, as a worst case the TRVs of the parent can be used for this metabolite.) **Clethodim imine sulfoxide** Code: RE-47718, M21R Genotoxicity hazard identified?: Open (Read-across to Clethodim imine sulfone seems suitable, however, there is a remaining uncertainty about the impact of the sulfoxide vs sulfone group on the genotoxicity of the molecules.) Reference values of parent applied?: Not triggered. **Clethodim imine sulfone** Code: RE-47719, M23R, M24R Genotoxicity hazard identified?: No (Based on an in vitro test battery (not including the in vitro mammalian cell mutation assay).) Reference values of parent applied?: Not triggered. **3-[(2-Ethylsulfonyl)propyl]-pentanedioic acid (DME sulfone acid)** Code: M18R, M19R Genotoxicity hazard identified?: Open (Read-across to DME sulfoxide acid inconclusive. Impact of organic functional groups (sulfone vs sulfoxide) not clarified.) Reference values of parent applied?: Open (Read-across to DME sulfoxide acid inconclusive. Impact of organic functional groups (sulfone vs sulfoxide) not clarified.)
Regarding groundwater metabolites, the following metabolites may need to be discussed pending the assessment regarding fate. - clethodim sulfone (RE-47253, also residue metabolite) - clethodim sulfoxide (RE-45924, also residue metabolite)	**Hydroxy clethodim imine sulfone glucoside** Code: M20R(a) Genotoxicity hazard identified?: Open (Read-across to Clethodim imine sulfone not accepted. The aglycon for hydroxy clethodim imine sulfone glucoside is not hydroxy clethodim imine sulfone, as hydroxy clethodim imine sulfone contains an imine group (C=N-H) and the aglycon of hydroxy clethodim imine sulfone glucoside contains an oxime group (C=N-OH), according to the structures presented. The genotoxicity assessment for the metabolite remains inconclusive.) Reference values of parent applied?: Not triggered.

Subject	Conclusions Pesticides Peer Review Meeting
- clethodim oxazole sulfone (RE-47797, M4, also residue metabolite) - clethodim oxazole sulfoxide (RE-47796, also residue metabolite) - trans-3-chloroacrylic acid (CAA, no residue metabolite) - 2-[3-chloroallyloxyimino] butanoic acid (CBA, no residue metabolite)	**Clethodim imine sulfone glucoside** Code: M20R(b) Genotoxicity hazard identified?: Open (Read-across to clethodim imine sulfone not accepted. The aglycon for clethodim imine sulfone glucoside is not clethodim imine sulfone (#8), as clethodim imine sulfone contains an imine group (C=N-H) and the aglycon of clethodim imine sulfone glucoside contains an oxime group (C=N-OH), according to the structures presented. The genotoxicity assessment for the metabolite remains inconclusive.) Reference values of parent applied?: Not triggered. **3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid (DME sulfoxide acid)** Code: M16R, M17R Genotoxicity hazard identified?: Open (Based on eligible information (i.e., the in vivo MN study cannot be taken into account), the metabolite is clastogenic in vitro, inconclusive in vivo.) Reference values of parent applied?: Open (The toxicity profile appears to qualitatively different. Once the genotoxicity of the metabolite is clarified: considering the lack of significant adverse effects in the 28-day study and that the liver was not identified as a critical target organ for the metabolite, the experts overall agreed that using the reference values of the parent for the metabolite would be sufficiently protective, acknowledging the different toxicological profiles of the parent and this metabolite.) **Hydroxy 3-[(2-Ethylsulfinyl)propyl]-pentanedioic acid** Code: M14R, M15R Genotoxicity hazard identified?: Open (Read-across to DME sulfoxide acid appropiate. Same conclusions apply.) Reference values of parent applied?: Open (Read-across to DME sulfoxide acid not supported.) **3-Chloroallyl alcohol glucoside** Code: M14A, M15A Genotoxicity hazard identified?: No (Covered by its aglycon, 3-chloroallyl alcohol, same conclusions apply.)

Subject	Conclusions Pesticides Peer Review Meeting
	Reference values of parent applied?: No (Covered by its aglycon, 3-chloroallyl alcohol, same conclusions apply.) **3-Chloroallyl alcohol** Genotoxicity hazard identified?: No (Based on experimental data. In line with the ccWG on genotoxicity.) Reference values of parent applied?: No (The metabolite is more toxic than the parent). The RMS proposed to set an ADI of 0.015 mg/kg bw per day (13-week study, NOAEL: 3 mg/kg bw per day); UFs: standard 100 for intra- and interspecies differences and 2 for 90-day to chronic. The RMS proposed to set an ARfD of 0.1 mg/kg bw (dev. tox rat + 28-day rat studies, NOAEL: 10 mg/kg bw/day); UFs: standard 100 for intra- and interspecies differences. **2-(Glutamylcysteinyl)-3-chloropropanol** Code: M19A Genotoxicity hazard identified?: Yes (In silico analysis indicated a concern for genotoxicity.) Reference values of parent applied?: Not triggered. **Clethodim oxazole sulfoxide** Code: RE-47796 Genotoxicity hazard identified?: No (Based on negative in vitro test battery in line with the GW guidance.) Reference values of parent applied?: Yes (Lower toxicity than parent. Reference values of parent as worst-case.) Groundwater relevance; other hazards identified?: No (Parent not classified as Carcinogenic or Reproductive toxicant). **Clethodim oxazole sulfone** Code: RE-47797, M4 Genotoxicity hazard identified?: No (Genotoxic in vitro (positive results in the in vitro CA test) but not in vivo (negative in vivo MN with proof of bone marrow exposure).) Reference values of parent applied?: Open (Read-across to clethodim oxazole sulfoxide proposed. Read-across suitable

Subject	Conclusions Pesticides Peer Review Meeting
	but uncertainty remains regarding the impact of sulfide versus sulfone groups.) Groundwater relevance; other hazards identified?: No (Parent not classified as Carcinogenic or Reproductive toxicant). **S-methyl sulfoxide** Code: RE-47507 Genotoxicity hazard identified?: No (Major rat metabolite, covered by parent.) Reference values of parent applied?: Yes (Major rat metabolite, covered by parent.) **2-[3-chloroallyloxyimino]butanoic acid (CBA)** Genotoxicity hazard identified?: Open (Assessment as residue not triggered. As a groundwater metabolite, if exceeding 0.1 ug/L a genotoxicity test battery would be required; no data have been submitted by the applicant. As regards the read-across approach, the metabolite is structurally not similar to the parent.) Reference values of parent applied?: Assessment as residue not triggered (As a groundwater metabolite, if exceeding 0.75 ug/L, consumer risk assessment would be triggered. As regards the read-across approach the metabolite is structurally not similar to the parent.) Groundwater relevance; other hazards identified?: Yes (Parent not classified as Carcinogenic or Reproductive toxicant. Should the metabolite exceeds 0.1 ug/L, relevant based on its acute toxicity (cat. 3)). **Trans-3-chloroacrylic acid (CAA)** Genotoxicity hazard identified?: Open (Assessment as residue not triggered. As a groundwater metabolite (if above 0.1 ug/L) a genotoxicity test battery would be required; no data have been submitted by the applicant. Based on existing data under 1,3-dichloropropene the genotoxic potential of this metabolites remains open.) Reference values of parent applied?: Assessment as residue not triggered (As a groundwater metabolite, if exceeding 0.75 ug/L, consumer risk assessment would be triggered.) Groundwater relevance; other hazards identified?: No (Parent not classified as Carcinogenic or Reproductive toxicant).

Subject	Conclusions Pesticides Peer Review Meeting
	Clethodim oxazole Genotoxicity hazard identified?: No (Read-across to clethodim oxazole sulfoxide and clethodim oxazole sulfone.) Reference values of parent applied?: Yes (Read-across to clethodim oxazole sulfoxide failed. Repeated dose toxicity alert (HESS profiler) present in the this metabolite. Liver is the target organ for parent. Reference values of parent as worst-case.) **Deoxy-M17R** Genotoxicity hazard identified?: Open (Read-across to DME sulfoxide acid appropiate. Same conclusion applies.) Reference values of parent applied?: Not triggered. **Hydroxy pentanoic acid glucoside (RT26)** Genotoxicity hazard identified?: Open (Read-across inconclusive. Not suitable anologues. The experts recommended to run two complentary QSARs.) Reference values of parent applied?: Open (Read-across inconclusive. Not suitable anologues.) **Open points:** • RMS to update the assessment (and related NOAEL setting) of the 5-week rat study of clethodim 5-hydroxy sulfone (RE-51228) in line with the agreement reached during the peer review meeting. • RMS to update the assessment (and related NOAEL setting) of the 5-week rat study for DME sulfoxide acid (M16R, M17R) in line with the agreement reached during the peer review meeting. • RMS to refer in the RAR to the outcome of the ccWG advice of 3-chloroallyl alcohol (3-CAA). • RMS to confirm that no more critical information is available for the assessment of 3-chloroallyl alcohol (3-CAA). • RMS to update the assessment (and related NOAEL setting) of the 5-week rat study of clethodim oxazole sulfoxide (RE-47796) in line with the agreement reached during the peer review meeting.

Subject	Conclusions Pesticides Peer Review Meeting
	• RMS to update the RAR based on the agreements reached during the Experts' Meeting.
Experts' consultation 2.11 Experts to discuss the toxicological reference values of clethodim and their applicability to the different isomers (or isomer ratio).	The agreed reference values are: • **ADI**: 0.16 mg/kg bw per day based on the NOAEL of 16 mg/kg bw per day obtained in the 2-year rat study and applying a standard uncertainty factor of 100 • **AOEL**: 0.25 mg/kg bw per day based on the NOAEL of 25 mg/kg bw per day obtained in the 90-day rat study and applying a standard uncertainty factor of 100 • **ARfD** and **AAOEL**: not needed. No information is available on possible differences in toxicity of isomers of clethodim. The racemic mixture of R- and S-isomers has been tested in the toxicological studies and reference values are based on these studies. No additional uncertainty factors are needed for the toxicological reference values, but additional considerations of possible differences in isomer toxicity will be given to the exposure assessment. Regarding the E- and Z- isomers, no information on their ratio in the toxicological batches is available and therefore no related conclusion can be drawn.
Experts' consultation 2.12 Experts to discuss the non-dietary exposure and risk assessment of Clethodim 120 EC.	Experts agreed that: 1. The NDE should be revised using the EFSA GD 2022. 2. An additional margin of exposure of 2 for workers and residents will have to be included to account for conversion between R and S isomers after application. 3. As for the E- and Z- isomers there is no information on their ratio in the toxicological batches and on their conversion after application, a conclusion cannot be drawn. **New open point** RMS to provide revised non-dietary exposure estimates with the agreed toxicological endpoints, including the additional scenario of removing bolting beets for the workers (as available in the EFSA 2022 guidance and related calculator). Furthermore, an additional margin of exposure of 2 for workers and residents will have to be considered in the final step.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.13 Experts to discuss the dermal absorption of clethodim.	Experts agreed to the dermal absorption values of 2.7% for the concentrate and 6.3% for the dilution (0.25 g a.s./L). **New open point** RMS to revise the derivation of the dermal absorption values and to provide the BfR Excel table revised accordingly.
Mammalian toxicity Experts' consultation 0.1 Experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation supported for the representative uses, based on the currently available information, for most of the co-formulants and/or co-formulant components, insufficient toxicological data are available (including genotoxicity, short- and long-term toxicity/carcinogenicity) and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. For one co-formulant, sufficient toxicological data are available, and it was concluded that it does not impact on the toxicity/classification and safety of the proposed formulation for the representative uses. **Open point**: RMS to integrate the additional information on the co-formulants provided during the peer review meeting, in a revised RAR.

REPORT OF PESTICIDES PEER REVIEW TC 171

PROPAMOCARB – AIR III after ED clock-stop Rapporteur Member State: PT

2. Mammalian toxicity

Date: 16 May 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Expert nominated by RMS PT	Direção Geral de Alimentação e Veterinária (DGAV) - PT
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS BE	Federal Public Service Health, Food Chain Safety, Environment - BE
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Norwegian Food Safety Authority - NO

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

Please note that information part of this report may have been masked by EFSA in accordance with Article 63 of Regulation (EC) No 1107/2009 as well as EFSA's Practical Arrangements concerning confidentiality in accordance with Articles 7 and 16 of Regulation (EC) No 1107/2009, or EFSA's Practical Arrangements concerning transparency and confidentiality as a consequence of confidentiality requests submitted by the applicant on application dossiers for pesticides active substances or Maximum Residue Levels, respectively. Please note that information disclosed in this report is without prejudice to pre-existing intellectual property rights and data exclusivity clauses set out in Union law, and particularly in Article 62 of Regulation (EC) No 1107/2009.

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	**Conclusions Pesticides Peer Review Meeting**
Additional experts' consultation 2.11 identified following the Applicant's arguments on the derivation of the toxicological reference values: Experts to discuss the **selection of NOAEL for the AOEL derivation.** EFSA note: EFSA agrees that there is unclarity on the NOAEL selected for the AOEL derivation as the mentioned decreased bodyweight (bw) gain in F0 female rats (week 3-4) of the 2-generation study (1998) is not confirmed from the review of the mean bw and bw gain tables reported in the RAR. A follow-up expert discussion on the identification of the parental NOAEL for this study and possibly of the AOEL	The experts agreed on - a revised **parental NOAEL of 57.6 mg/kg bw per day** in the 2-generation rat study, based on decreased body weight (gain) in females during the different phases of the study; - a revised **AOEL of 0.29 mg/kg bw per day** based on the 52-week rat study (based on vacuolar change, choroid plexus & lacrimal gland in females, relevant to humans), applying an uncertainty factor of 100. **Open point** RMS to provide a revised final RAR (Vol 1, Vol 3 B6 and LoEP) reflecting the agreements reached in the peer review meeting TC 171.

Subject	Conclusions Pesticides Peer Review Meeting
derivation is therefore warranted.	
Additional experts' consultation 2.12 identified: Experts to discuss the combined **non-dietary expsoure (NDE) assessment** for the 2nd active substance fluopicolide in the PPP Infinito /Volare.	The experts agreed that the combined exposure to propamocarb and fluopicolide (both present in the PPP) should be provided, with the agreed endpoints for fluopicolide (EFSA, 2009) and a pro-rata correction of the dermal absorption value for the dilution (11%). **Open point:** RMS is kindly requested to provide revised NDE estimates for the combined exposure to propamocarb hydrochloride and fluopicolide (AOEL, AAOEL and dermal absorption values) for the supported uses of the formulation SC Infinito / Volare. It is noted that such combined exposure is automatically calculated in the EFSA calculator related to the EFSA guidance 2022, provided that the respective endpoints for each active substance are entered in the tool (including the agreed endpoints for both compounds, and oral absorption 62% for fluopicolide). **Open point**: RMS is kindly requested to provide revised NDE estimates for the supported uses of the formulation Proplant, with the agreed toxicological endpoints for propamocarb (dermal absorption values and revised AOEL).
Additional experts' consultation (mammalian toxicity) included for completeness: MS experts to discuss whether the available information is sufficient to characterise the **full toxicological profile** of the formulation for representative use(s) **Proplant** with respect to the **acute, genotoxicity, short- and long-term toxicity**. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each	For the product **Proplant**, since the co-formulant(s) do(es) not present any toxicological concern, it can be concluded that it/they will not impact on the safety of the formulation.

Subject	Conclusions Pesticides Peer Review Meeting
individual component other than the active substance.	
Additional experts' consultation (mammalian toxicity) included for completeness: MS experts to discuss whether the available information is sufficient to characterise the **full toxicological profile** of the formulation for representative uses **Infinito/Volare** with respect to the **acute, genotoxicity, short- and long-term toxicity.** If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation **Infinito/Volare** (supported for the representative uses), based on the currently available information, sufficient toxicological data are not available for most components (including genotoxicity, short- and long-term toxicity/carcinogenicity) and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. **Open point**: RMS to revise the RAR Vol.4 in line with the discussion held during the peer review meeting.

REPORT OF PESTICIDES PEER REVIEW

TC 163 and TC 164

CINMETHYLIN – NAS 1107

Rapporteur Member State: NL

2. Mammalian toxicity

Date: 14 March 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS NL	Ctgb - NL
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	The National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Expert nominated by MS EL	Benaki Phytopathological Institute (BPI) - EL
National Experts nominated by MS ES	Ministerio De Sanidad - ES
National Expert nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS IE	Pesticide Registration and Controls Division / Department of Agriculture, Food and the Marine - IE
National Expert nominated by MS NL	Ctgb - NL

Status	Name of institution/attendee
National Expert nominated by MS PL	Merit Mark Polska Sp.z o.o. on behalf the Ministry of the Agriculture and Rural Development - PL
External expert	Andrea Terron
External expert	Emily McVey
Observers	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Pesticide Registration and Controls Division / Department of Agriculture, Food and the Marine - IE
Observer	International Centre for Pesticides and Health Risk Prevention – ICPS - IT
Technical hearing (Applicant)	BASF

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 MSs to discuss the setting of short-term toxicity NOAELs of cinmethylin including: - the need for repeated dose inhalation toxicity study for cinmethylin. - NOAEL 28-day mouse study (CA 5.3.1/2, 2016a) - adverse outcomes in the 90-day rat study (CA 5.3.2/1) - results of the 1-year dog study (CA 5.3.2/7) and agree on the study NOAEL. - results of the 28-day dermal rat study (CA	**28-day mouse study** The NOAEL of the 28-day mouse study is 1200 ppm (corresponding to 296 and 254 mg/kg bw per day in males and females, respectively), based on decreased bwg, decreased levels of albumin, protein, globulin, cholesterol, and triglycerides, and increased liver weight at 4000 ppm. **Adverse outcomes in the 90-day rat study** The NOAEL of the 90-day study is 1000 ppm (corresponding to 67 and 79 mg/kg bw per day in males and females, respectively), based on (relative) liver weight increase with corresponding histopathology (hepatocellular hypertrophy (males and females, clinical chemistry changes (mainly GGT; males and females), ovary findings (interstitial cell vacuolation; females), thyroid hypertrophy/hyperplasia (males), and nasal cavity findings (males and females) at 3000 ppm **1-year dog study (CA 5.3.2/7)** The NOAEL of the study is 200 ppm (corresponding to 4.7 and 4.3 mg/kg bw per day for males and females, respectively) based on increased relative liver weight in males, changes in haematology (mainly in males: elevated WBC counts, increased neutrophils, decreased lymphocytes), increased serum ALP activity (females), and increased thyroid weight (both sexes) at 3000 ppm.

Subject	Conclusions Pesticides Peer Review Meeting
5.3.3/1-2) and agree on the study NOAEL.	**28-day dermal rat study** The systemic NOAEL is 1000 mg/kg bw per day, the highest dose tested and the local NOAEL is 100 mg/kg bw per day, based on skin irritation observed at 300 mg/kg bw per day. **Need for repeated dose inhalation toxicity study** Based on the available information and a related weight of evidence analysis (including a detailed evaluation of the type and localization of histopathological lesions), nasal cavity findings are concluded to be most likely the consequence of systemic exposure. The possible contribution of inhalation would be considered in the risk management. Therefore, there is no need for a repeated dose inhalation study for cinmethylin. **Open point** The RMS to revise the DAR in line with the PRM discussion.
Experts' consultation 2.2 MS experts to discuss the genotoxicity assessment of cinmethylin.	The majority of experts concluded, based on a weight of evidence approach, that cinmethylin is unlikely to be genotoxic in vivo.
Experts' consultation 2.3 MSs experts to discuss long term toxicity and carcinogenicity NOAELs in mice and rats for cinmethylin.	**Long term toxicity and carcinogenicity study in rats (B.6.5.1.)** The NOAEL for systemic toxicity is 200 ppm based on nasal cavity effects (degeneration/regeneration of the olfactory epithelium) at 24 months in males (8.7 mg/kg bw per day) and reduced bw at 12 months in females (13 mg/kg bw per day). The majority of experts agreed that the NOAEL for carcinogenicity is 5000 ppm (corresponding to 242 and 317 mg/kg bw per day for males and females, respectively), the highest dose tested. **Long term toxicity and carcinogenicity study in rats (B.6.5.2.)**

Subject	Conclusions Pesticides Peer Review Meeting
	The NOAEL for systemic toxicity is 100 ppm (corresponding to 4.7 and 5.8 mg/kg bw per day for males and females, respectively) based on decreased food consumption (females) and body weight development (males and females), increased relative liver weight (males), increased GGT (males and females) and increased relative kidney weights (males and females) observed at 3000 ppm. The NOAEL for carcinogenicity is 3000 ppm (corresponding to 144 and 177 mg/kg bw per day for males and females, respectively), the highest dose tested. **Long term toxicity and carcinogenicity study in mouse (B.6.5.3.)** The reference point for systemic toxicity is the BMDL10 (9.1 mg/kg bw per day) based on reduced body weight gain in females. The NOAEL for carcinogenicity is 5000 ppm (corresponding to 904 and 939 mg/kg bw per day for males and females, respectively), the highest dose tested. **Long term toxicity and carcinogenicity study in mouse (B.6.5.4.)** The study is considered not acceptable, since active mouse hepatitis virus infection was demonstrated across all groups (including controls) and could have impacted the general interpretation of the study. **Open point** The RMS to revise the DAR in line with the PRM discussion
Experts' consultation 2.4 Experts to discuss the outcomes of the generational studies (parental, reproductive and offspring NOAELs).	In the first 2-generation study in the rat (CA 5.6.1/1), the following NOAEL values were agreed: **1000 ppm** (79.4/81.3 mg/kg bw per day) for **parental NOAEL, both F0 and F1,** based on decreased food consumption and body weight/body weight gain in F0 dams during gestation/lactation, and organ weight/histopathological findings (liver, kidney, thyroid and nasal cavity) **5000 ppm for both reproductive and offspring NOAELs** (412/395 mg/kg bw per day), the highest dose tested. No reference values were derived from the second 2-generation study (CA 5.6/1) as it was agreed that the study is not reliable.

Subject	Conclusions Pesticides Peer Review Meeting
	Open point The RMS to revise the DAR in line with the PRM discussion.
Experts' consultation 2.5 MSs experts to discuss the developmental toxicity studies (rat and rabbit).	The following NOAEL values were agreed for the different Developmental toxicity studies: **Rat study (CA 5.6.2/1)** Maternal NOAEL 30 mg/kg bw/d based on clinical signs, reduced body weight gain; Developmental NOAEL 300 mg/kg bw/d based on delayed ossification, increased incidence of lateral ventricles dilation and of wavy ribs **Rabbit study (CA 5.6.2/2)** Maternal NOAEL 80 mg/kg bw/d based reduced food consumption and body weight gain, increased liver weight and increased GGT activity; Developmental NOAEL 80 mg/kg bw/d based on lower foetal weight and skeletal findings. It was agreed not to derive reference values were derived for Developmental studies 3 and 4 (CA 5.6.2/3 and CA 5.6.2/4) in rabbits, due to major deviations and high mortality observed in the studies. **Open point** The RMS to revise the DAR in line with the PRM discussion.
Experts' consultation 2.6 MSs experts to discuss the adversity of the observations in the neurotoxicity study and the possible waiver or need of further testing regarding cinmethylin neurotoxicity	Considering the lack of neurotoxicity MoA, that in the acute neurotoxicity study transient reduced motor activity only was noted (at 300 mg/kg bw per day), that no specific stand-alone neurotoxic effects were noted in the other acute toxicity studies and in repeated dose studies (including FOBs), no repeated dose neurotoxicity study (including DNT) is necessary and no extra UF are needed for the setting of TRVs.

Subject	Conclusions Pesticides Peer Review Meeting
including neurodevelopment toxicity.	
Experts' consultation 2.7 MSs to discuss the overall conclusion of the assessment of T-modalities, this should include the discussion of: - adequacy of the postulated Mode of Action (MoA) - The reliability/validity of the in vitro comparative study on Phase I and Phase II induction potential of cinmethylin (CA 5.8.2/13), including discussion of the adequacy of the concentrations, test system quality assurance (e.g. reference compounds) and conclusion on human relevancy - The reliability/validity of the Thyroid hormone and enzyme induction in Wistar rats study (CA 5.8.2/11-12) - The need of additional studies to explore DNT effects of cinmethylin	A pattern of T-mediated adversity was observed in a sufficiently investigated dataset. The experts agreed that the postulated MoA i.e., extrathyroidal mechanism with increase in the hepatic clearance of the THs, is plausible. A slight majority of the experts, including the RMS, noted that based on the observed in vitro quantitative differences, and in the absence of effects in other species (in vivo studies in dog and mouse), there is the possibility that following cinmethylin exposure, the effect leading to the perturbation of the HPT axis, may be specific to the rat. Considering the number of uncertainties highlighted during the discussion, a slight minority of the experts agreed that human relevance cannot be excluded based on the data presented. It is noted that the same conclusion was reached at the EFSA ED WG meeting in June 2024, before submission of the last in vitro study (CA 5.8.2/14) that was therefore not available to EFSA ED WG. All experts agreed that Scenario 1b of the ECHA/EFSA ED Guidance is applicable and the ED criteria for T-modality are met. **Open point** The RMS to revise the DAR in line with the PRM discussion.

Subject	Conclusions Pesticides Peer Review Meeting
- The need of additional Comparative Thyroid Assay (CTA, US-EPA) including histopathology of thyroid gland and measurement of THs and TSH - Inclusion of B.6.1.2.1. Study 1 – comparative in vitro metabolism to the WoE	
Summary discussion with technical hearing (applicant) under experts' consultation 2.7	Upon request from RMS, the applicant was given the opportunity to provide clarifications on the following agreed-upon in relation to the study on **phase I/II induction comparative in vitro study** with rat and human hepatocytes. *1. A new in vitro comparative assay was provided after the commenting round (and after discussion by the EFSA ED WG). Please explain how this study compares to the previous one (regarding set-up and findings).* *1.1. Why Human relevance should be dismissed in comparison with rat effects, when the profile of response to test compound, in comparison to positive chemicals, is similar (lower in humans but in a similar range as the reference compounds).* *1.2. Regarding the cell culture, having a validated (ECVAM) method for cryopreserved hepatocytes for CYP enzyme induction studies, it is not clear why such method is not followed. For instance, post-thawing time different; exposure time; cytotoxicity measurements.* *1.3. Having guidance's or validation studies using the 2-fold change in mRNA and enzymatic activity as reference to induction, it is not clear why sometimes it is opted by the use of 1.5-fold or delta analysis, and what is the scientific validity to dismiss the 2-fold –induction.* ▪ 1.3.1 *Is there scientific support that 2x increase of enzymatic activity even if remains low, would not have a physiological impact? In this specific case, what is the scientific evidence that a 2-fold increase of low UGT-T4*

Subject	Conclusions Pesticides Peer Review Meeting
	activity will not have consequence in T4-T3 clearance and consequently not relevant to DNT. ▪ *1.3.2 There is no fold-induction threshold validated or scientifically agreed for T4-UGT (there is for CYP activity in the ECVAM study), but this is still relative analysis as the one used for other endpoints (i.e., % from control).* *1.4.Why do the studies not include statistical analysis to show statistically significant changes, in any of the two in vitro induction studies?* The replies provided by the applicant's experts were considered during the experts' discussion on the available assessment.
Experts' consultation 2.8 MSs to discuss the relevance of the EAS-mediated effects of cinmethylin in the overall ED assessment.	**EAS-modality** A pattern of EAS-mediated adversity was not observed in a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED Guidance is applicable and the ED criteria for EAS-modality are not met. **Open point** The RMS to revise the DAR in line with the PRM discussion.
Experts' consultation 2.9 MSs expert to discuss the toxicity profile of cinmethylin metabolites available in DocID 2023/2001851 but also other relevant metabolites such as M684H001; M684H009; M684H010; M684H021; M684H022; M684H026; M684H039 and M684H059; M684F001, M684F011 and M684F013.	Considering ADME data of the rat, metabolites M684H001, M684H002, M684H005, M684H006, M684H007, M684H008, M684H011, M684H012, M684H015, M684H016, M684H022, M684H034, M684H039, M684H047, M684H048, M684H052, M684H055, M684H056, and M684H057 are considered covered by the toxicological profile of parent (including genotoxicity) and TRVs of the parent apply to these metabolites, if needed. Metabolites M684H021 and M684H059 are considered not covered by the parent. Based on the availbale in silico assessment, these metabolites are considered negative for Ames mutagenicity, but the assessment was considered inconclusive for chromosomal abberation.

Subject	Conclusions Pesticides Peer Review Meeting
	Experimental data on genotoxicity (Ames test and in vivo micronucleus test) have been submitted by the applicant (both negative according to applicant assessment), but that data were provided outside the time frame for the submission of additional information and, therefore, these cannot be taken into account for the current assessment. **Post-meeting note:** Residues experts asked confirmation whether the toxicological profile of M684H026 is covered by parent compound. Based on RMS' assessment it is covered by the parent based on ADME properties (considered a major rat metabolite). EFSA agreed with this assessment.
Experts' consultation 2.10 MSs experts to discuss toxicological reference values for cinmethylin.	The following toxicological references values were set for Cinmethylin. **ADI (acceptable daily intake)** The ADI of Cinmethilin was updated to 0.08 mg/kg bw per day based on the (human-relevant) NOAEL of 7.9 mg/kg bw per day from the 1-year dog studies and supported by the long-term rat and mouse studies, applying the standard uncertainty factor of 100. **ARfD (acute reference dose)** The ARfD for Cinmethylin is 0.3 mg/kg bw per day based on the (human-relevant) maternal NOAEL of 30 mg/kg bw per day from the developmental toxicity study in rats, applying the standard uncertainty factor of 100. **AOEL (acceptable operator exposure level)** The AOEL for Cinmethylin is 0.06 mg/kg bw per day based on the (human-relevant) parental NOAEL of 7.9 mg/kg bw per day from combined 1-yr dog studies and rodents long term studies, applying the standard uncertainty factor of 100 and a correction for bioavailability of 70%. **AAOEL (acute acceptable operator exposure level)**

Subject	Conclusions Pesticides Peer Review Meeting
	The AAOEL for Cinmethylin is 0.2 mg/kg bw per day based on the (human-relevant) parental NOAEL of 30 mg/kg bw per day from the the developmental toxicity study in rats, applying the standard uncertainty factor of 100 and a correction for bioavailability of 70%. It was noted that the reference values are based on the fact that a racemic mixture was tested and no information is available on the toxicity of individual isomers or shift in ADME studies. A factor of 2 (as a worst case) might be applied to non-dietary (residents and workers) and dietary risk assessment to cover shifts in the ratio between isomers (to be decided by experts on exposure). **Open point** The RMS to revise the DAR in line with the PRM discussion.
Experts' consultation 2.11 Experts to discuss non-dietary exposure assessment for the representative uses of cinmethylin.	**Open point** RMS is requested to provide revised non-dietary exposure estimates to demonstrate negligible exposure to cinmethylin • including the oral absorption value of 70% (bioavailability) • considering the lower application rate with a dermal absorption value of 22 % (pro-rata correction) • including all available risk mitigation measures from the model including a conclusion, for workers and resident, on margin of exposure when considering potential shift of isomers.
Experts' consultation 2.12 Experts to discuss dermal absorption values for cinmethylin in the representative formulation.	Based on an in vitro dermal absorption study with human skin performed with the formulation BAS 684 H, the agreed dermal absorption values are 0.4% for the concentrate and 11% for the dilution (125 g/L) (with a value of 22% after pro-rata correction for the dilution of 0.625 g/L). **Open point** The RMS to revise the DAR in line with the PRM discussion.
Experts' consultation 1.2	Regarding the co-formulants contained in the formulation supported for the representative uses (`BAS 684 03 H`), based on the currently available information, sufficient toxicological

Subject	Conclusions Pesticides Peer Review Meeting
MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	data were available for most components. However, for some components, toxicological data is insufficient (including genotoxicity and/or short, long term toxicity/ carcinogenicity) and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. **Open point** The RMS to revise the DAR Vol.4 in line with the Open Points identified during the Written Consultation on co-formulants.

REPORT OF PESTICIDES PEER REVIEW TC 165

BACILLUS PARALICHENIFORMIS STRAIN FMCH001 – NAS 1107

Rapporteur Member State: NL

6. Microorganisms - Mammalian toxicity

Date: 14 March 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Expert nominated by RMS NL	Ctgb - NL
National Experts nominated by MS AT	AGES - Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
Observer	AGES - Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 Experts to discuss the revised assessment of the secondary metabolites of *B.paralicheniformis* FMCH001.	The identification of secondary metabolites of potential toxicological relevance for *B. paralicheniformis* strain FMCH001 was based on a preliminary literature search, followed by molecular analysis on the strain and by a subsequent literature search to corroborate the toxicological information for (potential) metabolites. In addition, the Microbial Pest Control Agent As Manufactured (MPCA-AM) was analytically evaluated for some metabolites. Secondary metabolites of potential toxicological concern were discussed. **Bacitracin** is known to have antibiotic properties and it has not been possible to exclude its production in the MPCA-AM. Therefore, bacitracin levels should be analytically determined in the MPCA-AM (**data gap**), considering the proposed threshold (8 µg/L for bacitracin in the environment, expected to prevent the induction of antimicrobial resistance). **Subtilisin** levels should be analytically determined in the MPCA-AM and demonstrated to be below the threshold for classification in the technical material (**Data gap**). No toxicological concerns were identified for surfactins and iturins, based on the available toxicological information and measured levels in the MPCA-AM.
Experts' consultation 6.2 Experts to discuss the clearance in the acute	Clearance was sufficiently demonstrated in the available acute toxicity/infectivity/pathogenicity studies with *Bacillus paralicheniformis* strain FMCH001, concluded as having a low potential for infectivity.

Subject	Conclusions Pesticides Peer Review Meeting
intravenous study with *B. paralicheniformis* FMCH001.	
Experts' consultation 0.1 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	Regarding the co-formulants contained in the formulation supported for the representative uses ('F4018-4") based on the currently available information, sufficient toxicological data were available for most components. However, for some components, toxicological data is insufficient (including genotoxicity and/or short, long-term toxicity/ carcinogenicity) and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. **Open point** RMS to revise the DAR Vol.4 in line with the information discussed at the peer review meeting.

REPORT OF PESTICIDES PEER REVIEW TC 165

BACILLUS SUBTILIS STRAIN FMCH002 – NAS 1107

Rapporteur Member State: NL

6. Microorganisms - Mammalian toxicity

Date: 14 March 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Expert nominated by RMS NL	Ctgb - NL
National Experts nominated by MS AT	AGES - Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
Observer	AGES - Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH

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Discussion points/Outcome

6. Microroganisms - Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 Experts to discuss the revised assessment of the secondary metabolites of *B. subtilis* FMCH002.	The identification of secondary metabolites of potential toxicological relevance for *Bacillis subtilis* strain FMCH002 was based on a preliminary literature search, followed by molecular analysis on the strain and by a subsequent literature search to corroborate the toxicological information for (potential) metabolites. In addition, the MPCA-AM (Microbial Pest Control Agent As Manufactured) was analytically evaluated for some metabolites. Secondary metabolites of (potential) toxicological concern were discussed at the meeting. **Subtilisin** levels should be analytically determined in the MPCA-MA and demonstrated to be below the threshold for classification in the technical material (data gap). No toxicological concerns were identified for surfactins and iturins, based on the available toxicological information and measured levels in the MPCA-MA.
Experts' consultation 0.1 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity	Regarding the co-formulants contained in the formulation supported for the representative uses ('F4018-4") based on the currently available information, sufficient toxicological data were available for most components. However, for some components, toxicological data is insufficient (including genotoxicity and/or short, long-term toxicity/ carcinogenicity) and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. **Open point**

Subject	Conclusions Pesticides Peer Review Meeting
and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	RMS to revise the DAR Vol.4 in line with the information discussed at the peer review meeting.

REPORT OF PESTICIDES PEER REVIEW

TC 163 and TC 164

ZIRAM – AIR III, after ED clock stop

Rapporteur Member State: IT

2. Mammalian toxicity

Date: 14 March 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Experts nominated by RMS IT	International Centre for Pesticides and Health Risk Prevention – ICPS - IT
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	The National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS EL	Benaki Phytopathological Institute (BPI) - EL
National Experts nominated by MS ES	Ministerio de Sanidad - ES
National Experts nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR

Status	Name of institution/attendee
National Experts nominated by MS IE	Pesticide Registration and Controls Division / Department of Agriculture, Food and the Marine - IE
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS PL	Merit Mark Polska Sp.z o.o. on behalf the Ministry of the Agriculture and Rural Development - PL
External expert	Andrea Terron
External expert	Emily McVey
Observers	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Danish Environmental Protection Agency (DEPA) - DK
Observers	International Centre for Pesticides and Health Risk Prevention – ICPS - IT

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting

Experts' consultation 2.16
 	
MSs experts to discuss the TDC potential of ziram in an experts' meeting. The full dataset available for ziram T-modality should be presented for discussion, including the following points:
- acceptability and results of the new level 5 study – the Extended One-Generation Reproductive Toxicity Study (EOGRT, CA 5.6.1/03) including:
  ○ Adequacy of the dose test range;
  ○ Haematology effects (table provided after commenting phase);
	The doses used in the extended-one-generation reproductive toxicity (EOGRT) study are considered appropriate for the evaluation of any perturbation of the hypothalamus-pituitary-thyroid (HPT) axis based on the observed changes in body weight, body weight gain, haematological and clinical chemistry.
	
	T-modality
	
	A clear pattern of T-mediated adversity is not observed in a sufficiently investigated dataset, including the EOGRT study. **Scenario 1a** of the EFSA-ECHA ED Guidance is applicable and the ED criteria for T-modality are not met.
	
	About the potential impact of thiram and ETU on the T-modality for the ED assessment of ziram, it is noted that thiram is not a major metabolite of ziram and that ziram does not metabolise to ETU.
	
	Despite a concern regarding the DNT adversity and uncertainties on potential T-mediated effects in sensitive population being raised during the last PPR 01 & TC 07 in 2019, a DNT cohort has not been included in the EOGRT study design. Nevertheless, having concluded that the HPT axis was not sufficiently disrupted, no concern remains for DNT.
	
	EAS-modalities
	
	A clear pattern of EAS-mediated adversity is not observed in a sufficiently investigated dataset, including the EOGRT study.

Subject	Conclusions Pesticides Peer Review Meeting
○ T-mediated adverse effects including the observed changes in THs and TSH for P and F1 generations; - Adequacy of the historical control data provided for the THs and TSH in the EOGRT study. In this context the following information has to be provided and presented at the peer review experts' discussion meeting: - The analytical methods used to measure THs and TSH in the study - The sampling procedure (time of the day of the sampling procedure; method of euthanasia and randomization of the animals) in the study - The two above mentioned request should be also retrieved and presented for the HCD - The assessment of the T-modality should also include the assessment of the available results on DNT. Justification on the non-inclusion of DNT harm in the new EOGRT study, should be brought forward to the experts' consultation	**Scenario 1a** of the EFSA-ECHA ED Guidance is applicable and the ED criteria for EAS-modality are not met. For the study NOAEL please refer to EC 2.7. **Open point** The RMS to revise the RAR in line with the PRM discussion.

Subject	Conclusions Pesticides Peer Review Meeting
(considering that the available DNT study is lacking relevant endpoints like the startle reflex and the assessment of learning and memory). - The proposed study NOAEL for the new EOGRT should be presented for discussion and agreement. - The kinetic profile of Ziram (CA 5.1.1/03), should be presented and contextualised for any sex-related differences in the evaluated endpoint including THs and TSH. - The EAS-mediated endpoints included in the new EOGRT study, should be presented for discussion and agreement. - It is highly recommended that the presentation should follow the EFSA template in line with the decision tree of the EFSA/ECHA ED guidance.	
New experts' consultation point 2.17 MS experts to discuss the implications on the toxicological endpoints and	For the new OECD TG 443 -compliant Extended One-Generation Reproductive Toxicity Study the agreed NOAELs are: **NOAEL for systemic toxicity:** P: 70 ppm, 5.41 to 11.65 mg/kg bw/day; F1 Adult 1A: 70 ppm, 7.19 to 8.87 mg/kg bw/day; F1 Adult 1B: 70 ppm, 5.95 to 13.04 mg/kg bw/day

Subject	Conclusions Pesticides Peer Review Meeting
human health (based on the new study provided for ED)	**NOAEL for Fertility:** P1: 650 ppm, 38.24 to 106.02 mg/kg bw/day; F1 Adult 1B: 650 ppm, 52.07 to 120.91 mg/kg bw/day **NOAEL for reproductive toxicity:** P1: 650 ppm, 38.24 to 106.02 mg/kg bw/day; F1 Ault 1A: 650 ppm, 68.81 to 83.19 mg/kg bw/day; F1 Adult 1B: 650 ppm, 52.07 to 120.91 mg/kg bw/day <u>Parent NOAEL's are based on:</u> Lower body weight and body weight gain; increase of absolute and relative weight and histopathological lesions of the spleen; Haematological findings (decreased RBC, haemoglobin, and haematocrit); decrease in serum T4 level of female rats. F1 (adult) NOAEL's are based on: Lower food consumption; Lower body weight and body weight gain; Increase in the absolute and relative weight of the spleen corresponding with histopathological lesions at 650 and 200 ppm. For Adult 1A, it was also based on Haematological findings (decreased RBC, haemoglobin, and haematocrit). **NOAEL for Developmental toxicity**: F1 pups: 200 ppm; F2 pups: 200 ppm. Based on the decrease of body weight and body weight gain, increased mortality index, reduced litter size and lower organ weight Since the NOAELs from the new EOGRT study are higher of those in the studies used for the PoD they have no impact on toxicological endpoints and TRVs for ziram. Based on the previous 2-generation toxicity study and the new EOGRT, the agreed **relevant parental, reproductive and offspring NOAELs** are respectively **5**, **25** and **10 mg/kg bw per day.** **Open point** The RMS to revise the RAR in line with the PRM discussion.
New experts' consultation point 2.18 proposed by EFSA for	Regarding the co-formulants contained in the formulation supported for the representative uses (Ziram 76 WG), based on the currently available information, sufficient toxicological

Subject	Conclusions Pesticides Peer Review Meeting
completeness of discussion MS experts to discuss whether the available information is sufficient to characterise the **full toxicological** profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	data were available for most components. However, for some/a component(s), toxicological data is insufficient (including on genotoxicity, short- and long -term toxicity/ carcinogenicity/due to lack of information on its composition) and it is not possible to conclude whether they/it impact(s) on the toxicity/classification and safety of the proposed formulation. **Open point** RMS to revise the RAR Vol.4 in line with the discussion and open point identified at the peer review meeting.

REPORT OF PESTICIDES PEER REVIEW TC 164

FATTY ACIDS - CAPRIC ACID – AIR IV

Rapporteur Member State: EL

2. Mammalian toxicity

Date: 14 March 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS EL	Benaki Phytopathological Institute (BPI) - EL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS ES	Ministerio de Sanidad - ES
National Expert nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IE	Pesticide Registration and Controls Division / Department of Agriculture, Food and the Marine - IE
National Expert nominated by MS IT	International Centre for Pesticides and Health Risk Prevention – ICPS - IT
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS PL	Merit Mark Polska Sp.z o.o. on behalf the Ministry of the Agriculture and Rural Development - PL
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Pesticide Registration and Controls Division / Department of Agriculture, Food and the Marine - IE
Observers	International Centre for Pesticides and Health Risk Prevention – ICPS - IT

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

Please note that information part of this report may have been masked by EFSA in accordance with Article 63 of Regulation (EC) No 1107/2009 as well as EFSA's Practical Arrangements concerning confidentiality in accordance with Articles 7 and 16 of Regulation (EC) No 1107/2009, or EFSA's Practical Arrangements concerning transparency and confidentiality as a consequence of confidentiality requests submitted by the applicant on application dossiers for pesticides active substances or Maximum Residue Levels, respectively. Please note that information disclosed in this report is without prejudice to pre-existing intellectual property rights and data exclusivity clauses set out in Union law, and particularly in Article 62 of Regulation (EC) No 1107/2009.

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.2 MS experts to discuss the non-dietary exposure to capric acid taking into consideration: • the combined presence of caprylic acid (also an active substance) • the respective [redacted] • the intended uses of the formulation (including non-professional uses) • the [redacted] impurities MS experts to discuss toxicological profile of the concerned impurities	The default dermal absorption values, in line with the EFSA GD 2017, were used. Non-dietary exposure calculations for the representative uses of capric acid are well below the background dietary exposure level (821 mg/kg bw per day) for all groups (operators, workers, residents and bystanders). Some non-dietary exposure estimates to the concerned impurities (at their LODs) from the representative uses of capric acid as PPP may be higher than the pertinent reference points /Health Based Guidance Values. A specification for [redacted] would also be needed (see below data gap). Several uncertainties impact these non-dietary exposure estimates, e.g. the applicability to these impurities of the default dermal absorption value used for fatty acids; their unknown actual levels in the 5-batch analysis; the comparison of non-dietary exposure estimates with dietary limits. Available specification limits for these impurities as set in the pertinent EU legislation might not be sufficiently protective as recommended by EFSA. **Open point**: RMS to include the exposure estimates to the concerned impurities in a revised RAR and describe the related uncertainties. **Data gap**:

Subject	Conclusions Pesticides Peer Review Meeting
	determination of an acceptable level for impurity [redacted] in the technical specification of capric acid.
Expert consultation 1.1 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative uses with respect to acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	The available information on co-formulants contained in the formulation for representative uses ('HERBICLEAN AL') does not raise any concern about genotoxicity, short- and long-term toxicity. This information is sufficient to conclude that co-formulants do not impact the toxicity/classification and safety of the formulation for representative uses.

REPORT OF PESTICIDES PEER REVIEW TC 164

FATTY ACIDS - CAPRYLIC ACID – AIR IV

Rapporteur Member State: EL

2. Mammalian toxicity

Date: 14 March 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS EL	Benaki Phytopathological Institute (BPI) - EL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS ES	Ministerio de Sanidad - ES
National Expert nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IE	Pesticide Registration and Controls Division / Department of Agriculture, Food and the Marine - IE
National Expert nominated by MS IT	International Centre for Pesticides and Health Risk Prevention – ICPS - IT
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS PL	Merit Mark Polska Sp.z o.o. on behalf the Ministry of the Agriculture and Rural Development - PL
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Pesticide Registration and Controls Division / Department of Agriculture, Food and the Marine - IE
Observers	International Centre for Pesticides and Health Risk Prevention – ICPS - IT

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.2 Experts to discuss the revised non-dietary exposure assessment and risk assessment approach for the representative uses of caprylic acid.	The default dermal absorption values, in line with the EFSA GD 2017, were used. Non-dietary exposure calculations for the representative uses of caprylic acid are well below the background dietary exposure level (821 mg/kg bw per day) for all groups (operators, workers, residents and bystanders).
Expert consultation 2.3 Experts to discuss the acceptable levels of the toxicologically relevant impurities [redacted], considering the proposed lower levels and the comparison of exposure estimates from the representative uses of caprylic acid against the [redacted] from relevant sources.	Some non-dietary exposure estimates to the concerned impurities (at their LODs) from the representative uses of caprylic acid as PPP may be higher than the pertinent reference points /Health Based Guidance Values. A specification for [redacted] would also be needed (data gap). Several uncertainties impact these non-dietary exposure estimates, e.g. the applicability to these impurities of the default dermal absorption value used for fatty acids; their unknown actual levels in the 5-batch analysis; the comparison of non-dietary exposure estimates with dietary limits. Available specification limits for these impurities as set in the pertinent EU legislation might not be sufficiently protective as recommended by EFSA. **Open point**

Subject	Conclusions Pesticides Peer Review Meeting
	RMS to include the exposure estimates to the concerned impurities in a revised RAR and describe the related uncertainties. **Data gap** A specification for [redacted] would be needed.
Expert consultation 2.4 Experts to discuss the skin sensitisation potential of caprylic acid based on the available data.	Caprylic acid is non-sensitising to the skin. The skin sensitisation potential of the formulation should be considered at MS level for national authorisation.
Expert consultation 1.1 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative uses with respect to acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation supported for the representative uses ('DESHERB'NAT'), based on the currently available information, sufficient toxicological data were available for most components. However, for some component(s), toxicological data are insufficient (including long-term toxicity) and it is not possible to conclude whether this impacts the toxicity/classification and safety of the proposed formulation. **Open point** The RMS to revise the RAR Vol.4 in line with the information discussed at the peer review meeting.

REPORT OF PESTICIDES PEER REVIEW TC 164

FATTY ACIDS – POTASSIUM SALTS (FATTY ACIDS FROM HYDROLYSED VEGETABLE OILS) – AIR IV
Rapporteur Member State: EL

2. Mammalian toxicity

Date: 14 March 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS EL	Benaki Phytopathological Institute (BPI) - EL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS ES	Ministerio de Sanidad - ES
National Expert nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IE	Pesticide Registration and Controls Division / Department of Agriculture, Food and the Marine - IE
National Expert nominated by MS IT	International Centre for Pesticides and Health Risk Prevention – ICPS - IT
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS PL	Merit Mark Polska Sp.z o.o. on behalf the Ministry of the Agriculture and Rural Development - PL
Observer	Austrian Agency for Health and Food Safety (AGES) - AT

Status	Name of institution/attendee
Observer	Pesticide Registration and Controls Division / Department of Agriculture, Food and the Marine - IE
Observers	International Centre for Pesticides and Health Risk Prevention – ICPS - IT

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.2 Experts to discuss the revised non-dietary exposure assessment and risk assessment approach (including non-professional uses) for the representative uses of NEU 1128 I and ABP 617.	The default dermal absorption values, in line with the EFSA Guidance 2017, were used. Non-dietary exposure estimates for the representative uses of fatty acids from hydrolysed vegetable oils are well below the background dietary exposure level (821 mg/kg bw per day) for all groups (operators, workers, residents and bystanders). Some non-dietary exposure estimates to the concerned impurities (at their LODs) from the representative uses of fatty acids from hydrolysed vegetable oils as PPP may be higher than the pertinent reference points /Health Based Guidance Values. Several uncertainties impact these non-dietary exposure estimates, e.g. the applicability to these impurities of the default dermal absorption value used for fatty acids; their unknown actual levels in the 5-batch analysis; the comparison of non-dietary exposure estimates with dietary limits. Available specification limits for these impurities as set in the pertinent EU legislation might not be sufficiently protective as recommended by EFSA. **Open point** RMS to include the exposure estimates to the concerned impurities in a revised RAR and describe the related uncertainties. **Data gap** A specification for [redacted] would be needed.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 1.3 MS experts to discuss whether the available information is sufficient to characterise the full **toxicological** profile of the formulation for representative uses with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulant(s) contained in the formulation 'ABP 617' supported for the representative uses, based on the currently available information, sufficient toxicological data were available for all components. It can be concluded that the co-formulant(s) do not impact the toxicity/classification and safety of the proposed formulation.
Experts' consultation 1.2 MS experts to discuss whether the available information is sufficient to characterise the full **toxicological** profile of the formulation for representative uses with respect to acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulant(s) contained in the formulation 'NEU 1128I' supported for the representative uses, based on the currently available information, sufficient toxicological data were available for all components. It can be concluded that the co-formulant(s) do not impact the toxicity/classification and safety of the proposed formulation.

REPORT OF PESTICIDES PEER REVIEW

TC 163 and TC 164

PHENMEDIPHAM – AIR III, re-assessment of ED following mandate

Rapporteur Member State: FI

2. Mammalian toxicity

Date: 14 March 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff members	EFSA
National Experts nominated by RMS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	The National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS IE	Pesticide Registration and Controls Division / Department of Agriculture, Food and the Marine - IE
National Experts nominated by MS IT	International Centre for Pesticides and Health Risk Prevention – ICPS - IT
National Expert nominated by MS NL	Ctgb - NL
External Expert	Andrea Terron
External Expert	Emily McVey

Status	Name of institution/attendee
Observers	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Danish Environmental Protection Agency - DK
Observer	Department of Agriculture, Food and the Marine; Pesticide Control and Registration Division - IE
Observers	International Centre for Pesticides and Health Risk Prevention – ICPS - IT

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Open point linked to Experts' consultation 2.8 (inserted following update of the ED mandate to cover aspects other than ED (Jan 2024)). **This open point was followed up with the setting of an additional experts' consultation 2.8 (bis)** In the light of the latest available status of knowledge and risk assessment methodologies in relation to the genotoxicity assessment of phenmedipham, i.e. availability of the ECHA RAC Opinion (2019) and the EFSA Scientific Committee Opinion to assess the lines of evidence of bone marrow exposure (EFSA SC; 2017), the RMS is kindly requested	The experts agreed that phenmedipham is clastogenic *in vitro*. All experts agreed that the outcomes of the *in vivo* MN tests are negative and that the bone marrow was reached (based on plasma analysis and QWBA). A consensus was not reached whether the bone marrow was exposed sufficiently. A slight majority of Member States, including the RMS, considered that there is no evidence of sufficient bone marrow exposure; whereas other experts considered that, in the absence of an agreed definition of a quantitative value in plasma to be considered sufficient, and considering all the lines of evidence, there is sufficient evidence of bone marrow exposure. Overall, the experts concurred that further guidance/methodology on the quantitative assessment of bone marrow exposure would be welcomed. **Open point** EFSA noted that toxicological reference values as agreed during the previous peer review meeting (TC 168[3]) are applicable. The RMS to update the RAR in line with the conclusions of the experts' consultation on genotoxicity, including pertinent RAR/LoEP sections to address non-dietary and consumer dietary risk assessment.

[3] See in open EFSA peer review report for EFSA-Q-2015-00111: https://open.efsa.europa.eu/questions/EFSA-Q-2015-00111

Subject	Conclusions Pesticides Peer Review Meeting
to include a revised genotoxicity assessment Following the setting of this open point, it was decided to follow it up through a collegial discussion with MSs on the bone marrow exposure in *vivo* micronucleus tests Phenmedipham	
Follow up to EC 2.20 MSs experts to discuss the updated weight of evidence for a potential ED regarding T-modality in an experts' meeting. See also 2(32) (ED assessment for humans); 5(44) (ED assessment for non-target organisms), and public comment PCSF-435769, Vol 1, p. 192 See Reporting table after ED clock stop_2022, ED assessment for human 2(15)	The T-mediated parameters were considered sufficiently investigated, and a clear and consistent pattern of hypothalamic-pituitary-thyroid (HPT) axis perturbation is not observed for phenmedipham. With regard to the thyroid hormones and TSH measurements in the extended one-generation reproductive toxicity (EOGRT) study, it is concluded that the effects observed are variable and not consistent throughout the different populations tested in the study. The results of the high throughput screening (HTS) in vitro assays available in ToxCast[4] show that phenmedipham is positive for TPO inhibition. Phenmedipham activity for TPO inhibition could be considered comparable with other potent TPO inhibitors in ToxCast e.g., 6-Propyl-2-thiouracil (PTU). It is noted that, with this potency, it is expected that the substance would have led to a substantial and extensive effects on all aspects of the HPT axis in mammals; however, this is not the case for phenmedipham. In conclusion, taking into account the updated weight-of-the-evidence, a clear and consistent pattern of T-mediated adversity is not observed for phenmedipham. Scenario 1a of the ECHA/EFSA ED Guidance is applicable and the ED criteria for T-modality are not met. **Open point** The RMS to revise the RAR in line with the PRM discussion.

[4] From Comptox Chemical Dashboard; available at this link https://comptox.epa.gov/dashboard/chemical/invitrodb/DTXSID1024255 , last accessed by EFSA in March 2025.

REPORT OF PESTICIDES PEER REVIEW TC 159

***TRICHODERMA GAMSII* ICC080 – AIR IV** **Rapporteur Member State: SE**

6. Microorganisms - Mammalian toxicity

Date: 31 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency - SE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS NL	Ctgb - NL
External Expert	Margarita Aguilera-Gomez - ES
External Expert	Lieve Herman - BE
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH

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Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 **Experts to discuss the toxicological assessment provided for the (potential) secondary metabolites of *T. gamsii* ICC080, as well as the relevant conclusions for the non-dietary risk assessment. In addition, it should be discussed whether it can be narrowed down to include only *T. atrobrunneum* and *T. harzianum*.**	**The information from the literature on the secondary metabolites potentially produced by *T. gamsii* ICC080 is limited, however points to some toxicological properties. EFSA is of the opinion that the lack of analysis of metabolites in the technical material, together with the lack of sufficient robust information on *in situ* production, does not allow to exclude potential concerns.** **This view is in line with the previous EFSA conclusions and supported by the fact that there is increasing information on secondary metabolites produced by *Trichoderma* species in recent literature (not representing yet a consolidated knowledge on secondary metabolites of *Trichoderma* species).** **It is noted that the RMS and MS experts present in the meeting supported the view that no metabolites of concern are identified.**
Experts' consultation point identified by EFSA **MS experts to discuss whether the available information**	**Regarding the co-formulants contained in the formulation supported for the representative uses ('REMEDIER'), based on the currently available information, sufficient toxicological data were available for some of the components. However, for other components, toxicological data were insufficient (including genotoxicity, long term toxicity, and/or carcinogenicity), and it is not possible to**

Subject	Conclusions Pesticides Peer Review Meeting
is sufficient to characterise the full toxicological profile of the formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	conclude whether they impact on the toxicity/classification and safety of the proposed formulation. **Open point:** RMS to revise the RAR Vol.4 in line with the discussion at the peer review meeting.

REPORT OF PESTICIDES PEER REVIEW TC 159

***TRICHODERMA ATROVIRIDE* T11– AIR IV** **Rapporteur Member State: SE**

6. Microorganisms - Mammalian toxicity

Date: 31 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency - SE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS NL	Ctgb - NL
External Expert	Margarita Aguilera-Gomez - ES
External Expert	Lieve Herman - BE
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 **Experts to discuss the toxicological assessment provided for the (potential) secondary metabolites of *T. atroviride* T11, as well as relevant conclusions for the non-dietary risk assessment. In addition, it should be discussed whether it can be narrowed down to include only *T. atrobrunneum* and *T. harzianum*.**	**The information from the literature on the secondary metabolites potentially produced by *T. atroviride* T11 is limited, however points to some toxicological properties. EFSA is of the opinion that the lack of WGS analysis, together with a lack of sufficient robust information on *in situ* production, does not allow to exclude potential concerns.** **This view is in line with the previous EFSA conclusions and supported by the fact that there is increasing information on secondary metabolites produced by *Trichoderma* species in recent literature (not representing yet a consolidated knowledge on secondary metabolites of *Trichoderma* species).** **It is noted that the RMS and MS experts present in the meeting supported the view that no metabolites of concern are identified.**
Experts' consultation point identified by EFSA **MS experts to discuss whether the available information**	**Regarding the co-formulants contained in the formulation supported for the representative uses ('TUSAL'), based on the currently available information, sufficient toxicological data were available for all the components.** **Open point: RMS to revise the RAR Vol.4 in line with the discussion at the peer review meeting**

Subject	Conclusions Pesticides Peer Review Meeting
is sufficient to characterise the full toxicological profile of the formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	

REPORT OF PESTICIDES PEER REVIEW TC 159

***TRICHODERMA ATROBRUNNEUM* ITEM908 – AIR IV** **Rapporteur Member State: SE**

6. Microorganisms - Mammalian toxicity

Date: 31 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency - SE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS NL	Ctgb - NL
External Expert	Margarita Aguilera-Gomez - ES
External Expert	Lieve Herman - BE
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH

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Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 Experts to discuss the toxicological assessment provided for the (potential) secondary metabolites of *T. atrobrunneum* ITEM 908, as well as relevant conclusions for the non-dietary risk assessment. In addition, it should be discussed whether it can be narrowed down to include only *T. atrobrunneum* and *T. harzianum.*	The information from the literature on the secondary metabolites potentially produced by *T. atrobrunneum* ITEM908 is limited, however points to some toxicological properties. EFSA is of the opinion that the lack of detection of metabolites in the technical material is not sufficient to exclude their production, and therefore potential concerns, in particular considering the lack of sufficient information on *in situ* production. This view is in line with the previous EFSA conclusions and supported by the fact that there is increasing information on secondary metabolites produced by *Trichoderma* species in recent literature (not representing yet a consolidated knowledge on secondary metabolites of *Trichoderma* species). It is noted that the RMS and MS experts present in the meeting supported the view that no metabolites of concern are identified.
Experts' consultation point identified by EFSA MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for	Regarding the co-formulants contained in the formulation supported for the representative uses ('TH908'), based on the currently available information, sufficient toxicological data were not available, and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. **Open point:** RMS to revise the RAR Vol.4 in line with the discussion at the peer review meeting.

Subject	Conclusions Pesticides Peer Review Meeting
representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	

REPORT OF PESTICIDES PEER REVIEW TC 159

***TRICHODERMA ASPERELLUM* TV1 – AIR IV** **Rapporteur Member State: SE**

6. Microorganisms - mammalian toxicity

Date: 31 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency - SE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS NL	Ctgb - NL
External Expert	Margarita Aguilera-Gomez - ES
External Expert	Lieve Herman - BE
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

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Discussion points/Outcome

6. Microorganisms - mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 **Experts to discuss the infectivity potential of *T. asperellum* TV1 considering the supportive results of the acute oral toxicity study.**	**Based on the results of the available acute toxicity studies, it is concluded that *Trichoderma asperellum* TV1 has a low potential for infectivity.**
Experts' consultation 6.2 **Experts to discuss the potential of *T. asperellum* TV1 for acute inhalation toxicity.**	**See conclusion above.**
Experts' consultation 6.3 **Experts to discuss the toxicological assessment provided for the (potential)**	**The information from the literature on the secondary metabolites potentially produced by *T. asperellum* TV1 is limited, however points to some toxicological properties. EFSA is of the opinion that the lack of analysis of metabolites in the technical material, together with the lack of sufficient robust information on *in situ* production, does not allow to exclude potential concerns.**

Subject	Conclusions Pesticides Peer Review Meeting
secondary metabolites of *T. asperellum* TV1, as well as relevant conclusions for the non-dietary risk assessment. In addition, it should be discussed whether it can be narrowed down to include only T. *atrobrunneum* and T. *harzianum*.	This view is in line with the previous EFSA conclusions and supported by the fact that there is increasing information on secondary metabolites produced by *Trichoderma* species in recent literature (not representing yet a consolidated knowledge on secondary metabolites of *Trichoderma* species). It is noted that the RMS and MS experts present in the meeting supported the view that no metabolites of concern are identified.
Experts' consultation point identified by EFSA MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	Regarding the co-formulants contained in the formulation supported for the representative uses ('XEDAVIR'), based on the currently available information, toxicological data for all the components is insufficient, and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. Open point: RMS to revise the RAR Vol.4 in line with the discussion at the peer review meeting.

REPORT OF PESTICIDES PEER REVIEW TC 159

***TRICHODERMA ASPERELLUM* T25 – AIR IV** **Rapporteur Member State: SE**

6. Microorganisms - Mammalian toxicity

Date: 31 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency - SE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS NL	Ctgb - NL
External Expert	Margarita Aguilera-Gomez - ES
External Expert	Lieve Herman - BE
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH

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Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 **Experts to discuss the infectivity potential of *T. asperellum* T25 considering the results of the acute studies performed as well as other relevant information.**	**Based on the results of the available acute toxicity studies, it is concluded that *Trichoderma asperellum* T25 has a low potential for infectivity.**
Experts' consultation 6.2 **Experts to discuss the toxicological assessment provided for the (potential) secondary metabolites of *T. asperellum* T25, as well as relevant conclusions for the non-dietary risk assessment. In addition, it should be discussed whether it can be narrowed**	**The information from the literature on the secondary metabolites potentially produced by *T. asperellum* T25 is limited, however points to some toxicological properties. EFSA is of the opinion that the lack of Whole Genome Sequencing (WGS) analysis, together with a lack of sufficient robust information on *in situ* production, does not allow to exclude potential concerns.** **This view is in line with the previous EFSA conclusions and supported by the fact that there is increasing information on secondary metabolites produced by *Trichoderma* species in recent literature (not representing yet a consolidated knowledge on secondary metabolites of *Trichoderma* species).** **It is noted that the RMS and MS experts present in the meeting supported the view that no metabolites of concern are identified.**

Subject	Conclusions Pesticides Peer Review Meeting
down to include only T*. atrobrunneum* and T*. harzianum*.	
Experts' consultation point identified by EFSA MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	Regarding the co-formulants contained in the formulation supported for the representative uses ('TUSAL'), based on the currently available information, sufficient toxicological data were available for all the components. **Open point:** RMS to revise the RAR Vol.4 in line with the discussion at the peer review meeting.

REPORT OF PESTICIDES PEER REVIEW TC 159

***TRICHODERMA ASPERELLUM* ICC012 – AIR IV** **Rapporteur Member State: SE**

6. Microorganisms - Mammalian toxicity

Date: 31 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency - SE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS NL	Ctgb - NL
External Expert	Margarita Aguilera-Gomez - ES
External Expert	Lieve Herman - BE
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH

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Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 **Experts to discuss the toxicological assessment provided for the (potential) secondary metabolites of *T. asperellum* ICC012, as well as the relevant conclusions for the non-dietary risk assessment. In addition, it should be discussed whether it can be narrowed down to include only *T. atrobrunneum* and *T. harzianum*.**	**The information from the literature on the secondary metabolites potentially produced by *T. asperellum* ICC012 is limited, however points to some toxicological properties. EFSA is of the opinion that the lack of analysis of metabolites in the technical material, together with the lack of sufficient robust information on *in situ* production, does not allow to exclude potential concerns.** **This view is in line with the previous EFSA conclusions and supported by the fact that there is increasing information on secondary metabolites produced by *Trichoderma* species in recent literature (not representing yet a consolidated knowledge on secondary metabolites of *Trichoderma* species).** **It is noted that the RMS and MS experts present in the meeting supported the view that no metabolites of concern are identified.**
Experts' consultation point identified by EFSA **MS experts to discuss whether the available information is sufficient to**	**Regarding the co-formulant(s) contained in the formulation supported for the representative uses ('REMEDIER'), based on the currently available information, sufficient toxicological data were available for some of the components. However, for other components, toxicological data were insufficient (including genotoxicity, long term toxicity, and/or carcinogenicity), and it is not possible to conclude whether they impact on the toxicity/ classification and safety of the proposed formulation.**

Subject	Conclusions Pesticides Peer Review Meeting
characterise the full toxicological profile of the formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	**Open point: RMS to revise the RAR Vol.4 in line with the discussion at the peer review meeting.**

REPORT OF PESTICIDES PEER REVIEW TC 159

***TRICHODERMA AFROHARZIANUM* T-22 – AIR IV** **Rapporteur Member State: SE**

6. Microorganisms - Mammalian toxicity

Date: 31 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency - SE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS NL	Ctgb - NL
External Expert	Margarita Aguilera-Gomez - ES
External Expert	Lieve Herman - BE
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

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Discussion points/Outcome

6. Microorganisms - Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 **Experts to discuss the infectivity potential of T. *afroharzianum* T-22 based on results of the available acute toxicity studies (and considering their limitations).**	**Based on the results of the available acute toxicity studies, it is concluded that *Trichoderma afroharzianum* T-22 has a low potential for infectivity.**
Experts' consultation 6.2 **Experts to discuss the toxicological assessment provided for the (potential) secondary metabolites of *T. afroharzianum* T-22, as well as the relevant conclusions for the non-dietary risk assessment. In**	**The information from the literature on the secondary metabolites potentially produced by *T. afroharzianum* T-22 is limited, however points to some toxicological properties. EFSA is of the opinion that the lack of detection of metabolites in the technical material is not sufficient to exclude their production, and therefore potential concerns, in particular considering the lack of sufficient information on *in situ* production.** **This view is in line with the previous EFSA conclusions and supported by the fact that there is increasing information on secondary metabolites produced by *Trichoderma* species in recent literature (not representing yet a consolidated knowledge on secondary metabolites of *Trichoderma* species).**

Subject	Conclusions Pesticides Peer Review Meeting
addition, it should be discussed whether it can be narrowed down to include only *T. atrobrunneum* and *T. harzianum*.	It is noted that the RMS and MS experts present in the meeting supported the view that no metabolites of concern are identified.
Experts' consultation point identified by EFSA MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative use(s) with respect to the acute toxicity, genotoxicity, pathogenicity and infectiveness. For the endpoints not addressed by the studies with the formulation, MS experts to discuss the toxicological profile of each individual component other than the microbial active substance considering also the short- and long-term toxicity.	Regarding the co-formulants contained in the formulation supported for the representative uses ('TRIANUM-P'), based on the currently available information, sufficient toxicological data were available for some of the components. However, for other component(s), toxicological data is insufficient, and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. Open point: RMS to revise the RAR Vol.4 in line with the discussion at the peer review meeting.

REPORT OF PESTICIDES PEER REVIEW TC 158

PYDIFLUMETOFEN – Art. 31 mandate **Rapporteur Member State: FR**

2. Mammalian toxicity

Date: 30 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS BE	Federal Public Service Health Food Chain Safety and Environment - BE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Expert nominated by MS EL	Benaki Phytopathological Institute - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Expert nominated by MS IE	Department of Agriculture Food and the Marine - IE
National Expert nominated by MS MT	ICPS Milano – IT on behalf of MT
National Expert nominated by MS NL	Ctgb - NL
Hearing Expert	Camilla Recordati
Hearing Expert	Eugenio Scanziani
Observer	Federal Food Safety and Veterinary Office - CH
Observer	Malta Competition and Consumer Affairs Authority - MT

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Preparatory meeting to Pesticide Peer Review TC 158 on "Short-term repeated dose 28-day inhalation toxicity study of Pydiflumetofen" **6 December 2025 (9:00-15:00, online meeting)**	**A preparatory meeting to the Pesticide Peer Review TC 158 on the "Short-term repeated dose 28-day inhalation toxicity study of Pydiflumetofen (Ares(2024)7751893 31/10/2024)" was held on 6 December, chaired by EFSA staff.** **a. Participants: EFSA staff, Eugenio Scanziani (hearing expert, University of Milan) and Camilla Recordati (Hearing expert, University of Milan).** **b. Discussion points: Experts discussed the pathology findings in the new short-term repeated dose inhalation study in the rat with Pydiflumetofen; a pathology expert advice was prepared to assist in the Member States Experts consultation on Pydiflumetofen in Pesticide Peer Review TC 158. The new 28-day inhalation toxicity study in the rat with pydiflumetofen (0, 50, 200 and 500 mg/m^3 with recovery groups) was discussed.**
Experts to discuss the new 28-day inhalation toxicity study in the rat with pydiflumetofen (2019) and the study NOAEC, (based on the revised DAR January 2025.	**In TC 158, the study was considered acceptable with limitations.** **Effects related to the systemic exposure to Pydiflumetfoen were observed in the liver (statistically significant weight increase at 200 and 500 mg/m^3) line with the toxicological profile of the substance.** **Treatment related effects in the lungs (increased alveolar macrophage aggregates and type II pneumocyte hypertrophy/ hyperplasia) were seen at all concentrations. The majority of experts considered these pulmonary effects a local reaction to inhaled particles. The NOAEC was set at 50 mg/m^3 because of the nature of the findings (local response to inhaled**

Subject	Conclusions Pesticides Peer Review Meeting
	particles) and severity of the findings at this concentration (up to mild or minimal). The RMS did not agree and was still of the opinion that the effect at the low dose should be considered systemic and adverse.
Experts' consultation: Impact of the new 28-day inhalation study on the AOEL	Considering the conversion of the NOAEC into a systemic dose the current AOEL would be sufficiently protective. A revision of the non-dietary exposure estimates is not triggered by the results of this new 28-day study. Regarding occupational exposure, it was noted that use of PPE could be recommended for local effects.

REPORT OF PESTICIDES PEER REVIEW TC 158

DICHLORPROP-P – amendment of approval conditions **Rapporteur Member State: IE**

2. Mammalian toxicity

Date: 30 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS IE	Department of Agriculture Food and the Marine - IE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS BE	Federal Public Service Health Food Chain Safety and Environment - BE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Expert nominated by MS EL	Benaki Phytopathological Institute - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Expert nominated by MS HU	National Food Chain Safety Office - HU
National Expert nominated by MS IT	ICPS Milano - IT
National Expert nominated by MS NL	Ctgb - NL
Observer	Federal Food Safety and Veterinary Office FSVO (FSVO) - CH

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the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 1.1 CONFIDENTIAL (NUFARM) Experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative uses with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation supported for the representative uses ('Nufarm Code CA2134'), based on the currently available information, sufficient toxicological data were available for some components. However, for other components, toxicological data were insufficient (including genotoxicity and repeated dose toxicity information over the short- and long-term) and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. **Data gap** Data are missing for some co-formulants, in relationship with their identity and respective toxicity profile (including genotoxicity and repeated dose toxicity information over the short- and long-term), in order to conclude on their impact on the safety of the plant protection product. **Open point** RMS to integrate the additional information discussed in the meeting and the achieved conclusion in the revised RAR.

REPORT OF PESTICIDES PEER REVIEW TC 158

MALEIC HYDRAZIDE – amendment of approval conditions **Rapporteur Member State: BE**

2. Mammalian toxicity

Date: 30 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS BE	Federal Public Service Health Food Chain Safety and Environment - BE
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Expert nominated by MS EL	Benaki Phytopathological Institute - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Expert nominated by MS HU	National Food Chain Safety Office - HU
National Expert nominated by MS IE	Department of Agriculture Food and the Marine - IE
National Expert nominated by MS MT	ICPS Milano – IT on behalf of MT
National Expert nominated by MS NL	Ctgb - NL
Observer	Federal Food Safety and Veterinary Office FSVO (FSVO) - CH

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the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Member State Experts to discuss the genotoxicity profile of 3-pyridazinone in an experts' meeting.**	**3-pyridazinone is devoid of mutagenic, clastogenic or aneugenic potential based on the overall *in vitro* genotoxicity data package.**
Experts' consultation 2.2 **Member State Experts to discuss in an experts' meeting the 90-day rat study with 3-pyridazione and, in particular, changes in forelimb strength and motor activity, changes in hematological parameters and their possible relation to stress, effects on testes, epipidymides, ovaries and uterus. In addition, to discuss and agree on the NOAEL and BMD analysis.**	**For the 90-day study performed with 3-pyridazinone in rats by gavage the experts agreed:** • **the haematological changes observed could be dismissed on the basis of stress, but could also be considered treatment-related and associated with nasal turbinate effects, particularly in males;** • **the effects observed in testes, epididymis, ovaries and uterus and fertility were concluded to be likely not ED-mediated and associated with systemic toxicity and stress;** • **the increase in motor activity and forelimb grip strength were concluded to be possibly linked to the general discomfort of rats due to the irritating properties of the metabolite on the respiratory tract, and not the expression of a neurotoxic effect;** • **the LOAEL is 267 mg/kg bw per day and the critical effects at the LOAEL are: increased relative liver weight and increased incidences of vacuolation in the liver in males and females, reduced body weight gain. BMD analysis provided on different sets of quantal data was considered**

Subject	Conclusions Pesticides Peer Review Meeting
	not appropriate in case of limitations of the dataset (i.e. very flat dose-response observed for hepatocellular vacuolation, the most sensitive effect with almost all treated rats showing a response). LOAEL was considered more appropriate as PoD for ADI derivation. **Open point:** RMS to include in the updated DAR the revised BMD analysis presented during the experts' meeting.
Experts' consultation: 2.3 Member Sate Experts to discuss and agree on the toxicological reference values of 3-pyridazinone in an experts' meeting.	The ADI of 3-pyridazinone is 0.13 mg/kg bw per day based on the LOAEL of 267 mg/kg bw per day for hepatic changes observed in the 90-day study in rats, applying an overall UF of 2000 (standard UF of 100, plus an extra UF of 2 to extrapolate from sub-chronic to chronic, plus an extra UF of 10 for LOAEL to NOAEL extrapolation and incomplete data package).

REPORT OF PESTICIDES PEER REVIEW

TC 157 and158

BENZOBICYCLON – NAS 1107 **Rapporteur Member State: MT**

2. Mammalian toxicity

Date: 30 January 2025

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS MT	ICPS – IT on behalf of MT
National Expert nominated by RMS MT	Malta Competition and Consumer Affairs Authority (MCCAA) - MT
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS BE	Federal Public Service Health Food Chain Safety and Environment - BE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency (DEPA) - DK
National Experts nominated by MS EL	Benaki Phytopathological Institute - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS HU	National Food Chain Safety Office - HU
National Expert nominated by MS HR	Center for Plant Protection - HR
National Expert nominated by MS IE	Department of Agriculture Food and the Marine - IE

Status	Name of institution / attendee
National Experts nominated by MS NL	Ctgb - NL
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH
Observer	Swiss Federal Office for the Environment - CH
Observer	Malta Competition and Consumer Affairs Authority (MCCAA) - MT

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **MS experts to discuss ADME data and agree on:** - **the oral absorption value of benzobycyclon;** - **tissue distribution focusing g on the relevance for kidneys changes.**	**The oral absorption of Benzobicyclon is 11% at the low dose (10 mg/kg bw) and 4-5% at the high dose (500 mg/kg bw). The available ADME data point to a similar ADME profile of Benzobicyclon (total radioactivity) in male and female rats, including a similar kidney exposure.**
Experts' consultation 2.2 **MS experts to discuss the adequacy of the in vitro metabolism study considering the comments received (gender mixed hepatocytes, low recovery in human hepatocytes).**	**The available comparative in vitro metabolism study for Benzobicyclon is considered adequate and sufficiently robust for evaluation of potential unique human metabolites (UHM) and/or disproportionate human metabolites (DHM). No UHM and/or DHM were identified.** **Open point** **RMS to revise the DAR by including information on the justification for the acceptability of the study, including the use of mixed-gender hepatocytes and despite the low recovery at 15 and 30 minutes incubations with human hepatocytes, and the justification for the use of rat and human hepatocytes only.**

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.3 MS experts to discuss the findings and the NOAEL of the subchronic oral toxicity study in rats CA 5.3.2/01.	In a subchronic oral (dietary) toxicity study with Benzobicyclon adverse renal findings were observed in male rats at ≥ 100 ppm. These findings are consistent with α2u-globulin nephropathy. No other adverse effects were found in the study. The NOAEL for male rats is 20 ppm (1.13 mg/kg bw per day), based on kidney effects (α2u-globulin nephropathy, including changes at histopathology, clinical chemistry and urinalysis). Excluding kidney effects in male rats (considered specific to the test system and not relevant to humans), the NOAEL relevant for humans is 400 ppm (22.72 mg/kg bw per day), the highest dose tested in male rats. The NOAEL for female rats is 10000 ppm (630 mg/kg bw per day), the highest dose tested in females. **Open point** RMS to adjust in the revised DAR the interpretation of haematological findings in male rats (considered not adverse because of the low magnitude of change and lack of such effects in the rat study after chronic exposure).
Experts' consultation 2.4 MS experts to discuss the NOAELs for the subchronic and chronic (dog) toxicity studies on benzobicyclon.	The NOAEL in the 90-day dog study is 2000 mg/kg bw per day for males and females (the highest dose tested). The NOAEL in the 1-year dog study is 1000 mg/kg bw per day for males and females (the highest dose tested). **Open point** RMS to provide information in a revised DAR regarding: the congenital/background nature of pituitary and parathyroid cysts, duodenal cysts and pulmonary findings in the dog and the lack of toxicological relevance in this study; the interpretation of the clinical findings (related to very high amount of test substance, high faecal excretion, use of capsules, and occurrence also in controls).
Experts' consultation 2.5 MS experts to discuss the genotoxicity assessment of benzobicyclon (chromosomal aberration in vitro, Ames test, in vivo micronucleus test).	Benzobicyclon is unlikely to be genotoxic in vivo based on a weight of evidence approach. This overall conclusion is in line with the conclusion of ECHA RAC.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.6 MS experts to discuss the NOAELs (systemic toxicity and carcinogenicity) of the mouse study B.6.5.2.	The NOAEL for systemic toxicity in the chronic mouse study is 3000 ppm (equal to 373 mg/kg bw per day for males and 473 mg/kg bw per day for females), based on effects in the liver (organ weight and histopathology findings) at 30000 ppm. The NOAEL for carcinogenicity in the chronic mouse study is 30000 ppm (equal to 3817 mg/kg bw per day for males and 4807 mg/kg bw per day for females), the highest dose tested.
Experts' consultation 2.7 MS experts to discuss the mode of action of renal changes observed in male rat studies.	Renal findings in male rats given Benzobicyclon rat are in line with the process of α 2u-globulin nephropathy, a male rat specific condition, not relevant for humans. NOAELs excluding male rat renal findings (α 2u nephropathy-related) in all Benzobicyclon toxicity studies in the dataset are to be used for the human hazard and risk assessment of Benzobicyclon.
Experts' consultation 2.8 - MS experts to discuss the adequacy of the selected dose levels and spacing of the chronic toxicity/carcinogenicity studies in rats (OECD TG 453) CA 5.5/01, in particular as regards to renal toxicity. - MS experts to discuss the NOAELs (systemic toxicity and carcinogenicity) of the chronic oral toxicity and carcinogenicity study in rat.	The dose setting for the chronic toxicity/carcinogenicity study for Benzobicyclon in the rat is considered adequate, since selected based on a preliminary dose range finding study. The NOAEL for systemic toxicity for male rats is 50 ppm (equal to 1.696 mg/kg bw per day), based on α 2u-globulin nephropathy and aggravated chronic nephropathy at 100 ppm. Excluding kidney effects in males, which were considered specific to the test system and not relevant to humans, the NOAEL for systemic toxicity is 100ppm (equal to 3.43 mg/kg bw per day), the highest tested dose. The NOAEL for systemic toxicity for female rats is 10000 ppm (equal to 427 mg/kg bw per day), the highest tested dose. The NOAEL for carcinogenicity is 100 ppm for males (equal to 3.43 mg/kg bw per day), and 10000 ppm for females (equal to 427 mg/kg bw per day), the highest tested doses. **Open point** RMS to clarify that the hyalin droplet disposition in the kidney from females is considered not adverse, because present in concurrent controls, while consideration of their nature is not determined because of the lack of specific investigation.
Experts' consultation 2.9	In a two-generation study in the rat, histopathological pituitary findings were seen in some males from both generations; these are considered treatment related, but not adverse.

Subject	Conclusions Pesticides Peer Review Meeting
MS experts to discuss pituitary findings and the NOAEL of the2-gen reproductive toxicity study in the rat (CA B.6.6.1).	The following NOAEL values were agreed. Parental toxicity: For males, the NOAEL (considering kidney effects) is 100 ppm (equal to 7 mg/kg bw per day), based on effects on kidneys (pale in colour, enlargement (F1), significantly increased relative kidney weights (F0 and F1), increased hyaline droplet degeneration in the proximal tubular cells, tubular basophilic change, and granular casts in the dilated tubules (F0 and F1). Excluding kidney effects (considered specific to the test system and not relevant to humans), the NOAEL relevant for humans is 20000 ppm (equal to 1176 mg/kg bw per day), the highest dose tested. For females, the NOAEL is 20000 ppm (1741 mg/kg bw per day), the highest dose tested. Reproductive toxicity: The NOAEL is 20000 ppm (equal to 1515 mg/kg bw per day), the highest dose tested. Offspring toxicity: The NOAEL is 20000 ppm (equal to 1250 mg/kg bw per day), the highest dose tested
Experts' consultation 2.10 MS experts to discuss ED properties of benzobicyclon.	T-modality A pattern of T-mediated adversity was not observed ina a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED Guidance is applicaable and the ED criteria for T-modality are not met. EAS-modality A pattern of EAS-mediated adversity was not observed ina a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED Guidance is applicaable and the ED criteria for EAS-modality are not met. Open point The RMS to revise the DAR in line with the ocome of the Peer Review Meeting discussion.
Experts' consultation 2.11	Based on the information available in the DAR was discussed, and the following conclusions were reached on metabolites 1315P-076, 1315P-070, 1315P-966, 1315P-570, 1315P-960, 1315P-962, 1315P-683 and transformation products.

Subject	Conclusions Pesticides Peer Review Meeting
MS experts to discuss the toxicological profile of relevant metabolites.	**Genotoxicity** Available data in the dossier do not raise a concern for gene mutation and/or chromosome aberration based on experimental data for the following metabolites: 1315P-076, 1315P-070, 1315P-966, 1315P-570, 1315P-960, and 1315P-962 do not raise a concern for gene mutation and/or chromosome aberration. However, as regards 1315P-076, 1315P-966, 1315P-570, 1315P-960, and 1315P-962, as groundwater metabolites, an in vitro mamalian gene mutation assay should be provided and its relevance assessment remains currently open. Furthermore, additional experimental data on the common metabolite 1315P-966 is available in the sulcotrione dossier (currently under re-assessment), which should be considered in the overall weight of evidence for genotoxicity. Therefore, the genotoxic potential of metabolite 1315P-966 remains open. For metabolite 1315P-683, the assessment of its clastogencic/aneugenic potential remains open. The assessment of the genotoxic potential of thiophenol remains open, since very limited information was provided. Available information pointed out to a non genotoxic concern for transformation products, however the experts suppport that a more robust assessment including reporting shoud be provided to have a firm conclusion (in particular whether structural changes of the transformation products compared to their precursors). **General toxicity** The following toxicological reference values (TRVs) were set for metabolite 1315P-070: ADI (acceptable daily intake): 0.0015 mg/kg bw per day, based on the NOAEL of the 90-day rat study of 0.3 mg/kg bw per day applying the standard UF of 100 and an extra UF of 2 because of lack of a chronic study. AOEL (acceptable operator exposure level): 0.003 mg/kg bw per day, based on the NOAEL of the 90-day rat study of 0.3 mg/kg bw per day, applying the standard UF of 100. No correction for oral absorption. ARfD (acute reference dose): 1.5 mg/kg bw, based on the developmental NOAEL of 150 mg/kg bw per day of the developmental toxicity study in rabbits, applying the standard UF of 100.

Subject	Conclusions Pesticides Peer Review Meeting
	AAOEL (acute acceptable operator exposure level): 1.5 mg/kg bw, based on the developmental NOAEL of 150 mg/kg bw per day of the developmental toxicity study in rabbits, applying the standard UF of 100. No correction for oral absorption. **For the other metabolites and transformation products, toxicological information available in DAR (and dossier) of Benzobicyclon did not allow assessment of their general toxicity. Therefore, no TRVs could be set for these.** **Open point** **RMS to update the DAR on the outcomes of the discussion on metabolites and to provide reference to the US-EPA report on HPPD inhibitors.**
Experts' consultation 2.12 - **MS experts to discuss the derivation of toxicological endpoints based on the final conclusion on toxicological data with possible consideration of additional uncertainty factor, if appropriate.** - **MS experts to take into account that benzobicyclon is a racemate.**	**The following toxicological references values were set for Benzobicyclon.** **ADI (acceptable daily intake)** **The ADI of Benzobicyclon is 0.034 mg/kg bw per day based on the (human-relevant) NOAEL of 3.4 mg/kg bw per day from a 2-year chronic toxicity/carcinogenicity study in rats, applying the standard uncertainty factor of 100.** **ARfD (acute reference dose)** **Not required, since no acute effects observed in the data package.** **AOEL (acceptable operator exposure level)** **The AOEL for Benzobicyclon is 0.6 mg/kg bw per day based on the (human-relevant) parental NOAEL of 1176 mg/kg bw per day from the 2-generation reproductive toxicity study in rats, applying the standard uncertainty factor of 100 and a correction for an oral absorption of 5%.** **AAOEL (acute acceptable operator exposure level)** **Not required, since no acute effects observed in the data package.**

Subject	Conclusions Pesticides Peer Review Meeting
	Open point for EFSA: to communicate to Residues that the ADI of Benzobicyclon is based on the toxicological profile of the racemic mixture of the 2 isomers, and the specific toxicity profile of the individual isomers is unknown.
Experts' consultation 2.13 **MS experts to discuss non-dietary exposure of benzobicyclon and relevant metabolites; to consider that benzobicyclon is a racemate.**	**The dermal absorption values for Benzobicyclon in the representative formulation GWN-10235 are 0.66% for the concentrate and 16% for the dilution, while for the metabolite 131P-070 are 10% for the concentrate and 50% for the dilution (default values).** **Open point** **The RMS is requested to provide revised non-dietary exposure calculations taking into account the agreed toxicological endpoints (dermal absorption and AOEL/AAOEL) and agreed degradation values (from hydrolysis and flooded paddy field studies) for Benzobicyclon and the metabolite 1315P-070 for** • **operators considering they will be exposed to Benzobicyclon during M/L and to Benzobicyclon (70%) and the metabolite 1315P-070 (30%) during application** • **bystander considering they will be exposed to the parent (70%) and the metabolite 1315P-070 (30%)** • **workers and resident considering they will be exposed only to the metabolite 1315P-070** **The RMS is requested to calculate the worker exposure for inspection in rice crops, summing the potential exposure to dry residues and the exposure by walking into the flooded paddy field (with the agreed parameters for body surface area and film thickness).**
Experts' consultation (mammalian toxicity section) 1.1 **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute,**	**Regarding the co-formulants contained in the formulation supported for the representative uses ('GWN 10235'), based on the currently available information, sufficient toxicological data were available for most components. However, for some components, toxicological data is insufficient (including genotoxicity and/or short, long-term toxicity/ carcinogenicity) and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation.** **Open point: the RMS to revise the RAR Vol.4 in line with the discussion at the peer review meeting.**

Subject	Conclusions Pesticides Peer Review Meeting
genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	

REPORT OF PESTICIDES PEER REVIEW TC 153

Mecoprop-P – MRL Art. 10 **Evaluating Member State: IE**

2. Mammalian toxicity

Date: 25 November 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by EMS IE	Pesticide Registration Division, Dept. of Agriculture, Food & the Marine Laboratories - IE
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR)- DE
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Federal Food Safety and Veterinary Office - CH

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the toxicological profile (genotoxicity and general toxicity) of the metabolite hydroxymethyl-mecoprop-P (HMCPP) in an experts' meeting.**	**Open point for the EMS to confirm two points:** **1) Whether HMCPP is a major rat metabolite (i.e. higher than 10% in urine in both male / female)** **2) *In vivo* MN test on HMCPP is reliable.** **Based on the 28-day study with the metabolite, showing lower toxicity than mecoprop-P, but pending on the confirmation of the lack of a genotoxic potential for the metabolite HMCPP (see points of clarification above), TRVs of the parent may apply to the metabolite as a conservative approach (NOAEL > 1487 mg/kg bw per day in the 28-day study).**
Experts' consultation 2.2 **MSs experts to discuss the toxicological profile (genotoxicity and general toxicity) of the metabolite carboxy-mecoprop-P (CCPP) in an experts' meeting.**	**Based on experimental data, the metabolite CCPP is unlikely to be genotoxic.** **No conclusion can be reached on the general toxicity profile of the metabolite CCPP based on the available toxicological data, either a 28-day study or read across/grouping analysis could be considered to address general toxicity.**
Experts' consultation 2.3 **MSs experts to discuss the toxicological profile (genotoxicity and general toxicity) of the metabolite 4-glucosyl-MPP in an experts' meeting.**	**Based on lack of an *in vitro* MN test or reliable in silico analysis the genotoxicity potential of the metabolite 4-glucosyl-MPP is inconclusive for chromosome aberration, either in vitro MN test with the aglicon or a more robust in silico analysis should be provided to conclude on the genotoxicity potential of the metabolite.** **No conclusion can be reached on the general toxicity profile of the metabolite 4-glucosyl-MPP. Either a 28-day study with the**

Subject	Conclusions Pesticides Peer Review Meeting
	aglicon or read across/grouping analysis should be considered to address general toxicity. **Note: The EMS noted that according to residues exposure situation, there will be no consumer exposure and therefore no additional data should be provided. However EFSA noted that this data has been requested following residues advice.**

REPORT OF PESTICIDES PEER REVIEW TC 153

Imazalil – MRL Art. 10 **Evaluating Member State: NL**

2. Mammalian toxicity

Date: 25 November 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by EMS NL	Ctgb - NL
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR)- DE
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IE	Pesticide Registration Division, Dept. of Agriculture, Food & the Marine Laboratories - IE
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Federal Food Safety and Veterinary Office - CH

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Discussion points/Outcome

2. Mammalian toxicity

Please note that information part of this report may have been masked by EFSA in accordance with Article 63 of Regulation (EC) No 1107/2009 as well as EFSA's Practical Arrangements concerning confidentiality in accordance with Articles 7 and 16 of Regulation (EC) No 1107/2009, or EFSA's Practical Arrangements concerning transparency and confidentiality as a consequence of confidentiality requests submitted by the applicant on application dossiers for pesticides active substances or Maximum Residue Levels, respectively. Please note that information disclosed in this report is without prejudice to pre-existing intellectual property rights and data exclusivity clauses set out in Union law, and particularly in Article 62 of Regulation (EC) No 1107/2009.

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the genotoxic and general toxicity profile of metabolite R014821 in comparison with parent.**	**Based on experimental data, metabolite R014821 is unlikely to be genotoxic.** **Based on commonalities of the effects observed in toxicological studies between R014821 and imazalil, the toxicological reference values of imazalil are applicable to the metabolite R014821.**
Experts' consultation 2.2 **Experts to discuss the genotoxic and general toxicity profile of metabolite FK-284 in comparison with parent.**	**Based on the limitations of the in vivo MN test and taking into consideration the positive results obtained in the vitro MN test, all experts agreed that the genotoxicity of metabolite FK-284 is inconclusive with regards to its clastogenic and aneugenic potential.** **Since the genotoxicity of the metabolite FK-284 is inconclusive with regards to its clastogenic and aneugenic potential , no TRVs can be set for the metabolite.** **Open point: EMS to check whether the plasma analysis performed in the in vivo MN test performed with the metabolite FK-284 is acceptable taking into consideration the possible contamination observed in the control group.** **Stop the clock for the applicant: Applicant to provide further details of the results of the statistical analysis performed in the in vivo MN test conducted with the metabolite FK-284.**
Experts' consultation 2.3	**Based on experimental data, the metabolite FK-772 is unlikely to be genotoxic.** **Based on a comparative 90-day, rat study, the toxicological reference values of imazalil can apply to the metabolite FK-**

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the genotoxic and general toxicity profile of metabolite FK-772 in comparison with parent.	772 as a worst-case approach (since there are indications that it is of lower toxicity than parent). Open point for the EMS to check whether the MLA test with the metabolite FK-772 was performed according to the latest OECD TG.

REPORT OF PESTICIDES PEER REVIEW

TC 152 and TC 153

Paraffin oils (CAS 97862-82-3) – AIR IV **Rapporteur Member State: EL**

2. Mammalian toxicity

Date: 25 November 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS EL	Benaki Phytopathological Institute - EL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	Central Institute for Supervising and Testing in Agriculture - CZ
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Expert nominated by MS NL	Ctgb - NL
Observer	Austrian Agency for Health and Food Safety (AGES) - AT

MEETING MINUTES – 25 November 2024
Pesticides Peer Review TC 152 and TC 153
Paraffin oils (CAS 97862-82-3)

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the criteria related to the relevance of test items used in the studies present in Vol. 3CA B6.**	**A study was considered relevant when the test material complied with at least one of the following criteria:** • **CAS No 64742-46-7, 72623-86-0 or 97862-82-3.** • **Fulfils the technical specification of European, British, US or International Pharmacopoeia.** • **It is a highly refined white oil with carbon chain length in the following ranges:** o **CAS No 64742-46-7: C11 – C25 (in agreement with REACH Registration Dossier)** o **CAS No 72623-86-0: C15 – C30 (in agreement with REACH Registration Dossier)** o **CAS No 97862-82-3: C11 – C30 (blend of other two paraffin oils, RAR/Confidential)** • **Other information on the identity of the test material complies with the physico-chemical properties of the active substance as included in RARs, Section B.2.**
Experts' consultation 2.2 **Experts to discuss the waivers for the *in vitro* comparative metabolism study, the carcinogenicity study in mouse, the developmental toxicity study in rabbit and neurotoxicity studies of paraffin oil (CAS 97862-82-3).**	**A waiver of the *in vitro* comparative metabolism study is considered acceptable, as, based on the available information, unique or disproportionate human metabolites of toxicological concern are not expected. A comparative *in vitro* metabolism study is not expected to alter this outcome.** **A waiver of the carcinogenicity study in mouse is considered acceptable, based on i) the absence of MOSH long-term toxicity/carcinogenicity in rats (via oral and inhalation routes) and mice (via dermal and inhalation routes), ii) no evidence of cancer in humans despite the long-term use of highly purified white mineral oils in medicine and cosmetics, iii) the negative human epidemiology study on kerosene, and iv) the absence of reported adverse effects with use of highly refined mineral oils as placebos in human studies.**

Subject	Conclusions Pesticides Peer Review Meeting
	Open point: **RMS to include in a revised RAR reference to the available data on effects of highly refined mineral oils applied as placebo in human studies to substantiate the waiver for the mouse carcinogenicity study.** **A waiver of the developmental toxicity study is considered acceptable, given that i) there is no evidence of adversity on reproductive organs in any study in the data set and that white oils have been used extensively as solvent controls in teratogenicity studies in the context of veterinary medicinal product assessment, causing no teratogenic effects, and ii) based on available information on paraffin oils, it can be concluded that developmental effects in the absence of PAHs are unlikely.** **Open point:** **RMS to include information in a revised RAR on developmental toxicity of the gas-to-liquid (GTL)-products to support the waiver.** **A waiver of neurotoxicity studies is considered acceptable, given that no signs of neurotoxicity have been reported from human studies and from the use of paraffin oils as human medicines, supported by the reported lack of bioactivity for non-aromatic saturated hydrocarbons (MOSH) in neuronal cells (as reported in the latest EFSA CONTAM Panel Opinion on mineral oil hydrocarbons in food (EFSA, 2023)).** **Open point:** **RMS to include considerations of human data to substantiate the waiver for neurotoxicity studies.**
Experts' consultation 2.3 **Experts to discuss the genotoxic potential of Paraffin oil (CAS 97862-82-3) considering the available information and the previous assessment in the Report of "PESTICIDE PEER REVIEW TC 100; PARAFFIN OIL CAS 8042-47-5 – AIR IV" (C17-C31) (Experts' consultation 2.4; 2.9).**	**Paraffin oils (CAS No 64742-46-7, 72623-86-0, 97862-82-3) are unlikely to be genotoxic. No further testing is needed.**

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.4 Experts to discuss the waiver for an ED assessment of paraffin oil (CAS 97862-82-3).	A waiver of the ED assessment for the EATS-modalities is considered acceptable based on i) the lack of toxicological concern from the available studies (from public literature) conducted with mineral oils relevant to the active substance paraffin oil, ii) absence of adverse effects or lipid accumulation in endocrine organs, iii) absence of alerts from the available QSAR data investigating the EATS-modalities, iv) history of safe use of paraffin oil and refined mineral oils in medicine[3], cosmetic[4] and food[5]. **Open point** The RMS is asked to include in a revised RAR the reference to any other uses, e.g., cosmetic and medicinal, for which there is no report of endocrine disturbance and human health concern.
Experts' consultation 2.5 Experts to discuss the toxicological reference values for paraffin oil (CAS 97862-82-3).	Health-based guidance values are not considered necessary for paraffin oil CAS 64742-46-7, paraffin oil CAS 72623-86-0, paraffin oil CAS 97862-82-3, as there is no evidence of (human-relevant) systemic adverse effects in animal studies and given that available human data do not point to adverse effects. In case a reference value for inhalation exposure assessment is needed, the MAK (Maximum workplace concentration = MCW) value of 5 mg/m³ could be used as an AOEC for route (inhalation)-specific risk characterisation for CAS No 64742-46-7, 72623-86-0, 97862-82-3. **Open point:** RMS to include information in a revised RAR indicating that spleen effects are only observed in F344 rats, and to include information on the uncertainty of the spleen effects being secondary to liver effects as described in the CONTAM Panel Opinion (2023).
Experts' consultation 2.6 Experts to discuss the non-dietary exposure	The default dermal absorption values of 25% and 70% for the concentrate and dilution, respectively, as proposed in the EFSA Guidance (2017), are applicable, in case needed.

[3] https://www.ema.europa.eu/en/documents/mrl-report/mineral-hydrocarbons-summary-report-committee-veterinary-medicinal-products_en.pdf
[4] https://mobil.bfr.bund.de/cm/349/highly-refined-mineral-oils-in-cosmetics-health-risks-are-not-to-be-expected-according-to-current-knowledge.pdf
[5] EFSA 2023, Update of the risk assessment of mineral oil hydrocarbons in food https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2023.8215, EFSA Journal, 2012; 10(6):2704, Scientific Opinion on Mineral Oil Hydrocarbons in Food https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2704

Subject	Conclusions Pesticides Peer Review Meeting
assessment for operators, residents and bystander and workers.	**Open point:** RMS to provide revised non-dietary exposure estimates, for the representative uses of POLITHIOL, comparing the estimates for the inhalation route to the MAK value of 5 mg/m³ (8h -10 m³) for all exposed populations, considering also the following recommendations: - default average air concentration (0.015 mg/m³) for moderately volatile compounds should be used; - exposure estimates for re-entry activities of workers are not required; - risk assessment for bystander is not required as average exposure over a longer duration (resident) will also cover bystander exposure; - exposure estimates for resident should include both the vapour and spray drift pathways.
Expert consultation points from the Confidential Evaluation Tables	
Experts' consultation 2.1 Experts to discuss the Margin of Exposure approach related to the potential presence of 0.3 ppm polycyclic aromatic hydrocarbons (PAHs) in the a.s.	There is no human health concern from the potential presence of polycyclic aromatic hydrocarbon (PAH) impurities at levels equal or below 0.3 ppm in the active substance, as the Margin of Exposure between estimated non-dietary PAH exposure to the BMDL10 of the available carcinogenicity study is >> 10.000. **Open point:** RMS to present Margin of Exposure assessments for the potential presence of 0.3 ppm PAHs in the active substance, tailored for the three paraffin oils (i.e., with CAS numbers 64742-46-7, 72623-86-0 and 97862-83) in their respective RAR Vol. 4. RMS to clearly indicate in the Vol. 4 that exposure is estimated for the paraffin oil active substance, resulting in the highest exposure to the active substance, and that PAH exposure was extrapolated from that exposure estimate assuming a maximum PAH content of 0.3 ppm.
Experts' consultation (mammalian toxicity) 2.2 & 2.3 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with	Not for all co-formulants was sufficient information available to conclude on their safety. Open points were set for the RMS for the following co-formulants: [redacted] **Open point:** RMS to include the toxicological information on the co-formulant [redacted] presented during the Peer Review Meeting in an updated RAR, including its assessment and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity

Subject	Conclusions Pesticides Peer Review Meeting
respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	potential over the short- and long-term, and whether a safety concern exists. [redacted] **Open point:** RMS to include the information on the co-formulant [redacted] from the previous discussion of this co-formulant (Peer Review Meeting Report TC118-TC119) in an updated RAR, including its assessment and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term, and whether a safety concern exists. [redacted] **Open point:** RMS to include the toxicological information on the co-formulant [redacted] presented during the Peer Review Meeting in an updated RAR, including its assessment and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term, and whether a safety concern exists. [redacted] **Open point:** RMS to include the toxicological information on the co-formulant [redacted] presented during the Peer Review Meeting in an updated RAR, including its assessment and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term, and whether a safety concern exists. [redacted] **Open point:** RMS to include the toxicological information on the co-formulant [redacted] presented during the Peer Review Meeting in an updated RAR, including its assessment and related conclusion whether

Subject	Conclusions Pesticides Peer Review Meeting
	sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term, and whether a safety concern exists. [redacted] **Open point:** **RMS to include the toxicological information on the co-formulant [redacted] presented during the Peer Review Meeting in an updated RAR, including its assessment and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term, and whether a safety concern exists.** **The plant protection product information is property of UPL, thus information on the co-formulant(s) of the representative product are presented in Volume 4 for UPL.**

REPORT OF PESTICIDES PEER REVIEW

TC 152 and TC 153

Paraffin oils (CAS 72623-86-0) – AIR IV **Rapporteur Member State: EL**

2. Mammalian toxicity

Date: 25 November 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS EL	Benaki Phytopathological Institute - EL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	Central Institute for Supervising and Testing in Agriculture - CZ
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Expert nominated by MS NL	Ctgb - NL
Observer	Austrian Agency for Health and Food Safety (AGES) - AT

MEETING MINUTES – 25 November 2024
Pesticides Peer Review TC 152 and TC 153
Paraffin oils (CAS 72623-86-0)

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the criteria related to the relevance of test items used in the studies present in Vol. 3CA B6.**	**A study was considered relevant when the test material complied with at least one of the following criteria:** • **CAS No 64742-46-7, 72623-86-0 or 97862-82-3.** • **Fulfils the technical specification of European, British, US or International Pharmacopoeia.** • **It is a highly refined white oil with carbon chain length in the following ranges:** o **CAS No 64742-46-7: C11 – C25 (in agreement with REACH Registration Dossier)** o **CAS No 72623-86-0: C15 – C30 (in agreement with REACH Registration Dossier)** o **CAS No 97862-82-3: C11 – C30 (blend of other two paraffin oils, RAR/Confidential)** • **Other information on the identity of the test material complies with the physicochemical properties of the active substance as included in RARs, Section B.2.**
Experts' consultation 2.2 **Experts to discuss the waivers for the in vitro comparative metabolism study, the carcinogenicity study in mouse, the developmental toxicity study in rabbit and neurotoxicity studies of**	**A waiver of the in vitro comparative metabolism study is considered acceptable, as, based on the available information, unique or disproportionate human metabolites of toxicological concern are not expected. A comparative *in vitro* metabolism study is not expected to alter this outcome.** **A waiver of the carcinogenicity study in mouse is considered acceptable, based on i) the absence of MOSH long-term toxicity/carcinogenicity in rats (via oral and inhalation routes) and mice (via dermal and inhalation routes), ii) no evidence of cancer in humans despite the long-term use of highly**

Subject	Conclusions Pesticides Peer Review Meeting
paraffin oil (CAS 72623-86-0).	purified white mineral oils in medicine and cosmetics, iii) the negative human epidemiology study on kerosene, and iv) the absence of reported adverse effects with use of highly refined mineral oils as placebos in human studies. Open Point: RMS to include in a revised RAR reference to the available data on effects of highly refined mineral oils applied as placebo in human studies to substantiate the waiver for the mouse carcinogenicity study. A waiver of the developmental toxicity study is considered acceptable, given that i) there is no evidence of adversity on reproductive organs in any study in the data set and that white oils have been used extensively as solvent controls in teratogenicity studies in the context of veterinary medicinal product assessment, causing no teratogenic effects, and ii) based on available information on paraffin oils, it can be concluded that developmental effects in the absence of PAHs are unlikely. Open Point: RMS to include information in a revised RAR on developmental toxicity of the gas-to-liquid (GTL)-products to support the waiver. A waiver of neurotoxicity studies is considered acceptable, given that no signs of neurotoxicity have been reported from human studies and from the use of paraffin oils as human medicines, supported by the reported lack of bioactivity for non-aromatic saturated hydrocarbons (MOSH) in neuronal cells (as reported in the latest EFSA CONTAM Panel Opinion on mineral oil hydrocarbons in food (EFSA, 2023)). Open Point: RMS to include considerations of human data to substantiate the waiver for neurotoxicity studies.
Experts' consultation 2.3 Experts to discuss the genotoxic potential of Paraffin oil (CAS 72623-86-0) considering the available information and the previous assessment in the Report of "PESTICIDE PEER REVIEW TC 100; PARAFFIN OIL CAS 8042-47-5 – AIR IV" (C17-C31) (Experts' consultation 2.4; 2.9).	Paraffin oils (CAS No 64742-46-7, 72623-86-0, 97862-82-3) are unlikely to be genotoxic. No further testing is needed.

Subject	Conclusions Pesticides Peer Review Meeting
See reporting table 2(61)	
Experts' consultation 2.4 Experts to discuss the waiver for an ED assessment of paraffin oil (CAS 72623-86-0).	A waiver of the ED assessment for the EATS modalities is considered acceptable based on i) the lack of toxicological concern from the available studies (from public literature) conducted with mineral oils relevant to the active substance paraffin oil, ii) absence of adverse effects or lipid accumulation in endocrine organs, iii) absence of alerts from the available QSAR data investigating the EATS modalities, iv) history of safe use of paraffin oil and refined mineral oils in medicine[3], cosmetic[4] and food[5]. Open point The RMS is asked to include in a revised RAR the reference to any other uses, e.g., cosmetic and medicinal, for which there is no report of endocrine disturbance and human health concern.
Experts' consultation 2.5 Experts to discuss the toxicological reference values for paraffin oil (CAS 72623-86-0).	Health-based guidance values are not considered necesarry for paraffin oil CAS 64742-46-7, paraffin oil CAS 72623-86-0, paraffin oil CAS 97862-82-3, as there is no evidence of (human-relevant) systemic adverse effects in animal studies and given that available human data do not point to adverse effects. In case a reference value for inhalation exposure assessment is needed, the MAK (Maximum workplace concentration = MCW) value of 5 mg/m³ could be used as an AOEC for route (inhalation)-specific risk characterization for CAS No 64742-46-7, 72623-86-0, 97862-82-3. Open Point: RMS to include information in a revised RAR indicating that spleen effects are only obsvered in F344 rats, and to include information on the uncertainty of the spleen effects being secondary to liver effects as described in the CONTAM Panel Opinion (2023).
Experts' consultation 2.6	The default dermal absorption values of 25% and 70% for the concentrate and dilution, respectively, as proposed in the EFSA Guidance (2017), are applicable, in case needed.

[3] https://www.ema.europa.eu/en/documents/mrl-report/mineral-hydrocarbons-summary-report-committee-veterinary-medicinal-products_en.pdf
[4] https://mobil.bfr.bund.de/cm/349/highly-refined-mineral-oils-in-cosmetics-health-risks-are-not-to-be-expected-according-to-current-knowledge.pdf
[5] EFSA 2023, Update of the risk assessment of mineral oil hydrocarbons in food https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2023.8215, EFSA Journal, 2012; 10(6):2704, Scientific Opinion on Mineral Oil Hydrocarbons in Food https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2704

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the non-dietary exposure assessment for operators, residents and bystander and workers for products OLIE-H and Finavestam-EMA.	**Open point: RMS to provide revised non-dietary exposure estimates, for the representative uses of the products Finavestam EMA and OLIE-H, comparing the estimates for the inhalation route to the MAK value of 5 mg/m³ (8h -10 m³) for all exposed populations, considering also the following recommendations:** **- default average air concentration (0.015 mg/m³) for moderately volatile compounds should be used;** **- exposure estimates for re-entry activities of workers are not required;** **- risk assessment for bystander is not required as average exposure over a longer duration (resident) will also cover bystander exposure;** **- exposure estimates for resident should include both the vapour and spray drift pathways.**
Experts' consultation 2.1 Confidential_certis **Experts to discuss the Margin of Exposure approach related to the potential presence of 0.3 ppm PAHs in the a.s.**	**There is no human health concern from the potential presence of polycyclic aromatic hydrocarbon (PAH) impurities at levels equal or below 0.3 ppm in the active substance, as the Margin of Exposure between estimated non-dietary PAH exposure to the BMDL10 of the available carcinogenicity study is >> 10.000.** **Open Point:** **RMS to present Margin of Exposure assessments for the potential presence of 0.3 ppm PAHs in the active substance, tailored for the three paraffin oils (i.e., with CAS numbers 64742-46-7, 72623-86-0 and 97862-83) in their respective RAR Vol. 4. RMS to clearly indicate in the Vol. 4 that exposure is estimated for the paraffin oil active substance, resulting in the highest exposure to the active substance, and that PAH exposure was extrapolated from that exposure estimate assuming a maximum PAH content of 0.3 ppm.**
Experts' consultation 2.3 (mammalian toxicity) Confidential_certis **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with**	**Not for all co-formulants, sufficient information was available to conclude on their safety. Open Points were set for the RMS for the following co-formulants:** [redacted] **Open Point:** **RMS to include the toxicological information on the co-formulant** [redacted] **presented during the Peer Review Meeting in an updated**

Subject	Conclusions Pesticides Peer Review Meeting
respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance. Experts to discuss the relevance of the eye irritation study performed on the active substance (TOT-XV 100% paraffin oil) to address the eye irritation potential of the formulation for representative uses OLIE-H.	RAR, including its assessment and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term and whether a safety concern exists. [redacted] **Open Point:** RMS to include the toxicological information on the co-formulant [redacted] presented during the Peer Review Meeting in an updated RAR, including its assessment and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term and whether a safety concern exists.
Experts' consultation 2.1 Confidential_Total Energies Experts to discuss the Margin of Exposure approach related to the potential presence of 0.3 ppm PAHs in the active substance.	There is no human health concern from the potential presence of polycyclic aromatic hydrocarbon (PAH) impurities at levels equal or below 0.3 ppm in the active substance, as the Margin of Exposure between estimated non-dietary PAH exposure to the BMDL10 of the available carcinogenicity study is >> 10.000. **Open Point:** RMS to present Margin of Exposure assessments for the potential presence of 0.3 ppm PAHs in the active substance, tailored for the three paraffin oils (i.e., with CAS numbers 64742-46-7, 72623-86-0 and 97862-83) in their respective RAR Vol. 4. RMS to clearly indicate in the Vol. 4 that exposure is estimated for the paraffin oil active substance, resulting in the highest exposure to the active substance, and that PAH exposure was extrapolated from that exposure estimate assuming a maximum PAH content of 0.3 ppm.
Experts' consultation 2.3 (mammalian toxicity) Confidential_Total Energies MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the	Not for all co-formulants, sufficient information was available to conclude on their safety. Open Points were set for the RMS for the following co-formulants: [redacted] **Open Point:** RMS to include the toxicological information on the co-formulant [redacted] presented during the Peer Review Meeting in an updated RAR, including its assessment

Subject	Conclusions Pesticides Peer Review Meeting
formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term and whether a safety concern exists. [redacted] **Open Point:** RMS to include the toxicological information on the co-formulant [redacted] presented during the Peer Review Meeting in an updated RAR, including its assessment and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term and whether a safety concern exists.

REPORT OF PESTICIDES PEER REVIEW

TC 152 and TC 153

Paraffin oils (CAS 64742-46-7) – AIR IV **Rapporteur Member State: EL**

2. Mammalian toxicity

Date: 25 November 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS EL	Benaki Phytopathological Institute - EL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	Central Institute for Supervising and Testing in Agriculture - CZ
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Expert nominated by MS NL	Ctgb - NL
Observer	Austrian Agency for Health and Food Safety (AGES) - AT

MEETING MINUTES – 25 November 2024
Pesticides Peer Review TC 152 and TC 153
Paraffin oils (CAS 64742-46-7)

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' Consultation 2.1 **Experts to discuss whether test items used in studies are conform the criteria related to the relevance of test items used in the studies present in Vol. 3CA B6.**	**A study was considered relevant when the test material complied with at least one of the following criteria:** • **CAS No 64742-46-7, 72623-86-0 or 97862-82-3.** • **Fulfils the technical specification of European, British, US or International Pharmacopoeia.** • **It is a highly refined white oil with carbon chain length in the following ranges:** o **CAS No 64742-46-7: C11 – C25 (in agreement with REACH Registration Dossier)** o **CAS No 72623-86-0: C15 – C30 (in agreement with REACH Registration Dossier)** o **CAS No 97862-82-3: C11 – C30 (blend of other two paraffin oils, RAR/Confidential)** • **Other information on the identity of the test material complies with the physicochemical properties of the active substance as included in RARs, Section B.2.**
Experts' Consultation 2.2 **Experts to discuss the waivers for the in vitro comparative metabolism study, the carcinogenicity study in mouse, the developmental toxicity study in rabbit and neurotoxicity**	**A waiver of the *in vitro* comparative metabolism study is considered acceptable, as, based on the available information, unique or disproportionate human metabolites of toxicological concern are not expected. A comparative *in vitro* metabolism study is not expected to alter this outcome.** **A waiver of the carcinogenicity study in mouse is considered acceptable, based on i) the absence of MOSH long-term toxicity/carcinogenicity in rats (via oral and inhalation routes)**

Subject	Conclusions Pesticides Peer Review Meeting
studies of paraffin oil (CAS 64742-46-7).	and mice (via dermal and inhalation routes), ii) no evidence of cancer in humans despite the long-term use of highly purified white mineral oils in medicine and cosmetics, iii) the negative human epidemiology study on kerosene, and iv) the absence of reported adverse effects with use of highly refined mineral oils as placebos in human studies. **Open Point:** RMS to include in a revised RAR reference to the available data on effects of highly refined mineral oils applied as placebo in human studies to substantiate the waiver for the mouse carcinogenicity study. A waiver of the developmental toxicity study is considered acceptable, given that i) there is no evidence of adversity on reproductive organs in any study in the data set and that white oils have been used extensively as solvent controls in teratogenicity studies in the context of veterinary medicinal product assessment, causing no teratogenic effects, and ii) based on available information on paraffin oils, it can be concluded that developmental effects in the absence of PAHs are unlikely. **Open Point:** RMS to include information in a revised RAR on developmental toxicity of the gas-to-liquid (GTL)-products to support the waiver. A waiver of neurotoxicity studies is considered acceptable, given that no signs of neurotoxicity have been reported from human studies and from the use of paraffin oils as human medicines, supported by the reported lack of bioactivity for non-aromatic saturated hydrocarbons (MOSH) in neuronal cells (as reported in the latest EFSA CONTAM Panel Opinion on mineral oil hydrocarbons in food (EFSA, 2023)). **Open Point:** RMS to include considerations of human data to substantiate the waiver for neurotoxicity studies.
Experts' Consultation 2.3 Experts to discuss whether the conclusion on the human relevance of inflammatory granuloma in the liver of F-344 rats by mineral oils reached for paraffin oil (CAS 8042-47-5) during PREV TC 100, in line with the most recent EFSA CONTAM Panel Opinion on MOH in the revised RAR (2023;	The conclusion on the human relevance of inflammatory granuloma in the liver of F-344 rats by mineral oils reached for paraffin oil CAS 8042-47-5, i.e., that the related mode of action is only relevant for the particularly sensitive F344 rats, also applies to paraffin oil CAS 64742-46-7, paraffin oil CAS 72623-86-0, and paraffin oil CAS 97862-82-3.

Subject	Conclusions Pesticides Peer Review Meeting
https://www.efsa.europa.eu/en/efsajournal/pub/8215), also applies to paraffin oil (CAS 64742-46-7).	
Experts' Consultation 2.4 Experts to discuss the genotoxic potential of Paraffin oil (CAS 64742-46-7) considering the available information and the previous assessment in the Report of "PESTICIDE PEER REVIEW TC 100; PARAFFIN OIL CAS 8042-47-5 – AIR IV" (C17-C31) (Experts' consultation 2.4; 2.9).	Paraffin oils (CAS No 64742-46-7, 72623-86-0, 97862-82-3) are unlikely to be genotoxic. No further testing is needed.
Experts' Consultation 2.5 Experts to discuss the waiver for an ED assessment of paraffin oil (CAS 64742-46-7).	A waiver of the ED assessment for the EATS modalities is considered acceptable based on i) the lack of toxicological concern from the available studies (from public literature) conducted with mineral oils relevant to the active substance paraffin oil, ii) absence of adverse effects or lipid accumulation in endocrine organs, iii) absence of alerts from the available QSAR data investigating the EATS modalities, iv) history of safe use of paraffin oil and refined mineral oils in medicine[3], cosmetic[4] and food[5]. **Open point** The RMS is asked to include in a revised RAR the reference to any other uses, e.g., cosmetic and medicinal, for which there is no report of endocrine disturbance and human health concern.

[3] https://www.ema.europa.eu/en/documents/mrl-report/mineral-hydrocarbons-summary-report-committee-veterinary-medicinal-products_en.pdf
[4] https://mobil.bfr.bund.de/cm/349/highly-refined-mineral-oils-in-cosmetics-health-risks-are-not-to-be-expected-according-to-current-knowledge.pdf
[5] EFSA 2023, Update of the risk assessment of mineral oil hydrocarbons in food https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2023.8215, EFSA Journal, 2012; 10(6):2704, Scientific Opinion on Mineral Oil Hydrocarbons in Food https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2704

Subject	Conclusions Pesticides Peer Review Meeting
Experts' Consultation 2.6 **Experts to discuss the toxicological reference values for paraffin oil (CAS 64742-46-7).**	**Health-based guidance values are not considered necesarry for paraffin oil CAS 64742-46-7, paraffin oil CAS 72623-86-0, paraffin oil CAS 97862-82-3, as there is no evidence of (human-relevant) systemic adverse effects in animal studies and given that available human data do not point to adverse effects.** **In case a reference value for inhalation exposure assessment is needed, the MAK (Maximum workplace concentration = MCW) value of 5 mg/m³ could be used as an AOEC for route (inhalation)-specific risk characterisation for CAS No 64742-46-7, 72623-86-0, 97862-82-3.** **Open Point: RMS to include information in a revised RAR indicating that spleen effects are only observed in F344 rats, and to include information on the uncertainty of the spleen effects being secondary to liver effects as described in the CONTAM Panel Opinion (2023).**
Experts' consultation 2.7 **Experts to discuss the dermal absorption and non-dietary exposure assessment for operators, residents and bystander and workers. See also 2(106), 2(110), 2(111), 2(113), 2(114).**	**The default dermal absorption values of 25% and 70% for the concentrate and dilution, respectively, as proposed in the EFSA Guidance (2017), are applicable, in case needed.** **Open point: RMS to provide revised non-dietary exposure estimates, for the representative uses of CITROLE, comparing the estimates for the inhalation route to the MAK value of 5 mg/m³ (8h -10 m³) for all exposed populations, considering also the following recommendations:** **- default average air concentration (0.015 mg/m³) for moderately volatile compounds should be used;** **- exposure estimates for re-entry activities of workers are not required;** **- risk assessment for bystander is not required as average exposure over a longer duration (resident) will also cover bystander exposure;** **- exposure estimates for resident should include both the vapour and spray drift pathways.**
Experts' Consultation 1.1 **Experts to discuss the Margin of Exposure approach related to the potential presence of 0.3 ppm PAHs in the active substance.**	**There is no human health concern from the potential presence of polycyclic aromatic hydrocarbon (PAH) impurities at levels equal or below 0.3 ppm in the active substance, as the Margin of Exposure between estimated non-dietary PAH exposure to the BMDL10 of the available carcinogenicity study is >> 10.000.** **Open Point:**

Subject	Conclusions Pesticides Peer Review Meeting
	RMS to present Margin of Exposure assessments for the potential presence of 0.3 ppm PAHs in the active substance, tailored for the three paraffin oils (i.e., with CAS numbers 64742-46-7, 72623-86-0 and 97862-83) in their respective RAR Vol. 4. RMS to clearly indicate in the Vol. 4 that exposure is estimated for the paraffin oil active substance, resulting in the highest exposure to the active substance, and that PAH exposure was extrapolated from that exposure estimate assuming a maximum PAH content of 0.3 ppm.
Experts' Consultation (mammalian toxicity section) 2.1 **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.** **Experts to discuss the skin sensitizing potential of CITROLE (see 2(108) of the non-confidential reporting table).**	**Not for all co-formulants, sufficient information was available to conclude on their safety. Open Points were set for the RMS for the following co-formulants:** [redacted] **Open Point:** **RMS to include the toxicological information on the co-formulant** [redacted] **presented during the Peer Review Meeting in an updated RAR, including its assessment and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term and whether a safety concern exists.** [redacted] **Open Point:** **RMS to include the toxicological information on the co-formulant** [redacted] **presented during the Peer Review Meeting in an updated RAR, including its assessment and related conclusion whether sufficient information is available to assess genotoxicity and/or repeated dose toxicity potential over the short- and long-term and whether a safety concern exists.**

REPORT OF PESTICIDES PEER REVIEW

TC 152 and TC 153

Metyltetraprole – NAS 1107 **Rapporteur Member State: FR**

2. Mammalian toxicity

Date: 25 November 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	Central Institute for Supervising and Testing in Agriculture - CZ
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency - DK
National Expert nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS NL	Ctgb - NL
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Federal Food Safety and Veterinary Office - CH
Observer	National Institute of Public Health - CZ
Observer	Ctgb - NL

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Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.1 **Member States experts to discuss oral absorption values, considering the results of the study [redacted] 2017 and the results of the new ADME study that should be submitted.**	**The oral absorption of metyltetraprole was agreed at 11.5%, from a study in the rat given 250 mg/kg bw (% of the total radioactivity considering Urine + Bile > 3h + Carcass).** **Open point:** **RMS to describe in detail in a revised DAR the new IVCM study and its results, also detailing the study limitations and concluding on whether based on the available data there is indication of the formation of a unique or a disproportionate human metabolite.**
Expert consultation 2.2 **Member State experts to discuss the acceptability of the phototoxicity study (see Vol. 3CA, B.6.2.7, phototoxicity, p. 71-73) following integration of the additional data required.**	**Metyltetraprole absorbs electromagnetic radiation in the range 290-700 nm. The study provided is not adequate to test phototoxicity for this active substance (UVB and UVC absorber). Thus, it is neither possible to conclude on phototoxicity, nor on photomutagenicity.** **An outstanding data gap (ODG) is set for phototoxicity and photomutagenicity.**
Expert consultation 2.3 **Member States experts to discuss target organs and the NOAEL of both the oral (dietary) 90-day rat studies provided ([redacted] 2016a and 2017a) in an expert meeting.**	**The NOAEL of 90-day study in rats is 6000 ppm (corresponding to 438 mg/kg bw per day in males, and 509 mg/kg bw per day in females), based on effects on the liver in males and females (increased absolute and relative liver weights with statistically significant minimal centrilobular hypertrophy in the kidneys of males (α2μ-globulin accumulation within the proximal tubules), in the blood (increased WBC count due to increased lymphocyte counts in males and females, and slight anaemia in females) at the LOAEL of 20000 ppm (corresponding to 1508 mg/kg bw per day in males, and 1715 mg/kg bw per day in females respectively).**

Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.4 Member States experts to discuss the NOAEL of the oral 90-day study in mice, including a discussion on the treatment relationship and adversity of the finding "increased X-zone vacuolation" in the adrenals of female mice, including considerations on the spontaneous occurrence of this finding in female mice and the possible relationship with hormonal imbalances (see Huang CC, Kang Y. The transient cortical zone in the adrenal gland: the mystery of the adrenal X-zone. J Endocrinol. 2019 Apr;241(1):R51-R63. doi: 10.1530/JOE-18-0632. PMID: 30817316; PMCID: PMC6675673).	The NOAEL of the 90-day study in mice is 3500 ppm (corresponding to 521 and 644 mg/kg bw per day in males and females, respectively), based on effects on the liver in males (statistically significant increase in absolute and relative weight, centrilobular hypertrophy, statistically significant decrease in albumin) and on lacrimal glands in females (inflammatory cell infiltrate) at the LOAEL of 7000 ppm (corresponding to 1057 and 2358 mg/kg bw per day in males and females, respectively). **Open point:** RMS to introduce in a revised DAR the new tables on histopathological findings on Harderian and lacrimal glands presented during the meeting, and the related considerations.
Expert consultation 2.5 Member States experts to discuss the NOAEL of the 1-year dog study in an expert meeting.	The NOAEL of the 90-day study in the dog is <100 mg/kg bw per day, based on effects on the liver (periportal inflammatory cell infiltrates rich in neutrophils, hepatocellular necrosis with inflammatory cell infiltrate and haemorrhage, decreased glycogen mainly in males) and decreased thymus weight in both sexes. The NOAEL of the 52-week study in the dog is 300 mg/kg bw per day based on effects observed in the blood (decreased haematocrit, haemoglobin concentration and erythrocyte count in both sexes and presence of hemosiderin in Kupffer cells in one male), and liver in both sexes (statistically significant increase in absolute and relative weight, hepatocellular hypertrophy, statistically significant decrease in albumin).
Expert consultation 2.6 Member State experts to discuss the genotoxicity of metyltetraprole.	Metyltetraprole is unlikely to be genotoxic. **Open point:** RMS to further expand in the updated DAR the key elements related to genotoxicity assessment.
Expert consultation 2.7	The NOAELs for the long-term toxicity/carcinogenicity study in the rat are:

Subject	Conclusions Pesticides Peer Review Meeting
Member States experts to discuss the NOAELs (systemic and carcinogenicity) for the rat study ([redacted] 2017b).	• Systemic NOAEL: 2000 ppm in females (corresponding to_111.8 mg/kg bw per day) based on increased white blood cell counts due to increased lymphocyte counts at 6000 ppm observed at all time points (stat. sign. in week 52); 6000 ppm in males (corresponding to 255 mg/kg bw per day) based on effects on kidney (increased weight, increased incidence and severity of tubular eosinophilic droplets- α2μ-globulin-and decreased urinary volume), heart (increased incidence of cardiomyopathy), blood (decreased haematocrit and haemoglobin concentration) • Carcinogenicity NOAEL: 2000 ppm (corresponding to 83.9 mg/kg bw per day) based on increased incidence of malignant lymphomas in both sexes at ≥6000ppm.
Expert consultation 2.8 Member States experts to discuss the NOAELs (systemic and carcinogenicity) for the mouse study ([redacted] 2017c).	The NOAELs for the long-term toxicity/carcinogenicity study in the mouse are: • Systemic NOAEL: 700 ppm in males (corresponding to 82.2 mg/kg bw per day) based on effects in the liver (increased in absolute and relative liver weight) • Carcinogenicity NOAEL: 700 ppm (corresponding to 82.2 mg/kg bw per day) based on increased incidence of malignant lymphomas in both sexes
Expert consultation 2.9 Member State experts to discuss and agree the NOAELs of the main 2-generation reproductive toxicity study in rats ([redacted] 2017d) by focusing in particular on: -irritability and vocalisation findings by taking into account all the other studies where these effects occurred; -changes in thyroid, liver, adrenals, thymus, spleen and kidney weights.	The following NOAELs were set for 2-generation reproductive toxicity study in rats: Parental NOAEL at 6000 ppm (corresponding to 409 mg/kg bw per day) on the basis of effects observed in the liver (increase in abs. and rel. weights in F, F0 and F1), thyroid (increase in abs. and rel. weights in F and F0) and uterus (decrease in abs. and rel. weights in F0) at the LOAEL of 20000 ppm (corresponding to 1385 mg/kg bw per day). Offspring NOAEL at 6000 ppm (corresponding to 409 mg/kg bw per day) on the basis of effects observed in pup BW and BWG (decrease in BW in F2 on LD21, both sexes↓ BWG in F1 on LD14-21, in F2 on LD14-21 and LD1-21), decrease in abs. and rel. thymus weight in F1, F pups and F2 M/F pups, decrease in abs. and rel. spleen weight in F2, M/F pups at the LOAEL of 20000 ppm (corresponding to 1385 mg/kg bw per day). Reproductive NOAEL at 20000 ppm (corresponding to 1385 mg/kg bw per day) in the absence of adverse effects on reproductive parameters.
Expert consultation 2.10 Member State experts to discuss in an expert	In the rabbit, the Maternal NOAEL is 100 mg/kg bw per day based on the increased number of females with markedly decreased food consumption, clinical signs (scant or no faeces), and abortion at 250 mg/kg bw per day.

Subject	Conclusions Pesticides Peer Review Meeting
meeting the increased incidence of misaligned sacral arch and abortions observed in the developmental toxicity study in rabbit ([redacted] 2017) and agree on the developmental NOAEL of the study.	The Developmental NOAEL is 100 mg/kg bw per day based on the increased incidence of skeletal alterations (misaligned sacral arch) at 250 mg/kg bw per day.
Expert consultation 2.11 Member State experts to discuss the neurotoxic potential of metyltetraprole by taking into consideration also the neurobehavioural and neuropathological findings observed in other studies.	The NOAELs for the acute neurotoxicity study are: • Systemic NOAEL: 2000 mg/kg bw per day (top dose) • Neurotoxicity NOAEL: 500 mg/kg bw per day based on tremors and landing footsplay in males. Data gap: A repeated dose neurotoxicity study is set due to equivocal evidence of neurotoxicity after repeated oral exposure to metyltetraprole in the available dataset and in the acute neurotoxicity study.
Expert consultation 2.12 Member State experts to discuss the ED potential of metyltetraprole in an expert meeting.	T-modality A pattern of T-mediated adversity was not observed in a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for T modality are not met. EAS-modality A pattern of EAS-mediated adversity was not observed in a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for EAS-modality are not met. Open point: RMS to revise the DAR in line with the PRM discussion.
Expert consultation 2.13 Member State experts to discuss the mitochondrial inhibition potential of metyltetraprole (and metabolites) in an expert meeting.	Metyltetraprole fungicidal Mode of Action (MoA) implies mitochondrial Complex III inhibition. Metyltetraprole also inhibits the mitochondrial complex III activity in human and rat liver mitochondrial fractions. ADME data support that the a.s. and metabolites can reach the brain. Complex III inhibition producing mitochondrial dysfunction and degeneration of dopaminergic neurons of nigrostriatal pathway can contribute as a risk factor to the development of parkinsonian motor deficits (AOP 3). Data gap: Testing in the *in vitro* battery of the AOP 3 with appropriate test system and development of an AOP-informed IATA based on AOP 3 with the inclusion of appropriate ADME data for IVIVE suitable for PBPK modelling.
Expert consultation 2.14	Treatment-related effects were noted in organs and tissues of the immune system in various studies. However, such changes were present in association with other critical effects

Subject	Conclusions Pesticides Peer Review Meeting
Member State experts to discuss the immunotoxic potential of metyltetraprole in an expert meeting.	(to other organs and tissues) and did not show a clearly consistent pattern across studies. Therefore, immunotoxicity by metyltetraprole is unlikely and no further immunotoxicity investigations are considered necessary.
Expert consultation 2.15 Member State experts to discuss the genotoxicological and/or toxicological profile of metabolites in an expert meeting. Pending the outcome of residues and fate expert discussions, the following metabolites should be discussed in this expert meeting: -3-CH2OH-S-2367 -Sulfate conjugate of 3-CH2OH-S-2367 -Glucose conjugate of 3-CH2OH-S-2367 -3-COOH-S-2367 -OHTM -Glucose conjugate of OHTM -OHTM conj. 2 -OHTM-COOH -3HM-OHTM-COOH -ISS7 -CPOH -Glucose conjugate of CPOH -1-MT-acetic acid -1-MT-lactic acid -1-MT-alanine	Metabolites 1-MT, 1-MT-alanine, 1-MT acetic acid, 1-MT lactic acid, OHTM, OHTM-COOH, 3-HM-OHTM-COOH, ISS7 and CPOH are unlikely to be genotoxic, based on experimental data showing negative results. 3-CH2OH-S-2367 and 3-COOH-S-2367, and their conjugates (Sulphate conjugate of 3-CH2OH-S-2367 and Glucose conjugate of 3-CH2OH-S-2367) are unlikely to be genotoxic based on in silico analysis, and structural similarity to the parent. The toxicity of the aglycones and their conjugates is considered to be covered by the parent's ADI of 0.082 mg/kg bw per day (ARfD not set for metyltetrapole) based on structural similarity to the parent, ADME data, and lower potential to inhibit mitochondrial complex III than the parent. Data gap: Hydrolysis study demonstrating that Sulfate conjugate of 3-CH2OH-S-2367 can be cleaved to aglycone under physiological conditions is missing. All other residue metabolites assessed have a qualitatively and quantitatively different toxicological profile than the parent, so specific RVs apply. The ADI for 1-MT alanine is 0.04 mg/kg bw per day (28-d rat NOAEL, UF 1000 for the incomplete database = 40 mg/kg bw per day for decreased bw/bwg). ARfD is also 0.04 mg/ kg bw per day in the absence of proper data. Data gap: For general toxicity is set for 1-MT acetic acid, 1-MT lactic acid, and 1-MT in the absence of data supporting data bridging from 1-MT alanine. The ADI for CPOH is 0.1 mg/kg bw per day (90-d oral (diet) rat NOAEL = 103 mg/kg bw per day UF 1000 for incomplete database) based on kidney effects. Glucose conjugate of CPOH: same genotoxicity and RVs conclusions as for CPOH. The ADI for OHTM is 0.05 mg/kg bw per day (28-d oral (diet) rat: NOAEL = 50 mg/kg bw per day (m/f); UF 1000 for the incomplete database) based on ↑ liver wt, ↓ prothrombin time, clinical chemistry parameters, urinalysis. ARfD is also 0.05 mg/kg bw per day, in the absence of proper data. Glucose conjugate of OHTM is covered by aglycone. No structure OHTM CONJ. 2 is considered covered by aglycone, if proven to be a glycoside/glucuronide conjugate of OHTM.

Subject	Conclusions Pesticides Peer Review Meeting
	Data gap: **For general toxicity is set for 3HM-OHTM-COOH and OHTM-COOH.** **The ADI for ISS7 is 0.036 mg/kg bw per day (90-d rat NOAEL = 36 mg/kg bw per day; UF 1000 for the incomplete database) based on thyroid histopathology, increased liver weight, abnormal coloration, increased globulin level, decreased A/G ratio, spleen. ARfD is also 0.036 mg/kg bw per day, in the absence of proper data. ISS7 is considered as a relevant GW metabolite, in the absence of long-term toxicity data that can dismiss its carcinogenic potential (noting the harmonised classification as carc 2 for the parent).** **CPOH is a common metabolite to pyraclostrobin. The same CPOH ADI of 0.1 mg/kg bw per day (90-d oral (diet) rat NOAEL = 103 mg/kg bw per day for kidney effects; UF 1000 for incomplete database) set during pyraclostrobin's peer review was confirmed. This ADI is sufficiently close to that of metyltetraprole to lift any potential concern associated with complex III inhibition MoA. To be conservative, an ARfD is also set at 0.1 mg/kg bw per day (equal to the ADI). The genotoxicity and RVs conclusions on CPOH also apply to the Glucose conjugate of CPOH.**
Expert consultation 2.16 **Member State experts to discuss and agree on reference values.**	**The ADI of Metyltetraprole is 0.082 mg/kg bw per day, based on the long-term toxicity and carcinogenicity NOAEL of 82.2 mg/kg bw per day from the 18-month mouse study (as also supported by the carcinogenic NOAEL of the 2-year rat study of 83.9 mg/kg bw per day) to which an overall UF of 1000 is applied.** **The 10x extra UF accounts for the:** • **incomplete dataset (data gap for subchronic neurotoxicity)** • **data gap for AOP-informed IATA based on AOP 3.** • **uncertainty about the limited (<10) rat-to-human relative potency factor for the in vitro inhibition of mitochondrial complex III** • **severity of the carcinogenic findings and adequate MoS** **The AOEL is 0.0115 mg/kg bw per day based on the LOAEL of 100 mg/kg bw per day from the 13-week dog study to which the following UFs are applied.** **- standard 100X UF for inter- and intra-species differences** **- extra UF of 10 accounting for the:** • **incomplete dataset (data gap for subchronic neurotoxicity)** • **data gap for AOP-informed IATA based on AOP 3.** • **Uncertainty about the limited (<10) rat-to-human relative potency factor for the in vitro inhibition of mitochondrial complex III** • **LOAEL-to-NOAEL extrapolation**

Subject	Conclusions Pesticides Peer Review Meeting
	- correcting factor of 11.5% for limited oral absorption ARfD and AAOEL are not necessary since acute neurotoxic effects are slight and transient nature; effects in the rabbit prenatal dev tox study are considered secondary to malnutrition (abortion) or not relevant for acute effects (skeletal variations).
Expert consultation 2.17 Member State experts to discuss dermal absorption values in an expert meeting.	The agreed dermal absorption values are: - 10% for the concentrate (60 g a.s./L). - 3% for the dilution 0.04 g a.s./L (for use on cucumber). - 10% for the dilution > 0.04 g a.s./L and <60 g a.s./L (for outdoor use on cereals, due to data variability in dermal absorption studies where several dilutions are tested).
Expert consultation 2.18 Member State experts to discuss non dietary exposure estimates in an expert meeting.	The approach taken by the RMS as regards non dietary exposure calculations for two different scenarios (one indoor on cucumbers, and one outdoor on cereals) was agreed by all experts. Open point: RMS to update non dietary exposure calculations based on the newly agreed AOEL value.
Expert consultation 1.1 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Based on the insufficient information provided by the applicant, the RMS could not conclude on the toxicological profile (i.e. acute toxicity, genotoxicity, short- and long-term/chronic toxicity, reproductive and developmental toxicity, neurotoxicity, immunotoxicity, endocrine disruptive properties) of the representative formulation for metyltetraprole, nor on the toxicological profile of each constituent other than the active substance. Post meeting note: Since this data requirement was already set for the applicant's consideration at the time of the clock-stop, a data gap is now set.

REPORT OF PESTICIDES PEER REVIEW

TC 152 and TC 153

Diflufenican – AIR III after ED clock stop **Rapporteur Member State: CZ**

2. Mammalian toxicity

Date: 25 November 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS CZ	Central Institute for Supervising and Testing in Agriculture - CZ
National Experts nominated by RMS CZ	National Institute of Public Health - CZ
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS EL	Benaki Phytopathological Institute - EL
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IE	Pesticide Registration Division, Dept. of Agriculture, Food & the Marine Laboratories - IE
National Experts nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS NL	Ctgb - NL
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	Federal Food Safety and Veterinary Office - CH

MEETING MINUTES – 25 November 2024
Pesticides Peer Review TC 152 and TC 153
Diflufenican

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.12 **Member State Experts to discuss and agree upon the NOAELs of the extended one generation reproductive toxicity study in an experts' meeting.**	**The NOAELs of the newly provided extended one generation reproductive toxicity study in rat were agreed as follows:** **Parental NOAEL: 30mg/kg bw per day based on statistically significantly decreased body weight gain > 10% in F0 animals and F1 Cohort 1A females; and statistically significantly decreased body weight > 10% in F1 Cohort 1A females at 100 mg/kg bw/day.** **Offspring/developmental NOAEL: 30 mg/kg bw/day based on the statistically significantly decreased body weight > 10% in F1 pups at 100 mg/kg bw/day.** **Reproductive toxicity NOAEL: 1000 mg/kg bw per day (top dose, due to absence of treatment related adverse effects on reproductive parameters).**
Experts' consultation 2.13 **Member State Experts to discuss reference values of diflufenican in an experts' meeting.**	**Since the NOAELs set in the newly provided EOGRS do not impact previously selected toxicological reference values (TRVs), all experts agreed to maintain the already established TRVs:** **ADI=0.2 mg/kg bw per day based on reduced bodyweight gain (BWG), reduced liver weight and clinical chemistry changes indicating mild liver toxicity observed in the 2-year chronic toxicity/carcinogenicity study in the rat (NOAEL=23 mg/kg bw per day; standard uncertainty factor of 100).** **AOEL=0.11 mg/kg bw per day based on decreased BWG and food consumption in the 90-day rat study (NOAEL of 18.46**

Subject	Conclusions Pesticides Peer Review Meeting
	mg/kg bw per day; standard uncertainty factor of 100; correction for 58% oral absorption). ARfD and AAOEL not needed.
Experts' consultation 2.14 MSs experts to discuss the ED potential of diflufenican for EAS and T modalities. For the EAS modalities the discussion should cover the results of level 2 and 3 studies and the outcome of the extended one generation reproductive toxicity study, e.g.: - methodology and uncertainties on the assessment of nipple/areolae retention and adequacy of HCD. - AGD index (AGDI) values and adequacy of HCD. - Gestation length and decreased incidence of pregnant dams. - Uncertainty related to the use of a different strain in the EOGRT compared to other studies in the dataset.	T-modality A pattern of T-mediated adversity was not observed in a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for T modality are not met. EAS-modality A pattern of EAS-mediated adversity was not observed in a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for EAS-modality are not met. Open point The RMS to revise the RAR in the line with the meeting discussion.
Experts' consultation TOX proposed by EFSA (AG-D1-500-SC, ADAMA) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute,	Open point: the RMS to revise the RAR Vol.4 by including the assessment of co-formulants for AG-D1-500-SC. RMS to consider previous conclusions for the co-formulants not discussed during the meeting but already assessed under other substances.

Subject	Conclusions Pesticides Peer Review Meeting
genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	
Experts' consultation TOX proposed by EFSA (Diflufenican 500 SC, SAPEC) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation supported for the representative uses (500 SC, SAPEC), based on the currently available information, sufficient toxicological data were available for some components. However, for some other component(s), toxicological data is insufficient (including on genotoxicity, short- and long term toxicity/ carcinogenicity/due to lack of information on its composition) and it is not possible to conclude whether they/it impact(s) on the toxicity/classification and safety of the proposed formulation. Open point: the RMS to revise the RAR Vol.4 in line with the discussion and open points identified at the peer review meeting. RMS to consider previous conclusions for the co-formulants not discussed during the meeting but already assessed under other substances.
Experts' consultation TOX proposed by EFSA (FH-020 WG, ROTAM) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each	Regarding the co-formulants contained in the formulation supported for the representative uses (FH-020 WG, ROTAM), based on the currently available information, sufficient toxicological data were available for some components. However, for some other component(s), toxicological data is insufficient (including on genotoxicity, short- and long term toxicity/ carcinogenicity/due to lack of information on its composition) and it is not possible to conclude whether they/it impact(s) on the toxicity/classification and safety of the proposed formulation. Open point: the RMS to revise the RAR Vol.4 in line with the discussion and open point identified at the peer review meeting. RMS to consider previous conclusions for the co-formulants not discussed during the meeting but already assessed under other substances.

Subject	Conclusions Pesticides Peer Review Meeting
individual component other than the active substance.	
Experts' consultation TOX proposed by EFSA (HCO01, UPL) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation supported for the representative uses (HCO01, UPL), based on the currently available information, sufficient toxicological data were available for some components. However, for some other component(s), toxicological data is insufficient (including on genotoxicity, short- and long term toxicity/ carcinogenicity/due to lack of information on its composition) and it is not possible to conclude whether they/it impact(s) on the toxicity/classification and safety of the proposed formulation. Open point: the RMS to revise the RAR Vol.4 in line with the discussion and open points identified at the peer review meeting. RMS to consider previous conclusions for the co-formulants not discussed during the meeting but already assessed under other substances.

REPORT OF PESTICIDES PEER REVIEW TC 152

Buprofezin – AIR IV after ED clock stop **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 19 November 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) -IT
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	Central Institute for Supervising and Testing in Agriculture - CZ
National Expert nominated by MS CZ	National Institute of Public Health – CZ
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL
Observer	Austrian Agency for Health and Food Safety (AGES) - AT
Observer	National Institute of Public Health - CZ
Observer	Ctgb - NL

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.13 **identified following consideration of comments received during the MS/APPL/public consultation on the assessments following the ED clock stop:** **Experts to assess and discuss the arguments provided by the applicant in the position paper for T-modality.** **Experts to discuss whether the applicant's new position paper modify the previous Peer Review Meeting conclusions.**	**Following consideration of comments received during the 3-month ED clock stop, buprofezin meets the ED criteria for T-modality for humans (Scenario 1b).**

REPORT OF PESTICIDES PEER REVIEW

TC 147 and TC 148

FLUROCHLORIDONE – AIR IV **Rapporteur Member State: AT**

2. Mammalian toxicity

Date: 30 September 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS HR	Croatian Agency for Agriculture and Food - HR
National Experts nominated by MS MT	Malta Competition and Consumer Affairs Authority (MCCAA) - MT
National Experts nominated by MS NL	Ctgb - NL
Observer	Finnish Safety and Chemicals Agency (Tukes) - FI
Observers	Malta Competition and Consumer Affairs Authority (MCCAA) - MT
Observer	Ctgb - NL

MEETING MINUTES – 30 September 2024
Pesticides Peer Review TC 147 and TC 148
Flurochloridone

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss oral absorption of flurochloridone, regarding inclusion of data on faecal levels for its calculation, considering the lack of a bile-caniculated study and the availability of a study with information on total radioactivity in urine and faeces upon oral and i.p. exposure (both single low dose), with data for time frames of 0-18 hours, 18-42 hours and 42-90 hours (without information on excretion in the first three hours).**	**Oral absorption of flurochloridone is >91%. Data on faecal levels can be included in the calculation, given that fecal levels upon i.p. exposure are similar as faecal levels upon oral exposure.** **Open point:** **The RMS to check, and amend as necessary, whether the justification of using data on fecal levels for calculation of oral absorption of flurochloridone is provided in Vol. 1.**
Expert consultation 2.2 **Experts to discuss the comparative in vitro metabolism studies, considering uncertainty in the presence of one or more metabolites in metabolite fractions, and lack of chiral analysis.**	**The comparative in vitro metabolism study is supportive. No unique or disproportionate human metabolites have been identified.**

Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.3 Experts to discuss the reliability of the literature studies KCA 5.3.2/03 (Zhang 2015), KCA 5.8.2/10 (Zhu et al. 2019) and KCA 5.8.2/11 (Li et al. 2019).	Please refer to expert consultation point 2.8 for the reliability assessments of the Zhu et al. (2019) study and the Li et al. (2019) study. The study by Zhang et al. (2015) is reliable with restrictions based on minor deviations. The study is in line with the regulatory 90-day study, and does not impact the risk assessment.
Expert consultation 2.4 Experts to discuss genotoxicity of flurochloridone, including the *in vitro* micronucleus assay from Bohnenberger S 2012 (KCA 5.4.1/12), the lack of insight into the nature of the findings (anuegenic or clastogenic response) and the appropriateness of the available follow-up *in vivo* genotoxicity data package (considering possible lack of potential site-of-contact effect in *in vivo* bone marrow MN test of clastogenic substances acting without metabolic activation).	Flurochloridone is genotoxic in vitro (clastogenic and/or aneugenic), but not in vivo based on available experimental genotoxicity data. This is in line with ECHA RAC that considered that classification and labelling for germ cell mutagenicity is not warranted.
Expert consultation 2.5 Experts to discuss NOAEL for carcinogenicity in mice (KCA5.5/02 [redacted] 1985b).	The carcinogenic NOAEL in mice is 25.7 mg/kg bw per day based on increase in liver adenocarcinoma at 100.1 mg/kg bw per day.
Expert consultation 2.6 Experts to discuss acceptability of the multigeneration reproduction study in rats ([redacted] 1983; KCA 5.6.1/01) based on its deviations from the current	No additional information (BMD modelling analysis) has been provided by the applicant. Please refer to expert consultation point 2.8 (ED assessment) where acceptability / reliability of the study was discussed.

Subject	Conclusions Pesticides Peer Review Meeting
OECD TG 416 (2001), as well as the BMD analysis of the data on fertility toxicity effects (see 2(37)).	
Expert consultation 2.7 Experts to discuss the BMD analysis of the data on developmental toxicity effects of the [redacted] 1983a study (KCA 5.6.2/01) and the [redacted] 1984 study (KCA 5.6.2/02).	No additional information (BMD modelling analysis) has been provided by the applicant.
Expert consultation 2.8 Experts to discuss the ED properties of flurochloridone in a Peer Review Meeting in line with the scientific criteria for the determination of ED properties and its reference point (NOAEL or BMD), laid down in Commission Regulation (EU) No 2018/605 and according to the ECHA/EFSA guidance, for EATS modalities for the active substance.	T-modality A pattern of T-mediated adversity was not observed in a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for T-modality are not met for flurochloridone. EAS-modalities The EAS-mediated parameters were not sufficiently investigated and a pattern of EAS-mediated adversity, (i.e., histopathological effects in epididymis and testis decrease epidydimis and testis weight and size, decrease sperm motility and sperm counts and increase sperm abnormalities) was observed in the available dataset of studies. The observed pattern of EAS-mediated adversity suggests an anti- androgenic mode of action (MoA). This is substantiated by the results of the OECD TG 441 – Hershberger assay study i.e., positive for anti-androgenic activity. Scenario 2b of the ECHA/EFSA ED guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for EAS-modalities are met for flurochloridone. The NOAEL for ED effects is 3.9 mg/kg bw per day from the 2-year toxicity study in rats based on reduced weights and size of testes and histopathological findings in testis/epididymides including tubular atrophy, interstitial cell hyperplasia, spermatic degeneration and microtubular hyperplasia observed at 15.7 mg/kg bw per day (LOAEL).
Expert consultation 2.9	Genotoxicity Inconclusive assessment for M7 and M8 based on available information submitted by the applicant on the in silico analysis.

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the toxicological profile of metabolites.	Concern for M1, M2 and M6 based on the in silico analysis. No concern for M3, M4, M5, and M9 based on the in silico analysis. General toxicity Experimental data only available for the parent compound. Available information submitted by the applicant on the in silico analysis not sufficiently robust to reach a conclusion on general toxicity of metabolites.
Expert consultation 2.10 Experts to discuss the setting of toxicological reference values (ADI, ARfD, AOEL and AAOEL), considering: 1) the results of the BMD analyses; 2) the possible need for the application of extra uncertainty factors; 3) the conclusion on the oral absorption.	The acceptable daily intake (ADI) is 0.04 mg/kg bw per day, based on the 2-year rat study in which a NOAEL of 3.9 mg/kg bw per day was set based on reduced testes weight and size with tubular atrophy, interstitial cell hyperplasia, reduced size of epididymides with spermatic degeneration and microtubular hyperplasia observed at a LOAEL of 15.7 mg/kg bw per day. The standard uncertainty factor (UF) of 100 was applied. This value is the same as from the previous peer review. The acute reference dose (ARfD) is 0.04 mg/kg bw, based on two developmental toxicity rat studies in which a NOAEL of 20 mg/kg bw per day identified in the second study. No NOAEL was identified in the first study. The NOAEL was set based on decreased fetal body weight (11%), increased visceral and skeletal malformations (visceral: diaphragmatic hernia, heart/great vessel anomaly; skeletal: exoccipital cervical vertebra defect) and variations. A LOAEL of 25 mg/kg bw per day was set in the first study (lowest dose level tested) and 100 mg/kg bw per day (second study). The increased UF of 500 was applied based on the severity and steep-dose response curve of the effects. This value is the same as during the previous peer review. The acceptable operator exposure level (AOEL) and acute AOEL (AAOEL) are 0.04 mg/kg bw per day, based on the same basis of the ARfD with no correction for oral absorption. The AOEL value is the same as during the previous peer review. No AAOEL was set during the previous peer review.
Expert consultation 2.11 Experts to discuss dermal absorption values of both formulations.	The agreed dermal absorption values for the AG-F8-250 CS formulation in the encapsulated form scenario are 0.8% for the concentrate, 4.6%, 7.0% and 9.2% for the in-use dilutions (5 g/L, 3.3 g/l and 2.5 g/L, respectively). These values should be used for operator exposure estimations during mixing/loading and application. The agreed dermal absorption values for the scenario of all capsules disrupted are 1.3% for the concentrate and 26%, 39% and 52% for the in-use dilutions (5 g/L, 3.3 g/l and 2.5 g/L, respectively). These values should be used for resident/bystander (and

Subject	Conclusions Pesticides Peer Review Meeting
	worker, in case of contact with soilborne residues) exposure estimations. The agreed dermal absorption values for the AG-F8-250 EC formulation to be used for non-dietary exposure calculations in a first-tier approach are 7.5% for the concentrate, 34% for the in-use dilution. The agreed dermal absorption values to be used in a second tier approach are 7.5 % for the concentrate and 6.4%, 12.8% and 9.7% for the in-use dilutions (5 g/L, 3.3 g/l and 2.5 g/L, respectively). Open point: The RMS is requested to provide the filled-in BfR templates for the setting of the dermal absorption values.
Expert consultation 2.12 Experts to discuss non-dietary exposure estimates.	For both formulations (AG-F8-250 CS/EC), exposure to soilborne residues should also be taken into account for workers, residents and bystanders (for children entering into treated crops). Open points: The RMS is requested to provide revised exposure estimates for the two formulations, for all representative uses (all application rates), using the agreed toxicological endpoints, and applying all available risk mitigation measures. The RMS is also requested to provide a negligible exposure assessment (including second tier with margin of exposure assessment) for risk management considerations.
Expert consultation 1.1 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	With regard to the mammalian toxicity information available for the formulation(s) for representative uses 'AG-F8-250 CS', studies were performed for acute toxicity endpoints. With regard to the co-formulants contained in 'AG-F8-250 CS', sufficient toxicological data were available for some components*, but not all. The collected information did not highlight any concern. *Open point: The RMS to update the RAR according to outcomes of the discussions and to include specific request for further assessment of one additional constituent of one component and three additional constituents of one component. Open point (for EFSA): EFSA to check outcome of a previous open point for a co-formulant share with another plant protection product. With regard to the mammalian toxicity information available for the formulation(s) for representative uses 'AG-F8-250 EC ', studies were performed for acute toxicity endpoints. With regard to the co-formulants contained in 'AG-F8-250 CS',

Subject	Conclusions Pesticides Peer Review Meeting
	sufficient toxicological data were available for all components.

REPORT OF PESTICIDES PEER REVIEW

TC 147 and TC 148

FLUAZAINDOLIZINE – NAS 1107 **Rapporteur Member State: MT**

2. Mammalian toxicity

Date: 30 September 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS MT	Malta Competition and Consumer Affairs Authority (MCCAA) - MT
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS HR	Croatian Agency for Agriculture and Food - HR
National Experts nominated by MS NL	Ctgb - NL
Observers	Malta Competition and Consumer Affairs Authority (MCCAA) - MT
Observer	Ctgb - NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **MS experts to discuss and agree on the oral absorption/bioavailability of fluazaindolizine based on ADME study results.**	**The systemic bioavailability of Fluazaindolizine is 51% after oral dosing in rats.**
Experts' consultation 2.2 **Experts to discuss the results and human relevance of the in vitro comparative metabolism study.**	**The in vitro comparative metabolism (IVCM) study indicates an in vitro disproportionate production of the metabolite IN-REG72 by human hepatocytes as compared to other species. Experimentally, IN-REG72 shows no genotoxic potential.** **To account for the possible disproportionate formation of this metabolite in humans in vivo, for risk assessment it is suggested to include an extra factor of 2 in the calculations when comparing the TRVs of fluazaindolizine with dietary and non-dietary exposure estimates.**
Experts' consultation 2.3 **Experts to discuss the phototoxic potential of fluazaindolizine on the basis of all the newly provided evidence.**	**Fluazaindolizine is phototoxic in vitro. It is acknowledged that as yet, there is no agreed guidance on how to follow-up a positive in vitro phototoxicity result.**

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.4 **Experts to discuss the adequate LD50 to consider in the KCA 5.2.1/02 study on acute oral toxicity study in rats ([redacted] 2018).**	**The rat oral LD50 is 940 mg/kg bw.**
Experts' consultation 2.5 **Experts to agree on the NOAELs of the 28-day, 90-day and 1-year study in dogs and set an overall short-term toxicity NOAEL in dogs.**	**As regards the oral 28-day dog study, no NOAEL is set as this is a dose range finding study.** **As regards the 90-day oral dog study, the NOAEL is 500 ppm (=20.4 mg/kg bw per day) based on liver toxicity consisting of histopathology and clinical chemistry parameters findings (liver single cell necrosis, statistically significant increase in ALP in males) and increased CYP3A enzyme activity in both males and females at the 1500 ppm dose (=58.6 mg/kg bw per day).** **As regards the 1-year dog study, the NOAEL is 500 ppm (=17.4 mg/kg bw per day) based on a significant increase in ALP levels in males throughout the study duration, minimal and transient increases in AST, ALT, and/or SDH in both males and females, centrilobular pigmented hepatocytes in 1 male and non-statistically significant increases in liver weight in males at 1000 ppm (= 35.8/36.6 mg/kg bw per day, M/F)** **The relevant dog short-term NOAEL is 17.4 mg/kg bw per day, based on the liver toxicity observed in the 1-year dog at 1000 ppm, as also supported by the NOAEL of the 90-day study.** **For the Mouse 28-Day, the NOAEL is 3000 ppm (=514/634 mg/kg bw per day, M/F) based on a LOAEL of 6000 ppm (1105 mg/kg bw per day, top dose) for liver and kidney histopathological findings in combination with increased spleen weight and decreased body weight gain.** **As regards the Mouse 90-Day study, the NOAEL is 1000 ppm (=146 mg/kg bw per day) based on a LOAEL of ≥ 3000 ppm for gall bladder (inflammation, hyperplasia of the epithelium, fibrosis at 7000 ppm in females) & kidney (perihilar nephropathy, shrunken tubules & interstitial**

Subject	Conclusions Pesticides Peer Review Meeting
	fibrosis), liver hypertrophy at 7000 ppm correlated with ↑ liver wt (relative ↑ 10%). The relevant mouse short-term NOAEL is 146 mg/kg bw per day based on the mouse 90-day study results. Open point: for the above concerned studies, the RMS should clearly list all the adverse toxicological effects underlying the NOAEL setting, e.g., histopathology, organ weights, clinical chemistry parameters seen at the LOAEL, and differentiate them from the adverse findings caused by higher exposure levels.
Experts' consultation 2.6 Experts to discuss the NOAELs and LOAELs of the 90-day rat studies ([redacted] 2013 and [redacted] 2013; KCA 5.3.2/04 and KCA 5.3.2/06).	The NOAEL of the rat oral 90-day study (= relevant oral short-term NOAEL in rats) is 84.4 and 96.9 mg/kg bw per day in males and females, respectively, for kidney effects (histopathology - pyelitis, pyelonephritis, urothelial hyperplasia - and increased urine volume) at 3000 ppm, equivalent to 166 mg/kg bw per day in males and 189 mg/kg bw per day in females (LOAEL).
Experts' consultation 2.7 Experts to discuss the genotoxic potential and photomutagenicity of fluazaindolizine in the light of all the available evidence including the new in vitro micronucleus study.	Based on the weight of the in vitro and in vivo evidence, fluazaindolizine is unlikely to be genotoxic. Based on the positive in vitro phototoxicity results, fluazaindolizine is concluded as photomutagenic. In the absence of a proper test and assessment guidance for photomutagenicity, a positive phototoxicity result is currently regarded as a surrogate for a positive photomutagenic result.
Experts' consultation 2.8 Experts to discuss the long-term oral toxicity and carcinogenicity study in the rat.	The rat systemic NOAEL of the long-term oral toxicity study is 1500 ppm equivalent to 76.1 and 77.7 mg/kg bw per day in males and females, respectively, based on renal/urinary tract effects in both sexes at 4500 ppm, consisting of histopathological findings (medullary tubular dilation, cyst(s), mineralisation, interstitial fibrosis, and chronic progressive nephropathy, papillary necrosis, deformed papilla, transitional cell hyperplasia, pelvic dilation, pelvic haemorrhage and urothelial cell hyperplasia), and related urinalysis effects.

Subject	Conclusions Pesticides Peer Review Meeting
	The rat carcinogenicity NOAEL is 4500 ppm, equivalent to 240.8 and 254.1 mg/kg bw per day in males and females, respectively (the highest dose tested).
Experts' consultation 2.9 **Experts to discuss the long-term oral toxicity and carcinogenicity study in the mouse.**	**The systemic NOAEL of the mouse long-term oral toxicity study is 1000 ppm equivalent to 141.7 and 176.6 mg/kg bw per day in males and females, respectively, based on increased incidence of amyloidosis at 3000 ppm in both sexes.** **The mouse carcinogenicity NOAEL is 3000 ppm, equivalent to 427.2 and 525.2 mg/kg bw per day in males and females, respectively (the highest dose tested)**
Experts' consultation 2.10 **Experts to discuss the NOAELs of the KCA 5.6.1/01 One-generation rat study ([redacted], 2017).**	**In the rat one-generation reproduction study:** **Parental NOAEL is 500 ppm (37 mg/kg per day) based on transitional cell hyperplasia and/or ulceration of the renal pelvis/papilla at 2500 ppm.** **Reproductive NOAEL is: 5000 ppm (361 mg/kg per day for P1 males; 369 mg/kg/day for P1 females), based on the lack of test substance-related effects in the P1 generation at any dietary concentration tested.** **Offspring NOAEL: 2500/1500 ppm (179 mg/kg bw per day) based on microscopic kidney findings in F1 adults (transitional cell hyperplasia in males and females, pyelonephritis in males, unilateral pelvic dilatation in females at 5000 ppm).** **The relevant parental, reproductive and offspring NOAELs are based on the results of the 2-generation reproductive toxicity study.** **Relevant parental NOAEL: 29.71 mg/kg bw per day, based on urinary tract effects (transitional cell hyperplasia, other histopathological changes)** **Relevant reproductive NOAEL: 265.10 mg/kg bw per day (top dose tested)** **Relevant offspring NOAEL: 37.91 mg/kg bw per day based on kidney and bladder histopathological changes**

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.11 Experts to discuss and agree on the NOAEL of the acute rat neurotoxicity study (KCA 5.7.1/02; [redacted] 2017)	**In the rat acute neurotoxicity study:** the NOAEL for systemic toxicity is 125 mg/kg bw for male rats based on effects observed at higher doses including decreased body weight and reduced motor activity secondary to systemic toxicity; the neurotoxicity NOAEL is 1750 mg / kg bw for both sexes based on the absence of primary neurotoxic effects at the highest tested dose. Open point: RMS to include the Mode of Action data presented during the peer review meeting in an updated DAR.
Experts' consultation 2.12 The evaluation of the ED properties should be discussed in an expert consultation in line with the ECHA/EFSA guidance. The outcome of this experts' consultation point will be considered for the ED assessment for wild mammals (5(84)).	*T-modality* T-modality has been sufficiently investigated in studies of different duration and in different species with no evidence of a pattern of T-mediated adversity. Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for the T modality are not met for fluazaindolizine. *EAS-modalities* EAS-modality has been sufficiently investigated in studies of different duration and in different species with no evidence of a pattern of EAS-mediated adversity. Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for the EAS modality are not met for fluazaindolizine. Open point: RMS should correctly assign - in a revised DAR - the prostatitis effects in the F1 generation to the 2-generation rat study rather than to the 28-day with 1-generation rat study (see Vol 1, p-531).
Experts' consultation 2.13	As regards residue metabolites, Genotoxicity was assessed for IN-REG72, IN-REG72 glucose conjugate and IN-RYC33; Both genotoxicity and general toxicity were assessed for IN-A5760, IN-F4106, IN-QEK31, IN-QZY47, IN-R3Z85, IN-

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the genotoxicity and/or general toxicity of the residue metabolites listed above. In addition, experts to discuss the genotoxicity and general toxicity of the metabolite trifluoroacetic acid, if its formation is confirmed.	RSU03, IN-TMQ01, IN-TQD54, IN-TUT81, IN-UGA20, IN-UGT08, IN-UJV12, IN-UJU44, IN-UNS90, IN-A5760 glucuronide conjugate, IN-A5760 sulfate conjugate, IN-RSU03 glucose conjugate, IN-RSU03 malonyl conjugate and IN-UNS90 glucose conjugate. Overall, there is no genotoxic concern for any of the residue metabolites above, based on experimental data and/or QSAR predictions, robust grouping and read-across approach. Only for IN-VM862, aneugenicity was not properly investigated. As for general toxicity, (except for IN-VM862), the parent's reference values are applicable to all residue metabolites assessed, based on repeated dose toxicity studies for some metabolites, robust grouping and read across, also taking into consideration target organ toxicity. For IN-VM862, there are qualitative and quantitative differences in target organ toxicity from the parent (see EC 2.15 conclusions below). Open point To account for the potential formation of the disproportionate human metabolite IN-REG72, the RMS should include an additional UF of 2 in the calculations when comparing non-dietary and consumer exposure with fluazaindolizine references values.
Experts' consultation 2.14 Experts to discuss the genotoxicity and/or general toxicity of the GW metabolites listed above.	In groundwater (GW), IN-REG72 occurs below 0.1 µg/L and is unlikely to be genotoxic. IN-QEK31, IN-F4106 and IN-A5760, IN- QZY47 (S-enantiomer) (all above 0.75 µg/L) are not relevant GW metabolites based on hazard assessment and the reference values of the parent are applicable. The concentration of IN-VM862 in GW is open. The ADI/ AOEL of IN-VM862 is 0.002 mg/kg bw per day based on the rat NOAEL of 2 mg/kg bw per day in the 90 day study (for ↑absolute neutrophil count, ↑total proteins and albumin, proteinuria, ↑adrenal gland and kidney weights, tubular

Subject	Conclusions Pesticides Peer Review Meeting
	changes in the kidneys, enlargement of mandibular lymph nodes with lymphoid hyperplasia and plasmocytosis, and ↑number of endometrial glands in the uterus at ≥10 mg/kg bw per day). An overall UF of 1000 is applied to also account for the sub-chronic to chronic extrapolation and missing toxicological data. Due to the lack of conclusions on the aneugenic potential of IN-VM862, its reference values might be affected in the future.
Experts' consultation 2.15 Experts to discuss the points of departure (PoD) underlying the derivation of the ADI (acceptable daily intake), the ArfD (acute reference dose), and the (A)AOEL (acute/acceptable operator exposure level) for fluazaindolizine including the appropriate uncertainty factors and correction factor for oral absorption in an experts' meeting.	The ADI is 0.17 mg/kg bw per day based on the NOAEL of 17 mg/kg bw per day and the effects observed at the LOAEL of 36 mg/kg bw per day in the 1-year dog study (statistically significant increase in ALP, minimal and transient increase in AST, ALT and SDH in both sexes and centrilobular pigmented hepatocytes in one male and not statistically significant changes in male liver weight). Standard UF of 100. The ARfD is 1.25 mg/kg bw based on the rat systemic NOAEL of 125 mg/kg bw from the acute neurotoxicity study. Standard UF of 100. The AOEL is 0.09 mg/kg bw per day based on the NOAEL of 17 mg/kg bw per day and the effects observed at the LOAEL of 36 mg/kg bw per day in the 1-year dog study with standard UF of 100 and correction of 51% for oral bioavailability; this value is supported by the 90-day study results in dogs. The RMS considered more appropriate to derive the AOEL from the multigeneration study in rats, but then agreed to the AOEL set on the basis of the 1-year dog study. The AAOEL is 0.64 mg/kg bw based on the rat acute neurotoxicity study and corrected for 51% oral bioavailability with standard UF of 100.
Experts' Consultation 2.16	Based on an *in vitro* study in human skin the dermal absorption values for fluazaindolizine are: 1.7% for the concentrate (500 g/L);

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss non-dietary exposure data including dermal absorption values for the product concentrate and dilutions.	6.5% for the dilution 1 g/L; 13% for the dilution 0.5 g/L (after pro-rata correction, for field in furrow application). For the drip irrigation in greenhouse, the default value of 50% for SC formulation is applicable for worker exposure estimates. Open point RMS to provide the latest and correct version of the BfR spreadsheet for the calculation of the dermal absorption values. *Greenhouse drip irrigation scenario*: For operators only the exposure during mixing/loading (ML) was considered relevant. For bystanders and residents, only exposure to vapour was considered relevant. For workers, only exposure to soilborne residues was considered relevant. *In-furrow field application scenario*: For bystanders and residents, mainly exposure pathways of spray drifts vapour and deposits are relevant, and no re-entry activities are foreseen for workers. Open point RMS to provide revised non-dietary exposure estimates for the representative uses, applying the agreed approaches and toxicological endpoints (dermal absorption values and AOEL/AAOEL).
Experts' consultation 0.1 Experts to discuss the toxicological relevance of the significant impurities.	None of the significant impurities is considered as toxicologically relevant based on the available experimental data and/or in silico predictions. Open point: RMS to update Vol 4 with the batches used in the new in vitro MN test.
Experts' consultation 0.2	Open point (for all co-formulants): RMS should complete the assessment of the toxicological profile of the co-formulants and report it in the revised RAR

Subject	Conclusions Pesticides Peer Review Meeting
MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative uses with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	(vol. 4) to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures. The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion, and referred to the safety of the co-formulant per se as well as in relation to the concentrations in the PPP. A disclaimer should be included for all evaluations, indicating the limitations of the database as to the reliance of the existing evaluations.

REPORT OF PESTICIDES PEER REVIEW TC 148

Trifloxystrobin – MRL Art. 10 **Evaluating Member State: NL**

2. Mammalian toxicity

Date: 30 September 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by EMS NL	Ctgb - NL
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment - DE
National Expert nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Expert nominated by MS PL	Merit Mark Polska Sp. z o.o. - PL
Observer	Finnish Safety and Chemicals Agency (Tukes) - FI
Observer	Ctgb - NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss ADME studies conducted with trifloxystrobin to conclude on the representativeness of metabolite M5 (CGA 321113) in the toxicity studies performed with the parent, trifloxystrobin, and if the toxicological reference values established for trifloxystrobin are applicable to M5 in an experts' meeting.**	**The metabolite M5 (CGA 321113) is a major rat metabolite based on its recovery in bile together with its unique downstream metabolites M12, M13 and M28.** **Accordingly, the metabolite is covered by the toxicity studies performed with the parent trifloxystrobin and the toxicological reference values of the parent may apply to the metabolite.**
Experts' consultation 2.2 **MSs experts to discuss the reliability of the comparative in vitro tests on cytotoxicity and cellular respiration with M2, M3 and M4 in an experts meeting.**	**The scientific information provided in the comparative in vitro tests on cytotoxicity and cellular respiration with M2, M3 and M4 must be considered in the overall weight of evidence and the studies are considered supportive of the metabolites' risk assessment.**
Experts' consultation 2.3	**M2 (CGA 357262, isomer ZZ):** **Based on commonality of the effects observed in available toxicity studies with the metabolite and parent, the toxicity**

Subject	Conclusions Pesticides Peer Review Meeting
MSs experts to discuss the short-term toxicity of metabolite M2, CGA 357262, isomer ZZ, and toxicological reference values applicable to the metabolite.	profile of the metabolite is considered covered by the toxicological endpoints for the parent compound trifloxystrobin. Therefore, the toxicological reference values of trifloxystrobin are applicable to the metabolite.
Experts' consultation 2.4 MSs experts to discuss the short-term toxicity of metabolite M3, CGA 357261, isomer ZE and toxicological reference values applicable to the metabolite.	**M3 (CGA 357261, isomer ZE):** Based on commonality of the effects observed in available toxicity studies with the metabolite and parent, the toxicity profile of the metabolite is considered covered by the toxicological endpoints for the parent compound trifloxystrobin. Therefore, the toxicological reference values of trifloxystrobin are applicable to the metabolite.
Experts' consultation 2.5 MSs experts to discuss the short-term toxicity of metabolite M4, CGA 331409, isomer EZ and toxicological reference values applicable to the metabolite.	**M4 (CGA 331409, isomer EZ):** Based on commonality of the effects observed in available toxicity studies with the metabolite and parent, the toxicity profile of the metabolite is considered covered by the toxicological endpoints for the parent compound trifloxystrobin. Therefore, the toxicological reference values of trifloxystrobin are applicable to the metabolite.
Experts' consultation 2.6 MSs experts to discuss the toxicological profile of metabolite M6, CGA 373466 and toxicological reference values applicable to the metabolite.	**M6, CGA 373466:** Based on commonality of the effects observed in available toxicity studies with the metabolite and parent, the toxicity profile of the metabolite is considered covered by the toxicological endpoints for the parent compound trifloxystrobin. Therefore, the toxicological reference values of trifloxystrobin are applicable to the metabolite. It is noted that the genotoxicity data package doesn't include an assessment of the aneugenicity potential of the metabolite; according to the current state of the art, aneugenicity should be investigated and could affect the setting of TRVs. Open point for the EMS to revise the ER taking into consideration the conclusion reached during the meeting on metabolites M2, M3, M4 (include the ARfD setting for these metabolites), M5 (confirmation of the EMS assessment) and M6 (revise 28-day study NOAEL and overall conclusion).

REPORT OF PESTICIDES PEER REVIEW TC 148

PINOXADEN – Confirmatory data **Rapporteur Member State: AT**

2. Mammalian toxicity

Date: 30 September 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment - DE
National Expert nominated by MS FI	Finnish Safety and Chemicals Agency (Tukes) - FI
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Expert nominated by MS NL	Ctgb - NL
National Expert nominated by MS PL	Merit Mark Polska Sp. z o.o. - PL
Observer	Finnish Safety and Chemicals Agency (Tukes) - FI
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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.6 **Experts to discuss the NOAEL setting in the developmental toxicity study on M3 in rabbits and its relevance as a groundwater metabolite.**	**In the developmental toxicity study in rabbits conducted with metabolite M3, the maternal toxicity NOAEL is 30 mg/kg bw per day based on reduced maternal body weight gain up to day 9 of gestation.** **The developmental toxicity NOAEL is 30 mg/kg bw per day based on skeletal finding (rib – one or more costal cartilage interrupted).** **The developmental effects observed with the metabolite M3 are not assessed as severe enough (delayed development) for classification purposes (acknowledging that classification is under ECHA's remit), M3 is not relevant according to stage 3 of step 3 (screening for toxicity) of the guidance document on the assessment of the relevance of metabolites in groundwater.** **The toxicological reference values established for M3 during the peer review in 2013 are confirmed (EFSA, 2013).** **Open point for the RMS to add details on HCD and conclusion in a revised RAR addendum.**
Experts' consultation 2.7 **Experts to discuss the general approach to consider data from M3 for relevance assessment of the downstream metabolites (grouping approach for the non-relevance assessment of M3, M11, M54, M55 and M56; as well as of the comparison to a threshold of concern of 0.02 µg/kg body**	**M3 metabolite: see experts' consultation 2.6 above.** **M11, M54, M55 and M56 metabolites: the justification for grouping and read across for general toxicity is not sufficient for concluding on the non-relevance of these groundwater metabolites.** **In addition, if metabolite M55 exceeds 0.1 µg/L, it should be already considered a relevant metabolite following the EC guidance document on the assessment of the relevance of**

Subject	Conclusions Pesticides Peer Review Meeting
weight per day at groundwater relevance assessment Step 4.). EFSA notes that if metabolite M55 exceed 0.1 µg/L; it should be already considered a relevant metabolite following the EC guidance document on the assessment of the relevance of groundwater metabolites since and M55 showed equivocal /positive results in the in the *in vivo* Comet assay (see 2(6)). The discussion should also consider potential differences on toxicity for those groundwater metabolites containing a chiral centre (i.e. all of them except M3 and M11).	groundwater metabolites since M55 showed equivocal/positive results in the in the *in vivo* Comet assay. As regards step 4 of the guidance, it is currently only applicable to M3 since the grouping approach has not been accepted for the other metabolites Open point to be transferred to section 3 (residues) for the RMS to perform a consumer risk asssessment to M3. Open point for the RMS to review volume 1 and B.6 addenda to include the conclusion of the current peer review.
Experts' consultation 2.8 Experts to consider additional ACCase activity in pinoxaden metabolites.	The available information on biological activity was presented and it was considered as part of the overall assessment in experts' consultation 2.7 above, but insufficient in itself to draw a conclusion on the general toxicity of the metabolites.
Experts' consultation 2.9 Experts to consider the additional Historical Control Data.	See experts' consultation 2.6 above.

REPORT OF PESTICIDES PEER REVIEW TC 148

Ethiprole – MRL Art. 10 **Evaluating Member State: NL**

2. Mammalian toxicity

Date: 30 September 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by EMS NL	Ctgb - NL
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment - DE
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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation point 1 (as follow up of Pesticides Peer Review Experts' Teleconference 120, 21-22 November 2023. Experts' Consultation point 2.7) **Re-discussion of toxicological reference values in view of missing developmental neurotoxicity**	There is no need to apply an extra UF for the derivation of toxicological reference values for ethiprole. The toxicological reference values remain as previously agreed: Acceptable Daily Intake (ADI): 0.002 mg/kg bw per day based on the NOAEL in the 1-yr dog study (related to increased relative liver weight) and an UF of 100. Acute Reference Dose (ARfD): 0.005 mg/kg bw based on the maternal NOAEL of the rabbit developmental toxicity study (related to decreased body weight gain) and an UF of 100.

REPORT OF PESTICIDES PEER REVIEW TC 147

FOSETYL – AIR III, mandated for re-assessment of ED **Rapporteur Member State: FR**

2. Mammalian toxicity

Date: 24 September 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS HR	Croatian Agency for Agriculture and Food - HR
National Experts nominated by MS NL	Ctgb - NL

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.8 **MSs to discuss the endocrine disruption (ED) assessment in an experts' meeting for the estrogen, androgen, steroidogenesis and thyroid (EAST) modalities, including the new level 2 and 3 mechanistic studies submitted.**	***T-modality*** **T-modality has been sufficiently investigated in studies of different duration and in different species with no evidence of a pattern of T-mediated adversity.** **Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for the T-modality are not met for fosetyl.** ***EAS-modalities*** **EAS-mediated activity has been sufficiently investigated and no EAS-mediated endocrine activity has been observed. Although the EAS-mediated parameters have not been sufficiently investigated, there is no sufficient evidence of a pattern of EAS-mediated adversity in the available dataset of studies.** **Scenario 2a(ii) of the ECHA/EFSA Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for the EAS-modalities are not met for fosetyl.**

REPORT OF PESTICIDES PEER REVIEW

TC 141 and TC 142

MCPA, MCPA-EHE, MCPA-THIOETHYL – AIR III **Rapporteur Member State: PL**

2. Mammalian toxicity

Date: 3 July 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS PL	EVA - PL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES)- AT
National Expert nominated by MS CZ	The National Institute of Public Health - CZ
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency - DK
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES)- FR
National Expert nominated by MS IE	Department of Agriculture food and the Marine Ireland - IE
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS SK	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

Please note that information part of this report may have been masked by EFSA in accordance with Article 63 of Regulation (EC) No 1107/2009 as well as EFSA's Practical Arrangements concerning confidentiality in accordance with Articles 7 and 16 of Regulation (EC) No 1107/2009, or EFSA's Practical Arrangements concerning transparency and confidentiality as a consequence of confidentiality requests submitted by the applicant on application dossiers for pesticides active substances or Maximum Residue Levels, respectively. Please note that information disclosed in this report is without prejudice to pre-existing intellectual property rights and data exclusivity clauses set out in Union law, and particularly in Article 62 of Regulation (EC) No 1107/2009.

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the revised assessment of the ADME (toxicokinetics) data, including:** **- *in vitro* comparative metabolism data for MCPA (and MCPA 2-EHE and MCPA-thioethyl);** **- the reliability of the toxicokinetic studies for MCPA-thioethyl;** **- the relevance of the dog species for the risk assessment of MCPA (MCPA acid, MCPA-thioethyl, MCPA-EHE);** **- consideration of the oral absorption value.**	**A data gap is confirmed for an in vitro interspecies comparative metabolism study.** **The available information is not sufficient to consider the dog of no relevance to humans for MCPA.** **Oral absorption exceeds 80% of the administered dose in rats, while in dogs, it was set at 58% (applicable to MCPA and its variants).** **HMCPA was identified as a major metabolite in rats, while in dogs, the major metabolite is MCPA glycine.** **Open point:** **RMS to calculate the values of plasma levels in Table CA 6.1.1/03-2 (p. 40 of RAR) into % of administered dose.** **Open point:** **RMS to revise the RAR in agreement with the experts' conclusions in both Vol. 3 and Vol. 1.**
Experts' consultation 2.2 **Experts to discuss the sensitisation potential of**	**MCPA might be considered a skin sensitiser, while MCPA-EHE (tested with a modified Buehler test, that is considered less sensitive than the other tests) and MCPA-thioethyl (M&K test) may not be considered skin sensitisers based on the available data.**

Subject	Conclusions Pesticides Peer Review Meeting
MCPA (as well as MCPA 2-EHE and MCPA-thioethyl).	
Experts' consultation 2.3 Experts to discuss the relevance of the adverse effects observed in rat short-term inhalation studies with MCPA and MCPA DMA for human risk assessment by inhalation.	The 28-day toxicity study by inhalation in rats presented a NOAEC of 0.02 mg/L, equivalent to 3.86 mg MCPA/kg bw per day based on local and systemic toxicity. Open point: In the 4-week toxicity study by inhalation in rats (2012b), RMS to check and amend the tabulated results on organ weight. Open point: RMS to check the equivalence of the NOAEC of 0.02 mg/L in mg/kg bw per day for both MCPA and MCPA DMA (because the two molecules have a different molecular weight).
Experts' consultation 2.4 Experts to discuss the setting of the single NOAELs and overall NOAEL(s) in the short-term rat studies with MCPA (also considering DMA salt), MCPA-thioethyl and MCPA 2-EHE, based on additional results and revised assessment included in the RAR, and to consider if they are of similar toxicity (qualitatively and quantitatively).	Regarding oral short-term toxicity studies in rats, three studies were considered reliable, the lowest NOAEL is observed in the 1994a study with MCPA-EHE at 5 mg/kg bw per day based on systemic toxicity (minimal decreased body weight, increased creatinine and focal testicular atrophy) and neurotoxicity (decreased motor activity in males). Open point: Discrepancies between Vol 1 vs. Vol 3 were noted regarding oral short-term toxicity in rats and should be addressed by the RMS.
Experts' consultation 2.5 Experts to discuss the setting of the single NOAELs and overall NOAEL(s) in the short-term dog studies with MCPA acid (also considering DMA salt), MCPA-thioethyl and MCPA 2-EHE, based on additional results and revised assessment included in the RAR, and to consider if they are of similar toxicity	In short-term toxicity studies in dogs, the overall NOAEL is 1 mg/kg bw per day based on clinical chemistry changes (statistically significant increased urea and creatinine levels), and histopathological changes (liver bile duct proliferation and kidney proximal tubules pronounced pigment deposition) in the 90-day and 1-year dog studies. Open point: RMS to correct the Table 6.3.2/08-2, indicating pre-dose instead Day 0. Open point: RMS to address the discrepancies observed between Vol 1 vs. Vol 3 regarding oral short-term toxicity in dogs.

Subject	Conclusions Pesticides Peer Review Meeting
(qualitatively and quantitatively). From experts consultation 2.11: Experts to discuss the NOAEL setting for systemic and carcinogenic effects in the 1-year and 2-year dog studies with MCPA and MCPA-thioethyl (and relevance for MCPA 2-EHE).	
Experts' consultation 2.6 Experts to discuss the short-term dermal toxicity studies with MCPA and MCPA-EHE (considering also their relative toxicity and the relevance for MCPA-thioethyl), based on additional results and revised assessment included in the RAR, and to consider if they are of similar toxicity (qualitatively and quantitatively).	With regards to short-term dermal toxicity in rats and rabbits, the overall systemic NOAEL is set at 1000 mg/kg bw per day in the absence of treatment related systemic adverse effects; the local NOAEL is 10 mg/kg bw per day due to slight erythema and oedema observed at 100 mg/kg bw per day in rabbits.
Experts' consultation 2.7 Experts to discuss the setting of the single NOAELs and overall NOAEL(s) in the short-term mouse studies with MCPA, MCPA-thioethyl and/or MCPA-EHE, based on additional results and revised assessment included in the RAR, and to consider if they are of similar toxicity (qualitatively and quantitatively).	In short-term mouse studies, no reliable NOAEL could be derived based on the limitations seen in the three available studies, including a dose range finding study, with a limited power to derive a NOAEL (5 animals/sex/group, limited investigations, statistical analysis not provided for some endpoints).

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.8 Experts to discuss the genotoxicity potential of MCPA (including MCPA-acid, MCPA 2-EHE and MCPA-thioethyl).	**Data gap:** The genotoxicity of MCPA is inconclusive regarding gene mutation in mammalian cells (based on positive results observed in vitro with metabolic activation with MCPA), clastogenicity and aneugenicity (based on positive results obtained in vitro with MCPA and insufficiently robust in vivo follow up).
Experts' consultation 2.9 Experts to discuss the NOAEL setting for systemic and carcinogenic effects in the long-term mouse studies with MCPA and MCPA-thioethyl (and relevance for MCPA 2-EHE).	Regarding long-term toxicity / carcinogenicity in mice, the overall NOAEL for chronic toxicity is 15.7 mg/kg bw per day based on renal changes, reduced body weight gains (intermittent) and haematological changes. The carcinogenic NOAEL is 75.9 mg/kg bw per day (highest dose tested) based on the 24-month study. This conclusion is pending a revision of the RAR according to the following open points: **Open point:** RMS to integrate the RAR with information supporting the NOAEL setting of the 24-month mice study (1988) (more detailed description of renal changes, body weight gain changes and haematological changes). **Open point:** RMS to integrate the RAR with a summary of the 18-month (1990) study (rationale and complete description of the experimental setting, methods and results). **Open point:** • RMS to check in the 18-month study with MCPA-thioethyl report the rationale for conducting the study, material and methods and list the limitations (i.e. which parameters were collected/investigated, as a deviation to OECD TG) in order to conclude on the relevance of this study for the setting of systemic NOAELs, considering the toxicological profile of this substance (i.e. clinical chemistry/haematology parameters have been used to set NOAELs in other study). • RMS to revise effects on body weight and food efficiency to conclude on their relevance; • This information should be integrated in a revised RAR.
Experts' consultation 2.10	With regards to long-term toxicity and carcinogenicity in rats, no evidence of treatment related carcinogenicity was observed with MCPA and its variants (pending the revisions requested in the open points below).

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the NOAEL setting for systemic and carcinogenic effects in the long-term rat studies with MCPA and MCPA 2-EHE (and relevance for MCPA-thioethyl).	**Based on the available information, the tentative NOAEL (chronic and carcinogenicity) is set at 320 ppm (equivalent to 17.6 mg/kg bw per day) - to be confirmed for MCPA.** **Open point:** - **RMS to check in the 1994 study report (study performed with a 25.3% MCPA formulation) the rationale for conducting the study, material and methods and check the limitations as compared to OECD TG (i.e. which parameters were collected/investigated), considering the toxicological profile of this substance (i.e. clinical chemistry/haematology parameters have been used to set NOAELs in other study).** - **Summary tables available in the RAR should be checked for correctness (see for instance brain weight, week 78)** - **This information should be integrated in a revised RAR.** **Open point:** **With regards to the 1988 study (2-year rat with MCPA), RMS to clarify in a revised RAR the conversion of ppm into mg/kg bw per day; check the summary tables in the RAR, clarifying aspects such as the timepoint where the findings were observed, statistical analysis results, and checking for consistency with the narrative; to transparently integrate in a revised RAR the conclusions as discussed in the meeting.** **For MCPA 2-EHE the NOAEL is confirmed at 29 mg/kg bw per day, due to decreased body weight gain and kidney and liver histopathological changes; no carcinogenic potential was observed with MCPA 2-EHE.** **Open point:** **With regards to the 2012 study (2-year rat study with MCPA 2-EHE) RMS to integrate in a revised RAR the conclusions reached by the experts.** **For MCPA-thioethyl, the following tentative NOAELs were set, pending the provision of additional details (as described in the open point below):** - **tentative NOAEL for chronic toxicity: 0.8 mg/kg bw per day (20 ppm) based on reduced body weight gain, equivocal renal histopathological findings; haematological and spleen changes (increased extramedullary haematopoiesis).** - **tentative carcinogenic NOAEL: 83.1 mg/kg bw per day (2000 ppm, highest dose tested) (see open point below).** **Open point:**

Subject	Conclusions Pesticides Peer Review Meeting
	With regards to the 1988 study (2-year rat study with MCPA-thioethyl) RMS to integrate the information in a revised RAR. In particular: - provide detailed summary tables of neoplastic findings; - check all tabulated summary table (histopathological findings); - clarify histopathological findings in the bone marrow (microgranulomas); - complete the tabulated summary of haematological findings (all lineages: red, white and platelets).
Experts' consultation 2.11 Experts to discuss the NOAEL setting for systemic and carcinogenic effects in the 1-year and 2-year dog studies with MCPA and MCPA-thioethyl (and relevance for MCPA 2-EHE).	See experts' consultation 2.5
Experts' consultation 2.12 Experts to discuss the parental, reproductive and offspring NOAELs in the 1 and 2-generation rat studies with MCPA and MCPA 2-EHE (and relevance for MCPA-thioethyl).	<u>In the 1-generation reproductive toxicity study with MCPA (2004):</u> tentative parental, offspring and reproductive toxicity NOAELs are identified at the top dose level of 89 mg/kg bw per day. Open point: RMS to check if macroscopic or histopathology were investigated in the 1-generation reproductive toxicity study with MCPA (2004). <u>In the 2-generation reproductive toxicity study with MCPA (1999)</u>, the parental NOAEL is 80 mg/kg bw per day (1000 ppm) based on reduced parental bodyweight. The reproductive toxicity NOAEL is 80 mg/kg bw per day, based on reduced litter size, lactation index and offspring survival, and increased gestation length in F0 and in F1 generations. The offspring NOAEL is 7.5 mg/kg bw per day (100 ppm) based on reduced pup weight gain at 1000 ppm. Open point: RMS to check the limitations of the study design compared with the current OECD TG (including stability of test material). <u>In the 2-generation reproductive toxicity study with MCPA (1986)</u>, the parental NOAEL is 150 ppm based on significant reduction of body weight from weaning through the premating period (F1b).

Subject	Conclusions Pesticides Peer Review Meeting
	The offspring NOAEL is open pending on the open point for the RMS to present the litter parameters and pup weight with % changes. **The reproductive NOAEL is open pending on the open point for the RMS to present the reproductive parameters.** **Open point:** **RMS to check the corresponding dose intake for each dietary concentration. Body weight results to be presented with % change. RMS to check if the batch is representative of the representative specification. Litter and reproductive parameters to be presented with % changes.** **In the 1-generation reproductive toxicity study with MCPA 2-EHE (2004), the parental NOAEL is 1200 ppm that was reduced to 800 ppm day 1 post-partum, based on reduced body weight in the F1 generation.** **The offspring NOAEL is 1200 ppm that was reduced to 800 ppm day 1 post-partum, based on reduced offspring weight gain at the highest dose level.** **The reproductive NOAEL is 1600 ppm (the highest dose tested).** **Open point:** **RMS to check whether the table mentioning MCPA DMA salt refers to MCPA-EHE, the corresponding test item intake (including the acid value) for the reduced dietary concentrations.**
Experts' consultation 2.13 **Experts to discuss the setting of NOAELs (maternal and developmental) in the rat developmental toxicity studies with MCPA and MCPA 2-EHE, considering also the study with MCPA PPP.**	**In the developmental toxicity study in rats with MCPA (1980), no conclusion could be reached due to missing/unclear information (see open point below).** **Open point:** **RMS to provide the list of deviations compared to the current OECD TG and provide revised results tables with % changes and clarify the groups size in the different tables vs. original statement that only 5 animal per dose were used.** **In the developmental toxicity study in rats with MCPA (1993), the maternal NOAEL is 60 mg/kg bw per day based on reduced body weight gain during 2 periods (day 6 to 15 and 0 to 20).** **The developmental toxicity NOAEL is 60 mg/kg bw per day based on reduced foetal weight, and decreased ossification of skull and sternebrae.** **Open point:** **RMS to describe the deviations from current OECD TG.** **In the developmental toxicity study in rats with MCPA 2-EHE (1999), the maternal toxicity NOAEL is 62.7 mg MCPA 2-EHE/kg bw**

Subject	Conclusions Pesticides Peer Review Meeting
	per day based on reduced body weight gain. The developmental toxicity NOAEL is 62.7 mg MCPA 2-EHE/kg bw per day based on increased incidence of foetal malformations and skeletal variations, increased post-implantation loss and reduced foetal weight at the top dose. **Open point:** RMS to check the conversion between MCPA-EHE and MCPA (acid).
Experts' consultation 2.14 Experts to discuss the setting of NOAELs (maternal and developmental) in the rabbit developmental toxicity studies with MCPA, their relevance for MCPA-thioethyl and MCPA 2-EHE, and to consider the acceptability of the mouse study.	In the developmental toxicity study in rabbits with MCPA (2005), a tentative NOAEL is set at 25 mg/kg bw per day for maternal toxicity since maternal bw was not significantly reduced (mortality incidence was not dose-related and cause of death unrelated to test-item treatment - pneumonia and aspiration caused by oral administration at 5 and 10 mg/kg bw per day, however the cause of death at the top dose remains unclear and should be clarified by the RMS). The tentative developmental toxicity NOAEL is 5 mg/kg bw per day based on skull anomalies (enlarged fontanella). **Open point:** RMS to add clarification on the maternal cause of death at the top dose. In the developmental toxicity study in rabbits with MCPA (1993), the maternal toxicity NOAEL is 15 mg/kg bw per day based on abortion, poor health status (resulting in human sacrifice in one animal) observed at the mid-dose. With the available information, a developmental NOAEL could not be set for this study (see open point below). **Open point:** RMS to clarify whether foetal data (variants and anomalies) are reported in the original study, and include these data in the RAR in a tabulated format, and whether maternal toxicity was correlated to post-implantation loss (check individual data). In addition, an open point was identified to include a full summary of a study mentioned in the list of available studies. **Open point:** RMS to check the RAC opinion and add as much as possible the details available on the developmental toxicity study in rabbits with MCPA-thioethyl (1984), check whether the study is available to the RMS and report it in the RAR.
Experts' consultation 2.15	In the acute neurotoxicity study in rats with MCPA (1994), the NOAEL for general toxicity is 200 mg/kg bw based on reduced weight gain and ataxia (males). The NOAEL for neurotoxicity is 300 mg/kg bw based on changes in motor activity observed at the top dose (females).

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the results of the neurotoxicity studies (including the more specific studies on brain toxicity and developmental neurotoxicity study) with MCPA, MCPA 2-EHE, and their relevance for MCPA- thioethyl.	In the acute neurotoxicity study in rats with MCPA 2-EHE (1994), the NOAEL for general toxicity and neurotoxicity is 250 mg/kg bw based on functional observations (gait impairment) observed at the mid dose and above. In a 90-day neurotoxicity study in rats with MCPA (2005), no neurotoxic effects were observed up to *ca*. 245 mg/kg bw per day. In another subchronic toxicity study in rats with MCPA with neurotoxicity investigations (1994), the NOAEL for neurotoxicity is 38 mg/kg bw per day (500 ppm) based on reduced motor activity at the top dose of 2500 ppm; in addition, at 2500 ppm, decreased grip strength and foot spread were also noted sporadically in males. In this study, the systemic NOAEL is also 38 mg/kg bw per day, based on body weight changes, changes in haematology and bone marrow histopathology (hypocellularity, sternum), and liver histopathology associated with clinical chemistry changes (ALT). Additionally, in a 90-day toxicity study in rats with MCPA 2-EHE (1994a): a systemic toxicity and neurotoxicity NOAEL was set at 5 mg/kg bw per day (see experts' consultation 2.4). The conclusions on neurotoxicity are supported by the available information from literature indicating that MCPA affects the blood-brain barrier (BBB) integrity at doses from 250 mg/kg bw onwards. In a developmental neurotoxicity (DNT) study in rats with MCPA 2-EHE (2010), insufficient details are available in the RAR to conclude on the developmental neurotoxicity NOAEL (e.g. open field observations are not detailed, limited data on offsprings are reported). Also, on the basis of the available information a treatment relationship of changes in brain morphometry and weight observed at the top dose cannot be discharged. **Open point:** RMS to integrate the information on the DNT study in order to decide on the NOAELs for this study in a revised RAR.
Experts' consultation 2.16 Experts to discuss the immunotoxicity potential of MCPA, MCPA 2-EHE and MCPA-thioethyl.	Based on the information currently available, no conclusion could be reached on the immunotoxic potential of MCPA. **Open point:** RMS to collect information on the effects on endpoints relevant for the assessment of the immune system from the available toxicological dataset and noting whether these effects were observed above the maximum tolerated dose (MTD) and/or with concomitant toxicological effects (to be identified). See also Experts' consultation 2.18 below.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.17 **Experts to discuss the assessment of the endocrine disruption (ED) properties for MCPA, MCPA 2-EHE and MCPA-thioethyl (and if read across can be done between the compounds).**	**For the EATS-modalities, all the experts agreed that a Weight of Evidence (WoE) approach using all the available data on MCPA and its variants is appropriate for the ED assessment of MCPA, MCPA 2-EHE and MCPA-thioethyl.** **T-modality** **T-mediated parameters have been considered sufficiently investigated in studies of different duration, in different species and using MCPA and its variants. A pattern of T-mediated adversity was not observed in a sufficiently investigated dataset.** **Considering the available data at the date of the Peer Review Meeting (TC 141, June 2024), scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for the T-modality are not met for MCPA and its variants.** **EAS-modalities** **The EAS-modalities for MCPA and its variants are considered insufficiently investigated. Scenario 2a(iii) of the ECHA/EFSA ED Guidance (2018) is applicable, in particular for the A-modality based on the lack of a Level 3 study (Hershberger Assay).** **If the above study is negative then the dataset would be considered sufficient. If endocrine activity is detected in the above assay, then further data will be needed to support a mode of action (MoA) analysis and an extended one-generation reproduction toxicity study (EOGRT) with inclusion of the cohort 1a and 1b, including the mating of cohort 1b to produce the F2 generation (OECD TG 443, Level 5) should be conducted.** **Open points:** **The RMS is kindly asked to revise the RAR Vol.1 and Vol. 3B6 in line with the discussion at the Peer Review Experts' TC 141.**
Experts' consultation 2.18 **Experts to discuss the relevance of the more detailed assessment of the supplementary studies for the risk assessment of MCPA, MCPA-EHE and MCPA-thioethyl.**	**Supplementary studies have been reported in more details in the revised RAR. They give supplementary information mainly on the mode of action (MoA).** **However, some of them may be relevant to the immunotoxicity endpoints and should be considered to address this point (see open point above in Experts' consultation 2.16).**
Experts' consultation 2.19	**No conclusion can be drawn on the genotoxicity and general toxicity of the metabolite HMCPA.** **No conclusion can be drawn on the genotoxicity potential of CCPA.**

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the genotoxicity and general toxicity profile of the metabolites CCPA and 4-chloro-2-hydroxymethylphenoxy acetic acid.	
Experts' consultation 2.20 Experts to discuss the toxicological reference values for MCPA, MCPA 2-EHE and MCPA-thioethyl, including - their applicability to MCPCA DMA or other salts; - the relevance of the dog species.	Since a number of toxicological parameters are still open, in particular the genotoxicity potential of MCPA that is inconclusive, no toxicological reference values can be derived based on the available data. Tentative toxicological reference values were discussed. Open point: RMS to check the basis for the acute reference dose (ARfD) set by the previous peer review (2008).
Experts' consultation 2.21 Experts to discuss the dermal absorption values for MCPA in the product DMA 500, including - the comparison of the detailed composition of the tested formulations (also with the representative formulation); - the deviations /acceptability of the studies and the proposed approaches for outliers, low recovery, combination of in vivo/in vitro data; - the complementary assessment following the EFSA guidance 2017.	For the formulation DMA 500, default dermal absorption values have to be applied, i.e. 10% for the concentrate and 50% for the dilution.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.22 **Experts to discuss the revised non-dietary exposure estimates (for operators, workers, residents and bystanders) for HF Calibra and MCPA DMA 500, and for the mixture formulation supporting MCPA-EHE.**	**Non-dietary exposure (NDE) from the formulation MCPA DMA 500:** **Open point:** **RMS to review the NDE estimates taking into consideration the suggestions agreed by the experts, using "old" as well as new models and all risk mitigation measures available as appropriate.** **Non-dietary exposure from the formulation HF Calibra:** **Open point:** **RMS to review the NDE estimates taking into consideration the suggestions agreed by the experts, using "old" as well as new models, and all risk mitigation measures available as appropriate, including lower application rates in case exposure estimates according to the higher application rates exceed the tentative (A)AOEL.** **Non-dietary exposure from the formulation UKS 151D:** **Open point:** **RMS to review the NDE estimates taking into consideration the suggestions agreed by the experts, using "old" as well as new models and all risk mitigation measures available as appropriate.**
Experts' consultation 2.23 **Experts to discuss the possible refinement of DFR (dislodgeable foliar residues) and DT_{50} values in the worker exposure estimates for HF Calibra.**	**The proposed refinement of the DFR and DT_{50} values in the worker exposure estimates for HF Calibra is not acceptable.**
Experts' consultation 2.24 **Experts to discuss the dermal absorption values for MCPA-thioethyl in the product HF Calibra.**	**Dermal absorption values for the formulation HF Calibra could not be concluded based on the available data (see open point below).** **Open point:** **RMS to provide the Excel file of the EFSA guidance 2017, reporting the values of the study (one for the rat and one for the human data) and clarify the different absorption values, whether derived from the 2012 or 2017 guidance.**
Experts' consultation 2.24bis **Experts to discuss the dermal absorption values for MCPA-2-EHE in the**	**Dermal absorption values for the formulation Evergreen (UKS 151D) could not be concluded based on the available data (see open point below).** **Open point:** **RMS to provide the Excel file of the EFSA guidance 2017, reporting the values of the study and clarify the different absorption values,**

Subject	Conclusions Pesticides Peer Review Meeting
product Evergreen (UKS 151D).	whether derived from the 2012 or 2017 guidance. RMS to present calculations according to both dermal absorption guidance.
Experts' consultation 2.25 transferred from section 1 to section 2: Experts to discuss the assessment of the toxicological relevance of the impurities relevant for SIPCAM for MCPA, MCPA 2-EHE and MCPA-thioethyl.	Due to time constraints, the discussion on this point was postponed.
Experts' consultation 2.25 transferred from section 1 to section 2: Experts to discuss the assessment of the toxicological relevance of the impurities relevant for Nufarm for MCPA, MCPA 2-EHE and MCPA-thioethyl.	Due to time constraints, the discussion on this point was postponed.
Experts' consultation 2.25 transferred from section 1 to section 2: Experts to discuss the assessment of the toxicological relevance of the impurities relevant for Ciech Sarzyna for MCPA, MCPA 2-EHE and MCPA-thioethyl.	Due to time constraints, the discussion on this point was postponed.
New experts' consultation point proposed by EFSA for completeness:	With regards to HF Calibra co-formulants, sufficient toxicological data were available for most components, except few; open points were set for the RMS to provide additional information (on

Subject	Conclusions Pesticides Peer Review Meeting
'HF Calibra' (from Sipcam Inagra, S.A.) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	the specific components of the co-formulants and their levels in the formulation and their toxicological profile from additional sources).
New experts' consultation point proposed by EFSA for completeness: 'Mixture formulation 'EVERGREEN COMPLETE' ('UKS 151D') (from Nufarm UK Limited) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual	With regards to "Evergreen complete" (UKS 151D) co-formulants, insufficient toxicological information was available for most components; open points were set for the RMS to provide additional information from sources that were identified (as discussed during the meeting).

Subject	Conclusions Pesticides Peer Review Meeting
component other than the active substance. Please note RMS Ireland is also evaluating the same mixture formulation ('UKS 151D') containing 3 a.s. in the context of the amendment of approval conditions for mecoprop-p-ester, and therefore careful considerations and consistency between the 2 assessments are required.	
New experts' consultation point proposed by EFSA for completeness: 'MCPA DMA 500 SL' (from EU MCPA Renewal Task Force – CIECH and Nufarm) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	With regards to MCPA DMA 500 SL co-formulants, sufficient toxicological data are available for all components to conclude that they do not impact the toxicity/classification and safety of this formulation. An open point was set for the RMS to gather additional information for further clarifications.

REPORT OF PESTICIDES PEER REVIEW

TC 141 and TC 142

MCPB – AIR III **Rapporteur Member State: PL**

2. Mammalian toxicity

Date: 3 July 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS PL	EVA - PL
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES)- AT
National Expert nominated by MS CZ	The National Institute of Public Health - CZ
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency - DK
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES)- FR
National Expert nominated by MS IE	Department of Agriculture food and the Marine Ireland - IE
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS SK	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **1) To discuss the ADME assessment of MCPB considering that:** **- the provided ADME study in rats on MCPB (1998) shows some deficiencies;** **- the argument that MCPB is promptly metabolized into MCPA, possibly justifying for read across from MCPA data in humans and animals, needs further consolidation;** **- no *in vitro* comparative metabolism study on MCPB has been provided;** **- new studies have been requested to the applicant (see data requirement).** **2) To discuss the relevance of the dog**	**A data gap is identified for an in vitro interspecies comparative metabolism study with MCPB.** **Based on the discussion on MCPA, the available information is not sufficient to consider the dog of no relevance to humans for MCPB.** **Oral absorption exceeds 80% of the MCPB administered dose in rats, no specific information is available in dogs for MCPB; with MCPA, oral absorption in dogs was set at 58%.**

Subject	Conclusions Pesticide Peer Review Meeting
as toxicological species for the risk assessment of MCPB (and MCPA) based on the ADME information.	
Experts' consultation 2.2 To discuss metabolites monitoring.	**EFSA post meeting note:** For the residue definition for body fluids and tissues, only MCPA needs to be monitored (see also E.C. 2.11).
Experts' consultation 2.3 To discuss the phototoxicity of MCPB.	**Data gap:** A phototoxicity test according to OECD TG 498 (corrected in 2023) on human skin cytotoxicity that can be used on UVB absorbers is needed to conclude on the phototoxicity potential of MCPB.
Experts' consultation 2.4 - To discuss the short-term toxicity assessment of MCPB, considering most studies have been conducted on MCPA - To discuss the relevance of the dog as a toxicological species for the short-term toxicity assessment of MCPB	In the 90-day toxicity study in rats with MCPB, the NOAEL is 6.3 mg/kg bw per day (100 ppm) based on increased kidney weight; this study shows a similar toxicity profile between MCPA and MCPB. In the 90-day toxicity study in dogs with MCPB, the NOAEL 2.5 mg/kg bw per day due to decreased body weight and body weight gain, clinical chemistry changes (increased creatinine) at 25 mg/kg bw per day and above; in addition, liver changes were observed at 44.1 mg/kg bw per day together with stress-related conditions. In these studies, toxicological effects are qualitatively comparable with those observed in short term studies on MCPA and the respective NOAELs are similar. The experts consider that both compounds should be taken into consideration for the risk assessment of MCPB, based on previous ADME considerations. It is noted that similar to MCPA, MCPB presents the dog as the lowest NOAEL for the short-term toxicity, however a more limited data package is available. **Open point:** RMS to integrate the conclusions in a revised RAR, and amend the summary table on MCPB studies. The NOAELs to be revised where necessary in vol. 3 and vol. 1.
Experts' consultation 2.5	With the information currently available no conclusion can be reached regarding the immunotoxicity potential of MCPB, and the need of dedicated immunotoxicity studies.

Subject	Conclusions Pesticide Peer Review Meeting
To discuss the potential effect on the immune system of MCPB.	Open point: RMS to collect information on the effects on endpoints relevant for the assessment of the immune system from available toxicological data set in a tabular format, noting whether these effects were observed above the MTD and/or associated with concomitant toxicological effects. RMS to conclude on the immunotoxicity potential based on the information available for both MCPA and MCPB.
Experts' consultation 2.6 To discuss the genotoxicity potential of MCPB on the basis of the available information, new study/ies and information in the bone marrow exposure study in mouse (2002).	The genotoxicity potential of MCPB is inconclusive (mainly for clastogenicity/aneugenicity). Open point: RMS to amend the RAR with regard to the suitability of the in vitro UDS test (the arguments provided in the RAR are applicable to in vivo UDS test). Open point: RMS to check if there is a justification in the in vitro mouse lymphoma study (2022) study for the lack of long-term treatment and whether the study has been conducted according to OECD TG. Limitations should be listed. Open point: RMS to integrate in a revised RAR the interpretation of studies and the conclusions as agreed in the meeting.
Experts' consultation 2.7 To discuss the long-term toxicity and carcinogenicity of MCPB in the rat and in the mouse. Please note that this assessment is mainly based on MCPA studies.	Long term toxicity and carcinogenicity studies waiving is tentatively agreed by all experts based on read across between MCPA and MCPB, pending further justification (see open point below for the RMS). Open point: RMS to further substantiate the read across from MCPA to MCPB checking other phenoxy acetic herbicides. Checking as a first step the published conclusions on the a.s. and reports from the experts' meetings, compare the critical effects, target organs, NOAELs/LOAELs, dose spacing and justify whether this corroborates the assessment of MCPB. RMS to check consistency between the 2 RARs with regards to the studies reported on MCPA and in both RARs.
Experts' consultation 2.8 Discuss the reproductive and developmental toxicity assessment of MCPB. It is noted that the assessment is mainly based on MCPA studies, based on an applicant statement (2015)	Reproductive toxicity studies waiving is tentatively agreed by all experts based on read across between MCPA and MCPB, pending further justification (see open point for the RMS). Open point: RMS to further substantiate the read across from MCPA to MCPB by checking other phenoxy acetic herbicides. Checking as a first step the published conclusions on the a.s. and reports from the experts' meetings, compare the critical effects, target organs, NOAELs/LOAELs, dose spacing and justify whether this corroborates the assessment of MCPB.

Subject	Conclusions Pesticide Peer Review Meeting
justifying for read-across from MCPA studies.	RMS to check the consistency between the 2 RARs with regards to the studies reported on MCPA and in both RARs. In the developmental toxicity study in rats, the maternal toxicity NOAEL was set at 25 mg/kg bw per day due to reduced maternal weight gain at 100 mg/kg bw per day. The foetal toxicity NOAEL was set at 25 mg/kg bw per day due to reduction in foetal weight and the higher proportion of foetuses showing delayed ossification at 100 mg/kg bw per day. MCPB did not show teratogenic effects in this study. In the developmental toxicity study in rabbits, a tentative maternal toxicity NOAEL was set at 5 mg/kg bw per day based on increased mortality, abortion and transient reduction in weight gain during gestation days 12-15 at the top dose and pending confirmation of the maternal findings related to clinical signs (hypoactivity, paresis, paralysis and ataxia), see open point below. The foetal toxicity NOAEL is 20 mg/kg bw per day (highest dose tested). Open point: RMS to prepare tabulated results on treatment-related clinical signs including hypoactivity, paresis, paralysis and ataxia, their incidence at each dose level in order to clarify the possible relationship with severe maternal toxicity (deaths) and/or conclude on specific neurotoxicity of MCPB in the main rabbit developmental toxicity study (1988). RMS to check whether there were deviations from the OECD TG and assess their impact on the study reliability (with regards to the rabbit study).
Experts' consultation 2.9 Discuss the neurotoxicity assessment of MCPB. It is noted that no studies on MCPB are available and the MCPB neurotoxicity assessment is based on MCPA studies (subchronic oral dietary toxicity and neurotoxicity study in Wistar rats (1994), and the developmental neurotoxicity study on MCPA 2EH in Wistar rats (2010)). This is	MCPA and MCPB neurotoxicity potential needs further elaboration from different studies and is currently inconclusive. Open point: RMS to check all available information on MCPB in order to conclude on the (lack of) neurotoxicity findings for this substance, e.g. identifying potential neurotoxic effects and identifying relevant deviations in available studies such as lack of FOB. To run a read across with all available information from MCPB and MCPA and other phenoxy acetic acid herbicides.

Subject	Conclusions Pesticide Peer Review Meeting
based on an applicant statement justifying for read-across from MCPA studies (2015). To confirm the relevance of the available MCPA studies to support the neurotoxicity toxicity assessment of MCPB taking into account: - in general the similarity in the toxicological profile of MCPB and MCPA needs clarification - no long term and carcinogenicity studies on MCPB have been provided - MCPB metabolism into MCPA is partially documented in ADME studies, in the rat only and with-out a plasmatic TK information	
Experts' consultation 2.10 To discuss ED assessment for MCPB, and the fact that it is in large part based on MCPA studies. Please consider also comments in the ecotox section.	T-modality Although the dataset is limited for MCPB, experts agreed to consider as part of the WoE for ED assessment the studies conducted with MCPA. Based on the WoE, a pattern of T-mediated adversity was not observed for both the substances and the dataset is considered sufficiently investigated. Considering the available data at the date of the Peer Review Meeting (TC 141, June 2024), scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for T-modality are not met. EAS-modalities The EAS modalities for MCPB are considered insufficiently investigated. Scenario 2a(iii) of the ECHA/EFSA ED Guidance, 2018 is applicable, in particular for A-modality based on the lack of a Level 3 study (Hershberger Assay). If the above study is negative then the dataset would be considered sufficient. If endocrine activity is detected in the above assay, then

Subject	Conclusions Pesticide Peer Review Meeting
	further data will be needed to support a MoA analysis and an extended one-generation reproduction study (EOGRT) with inclusion of the cohort 1a and 1b, including the mating of cohort 1b to produce the F2 generation (OECD TG 443, Level 5) should be conducted. **Open points:** **The RMS is kindly asked to revise the RAR Vol.1 and Vol. 3B6 in line with the discussion at the PRM TC 141.**
Experts' consultation 2.11 **To discuss the assessment of MCPB metabolites considering:** - **ADME of MCPB (see point 2(8)), in particular on metabolism of MCPB in MCPA in mammals.** - **Toxicological assessment on MCPA (see ongoing peer review on MCPA)**	**Metabolites:** **MCPA: covered by the respective assessment** **HMCPA: No conclusion can be drawn on the genotoxicity and general toxicity of the metabolite.** **MCPA methyl ester and MCPB methyl ester: no conclusion can be drawn on these two metabolites regarding genotoxicity and general toxicity due to lack of data.** **Open point: RMS to check if the applicant provided an answer to the data requirement set by EFSA on the metabolites MCPA methyl ester and MCPB methyl ester.**
Experts' consultation 2.12 **To discuss toxicological endpoints for the risk assessment of MCPB.**	**Since a number of toxicological parameters are still open, in particular the genotoxicity potential of MCPA and MCPB that is inconclusive, no toxicological reference values can be derived based on the available data.** **Tentative toxicological reference values were discussed.** **Open point: RMS to check the basis for the ARfD set by the previous peer review (2008).**
Experts' consultation 2.13 **To discuss dermal absorption of the PPP.**	**Dermal absorption values to be checked according to the revision requested to the RMS (see open point).** **Open point: RMS to provide the BfR template recommended for the assessment of the dermal absorption according to the EFSA GD 2017 (for the 2018/2019 in vitro dermal absorption study with human skin with CA 3115) and not excluding any outliers from the study.**

Subject	Conclusions Pesticide Peer Review Meeting
Expert consultation 2.14 **To discuss NDE.**	**Non-dietary exposure needs to be revised according to the open point below:** **Open point** **RMS to provide revised non-dietary exposure estimates with the agreed endpoints, ensuring harmonised update of Vol.1, Vol.3 CP B.6 (with appropriate screenshots of the EFSA calculator 2015/2022 in Appendix) and LoEP.** **RMS to present a revised assessment of the DFR study, including deviations/limitations with regards to weather conditions and maximum DFR values on post application day for both regions, Washington and North Dakota area, the highest value should be used for the risk assessment.**
Expert consultation 2.15 **Additional experts consultation point for completeness:** **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.** **MCPB Na 400**	**With regards to MCPB Na 400 co-formulants, sufficient toxicological data are available for most components, but one.** **An open point was set for the RMS to gather additional information on this compound.**

REPORT OF PESTICIDES PEER REVIEW

TC 141 and TC 142

LYSATE OF *WILLAERTIA MAGNA* C2C MAKY - NAS **Rapporteur Member State: AT**

2. Mammalian toxicity

Date: 3 July 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	The National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS IE	Department of Agriculture food and the Marine Ireland - IE
National Expert nominated by MS NL	Ctgb - NL
National Expert nominated by MS PL	E-V-A Sp. z o.o. - PL
National Expert nominated by MS SK	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK
Observers	PRCD, Department of Agriculture, Food and the Marine - IE

MEETING MINUTES – 3 July 2024
Pesticides Peer Review TC 141 and TC 142
Lysate of *Willaertia magna* C2c Maky

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the genotoxicity potential, including the waiving proposal, in an experts' meeting.**	**There is no concern regarding genotoxicity of Lysate of *Willaertia magna* C2c Maky. The waiver proposal for the conduction of additional genotoxicity studies was accepted.**
Experts' consultation 2.2 **Waiver for the assessment of the endocrine disruption (ED) potential will be discussed/confirmed during an expert meeting.**	**Based on the lysate of *Willaertia magna* C2c Maky composition (cell fragments consisting of different proteins, lipids and carbohydrates, nucleic acids, water and mineral salts) and available data from 90-day and prenatal developmental rat studies, all the experts agreed to waive further testing to support the ED assessment.** **Open point:** **RMS is kindly requested to include in a revised version of the DAR the available information on the historical control data (HCD) on TSH measurements in the control rats of prenatal developmental studies.** **Namely, study CA 5.6.2/02 should include the animal species, laboratory, and the route of administration for the animals for which the data were collected in the study.**
Experts' consultation 2.3	**The waiver proposals for the conduction of toxicological studies (90-day study in non-rodent species, and developmental toxicity study in second species) were accepted.**

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss/confirm in an experts' meeting: - **the waiver proposals for the conduction of toxicological studies,** - **the quantitative exposure assessment,** - **the risk assessment.**	**A semi-quantitative exposure and risk assessment using a dermal absorption value for dilution of 10% and a surrogate AOEL of 10 mg/kg bw per day indicates no concerns of Lysate of *Willaertia magna* C2c Maky for operators, bystanders and residents, and workers.** **Open point:** **RMS to update the semi-quantitative exposure and risk assessment using a dermal absorption value of 10% for dilution, and to add justification why performance of a (semi-) quantitative exposure and risk assessment was considered adequate.**
Experts' consultation 2.4 **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative use(s) 'AXP10' with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.**	**For the formulation for representative uses 'AXP10' wettable powder an assessment of co-formulants does not need to be performed.**

REPORT OF PESTICIDES PEER REVIEW

TC 141 And TC 142

MALTODEXTRIN - AIR V **Rapporteur Member State: IE**

2. Mammalian toxicity

Date: 3 July 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS IE	Department of Agriculture food and the Marine Ireland - IE
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety - AT
National Expert nominated by MS CZ	The National Institute of Public Health - CZ
National Expert nominated by MS DE	German Environment Agency (UBA)
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency - DK
National Experts nominated by MS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL
National Experts nominated by MS PL	EVA - PL
National Expert nominated by MS SK	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK

Status	Name of institution / attendee
Observers	PRCD, Department of Agriculture, Food and the Marine - IE

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the ED assessment of maltodextrin.**	**Based on the carbohydrate composition of maltodextrin and being of confirmed food-grade quality, all the experts agreed to waive further testing for the ED assessment.** **The following open points were agreed:** **The RMS is kindly requested to revise the RAR Vol.1, 2.10 Endocrine Disrupting Properties, to:** • **Include reference to the estimated levels of dietary exposure to maltodextrin, based on the report No 1905806, included in Chapter 6.** • **Include that ToxCast AR- and ER- pathway prediction models are not available, but there is *in silico* information provided by the CERAPP and COMPARA prediction models being negative. Also, to include the date when the search was done.** • **remove the scenario from the ED evaluation as no ED assessment was done.** **For the entire RAR:** **Since *Maltodextrins are considered as food ingredients and are excluded from the scope of European food additive legislation (Regulation (EC) No. 1333/2008), as are all starches treated with amylolytic enzymes* – the RMS is kindly requested to include a comment with this update, whenever maltodextrin is indicated to be a food additive.**
Experts' consultation 2.2 **Experts to discuss the risk assessment approach provided by the RMS.**	**A quantitative exposure and risk assessment for operators, workers and bystanders/residents is considered not necessary for the proposed application of the product.** **This conclusion was based on the nature of maltodextrin (carbohydrate), its rapid metabolisation into standard energy source (glucose), its common use as food ingredient, in cosmetics and in**

Subject	Conclusions Pesticide Peer Review Meeting
	medicinal products, and the absence of toxicological reference values. Open point: RMS to include the maltodextrin semi-quantitative exposure and risk assessment in Vol. 3CP B6 (PPP).
Experts' consultation 2.3 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, repeated dose toxicity and genotoxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Due to the absence of insight into the availability of mammalian toxicity data (including genotoxicity, short-term and long-term toxicity) on the co-formulant(s) in the formulation supported for the representative uses (Eradicoat), it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation. Open point: RMS to provide more information (if available) on the co-formulant(s) in Eradicoat, including mammalian toxicity data to assess genotoxicity, short-term toxicity and long-term toxicity, and to revise RAR Vol. 4 accordingly.

REPORT OF PESTICIDES PEER REVIEW TC 136

CLOMAZONE – AIR III after ED clock stop **Rapporteur Member State: DK**

2. Mammalian toxicity

Date: 22 May 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS DK	Danish Environmental Protection Agency - DK
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety - AT
National Experts nominated by MS CZ	National Institute of Public Health - CZ
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	Federal Environmental Agency (UBA) - DE
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS HU	National Food Chain Safety Office - HU
National Experts nominated by MS IT	ASST FBF Sacco - International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS NL	Ctgb -NL
National Expert nominated by MS PL	E-V-A Sp. z o.o. - PL
Observer	Swiss Federal Office for the Environment - CH
Observer	Ctgb -NL

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[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.12 **Experts to discuss the ED properties of the active substances in a Peer Review Meeting in line with the scientific criteria for the determination of ED properties laid down in Commission Regulation (EU) No 2018/605 and according to the ECHA/EFSA guidance, for EATS modalities for the active substance.** **The discussion should include not only the outcome of the studies used for the assessment of the EATS modalities but also the reliability of the studies, compliance to the test guideline used and deviations, if any, dose selection and any additional consideration necessary to conclude on the ED properties of the substance. Uncertainty analysis should be also included as relevant**	***T-modality*** **A pattern of T-mediated adversity was not observed in a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for T-modality are not met.** ***EAS-modalities*** **EAS-modalities were sufficiently investigated; no EAS-mediated adversity was observed in a complete dataset of studies.** **The endocrine acitivity was sufficiently investigated and the available studies (ToxCast ER prediction model, OECD TG 456, 458, 441 and aromatase assay).** **Clomazone has shown to be weak inhibitor of testosterone production (in the steroidogenesis assay, OECD TG 456) and of aromatese activity (in the Aromatase in vitro assay, OPPTS 890.1200).** **Overall, Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for EAS-modalities are not met.**

Subject	Conclusions Pesticides Peer Review Meeting
element of the WoE analysis.	
Experts' consultation 2.13 The NOAELs proposed by the RMS on the newly conducted 2 generation study should be discussed during the expert consultation and pending agreement on these, the impact on reference value should be discussed and agreed	In the new 2-generation reproductive toxicity study in rats, the parental toxicity NOAEL is 1000 ppm based on urinary tract findings (renal pelvis dilation associated with higher incidence of renal calculi, and kidney, urinary bladder and ureter inflammation) and liver changes (increased liver weight and hypertrophy) at 3500 ppm. The reproductive and offspring toxicity NOAEL are the highest dose tested of 3500 ppm. The outcome of the study does not have an impact on the TRVs. Open point for the RMS to clarify the conversion from ppm to mg/kg bw per day in a revised RAR.
New experts' consultation point 2.14 proposed by EFSA for completeness of discussion MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the FMC-Clomazone 360 CS formulation, sufficient toxicological data is available for the majority of the components in the formulation. For some co-formulants, the experts considered that the available toxicological information does not sufficiently address the genotoxicity and short/long term toxicity. With regards to another component of potential concern, its conclusion is pending on the ongoing REACH assessment. Open point for the RMS to include toxicological information from the biocide dossier on a component of a co-formulant. With regards to ALB 36 CL (Clomate) formulation, sufficient toxicological data is available for the majority of the components in the fomulation. For some co-formulants, the experts considered that the available toxicological information does not sufficiently address the genotoxicity and short/long term toxicity.

REPORT OF PESTICIDES PEER REVIEW TC 136

DIMETHACHLOR – AIR IV **Rapporteur Member State: HR**

2. Mammalian toxicity

Date: 22 May 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS HR	Croatian Agency for Agriculture and Food - HR
National Expert nominated by RMS HR	Institute for Medical Research and Occupational Health - HR
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS CZ	National Institute of Public Health - CZ
National Expert nominated by MS DE	Federal Environmental Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS HU	National Food Chain Safety Office (NEBIH) - HU
National Experts nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS NL	Ctgb – NL
Observer	Swiss Federal Office for the Environment - CH
Observers	Croatian Agency for Agriculture and Food, Center for Plant Protection - HR
Observer	Ctgb - NL

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the reliability, acceptability, and completeness of available comparative *in vitro* metabolism studies on dimethachlor.	Based on the available comparative metabolism studies, no unique or disproportionate human metabolites are formed as compared to other tested species. Mechanistic information on the observed toxicity showed limitations and uncertainties. It is noted that these studies have been considered by ECHA RAC, that has concluded that dimethachlor is carcinogenic category 2. Open point: RMS to clarify the LOQs values and if the concentrations of metabolites were above the LOQs.
Experts' consultation 2.2 Experts to discuss the NOAEL in the 28-day rat studies (feeding and gavage; KCA 5.3.1 / 01 and KCA 5.3.1 / 02).	In the rat 28-day feeding study the NOAEL was confirmed at 700 ppm (67 and 68 mg/kg bw per day, males and females respectively) with LOAEL at 3000 ppm (hepatic toxicity (increased liver weight, histopathology hepatocellular hypertrophy and accompanying clinical chemistry changes); hematological changes were also seen at the top dose. In the rat 28-day oral (gavage) study the NOAEL was confirmed at 150 mg/kg bw per day, with LOAEL at 350 mg/kg bw/day (↓ BW gain and food consumption; ↓ red blood cell parameters; liver toxicity - ↑ liver wt, liver enzyme activity, hepatocellular hypertrophy, and glycogen accumulation; and mortality at 750 mg/kg bw/day).
Experts' consultation 2.3 Experts to discuss the NOAEL in the 90-day mouse study (KCA 5.3.2/02).	The NOAEL of the 90-day mouse dietary study was set at 100 ppm (corresponding to 17.5 and 18.5 mg/kg bw per day in males and females respectively), with LOAEL at 1000 ppm due to liver toxicity (increased weight and hepatocellular hypertrophy) and increased kidney weight in males. At 7000 ppm renal tubular injury was also noted.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.4 Experts to discuss the NOAEL in the 1-year 90-day dog study (KCA 5.3.2/03, 1974).	The 90-day dog dietary study KCA 5.3.2/03, 1974 is considered supplementary due to various limitations. The study NOAEL is set at 350 ppm (corresponding to 10.1 and 10.4 mg/kg bw/day in males and females, respectively), with LOAEL at 1250 ppm due to liver toxicity (increased absolute and relative weights in females, increased alkaline phosphatase, and histopathological changes in both sexes).
Experts' consultation 2.5 Experts to discuss the NOAEL in the 90-day dog study (KCA 5.3.2 / 04.)	The NOAEL of the 90-day dog study (KCA 5.3.2 / 04.) was set at 300 ppm (corresponding to 9.96 and 10.81 mg/kg bw per day in males and females respectively), with LOAEL at 1000 ppm due to liver toxicity (increased relative to body liver weight, centrilobular hepatocellular hypertrophy and increased incidence of hepatocellular cytoplasmic vacuolisation).
Experts' consultation 2.6 Experts to discuss the appropriateness of the genotoxicity test battery on dimethachlor by considering: 1. Metabolic pathway: whether the metabolism leading to free aniline (contributing to the formation of quinone-imines) can be excluded. 2. Results *in vitro* with and without S9: is an *in vivo* Comet assay triggered? Study design of the *available in vivo* MN tests (suitability of the maximum dose, number of doses).	Dimethachlor is unlikely to be genotoxic *in vivo*, however limitations in the available dataset include: Lack of investigation of the nature of the micronucleus (MN) in the positive *in vitro* MN test. Lack of investigation of genotoxicity at the first site of contact (e.g. duodenum). Lack of investigation of genotoxicity at the target organs for toxicity/carcinogenicity.
Experts' consultation 2.7 Experts to discuss whether bone marrow has been	Dimethachlor is unlikely to be genotoxic *in vivo*, based on the available *in vivo* micronuclues studies in the mouse.

Subject	Conclusions Pesticide Peer Review Meeting
sufficiently exposed in available *in vivo* micronucleus test.	
Experts' consultation 2.8 Experts to discuss the NOAEL for long-term toxicity in the 18-month mouse study.	Based on a detailed analysis of individual histopathological data, the NOAEL for systemic toxicity is set at 300 ppm (32.3 mg/kg bw per day for males and 31.2 mg/kg bw per day for females), with a LOAEL at 4000 ppm (488 mg/kg bw per day for males and 451 mg/kg bw per day for females) driven by exacerbation of chronic progressive nephropathy, lower body weight and food utilisation and liver effects . The NOAEL for carcinogenicity at 4000 ppm (488 mg/kg bw per day for males and 451 mg/kg bw per day for females), the highest dose tested due to the lack of treatment related tumours.
Experts' consultation 2.9 Experts to discuss the NOAEL for carcinogenicity in rats (whereas classification and labelling is under consideration in the ECHA RAC process).	Both chronic and carcinogenic NOAELs are set at 300 ppm (11.1 and 12.9 mg/kg bw per day in males and females respectively) due to liver toxicity and nasopharyngeal adenomas and kidney lipomas at 4000ppm (157 and 183 mg/kg bw per day for males and females respectively).
Experts' consultation 2.10 Experts to discuss the developmental NOAEL in rats (KCA 5.6.2 / 02).	The maternal NOAEL is set at 50 mg/kg bw per day, with the LOAEL at 350 mg/kg bw per day (based on ↓ net bw change and ↓ food intake during gestation). The developmental NOAEL is set at 50 mg/kg bw per day with LOAEL at 350 mg/kg bw per day (↑ number of skeletal anomalies and variations poorly or non-ossified bones, in foetuses)
Experts' consultation 2.11 Experts to discuss endocrine disruption criteria following ED ECHA/EFSA Guidance (2018) and considering new studies conducted by the applicant.	EAS-modalities According to the ECHA/EFSA ED guidance, a positive result in the level 2 or 3 assays would trigger the conduction of a MoA analysis (scenario 2a(i) of the ECHA/EFSA ED Guidance) and as all ‚EAS-mediated' parameters have not been investigated, additional information e.g. from level 3, 4 or 5 studies may need to be generated. In the case of dimethachlor, ERTA Assay (OECD TG 455) is showing positive results for the ER antagonistic activity. Therefore, an extended one-generation with inclusion and mating of cohort 1B (OECD TG 443, Level 5) is requested. T-modality

Subject	Conclusions Pesticide Peer Review Meeting
	A pattern of T-mediated adversity was not observed in a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for T-modality are not met. **Open points** - **The RMS is asked to include in a revised RAR an assessment of OECD TG 456 in line with the latest update of the OECD TG 456 (July 2023).** - **For the ERTA and Steroidogenesis assays: the stability of the test item in solvent is missing. For the aromatase inhibition assay and ARTA assay the stability of the test item itself and of the test item in solvent is missing. The RMS is asked to include this information in a revised RAR.** - **The RMS is asked to include in a revised RAR which information is available in the US EPA Comptox Chemical Dashboard. For instance, ToxCast AR or ER models for the substance under assessment are not available; however, in silico models are available i.e. COMPARA (Consensus) (predictivity score = 1 for antagonist) and CERAPP Potency Level (Consensus) [*Comptox Chemical Dashboard accessed by EFSA in May 2024*].** - **It is suggested to provide in Vol. 1 an ED assessment in line with EFSA 's administrative guidance (EFSA, 2019[3]) - Appendix I; whereas, the assessment of the Level 2 studies has to be reported in Vol. 3 CA B.6.** - **The RMS is asked to check that an updated version of the Appendix E is submitted by the applicant during the ED stop-of-the-clock.**
Experts' consultation 2.12 **Experts to discuss the toxicological profile of metabolites found as residues in crops and/or livestock and/or found as a groundwater occurring at higher concentrations than 1µg/L.**	**CGA42443: unlikely to be genotoxic based on experimental data; ADI of 0.024 mg/kg bw per day.** **CGA39981: not discussed, nor a residue or groundwater metabolite.** **CGA354742: unlikely to be genotoxic based on experimental data; ADI of 0.0696 mg/kg bw per day.**

[3] European Food Safety Authority 2019. Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances, EFSA supporting publication 2019: 16(4): EN-1612. 49 pp. doi: 10.2903/sp.efsa.2019.EN-1612.

Subject	Conclusions Pesticide Peer Review Meeting
The discussion should also consider: a) Experts to discuss the NOAEL in the 28-day rat study with CGA42443. b) Experts to discuss the NOAEL in the 28-day rat study with CGA 373464.	**CGA48090: unlikely to be genotoxic based on experimental data; general toxicity inconclusive since proposed read-across not accepted.** **CGA48086: unlikely to be genotoxic based on acceptable read across to CGA354742 and CGA48090. General toxicity not discussed.** **SYN550004: unlikely to be genotoxic based on acceptable read across to CGA354742 and CGA48090. General toxicity not discussed.** **Open point: for SYN550004, RMS to add in a revised RAR the additional information on read across as provided by the applicant and presented during the meeting.** **SYN547047: unlikely to be genotoxic based on experimental data; general toxicity inconclusive since proposed read-across is not properly substantiated.** **CGA102935: unlikely to be genotoxic based on experimental data; Based on expert's judgment, the read across vs CGA50266 seems acceptable, however as a groundwater metabolite the available information is considered not sufficient to address its relevance.** **CGA50266: unlikely to be genotoxic based on experimental data; ADI of 0.4 mg/kg bw per day.** **SYN551032: unlikely to be genotoxic based on experimental data; general toxicity apparently not assessed, addressed by the applicant.** **Open point: the RMS to check whether admissible QSAR/read across information is available for SYN551032.** **CGA 373464: unlikely to be genotoxic based on experimental data; ADI of 0.48 mg/kg bw per day.**

Subject	Conclusions Pesticide Peer Review Meeting
	SYN 530561: unlikely to be genotoxic based on experimental data; general toxicity inconclusive since proposed read-across is not properly substantiated. **Some of the metabolites discussed above they might be also or only groundwater metabolites (PEC calculations will be under discussion by fate and behaviour experts). The experts agreed that since the parent compound has been classified as carcinogenic, all GW metabolites are considered relevant unless demonstrated they do not share the carcinogenic potential of the parent (data are missing to address this point for any of the potential groundwater metabolites); therefore, next steps in the guidance (e.g. derivation of reference values are not applicable).**
Experts' consultation 2.13 **Experts to discuss setting of health-based guidance values ADI, AOEL, ARfD and AAOEL**	**ADI: 0.1 mg/kg bw per day** **Based on the NOAEL of 11.1 mg/kg bw per day from 2-year chronic toxicity/carcinogenicity study in rats based on the LOAEL of 157 mg/kg bw per day in males: liver toxicity and nasopharyngeal adenomas** **Supported by the 90 day dog study: NOAEL of 300 ppm (9.96 and 10.81 mg/kg bw per day in M and F), based on LOAEL of 1000 ppm (32.3 and 36.0 mg/kg bw per day in M and F): increased relative liver wt, centrilobular hepatocellular hypertrophy, hepatocellular cytoplasmic vacuolisation** **Uncertainty factor of 100 (interspecies and intraspecies variations) applied** **A second long term mouse study was discussed; the dose spacing in this study is not suitable, and the 2-year rat study is more adequate to set the ADI.** **ARfD: 0.5 mg/kg bw** **Based on the NOAEL of 50 mg/kg bw per day from rat developmental toxicity, based on the LOAEL of 350 mg/kg bw per day: decreased body weight gain and food consumption** **Uncertainty factor of 100 (interspecies and intraspecies variations) applied.** **AOEL: 0.1 mg/kg bw per day** **Based on the NOAELs of 10 mg/kg bw per day from the two 90-day dog studies - liver was the main target organ, with an uncertainty factor of 100 (interspecies and intraspecies variations) applied.** **Systemic absorption of dimethachlor after oral administration was determined to be ≥94%, not requiring adjustment for absorption.** **AAOEL: 0.5 mg/kg bw**

Subject	Conclusions Pesticide Peer Review Meeting
	Based on the NOAEL of 50 mg/kg bw per day from rat developmental toxicity, based on the LOAEL of 350 mg/kg bw per day: decreased body weight gain and food consumption **Systemic absorption of dimethachlor after oral administration was determined to be ≥94%, not requiring adjustment for absorption.**
Experts' consultation 2.14 **Experts to confirm dermal absorption values of dimethachlor in the formulation for representative uses, i.e. A5089H.**	**Given the major limitations of available dermal absorption studies the MS experts agreed that the default values for an EC formulation (25% and 70%) should be applicable to A5089H.**
Experts' consultation 2.15 **Experts to discuss non-dietary exposure estimates, in particular:** **1) New DFR study** **2) Refined TC for residents and bystanders.**	**Based on the available DFR study, derivation of specific values of transfer coefficients for residents and bystanders (adults and children) were agreed, taking into account the uneven distribution of contamination on the different body parts of workers, and an appropriate correction for the light clothing in bystanders and residents (instead of workwear in workers).** **The resulting TC values are:** **601 cm²/h for workers** **977 cm²/h for adult residents** **2432 cm²/h for adult bystanders** **262 cm²/h for child residents** **620 cm²/h for child bystanders.** **Open point:** **RMS is kindly requested to provide the revised non-dietary exposure estimates with the agreed endpoints and parameters.**
Experts' consultation 2.1 (Confidential) **Experts to discuss the human safety of the formulation for the representative uses.**	**The RMS presented for all co-formulants an overview of available information reported in the MSDS, in ECHA database/REACH, and on assessment from other regulatory bodies (EU and international). However conclusions on the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures, were not presented; no further discusion took place during the experts' meeting.**

Subject	Conclusions Pesticide Peer Review Meeting
	Open point (applicable to all coformulants in the representative formulations): **RMS to complete the assessment of the toxicological profile of the co-formulants and report it in the revised RAR (Vol. 4) to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures.** **The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion, and referred to the safety of the co-formulant per se as well as in relation to the concentrations in the PPPs.** **A disclaimer should be included for all evaluations, indicating the limitations of the database as to the reliance of the existing evaluations.**
Additional experts' consultation 2.2 (Confidential) identified by the RMS **Experts to discuss the relevance of an impurity.**	**Not discussed during the experts meeting, this point will be under written procedure on additional information (see data requirement).**

REPORT OF PESTICIDES PEER REVIEW TC 136

SPINOSAD – AIR III, re-assessment of ED following mandate SANTE after ED clock stop

Rapporteur Member State: NL

2. Mammalian toxicity

Date: 22 May 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies	ECHA
National Experts nominated by RMS NL	Ctgb - NL
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS CZ	National Institute of Public Health - CZ
National Expert nominated by MS DE	Federal Environmental Agency (UBA) - DE
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS DK	Danish Environmental Protection Agency - DK
National Experts nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Expert nominated by MS HR	Croatian Agency for Agriculture and Food - HR
National Expert nominated by MS HR	Institute for Medical Research and Occupational Health - HR
National Expert nominated by MS HU	National Food Chain Safety Office - HU
National Experts nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
Observer	Swiss Federal Office for the Environment - CH
Observers	Croatian Agency for Agriculture and Food - HR
Observer	Ctgb - NL

MEETING MINUTES – 22 May 2024
Pesticides Peer Review TC 136
Spinosad

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.6 **The ED potential of spinosad after the submission of the new evidence should be discussed in an experts' meeting.** **For the EAS modalities the discussion should also cover:** - **WoE analysis for EAS-mediated adversity.** - **The outcome of the level 2 and 3 studies including the experimental design and the interpretation of the results for the steroidogenesis assay (see also points No. 3, 6, 25, 29) and the reliability of the ERTA (see also point No. 24).**	**T-modality** **A pattern of T-mediated adversity was not observed in a sufficiently investigated dataset. Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018[3]) is applicable and the ED criteria for T-modality are not met.** **EAS-modalities** **EAS-modalities were not sufficiently investigated; however, no EAS-mediated adversity was observed in the available dataset of studies.** **The endocrine acitivity was sufficiently investigated (OECD TG 455, 456, 458, 440, 441 and aromatase assay were available) and no EAS-mediated endocrine activity was observed. Scenario 2a(ii) of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for EAS-modalities are not met.** **Although dystocia is a "sensitive to, but not diagnostic of EAS" parameter, the MoA analysis provided by the applicant is valuable and considered as part of the Weight of Evidence (WoE) to assess the endocrine potential of spinosad. The MoA analysed is supporting the lack of an endocrine related activity and the MoA is non-ED related. Some uncertainties were identified concerning the human relevance of the MoA, since this cannot be excluded based on the available data.**

[3] ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Andersson N, Arena M, Auteri D, Barmaz S, Grignard E, Kienzler A, Lepper P, Lostia AM, Munn S, Parra Morte JM, Pellizzato F, Tarazona J, Terron A and Van der Linden S, 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. *EFSA Journal* 2018;16(6):5311, 135 pp. https://doi.org/10.2903/j.efsa.2018.5311. ECHA-18-G-01-EN.

Subject	Conclusions Pesticides Peer Review Meeting
- WoE analysis for EAS-mediated activity. - Mode of Action (MoA) (and alternative MoAs) analysis and the possible interaction with the endocrine pathway.	**Open points:** - the RMS is asked to check if T-mediated assays are available in the Comptox Chemical Dashboard for the substance Spinosad: CAS #168316-95-8, Spinosyn A: CAS# 131929-60-7 and Spinosyn D: CAS# 131929-63-0 and to include the results in the revised RAR. If no assay is available, the RMS is asked to mention this in the revised RAR. - The RMS is asked to update the RAR according to the discussion at the peer review experts' meeting. **Open point for EFSA** - EFSA to check with OECD the interpretation of the OECD TG 456.
Experts' consultation 2.7 The outcome of the newly submitted studies (e.g., comparative *in vitro* metabolism studies) and their potential implications on the toxicological endpoints and human health risk assessment should be discussed in an experts' meeting.	**Data gap:** An *in vitro* interspecies comparative metabolism study compliant with the recommendations in EFSA PPR Panel, 2021[4] is needed to conclude on the presence of unique human metabolites or disproportionate human metabolites upon spinosad administration.

[4] EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), Hernandez-Jerez AF, Adriaanse P, Aldrich A, Berny P, Coja T, Duquesne S, Focks A, Marinovich M, Millet M, Pelkonen O, Pieper S, Tiktak A, Top ping CJ, Widenfalk A, Wilks M, Wolterink G, Gundert-Remy U, Louisse J, Rudaz S, Testai E, Lostia A, Dorne J-L and Parra Morte JM, 2021. Scientific Opinion of the Scientific Panel on Plant Protection Products and their Residues (PPR Panel) on testing and interpretation of comparative *in vitro* metabolism studies. *EFSA Journal* 2021; 19(12):6970, 61 pp. https://doi.org/10.2903/j.efsa.2021.6970

REPORT OF PESTICIDES PEER REVIEW TC 136

HALOSULFURON-METHYL – AIR V **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 22 May 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS DE	Federal Environmental Agency (UBA) - DE
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National Expert nominated by MS HR	Croatian Agency for Agriculture and Food - HR
National Expert nominated by MS HR	Institute for Medical Research and Occupational Health - HR
National Experts nominated by MS NL	Ctgb - NL
National Experts nominated by MS PL	National Institute of Public Health - PL
Observer	Swiss Federal Office for the Environment - CH
Observers	Croatian Agency for Agriculture and Food - HR
Observer	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
Observer	Ctgb - NL

MEETING MINUTES – 22 May 2024
Pesticides Peer Review TC 136
Halosulfuron-methyl

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.1 **Experts to discuss *in vitro* comparative metabolism study on halosulfuron-methyl.**	**Based on the available comparative *in vitro* metabolism study with rat and human hepatocytes, there is no indication of the formation of unique or disproportionate human metabolites.** **Open point** **RMS to update the presentation of the comparative *in vitro* metabolism study in the RAR, highlighting its limitations by making a side-to-side comparison with the 2021 PPR scientific opinion recommendations.**
Expert consultation 2.2 **Experts to discuss the dog studies, including the haematological findings (90-day and 1-year), the HCD regarding pituitary cysts (1-year), body weight effects (1-year), and the NOAEL settings.**	**The NOAEL of the 90-day dog study is 10 mg/kg bw per day, based on reduced body weight gain in females and haematological changes in males.** **The NOAEL of the 1-year dog study is 10 mg/kg bw per day, based on reduced body weight gain and haematological changes in males and females.** **Open point** **RMS to update the RAR in relation to the critical effects underlying the NOAEL setting of the 90-day dog study.**
Expert consultation 2.3 **Experts to discuss the genotoxicity of halosulfuron-methyl, considering the new**	**Overall, the data package does not provide any indication of genotoxicity for halosulfuron-methyl, being in line with the ECHA RAC opinion.** **However, the genotoxicity data package is limited and the requested *in vitro* micronucleus test was not provided. A firm**

Subject	Conclusions Pesticides Peer Review Meeting
genotoxicity data to be provided by the applicant (*in vitro* MN test and if positive, adequate *in vivo* follow-up study), and the weight-of-evidence analysis to support bone marrow exposure for the available *in vivo* MN test.	conclusion on the clastogenicity and aneugenicity of halosulfuron-methyl remains open. **Open point** RMS to update the assessment of the mouse *in vivo* micronucleus test in line with the expert meeting discussion and update accordingly the conclusions of the overall assessment of the genotoxicity potential of halosulfuron-methyl.
Expert consultation 2.4 Experts to discuss the long term toxicity and carcinogenicity studies in rats and mice and the related NOAEL settings. Regarding the rat study, to consider the new data to be submitted by the applicant on the prostate, seminal vesicles, and testis with epididymis, as well as the HCD for atrophy of the seminal vesicles. Regarding the mouse study, to consider the new data to be submitted by the applicant regarding body weight, body weight gain and organ weights changes (including testis with epididymis organ weights), and, if available, HCD for microconcretions/ mineralisation in testis tubules.	In the rat, the NOAEL for chronic toxicity is 2500 ppm in males (corresponding to 108.3 mg/kg bw per day) and 1000 ppm in females (corresponding to 56.3 mg/kg bw per day), based on decreased BW and BWG. The NOAEL for carcinogenicity is the top dose, i.e. 5000 ppm in males (corresponding to 225.2 mg/kg bw per day) and 2500 ppm in females (corresponding to 138.6 mg/kg bw per day). In the mouse, the systemic NOAEL is the top dose of 7000 ppm for both sexes (corresponding to 972 and 1215 mg/kg bw per day in males and females, respectively). The carcinogenicity NOAEL is also 7000 ppm (corresponding to 972 and 1215 mg/kg bw per day in males and females, respectively) in the absence of any tumour up to and including the top dose.
Expert consultation 2.5 Experts to discuss the developmental toxicity studies in rat and rabbit. For what concern the rat study, experts to discuss findings related to foetal growth retardation, dilatation of lateral brain vesicles (considering also HCD if available), incidence	The rat maternal NOAEL is 250 mg/kg bw per day based on decrease in BW and BWG, alopecia and yellow stained fur. The rat developmental NOAEL is also 250 mg/kg bw per day based on reductions in foetal body weight, increased early resorptions and post implantation losses, increased rat external, skeletal and visceral malformations and skeletal variations. **Open point** RMS to include the finding of forked/fused ribs in the rat developmental toxicity study in the RAR and to update the basis for NOAEL setting as agreed by the experts.

Subject	Conclusions Pesticides Peer Review Meeting
of renal pelvic cavitation, and skeletal findings. For what concern the rabbit study, expert to discuss findings related to malformations in the form of forked/fused ribs. Finally, experts to discuss related setting of the NOAEL for developmental toxicity.	The rabbit maternal NOAEL is 50 mg/kg bw per day based on BWG decrease. The rabbit developmental NOAEL is 50 mg/kg bw per day based on early resorption, increased post-implantation loss, decreased foetal viability and increased incidence in forked/fused ribs. Open point RMS to include the finding of forked/fused ribs in the rabbit developmental toxicity study in the RAR and to update the basis for NOAEL setting as agreed by the experts.
Expert consultation 2.6 Experts to discuss the acute and subchronic neurotoxicity studies in rats and, in particular, FOB assessment and histopathological findings in the central and peripheral nervous system.	The acute neurotoxicity NOAEL is 600 mg/kg bw based on changes in the aerial righting reflex. The acute systemic NOAEL is 600 mg/kg bw based on mortality and decreased BWG. The subchronic NOAEL for systemic toxicity is 1000 ppm in males and 4000 ppm in females (corresponding to 62.8 and 315.9 mg/kg bw per day in males and females, respectively), based on statistically significant increased relative liver weight, liver histopathological findings and BW effects in males. The NOAEL for subchronic neurotoxicity is 10000 ppm in males and 4000 ppm in females (corresponding to 706 and 315.9 mg/kg bw per day, in males and females respectively, both top doses).
Expert consultation 2.7 Experts to discuss the ED properties of halosulfuron-methyl.	***For T-modality:*** Scenario 1a of the ECHA/EFSA ED Guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for T-modality are not met. ***For EAS-modalities:*** The following additional information was requested during the commenting phase to be able to conclude whether the approval criteria for endocrine disruption are met: • A study in line with OECD TG 455 (Stably Transfected Human Oestrogen Receptor-alpha Transcriptional Activation Assay (ER STTA assay)); • A study in line with OECD TG 440 (Uterotrophic assay) in case OECD TG 455 is negative; • A study in line with OECD TG 456 (H295R Steroidogenesis Assay); • A study in line with OPPTS 890.1200 (Aromatase assay); • A study in line with OECD TG 458 (Stably Transfected Human Androgen Receptor Activation Assay (AR STTA assay));

Subject	Conclusions Pesticides Peer Review Meeting
	• A study in line with OECD TG 441 (Hershberger Assay) in case OECD TG 456 and 458 and OPPTS 890.1200 are negative; In case of positive result/s for at least one modality, additional testing would be needed: OECD TG 443 (with the inclusion of cohort 1B) or OECD TG 416 (according to the latest version from 2001). However, no further data was submitted by the applicant. It is noted that the 2nd ED clock stop under Commission Implementing Regulation (EU) No 2018/1659 is not applicable for halosulfuron-methyl and the data requirement was not fulfilled for the ED assessment. Therefore, for the EAS-modalities the ED assessment is inconclusive (data gap and issue not finalized for the determination of endocrine disrupting properties -Commission Regulation (EU) 2018/605- according to the EFSA/ECHA Guidance for the identification of endocrine disruptors). All experts agreed.
Expert consultation 2.8 Experts to discuss toxicological profiles of halosulfuron-methyl metabolites.	Metabolite chlorosulfonamide acid (CSA; MON 5783), 3-chlorosulphonamide acid: The assessment of genotoxicity of the metabolite remains open. Although the metabolite does not share the developmental toxicity profile of the parent, no conclusion can be reached on the general toxicity of the metabolite given that the genotoxicity is not clarified. Open point RMS to clarify in the RAR the conclusion reached on the gene mutation assay in mammalian cells (CA 5.8.1/05). Also, to change the assessment of the *in vivo* mouse micronucleus test from not acceptable to supportive. Metabolite halosulfuron-methyl rearrangement, re-arranged halosulfuron-methyl (HSMR; A-891359): In the absence of a complete genotoxicity data package and limited information on general toxicity, the genotoxicity assessment of this metabolite remains open, and no conclusion on the general toxicity can be made. It cannot be concluded whether the metabolite shares the developmental toxicity profile of the parent. Metabolites halosulfuron rearrangement, (re-arranged halosulfuron, HSR), chlorosulfonamide (chlorosulfonamide ester, 3-chlorosulfonamide ester, CSE) and aminopyrimidine (AP): In the absence of genotoxicity and general toxicity data, no conclusion on the toxicological properties can be derived for the three metabolites. It cannot be concluded whether the metabolites share the developmental toxicity profile of the parent.

Subject	Conclusions Pesticides Peer Review Meeting
Expert consultation 2.9 **Experts to discuss the setting of reference values (ADI, ARfD, AOEL, AAOEL) for halosulfuron-methyl.**	**Since the assessment of the ED properties of the substance is inconclusive (data gap and issue not finalised), toxicological reference values (ADI, ARfD, AOEL and AAOEL) can only be postulated, which represents a critical area of concern.** **The postulated Acceptable daily intake (ADI): 0.063 mg/kg bw per day based on the offspring NOAEL of 6.3 mg/kg bw per day from the multigeneration study in rat with a 100-fold uncertainty factor applied.** **The postulated Acute reference dose (ARfD): 0.50 mg/kg bw based on the NOAEL of 50 mg/kg bw per day for maternal and developmental toxicity in rabbit with a 100-fold uncertainty factor applied.** **The postulated Acceptable operator exposure level (AOEL): 0.063 mg/kg bw per day based on the offspring NOAEL of 6.3 mg/kg bw per day from the multigeneration study in rat with a 100-fold uncertainty factor applied and no correction regarding oral absorption applied.** **The postulated Acute acceptable operator exposure level (AAOEL): 0.50 mg/kg bw based on the NOAEL of 50 mg/kg bw per day for maternal and developmental toxicity in rabbit with a 100-fold uncertainty factor applied and no correction regarding oral absorption applied.**
Expert consultation 2.10 **Experts to discuss the dermal absorption of halosulfuron-methyl 75WG.**	**The dermal absorption values for halosulfuron-methyl in the representative formulation are 0.31% for the concentrate and 0.34% for the spray dilution.** **Open point: RMS to include the Excel sheet for the results from the *in vitro* dermal absorption study using human skin in a revised RAR, and RMS to check the calculations for the dermal absorption value for the concentrate formulation and amend the RAR accordingly.**
Expert consultation 2.11 **Experts to discuss the non-dietary exposure risk assessment of halosulfuron-methyl 75WG for the representative use on rice.**	**For the representative use on rice, the relevant scenario for the worker re-entering the field for inspection activities should include exposure estimates from exposure to dry residues (on treated crops) and exposure from the re-entry in flooded rice fields.** **New open points:** - **RMS to recalculate the non-dietary exposure estimates taking into account the refined dermal absorption values.** - **RMS to recalculate the negligible exposure estimates taking into account the refined dermal absorption values (and considering only the lowest critical NOAEL of 50**

Subject	Conclusions Pesticides Peer Review Meeting
	mg/kg bw per day, based on findings triggering classification, for the MoE estimates). - RMS to calculate the worker exposure for inspection in rice crops, summing the potential exposure to dry residues and the exposure by walking into the flooded paddy field (with the agreed parameters and relevant application rates).
Expert consultation 1.1 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Additional information is needed on each component of the representative formulation to reach a conclusion. Open point RMS to complete the assessment of the toxicological profile of the co-formulants and report it in the revised RAR (Vol. 4) to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term toxicity of the chemically identified co-formulants, including mixtures. The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion, and referred to the safety of the co-formulant per se, as well as in relation to the concentrations in the PPPs. A disclaimer should be included for all evaluations, indicating the limitations of the database as to the reliance of the existing evaluations. The use of the EFSA template for presenting the toxicological data on co-formulants is appreciated.

REPORT OF PESTICIDES PEER REVIEW TC 131

PHOSPHINE – AIR V **Rapporteur Member State: ES**

2. Mammalian toxicity

Date: 8th March 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS ES	National Institute for Agricultural and Food Research and Technology (INIA-CSIC) - ES
National Experts nominated by RMS ES	Ministerio de Sanidad - ES
National Experts nominated by AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	Federal Environmental Agency (UBA) - DE
National Experts nominated by MS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS HR	Croatian Agency for Agriculture and Food - HR
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS PL	Ministry of Agriculture and Rural Development - PL
National Experts nominated by MS SE	Swedish Chemicals Agency (KEMI) - SE
Hearing expert	Francesca Marcon - IT
Observer	Federal Food Safety and Veterinary Office - CH
Observer	Swiss Federal Office for the Environment - CH
Observer	Swedish Chemicals Agency (KEMI) - SE

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the genotoxic potential of phosphine.**	**Overall, based on a weight of evidence approach, the experts expressed a concern over the genotoxicity (clastogenicity) of phosphine.** **One MS expert raised the question whether a new *in vivo* study might be appropriate to reduce uncertainties, which was supported by the RMS and another MS, while another MS disagreed. Should a new study be conducted, particular attention should be given of having a proper study design: dose selection (concentrations between 1 and 4.5 ppm should be included), route of administration (inhalation), length of exposure (13-week) and toxicity/cytotoxicity of phosphine to avoid mortality and severe clinical signs.** **Post-meeting notes:** **After the meeting it was noted that an additional *in vivo* chromosome aberration study in somatic cells, performed with aluminium phosphide (oral route, acute exposure) was not initially included in the EFSA cross cutting Genotoxicity WG advice or considered during the discussion held at the peer review meeting on phosphine. In this respect, the EFSA cc WG on genotoxicity was consulted (19.03.2024). The additional study was considered negative, but of limited relevance, considering that exact exposure to phosphine was not determined, similarly to the *in vivo* MN test in somatic cells performed by the same authors and using similar test conditions (doses, acute exposure, test item). The cc WG on genotoxicity confirmed the previous conclusion: "*In conclusion, although the evidence is limited, the available data raise concern for the genotoxicity of phosphine. No thresholded mode of action can be identified.*"**

Subject	Conclusions Pesticides Peer Review Meeting
	All MS experts also confirmed by written procedure (on 27/03/2024) the conclusions formerly reached during the peer review meeting considering the additional *in vivo* chromosome aberration study: '*Overall, based on a weight of evidence approach, the experts expressed a concern over the genotoxicity (clastogenicity) of phosphine' One MS expert raised the question whether a new in vivo study might be appropriate to reduce uncertainties, which was supported by the RMS and another MS, while another MS disagreed. Should a new study be conducted, particular attention should be given of having a proper study design: dose selection (concentrations between 1 and 4.5 ppm should be included), route of administration (inhalation), length of exposure (13-week) and toxicity/cytotoxicity of phosphine to avoid mortality and severe clinical signs.'*
Expert consultation 2.2 **Experts to discuss the NOAEL for carcinogenicity in rats.**	**All the experts agreed that phosphine is not carcinogenic under the conditions of the 2-year, inhalation rat study.** **The agreed carcinogenic NOAEL is higher or equal than 0.0042 mg/L or 0.81552 mg/kg bw per day, based on no evidence for carcinogenicity in both sexes at the highest dose tested, 3.01 ppm, for 104 weeks.**
Experts' consultation 2.3 **Experts to discuss human health endocrine disruption properties of phosphine.**	**Overall, no T-mediated adverse effects were consistently observed in a sufficient to conclude dataset. On this basis, phosphine occupies scenario 1a for mammalian T-modality.** **All experts agreed that EAS-mediated adversity and endocrine activity have not been sufficiently investigated according to the ED EFSA/ECHA guidance (2018), corresponding to scenario 2a (iii) for mammalian EAS-modality.** **Nevertheless, it was also agreed that a waiver for additional level 5 studies (i.e. OECD TG 416 or 443) should be granted based on the high toxicity of phosphine.** **ED criteria are therefore not met.** **Open point:** **RMS to update the assessment of the T-modality in accordance with the peer review meeting discussion and agreed conclusion.** **Open point:** **the RMS to substantiate better the waiver and, on top of information on classification, available data in the dataset indicating separation between tolerated and lethal dose, should be included. These data are considered relevant to substantiate the fact that any additional study will be not beneficial because doses will be or too low or too toxic.**

Subject	Conclusions Pesticides Peer Review Meeting
	Open point: the RMS to revisit the consideration on the endocrine activity in the RAR, i.e EAS-modality not sufficiently investigated.
Experts' consultation 2.4 **Experts to discuss the setting of refence values for phosphine including appropriate correction factors.**	**Overall, based on a weight of evidence approach, the experts expressed a concern over the genotoxicity of phosphine. One MS expert raised the question whether a new *in vivo* study might be appropriate to reduce uncertainties, which was supported by the RMS and another MS, while another MS disagreed (see expert's consultation 2.2 on genotoxicity).** **Therefore, the setting of reference values was considered as not possible.** **Nevertheless, the experts decided to discuss the toxicological reference values, should the uncertainty on the genotoxicity of phosphine be clarified and a negative conclusion reached.** **Open point** **the RMS to revise the ADI proposal as agreed by the experts in a revised RAR as well as the newly agreed NOAEL of the 2-year inhalation toxicity/carcinogenicity study in rats.**
Experts' consultation 2.5 **Experts to discuss non-dietary exposure estimates, in particular any risk mitigation measures that might be needed for the representative uses assessed.**	**The experts decided to perform non-dietary exposure estimates should the uncertainty on the genotoxicity of phosphine be clarified and a negative conclusion reached (see experts' consultations 2.2 and 2.4 on genotoxicity and on the setting of toxicological reference values, respectively).** **The approach and calculations from the RMS for non-dietary exposure assessment are acknowledged and were supported by all experts.** **Open point:** **RMS to include general recommendations for the level of protection required to obtain a safe use of phosphine fumigation at MS level (e.g. equivalent PPE available).**
Experts' consultation 0.1 (added by EFSA after column 4) **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and**	**There are no safety concerns for the co-formulants in the formulation for the representative uses.** **Open point: the RMS to include more details of this assessment in a revised RAR.**

Subject	Conclusions Pesticides Peer Review Meeting
long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	

REPORT OF PESTICIDES PEER REVIEW TC 131

PROQUINAZID – AIR IV **Rapporteur Member State: SE**

2. Mammalian toxicity

Date: 11 March 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency (KEMI) - SE
National Experts nominated by MS AT	AGES - Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	Federal Environmental Agency (UBA) - DE
National Expert nominated by MS EE	Agriculture and Food Board - EE
National Expert nominated by MS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Experts nominated by MS NL	Ctgb - NL
National Expert nominated by MS PL	E-V-A Sp. z o.o. - PL
National Expert nominated by MS PL	Ministry of Agriculture and Rural Development - PL
Hearing Expert	Gretchen Ritacco
Observer	Federal Food Safety and Veterinary Office - CH
Observer	Ctgb - NL
Observer	Ministry of Agriculture and Rural Development - PL
Observer	Swedish Chemicals Agency (KEMI) - SE

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation (mammalian toxicity section) 0.1 **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.**	**Regarding the co-formulants contained in the formulation supported for the representative uses (GF-4031), based on the currently available information, toxicological data is insufficient for any components, and it is not possible to conclude whether they impact on the toxicity/classification and safety of the proposed formulation.** **Open point: RMS to include an assessment of the available data on genotoxicity, short- and long-term toxicity of the (components of) co-formulants in the revised RAR.**
Experts' consultation 2.1 **Experts to discuss the phototoxic and photomutagenicity potential of proquinazid, including potential phototoxicty risk**	**Under the conditions of the available study (OECD TG 498, with topical application), the experts consider proquinazid unlikely to be phototoxic.** **Data are missing to address the photomutagenicity of proquinazid (at least a robust scientific justification should be provided regarding photomutagenicity).**

Subject	Conclusions Pesticides Peer Review Meeting
to non-dietary and consumer exposure groups.	
Experts' consultation 2.2 Experts to discuss the NOAEL in the 28-day mice study (relevance of liver findings).	KCA 5.3.1/01, 1997 28-day, rat: The agreed NOAEL is 1000 ppm (141/177 mg/kg bw per day) based on statistically significant increase in relative liver to body weight of (53.7%) in males and 33.8% in females at 3000 ppm (453/580 mg/kg bw per day).
Experts' consultation 2.3 Experts to discuss the NOAEL in the 90-day rat study (relevance of thyroid findings).	B.6.3.2 (1), Subchronic toxicity 90-day feeding study in rats, KCA 5.3.2, 2002. The agreed NOAEL is 100 ppm, 6.33 mg/kg bw per day based on morphological and hormonal changes in the thyroid at 300 ppm in males (19.45 mg/kg bw per day). Open point RMS to include more details on histopathological findings in the thyroid (including information on severity) in the RAR (KCA 5.3.2, 2002).
Experts' consultation 2.4 Experts to discuss the NOAEL in the 90-day and 1-year dog study.	<u>90-day, dog:</u> The NOAEL is lower than 500 ppm considering ocular findings in males and females (M:17 mg/kg bw per day, F: 18 mg/kg bw per day), and lower than 500 ppm in females considering liver findings (18 mg/kg bw per day). <u>1-year, dog:</u> The agreed NOAEL is 15 mg/kg bw per day based on increased relative liver to body weight, body weight losses and/or reductions in body weight gain, and inflammation in the epididymides and seminiferous tubules of the testes in males at 60 mg/kg bw per day.
Experts' consultation 2.5 Experts to discuss the endocrine disruption potential of proquinazid.	Overall, a pattern of T-mediated adverse effects was consistently observed in a complete dataset for proquinazid. Thyroid changes were characterised by follicular cell hypertrophy, hyperplasia and adenoma and the changes were dose- and time- dependent. All experts agreed on a liver mediated MoA through increase circulation of T4 and leading to thyroid hypertrophy/hyperplasia and adenoma not proved to be rodent-specific. On this basis proquinazid occupies scenario 1b for mammalian T modality, ED criteria met.

Subject	Conclusions Pesticides Peer Review Meeting
	Thyroid NOAEL was set at 30 ppm from the 90-day rat study (DuPont-1127, Revision No. 2 Malley, L.A. 2003) and the 2-year combined chronic toxicity/oncogenicity rat study (HL-1999-00644, Malley, L.A. 2002) corresponding to 1.16-189 mg/kg bw/d. **Regarding the EAS-modality, there are no evidence of an adverse pattern and on this basis, scenario 1a applies.** **Open point: the RMS to update the RAR in line with the discussion and agreements.** **Open point: some solubility issues were noted in the in vitro studies (in vitro comparative study, NIS, TR and TPO) especially when DMSO is used as solvent. However, the maximum solubility (in DMSO) varies from study to study. Therefore, the RMS is asked to doublecheck the maximum concentration used in the different studies and the reason behind in the discrepancy of the maximum DMSO solubility in the different MoA in vitro studies.** **Open point: the RMS to correct in revised RAR Vol. 1, (Table 2.10.2.1.1-1 Lines of evidence for adverse effects and endocrine activity related to T-modality) the exposure time of the Phase I and Phase II enzyme induction study (ID 26) to 1 and 0.43 weeks instead of 7 and 3 as it is (that would probably aim to refer to 7 and 3 days).**
Experts' consultation 2.6 **Experts to discuss data waiver for DNT.**	**The experts agreed on a data waiver for a DNT or CTA study. There was agreement that the young adult rat lacking thyroid binding globulin is likely representing the most sensitive population and the intraspecies uncertainty factor of 10 would in any case likely cover lack of additional investigation in the target population.**
Experts' consultation 2.7 **Experts to discuss the toxicological profile of metabolites:** **IN-MM671: including reliability of the Ames test (CA 6.8.1.002) as regards number of analysable concentrations needed and reliability of the *in vivo* MN test.** **IN-MM986**	**All the experts agreed the QSARs predictions for genotoxicity are considered <u>not reliable enough</u>, and a conclusion cannot be reached on this basis only.** **All experts agreed that initial grouping approach based on organic functional groups <u>may be</u> appropriate but should be further substantiated to reach a conclusion on genotoxicity and general toxicity.** **Genotoxicity is inconclusive (open) for the following metabolites based on the lack of experimental data, or they are not rat metabolites or major rat metabolites or the QSAR analysis was not reliable enough or the read-across was not properly substantiated:**

Subject	Conclusions Pesticides Peer Review Meeting
IN-MM991	A1
IN-MU715 (A3)	A4
IN-MW398	B3
IN-MY340	B4
IN-MY341	CRC-Soy-01
IN-MY788	IN-MY340
IN-NA250	IN-MY341
IN-NA251 (B1)	IN-MY788
IN-NA252 (B2)	IN-MM986
A1	IN-MM991
A4	IN-MW397
B3	IN-MW398
B4	IN-NA250
CRC-Soy-01	IN-NA251
Sulfate conjugated of the parent	IN-NA252
IN-MU210	A2
IN-MW397	
IN-MW977 and their glycosides	General toxicity is inconclusive (open) for the following metabolites the lack of experimental data, or they are not rat metabolites or major rat metabolites or the read-across was not properly substantiated: IN-MW977 (major) IN-MW977 (major) glucoside IN-MW977 (minor) IN-MW977 (minor) glucoside CRC-Soy-01 IN-MY341 IN-NA251 The following metabolites are covered by parent compound: IN-MU715 Sulfate conjugates of proquinazid. The following metabolites are unlikely to be genotoxic based on experimental data:

Subject	Conclusions Pesticides Peer Review Meeting
	IN-MW977 (major) (glucosides, covered by the aglycon). **IN-MW977 (minor) (glucosides, covered by the aglycon).** **IN-MM671** **IN-MU210** **IN-MU715**
Experts' consultation 2.8 **Experts to discuss the setting of reference values, ADI, ARfD, AOEL, AAOEL.**	**The ADI is 0.012 mg/kg bw per day based on a NOAEL of 1.16 mg/kg bw per day in the 2-year rat study related to changes in the liver and thyroid, using an uncertainty factor (UF) of 100.** **The ARfD is 0.06 mg/kg bw based on a LOAEL of 17 mg/kg bw per day in the 90-day dog study related to eye effects observed after first doses, using a standard UF of 100 plus an additional UF of 3 because of lack of NOAEL. The same basis is applied to the AAOEL (with no correction for oral absorption).** **The AOEL is 0.02 mg/kg bw per day, based on a NOAEL of 1.89 mg/kg bw per day in the rat combined subchronic and neurotoxicity study related to morphological changes in the liver and thyroid, changes in thyroid hormone homeostasis and with clinical pathology parameters, using an uncertainty factor of 100, considering a 100% oral absorption.**
Experts' consultation 2.9 **Experts to discuss non-dietary exposure estimates.**	**For the non-dietary exposure estimates, the dissipation results from a field study for workers re-entering vineyards were considered not applicable due to climatic conditions not representative of EU, while the dislodgeable foliar residue value of 0.53 µg/cm²/kg a.s per hectare (based on the highest individual residue value) was agreed.** **Open point** **RMS is requested to provide revised non-dietary exposure estimates in the revised RAR:** - **Using the agreed endpoints (dermal absorption, DFR, and toxicological reference values) and including bystanders;** - **including screenshots of the Excel calculator (EFSA 2014);** - **including also less critical uses (with lower application rate or number of applications within the same representative use).**
Experts' consultation 2.10	**Based on *in vitro* dermal absorption studies with human skin performed with Proquinazid (DPX-KQ926) 200 g/L EC, the agreed dermal absorption values are 1% for the concentrate and 6.5% for**

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss dermal absorption values.	the dilution of 0.033 g/L (with a value of 21% after prorata correction for the dilution of 0.01 g/L).

REPORT OF PESTICIDES PEER REVIEW TC 131

GIBBERELLIC ACID – AIR IV **Rapporteur Member State: SI**

2. Mammalian toxicity

Date: 11 March 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS SI	National Institute of Public Health - SI
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment - DE
National Expert nominated by MS EE	Estonian Agriculture and Food Board - EE
National Expert nominated by MS ES	Ministerio de Sanidad - ES
Observer	Federal Food Safety and Veterinary Office - CH
Observer	Estonian Agriculture and Food Board - EE

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.10 **Re-discussion of toxicological reference values (TRVs) (follow up TC 125)**	**The toxicological reference values (TRVs) set during the Peer Review Meeting 25 (March 2020) were confirmed since the available evidence (including reinterpretation of the developmental effects in the 2-generation rat study) was not sufficient to change the previous agreement.** **The acceptable daily intake (ADI) is 0.23 mg/kg bw per day, based on the offspring LOAEL of 233 mg/kg bw per day from the 2-generation study in rat and applying a standard uncertainty factor (UF) of 100 plus an additional factor of 10 (to cover extrapolation from sub-chronic to chronic, the use of a LOAEL, and the uncertainties related to the limited available dataset).** **The acceptable operator exposure level (AOEL) and acute AOEL are 0.23 mg/kg bw (per day), based on the LOAEL of 233 mg/kg bw per day from the 2-generation study, applying a standard UF of 100 plus an additional factor of 10 to cover the use of a LOAEL and the uncertainties related to the limited available dataset (including lack of data to set an oral absorption value).** **The acute reference dose (ARfD) is 0.78 mg/kg bw, based on the offspring LOAEL of 233 mg/kg bw per day from the 2-generation study, applying a standard UF of 100 plus an additional factor of 3 to cover the use of a LOAEL.**

REPORT OF PESTICIDES PEER REVIEW TC 131

***MELALEUCA ALTERNIFOLIA*, ESSENTIAL OIL (TEA TREE OIL) – AIR IV**

Rapporteur Member State: PL

2. Mammalian toxicity

Date: 11 March 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS PL	E-V-A Sp. z o.o.
National Experts nominated by RMS PL	Ministry of Agriculture and Rural Development - PL
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	Federal Environmental Agency (UBA) - DE
National Expert nominated by MS EE	Agriculture and Food Board - EE
National Expert nominated by MS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail - FR
National Experts nominated by MS NL	Ctgb - NL
National Experts nominated by MS SE	Swedish Chemicals Agency (KEMI) - SE
Observer	Federal Food Safety and Veterinary Office - CH
Observer	Ctgb - NL
Observer	Ministry of Agriculture and Rural Development - PL
Observer	Swedish Chemicals Agency (KEMI) - SE

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 1.1 **Experts to discuss the toxicological profile of the co-formulants taking into account the requested additional toxicological data and the corresponding RMS evaluation of these.**	**Regarding the co-formulants contained in the formulation supported for representative uses (Timorex Gold) based on the currently available information, sufficient toxicological data were available for most components. However, for a component toxicological data is insufficient (due to lack of information on its composition) and it is not possible to conclude whether it impacts on the toxicity/classification and safety of the proposed formulation.** **Open point** **The RMS to revise the RAR Vol. 4 in line with the discussion and open point identified at the peer review meeting.**
Experts' consultation 2.1 **Experts to discuss the genotoxicity potential of TTO considering and including 1) the component-based approach to address the genotoxicity potential of chemical mixture and 2) the available experimental data.**	**No concerns on genotoxicity for the different components were identified following a component-based approach.** **No concern was identified for the whole mixture based on experimental data.** **On this basis, tea tree oil is unlikely to be genotoxic.** **Open point** **The RMS to revise the RAR in line with the discussion and open point identified at the peer review meeting.**
Experts' consultation 2.2 **Experts to discuss in an experts' meeting the waiving proposed for the long-term**	**The majority of the experts, excluding the RMS, agreed that the waiving for long-term and carcinogenicity cannot be accepted.** **Waiving of inhalation toxicity studies was accepted by all the experts. Tea tree oil is classified as Acute Tox. 4 and Skin Irrit.**

Subject	Conclusions Pesticides Peer Review Meeting
toxicity and carcinogenicity studies on tea tree oil. The waiving of inhalation toxicity studies (e.g short term) should also be discussed.	2; therefore, local effects are likely occurring before systemic effects appear. **Open point** The RMS to revise the RAR in line with the discussion and open point identified at the peer review meeting.
Experts' consultation 2.3 Experts to discuss the following NOAELs • Reproductive, parental and offspring toxicity NOAELs in the newly submitted 2-generation study in rat KCA 5.6.1/01. • maternal and developmental toxicity NOAELs in the developmental toxicity study in rats and in rabbits, studies KCA 5.6.2/01 and 5.6.2/02 (newly submitted), respectively. Moreover, the skeletal findings observed at 30 mg/kg bw per day in the rat developmental toxicity study KCA 5.6.2/01 to be discussed by the experts.	2-generation toxicity study in rat (KCA 5.6.1/01): - NOAEL (reproductive) is 10 mg/kg bw per day based on statistically significant decrease No. of sperm per cauda epidydimis and No. of sperm per grams cauda epidydimis observed at 25 mg/kg bw per day in F1 generation. - NOAEL (parental) is 25 mg/kg bw per day based on reduction of body weight gain observed at 50 mg/kg bw per day in males of parental generation. - NOAEL (offspring) is 25 mg/kg bw per day based on decrease survival index, mean litter size and mean viable litter size observed at 50 mg/kg bw per day. Prenatal developmental toxicity study in rat (KCA 5.6.2/01): - NOAEL (maternal) is 30 mg/kg bw per day based on reduced maternal body weight gain and feed consumption observed at 60 mg/kg bw per day. - NOAEL (developmental) is 30 mg/kg bw per day based on delayed ossification in foetuses observed at 60 mg/kg bw per day in the presence of maternal toxicity. Tea tree oil: Embryo-fetal developmental toxicity study by oral gavage in New Zealand White rabbits (KCA 5.6.2/02): - NOAEL (maternal, developmental) and is 30 mg/kg bw per day based on increase post-implantation loss at 75 mg/kg bw per day. **Open point** The RMS to revise the RAR in line with the discussion and open points identified at the peer review meeting.
Experts' consultation 2.4 The ED potential of the active substance should be discussed in an experts' meeting.	<u>T-modality</u> The available evidence was considered sufficient to conclude on T-modality and a pattern of T-mediated adversity was not observed in the available dataset of studies. Scenario 1a of the

Subject	Conclusions Pesticides Peer Review Meeting
	EFSA/ECHA ED guidance (ECHA/EFSA, 2018) is applicable and the ED criteria for T-modality are not met. **EAS-modalities** **The EAS-modalities were sufficiently investigated. Effects on sperm motility, sperm number, sperm morphology, histopathological changes in testes and epididymis and changes in weights of testes and epididymis were observed in the available dataset of studies conducted in different species.** **The endocrine activity was not sufficiently investigated; however, the available studies (OECD TG 455 - agonism assay only - and OECD TG 441) were negative.** **A mode of action (MoA) analysis was performed. The experts agreed that the MoA is dealing with tea tree oil being a direct testicular toxicant. This was substantiated by several circumstantial evidence including the histopathological diagnostic description (i.e. effect not observed in all animals, patchy/focal or multi-focal distribution of the lesion, e.g., sperm granuloma and sperm retention), no effects in other endocrine sensitive organs (i.e prostate and seminal vesicle), no effects on female reproductive organs, and evidence of cell cycle arrest and cell death in the *in vitro* study conducted with tumoral cell line. Overall, the weight of evidence was suggestive that a pattern of EAS-mediated changes cannot be substantiated.** **The majority of the experts agreed that the ED criteria for EAS-modalities are not met.** **Open point** **The RMS to revise the RAR in line with the discussion and open points identified at the peer review meeting.**
Experts' consultation 2.5 **Expert to discuss the setting of toxicological reference values i.e. ADI, ARfD, AOEL, AAOEL, including the oral absorption values, for tea tree oil and the approach used for the risk assessment (lead-component or mixture).**	**The ADI is 0.05 mg/kg bw per day based on the NOAEL (reproductive) of 10 mg/kg bw per day from the 2-generation rat study, applying the standard uncertainty factor (UF) of 100 and an additional UF of 2 (for extrapolation from sub-chronic to chronic toxicity).** **The AOEL is 0.05 mg/kg bw per day based on the NOAEL (reproductive) of 10 mg/kg bw per day from the 2-generation rat study, applying the standard UF of 100 and an additional UF of 2 (due to lack of toxicokinetic data to derive the oral absorption value).** **The ARfD is 0.3 mg/kg bw based on the NOAEL of 30 mg/kg bw per day from the 90-d toxicity study in rats and applying an uncertainty factor of 100. The AAOEL is 0.3 mg/kg bw based on the same reasoning.**

Subject	Conclusions Pesticides Peer Review Meeting
	The major components are highly volatiles, and the persistence of the other components, including the minor ones, is less known. However, it was noted that the minor components, present in traces in tea tree oil, are considered unlikely to be genotoxic (see experts' consultation 2.1) and the NOAEL for the individual major components are higher than the NOAELs dervied for the whole tea tree oil mixture. Therefore, all experts agreed that the ADI and ARfD for tea tree oil are also applicable for consumer risk assessment (in case needed). **Due to its toxicological properties as natural potential carcinogen, methyleugenol is defined as a component of concern and as such it may be considered in the same way as 'relevant impurity' in line with Guidance document SANCO/11470/2012– rev. 8. For chemical mixture, the Scientific Committee (EFSA Scientific Committee, 2012)[3] stated that for unavoidable contaminants and impurities it might be possible to conclude that human exposure is likely to be of low concern from a public health perspective. Such a conclusion maybe reached based on a Margin of Exposure (MOE) approach when respective carcinogenicity data are available. For methyleugenol a carcinogenicity study is available in rats and mice (NTP, 2000[4]). From this study a BMDL10 of 22.2 mg/kg bw per day was derived in a recent FEEDAP Panel Opinion (EFSA FEEDAP Panel, 2023)[5]. All experts agreed that the application of a MOE approach is the most appropriate in such case considering the availability of experimental data (BMDL10 22.2 mg/kg bw per day).** **Open point** **The RMS to revise the RAR in line with the discussion and open points identified at the peer review meeting, these includes also the calculation of the MOE for methyleugenol.**
Experts' consultation 2.6 **Experts to discuss the dermal absorption values for TTO and the approach use for extrapolation of the**	**A human *in vitro* dermal absorption study conducted with the formulation for representative uses (Timorex Gold) radiolabelling terpinen-4-ol was available.** **Terpinen-4-ol was not considered as lead component and TRVs are derived for the whole mixture, therefore default dermal**

[3] EFSA Scientific Committee; Scientific Opinion on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Journal 2012; 10(3):2578. [5 pp.] doi:10.2903/j.efsa.2012.2578.

[4] National Toxicology Program (2000). NTP Toxicology and Carcinogenesis Studies of Methyleugenol (CAS NO. 93-15-2) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program technical report series, 491, 1–412. Available online: https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr491.pdf

[5] EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2023. Scientific Opinion on the safety and efficacy of a feed additive consisting of an essential oil from the leaves of Laurus nobilis L. (laurel leaf oil) for all animal species (FEFANA asbl). EFSA Journal 2023; 21(3):7875, 28 pp. https://doi.org/10.2903/j.efsa.2023.7875

Subject	Conclusions Pesticides Peer Review Meeting
dermal absorption, calculated for the main component Terpinen-4-ol, to the whole mixture TTO.	absorption values for the formulation type should be used, i.e. 25% for the concentration and 70% for the in-use dilution (EFSA, 2017[6]).
Experts' consultation 2.7 Experts to discuss the results of the operator and worker exposure study (Glass et al 2017) and the non-dietary assessment for Operator, Worker, Bystander and Resident.	The available study monitoring operator and worker inhalation exposure to Timorex Gold (tea tree oil) in greenhouse crops was acceptable; however, due to the low number of subjects replicates, the maximum residue values were used for the operator/worker exposure estimates (EFSA, 2022). For the worker exposure estimates , the assessment of the proposed DFR value on the basis of residue trials in grapes was not considered sufficient for a refinement of the dermal exposure estimates. Open point The RMS to revise the RAR in line with the discussion and open points identified at the peer review meeting. In particular the RMS to: - re-calculate the exposure estimates taking into account the newly agreed dermal absorption values (see experts' consultation 2.6); - re-calculate the risk assessment for operator, workers, bystander and residents taking into account the newly agreed AOEL and AAOEL (see experts' consultation 2.5) and agreed values from the monitoring study on operator and worker inhalation exposure (see experts' consultation 2.7).

[6] EFSA (European Food Safety Authority), Buist H, Craig P, Dewhurst I, Hougaard Bennekou S, Kneuer C, Machera K, Pieper C, Court Marques D, Guillot G, Ruffo F and Chiusolo A, 2017. Guidance on dermal absorption. EFSA Journal 2017; 15(6):4873, 60 pp. https://doi.org/10.2903/j.efsa.2017.4873

REPORT OF PESTICIDES PEER REVIEW TC 131

METRIBUZIN – AIR III **Rapporteur Member State: EE**

2. Mammalian toxicity

Date: 11 March 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS EE	Estonian Agriculture and Food Board - EE
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment - DE
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Expert nominated by MS SI	National Institute of Public Health - SI
Observer	Federal Food Safety and Veterinary Office - CH
Observer	Estonian Agriculture and Food Board - EE

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation **Consultation on extra UF, re-discussion of TRVs (follow up TC 40 and TC 99, post approval TC)**	**In 2021, the ADI for metribuzin was set at 0.0013 mg/kg bw per day based on the NOAEL of 1.3 mg/kg bw per day for decreased body weight gain, increased levels of circulating liver enzymes and thyroid follicular cell hyperplasia in a 2-year rat study and an overall UF of 1000 to account for the incomplete data set (lack of a developmental neurotoxicity, DNT study). Ruling out the DNT potential was considered relevant for addressing the concern associated with T4 increase at 1.3 mg/kg bw per day in the same 2 yr rat study.** **A comparative thyroid toxicity assay (CTA) submitted subsequently confirmed the perturbation by metribuzin of the HPT axis also in the most sensitive population (foetuses and new-born), and the unusual pattern of hormonal changes (↑ at low doses and ↓at high dose).** **Metribuzin was concluded as meeting the ED criteria for the T modality and a peer review conclusion was published in August 2023 setting the** **ADI at 0.0013 mg/kg bw per day and the ARfD, AOEL and the AAOEL at 0.002 mg/kg bw** **In the present meeting the experts agreed that the extra UF of 10 applied to all metribuzin TRVs for the lack of a DNT study is not justified given the availability of a CTA study that investigates the key T-mediated events in the sensitive target population.** **Nevertheless, the experts re-considered the adversity of the consistent T4 increase at low doses across the data package even if not accompanied by clear evidence of adverse histopathological**

Subject	Conclusions Pesticides Peer Review Meeting
	findings. It is in fact unknown the quantitative level of hormonal disruption that is necessary to induce developmental neurotoxicity. On this basis the experts set at 1.3 mg/kg bw per day the LOAEL for T4 increase in the 2-yr rat study. For what concerns the UF to be used for the derivation of the ADI an extra UF of 10 (on top of the standard 100 to cover for inter- and intra-species variability) was agreed based on: • the extrapolation from LOAEL to NOAEL for an endpoint predictive of an effect of particular concern, i.e. irreversible impact on brain development; • uncertainties related to the shape and steepness of the non-monotonic dose response curve for the observed effects on THs; • the likelihood of two overlapping MoAs that can mask the peak effects for hypo- and/or hyperthyroidism; • the uncertainty on how to qualify the sensitivity of the rat as a species able to capture hazards related to hyperthyroidism conditions. The final ADI value is therefore 0.0013 mg/kg bw per day. The ARfD, AOEL and the AAOEL are 0.002 mg/kg bw (per day) based on the NOAEL of 2 mg/kg bw from the rat acute oral neurotoxicity study and applying an overall UF of 1000. The extra UF of 10 accounts for the uncertainties related to the unknown impact of a transitory T4 increase on DNT potential, and to the lack of TH measurements in the acute neurotoxicity study.

REPORT OF PESTICIDES PEER REVIEW TC 131

PIRIMICARB – AIR III after ED clock stop **Rapporteur Member State: SE**

2. Mammalian toxicity

Date: 11 March 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS SE	Swedish Chemicals Agency (KEMI) - SE
National Experts nominated by AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	Federal Environmental Agency (UBA) - DE
National Expert nominated by MS ES	National Institute for Agricultural and Food Research and Technology (INIA-CSIC) - ES
National Experts nominated by MS ES	Ministerio de Sanidad - ES
National Experts nominated by MS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS HR	Croatian Agency for Agriculture and Food - HR
National Experts nominated by MS NL	Ctgb - NL
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Observer	Federal Food Safety and Veterinary Office - CH
Observer	Swiss Federal Office for the Environment - CH
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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.13 **MSs experts to discuss the evidence (*in vitro* and *in vivo*) for the assessment of the T-modality for human health assessment.**	**ED criteria for T-modality are not met for pirimicarb since a pattern for T-modality adversity has not been observed in a complete dataset (Scenario 1a of the ECHA/EFSA (2018) ED Guidance applies).**
Experts' consultation 2.14 **MSs experts to discuss the reliability of Hershberger assay in the context of the assessment of the EAS-modality (including the adequacy of the top dose and the statistical analysis).** **Experts' consultation 2.15** **MSs experts to discuss the adequacy of the**	**The Hershberger assay is considered reliable and negative. The new 2-generation study TG 416 dose-selection is considered sufficient to investigate endocrine adversity. No pattern of EAS-mediated adversity is observed in the study.** **Overall, no EAS-mediated adverse effects were consistently observed in a complete dataset, including a series of studies submitted following the ED clock stop. Pirimicarb showed anti-androgenic activity *in vitro* at high concentrations, and not reproducible. However, a pattern of A-activity is not observed *in vivo* level 3 or level 5 studies in a complete dataset.** **On this basis, pirimicarb occupies Scenario 1a for mammalian EAS modalities and that the ED criteria are therefore not met.** **Open point:** **RMS to update the RAR in line with the Peer Review Meeting discussion, specifically RMS to update the RAR regarding the assessment of the Hershberger assay; RMS to include the results of the AR model from Toxcast; RMS to include the discussion and**

Subject	Conclusions Pesticides Peer Review Meeting
measurements of AGD and HCD. Experts' consultation 2.16 MSs experts to discuss methodology and uncertainties in the assessment of the endpoint nipple retention. Experts' consultation 2.17 MSs experts to discuss the assessment of the EAS-mediated endpoints as part of the overall assessment of the EAS-modalities.	assessment of AGD, sexual maturation and nipple retention endpoints, including adequacy of HCD and PCD.
Experts' consultation 2.18 MSs to discuss and agree on the systemic NOAEL and LOAEL of the newly generated OECD 416 study and its impact of the setting of the TRVs. MSs to discuss and agree on the ED-mediated and sensitive endpoints for NOAEL and LOAEL of the newly generated OECD 416 study.	For the new 2-generation study with rats, the agreed NOAELs are: - for the parental toxicity: 300 ppm (equivalent to 24 mg/kg bw per day), based on decreased body weight observed in males and females of the F1 generation at 1000 ppm, and decreased bodyweight gain observed in males and females of both generations at 1000 ppm; - for the offspring toxicity: 300 ppm (equivalent to 24 mg/kg bw per day) based on body weight decrease and absolute brain weight decrease (6-7%) at 1000 ppm; - for the reproductive toxicity: 300 ppm based on effects on fertility and sperm count at 1000 ppm, with a very shallow dose response. Considering the lack of DNT investigations for a neurotoxic compound inducing cholinesterase inhibition, an additional uncertainty factor (UF) of 10 was applied to the derivation of the toxicological reference values, resulting in: - ADI /AOEL of 0.0035 mg/kg bw per day, based on the NOAEL of 3.5 mg/kg bw per day from the 1-year dog study (supported by the 2-year rat study with NOAEL of 3.7), applying an UF of 1000;

Subject	Conclusions Pesticides Peer Review Meeting
	- ARfD / AAOEL of 0.01 mg/kg bw, based on the NOAEL of 10 mg/kg bw from the acute neurotoxicity study, applying an UF of 1000. **Open point:** RMS is kindly requested to provide revised dietary and non-dietary exposure estimates with the new ADI and AOEL in a revised RAR.
Experts' consultation 2.19 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding co-formulants contained in the formulation supported for the representative uses (A10788A), based on the available information, insufficient toxicological data were available for some of them (genotoxicity, long term toxicity/ carcinogenicity and toxicity by inhalation) and it is not possible to conclude whether they impact on the toxicity/classification and safety of the formulation. **Open point:** The RMS to integrate the new information and the resulting assessment of the co-formulants in a revised RAR.

REPORT OF PESTICIDES PEER REVIEW TC 131

TRICLOPYR – AIR III **Rapporteur Member State: PL**

2. Mammalian toxicity

Date: 11 March 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS PL	Ministry of Agriculture and Rural Development - PL
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS SE	Swedish Chemicals Agency (KEMI) - SE
Observer	Federal Food Safety and Veterinary Office - CH
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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.12 **Experts to reassess the kidney changes in dogs including the derivation of endpoints.** **Follow up discussion from the Pesticides Peer Review Experts' Meeting 11 (Sept 2019) following updated RAR provided in 2023 with revised assessment of the additional information submitted by the applicant during the clock stop.** **See also revised RAR and Applicants relevant documents submitted during the clock stop.**	**Kidney changes in dogs including the derivation of endpoints in the 1-year dog study with triclopyr were discussed.** **On the basis of the available information, renal treatment-related adverse effects are confirmed at 2.5 mg/kg bw per day and above in both male and female dogs (increased serum BUN and creatinine as compared to concurrent controls and pre-dose values, exacerbation of pigment deposition in renal tubular cells and decreased PSP excretion). Consistently, 0.5 mg/kg bw per day is confirmed as the NOAEL in the 1-year dog study on triclopyr.** **In addition, the submitted toxicokinetic (TK) and in vitro data are not sufficient to dismiss the uncertainties and to consider the dog as a non-reliable model for the risk assessment.** **Open point:** **RMS to amend the evaluation of the plasma binding study in a revised RAR.**
Experts' consultation 2.13 **Experts to discuss the implications of relevance of the dog findings /potential reconsideration**	**Based on the discussion in experts' consultation point 2.12 above, the previously agreed toxicological reference values are confirmed.**

Subject	Conclusions Pesticides Peer Review Meeting
of the toxicological reference values (TRVs).	
Experts' consultation 2.14 Experts to discuss the toxicological relevance assessment of impurities. See also revised RAR and Applicants relevant documents submitted during the clock stop.	The toxicological relevance of most of impurities has not been sufficiently assessed and cannot be concluded on the basis of the available data.

REPORT OF PESTICIDES PEER REVIEW

TC 124 and TC 125

BIXLOZONE – NAS 1107 **Rapporteur Member State: NL**

2. Mammalian toxicity

Date: 30 January 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS Netherlands	Ctgb - NL
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS Czechia	National Institute of Public Health - CZ
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Germany	Federal Environmental Agency (UBA) - DE
National Expert nominated by MS Denmark	Danish Environmental Protection Agency - DK
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Expert nominated by MS Finland	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS France	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Expert nominated by MS Poland	E.V.A. - PL
National Expert nominated by MS Slovenia	National Institute of Public Health -SI

Status	Name of institution / attendee
National Expert nominated by MS Slovenia	GEEST s.p. Visoko, Slovenia on behalf of Slovenian Compentent Authority - SI
Observer	Swiss Federal Office for the Environment, Biocided & Plant Protection Products Section - CH
Observer	Danish Environmental Protection Agency - DK
Observer	Finnish Safety and Chemicals Agency (Tukes) - FI
Observer	Ctgb - NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MS experts to discuss and agree on the oral absorption value to be used for reference dose setting.**	**The oral absorption value was set at 70% based on the mean bioavailability of bixlozone for male and female rats upon multiple oral low dosing.**
Experts' consultation 2.2 **MS experts to discuss the systemic NOAEL of the 18-month oral carcinogenicity study in mice in an Expert Meeting.**	**The NOAEL for systemic toxicity in the 18-month oral carcinogenicity study in mice is 250 ppm (32 mg/kg bw per day) based on increased incidence and severity of hepatocellular hypertrophy in males.** **Open point:** **RMS to clarify in the DAR that in males the slight increase in absolute and relative liver weight at 1000 ppm was not statistically significant.**
Experts' consultation 2.3 **The potential of bixlozone to disrupt the endocrine system in humans needs to be further discussed and agreed upon in an Expert Meeting.**	**ED assessment** **There is no indication in the data set of perturbations of the T-mediated parameters and the applicable scenario is Scenario 1a „ED criteria were not met because no endocrine adversity has been observed for T-modality".** **Open point: RMS to include/revise the sentence clarifying the absence of changes indicative of a histopathological continuum in the 2 years rat study in the revised RAR Vol. 1 p. 249.** **There is no indication in the data set of perturbations of the EAS-mediated parameters. The applicable scenario is Scenario 1a „ED criteria were not met because no endocrine adversity has been observed for EAS-modalities".**

Subject	Conclusions Pesticide Peer Review Meeting
	Open point: the RMS is suggested to present the ED assessment in the revised DAR Vol. 1, in accordance with the template provided in the EFSA administrative guidance 2019 (Appendix I). Moreover, it is asked to report the Lines of Evidence for Human Health in two separate sheets for T- and EAS-modalities (in accordance with the above-mentioned template).
Experts' consultation 2.4 **MS experts to discuss the toxicity profile and the reference values for the mentioned metabolites.**	**The following conclusions were drawn regarding the metabolites discussed:** **2,4-dichlorobenzoic acid (2,4-DCBA), M190/1, free and conjugated, (residue and GW>0.75 µg/L, major rat metabolite)** **It is unlikely to be genotoxic *in vitro*. No experimental data on general toxicity are available. As a major rat metabolite based on ADME studies, the reference values of bixlozone apply (ADI: 0.29 mg/kg bw per day; ARfD: 0.75 mg/kg bw).** **Dimethylmalonic acid, M132/1, free and conjugated (residue)** **In the absence of data/information on this residue metabolite, data gaps were set for both genotoxicity and general toxicity.** **2,2-dimethyl-3-OH-propionic acid, M118/1, free and conjugated (residue)** **In the absence of data/information on this residue metabolite, data gaps were set for both genotoxicity and general toxicity.** **Dimethylmalonamide-F9600, M289/2 (residue)** **In the absence of data/information on this residue metabolite, data gaps were set for both genotoxicity and general toxicity.** **F9600-hydroxy-isobutyramide, M261/1 (residue)** **In the absence of data/information on this residue metabolite, data gaps were set for both genotoxicity and general toxicity.** **5-hydroxy-F9600, M289/1 (residue)** **As a major rat metabolite based on ADME studies, the reference values of bixlozone apply (ADI: 0.29 mg/kg bw per day; ARfD: 0.75 mg/kg bw per day).** **5'-OH-F9600, M289/3, free and conjugated, (residue)**

Subject	Conclusions Pesticide Peer Review Meeting
	In the absence of data/information on this residue metabolite, data gaps were set for both genotoxicity and general toxicity. F9600-3-OH-Propanamide, M275/1 (residue) In the absence of data/information on this residue metabolite, data gaps were set for both genotoxicity and general toxicity.
Experts' consultation 2.5 Toxicological end points for assessment of risk following long-term dietary exposure – ADI (acceptable daily intake), and acute dietary exposure – ArfD (acute reference dose), as well as Toxicological end points for assessment of occupational, bystander and residents risks (A)AOEL (acceptable operator exposure level) including the correction factor for oral absorption need to be agreed upon.	The following reference values were agreed. ADI: 0.29 mg/kg bw per day based on a NOAEL of 29 mg/kg bw per day in the rat oral 90-day study for increased liver weight accompanied by hepatocellular hypertrophy in females, and increased kidney weight in males (absolute and relative), using the standard UF of 100. AOEL: 0.2 mg/kg bw per day based on a NOAEL of 29 mg/kg bw per day in the rat oral 90-day study for increased liver weight accompanied by hepatocellular hypertrophy in females, and increased kidney weight in males (absolute and relative), using the standard UF of 100, and applying a correction for oral absorption of 70%. ARfD: 0.75 mg/kg bw based on a NOAEL of 75 mg/kg bw per day in the rat prenatal developmental toxicity study for decreased maternal body weight gain (GD6-9 at ≥ 225 mg/kg bw per day), using the standard UF of 100. AAOEL: 0.53 mg/kg bw based on a NOAEL of 75 mg/kg bw per day in the rat prenatal developmental toxicity study for decreased maternal body weight gain (GD6-9 at ≥ 225 mg/kg bw per day), using the standard UF of 100, and applying a correction for oral absorption of 70%.
Experts' consultation 2.6 MS experts to discuss non dietary exposure data including dermal absorption values for the product concentrate and spray dilutions.	The agreed dermal absorption values for bixlozone are 0.4% for the concentrate, 6% for the intermediate dilution, and 24% for the lowest dilution. The non-dietary exposure of operators, workers, and residents and bystanders is predicted to be below the (A)AOEL. Open point: RMS to indicate in the final DAR that TRVs will not be exceeded for any intended use, even in the case that the non-dietary exposure assessment is performed using dermal absorption values based on the 2017 EFSA guidance.
Experts' consultation 2.7 (added by EFSA after column 4)	Regarding the co-formulant(s) contained in the formulation used for representative uses, sufficient toxicological data were available for the majority of them. However, for some co-formulant(s) due to insufficient information on genotoxicity, short- and long-term

Subject	Conclusions Pesticide Peer Review Meeting
MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	toxicity, it is not possible to conclude whether they impact on the toxicity (genotoxicity and general toxicity)/classification and safety of the proposed formulation.
Experts' consultation 0.1 MS experts to discuss the validity of the newly submitted data/information on each impurity and the overall toxicological relevance of all these impurities.	The following conclusions were reached for the impurities discussed. **Impurity** [redacted] [redacted] is considered a [redacted] impurity, and it does not pose a toxicological concern at the proposed level of max [redacted]. **Impurity** [redacted] The impurity is not of concern regarding general toxicity, whereas no conclusion can be drawn as to the genotoxicity of [redacted], and a related data gap on genotoxicity was set. **Impurity** [redacted] [redacted] is considered a [redacted] impurity, but that there is no toxicological concern at the proposed level. **Impurity** [redacted] [redacted] cannot be formed at significant concentrations in technical bixlozone and, therefore, its relevance does not need to be addressed.

REPORT OF PESTICIDES PEER REVIEW

TC 124 and TC 125

INDOLYLBUTYRIC ACID – AIR IV **Rapporteur Member State: EL**

2. Mammalian toxicity

Date: 30 January 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS Czechia	National Institute of Public Health - CZ
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Germany	Federal Environmental Agency (UBA) - DE
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National Experts nominated by MS Spain	Ministerio de Sanidad - ES
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National Expert nominated by MS France	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Netherlands	Ctgb - NL
National Expert nominated by MS Poland	E.V.A. - PL
National Expert nominated by MS Slovenia	National Institute of Public Health -SI

Status	Name of institution / attendee
National Expert nominated by MS Slovenia	GEEST s.p. Visoko, Slovenia on behalf of Slovenian Compentent Authority - SI
Observer	Swiss Federal Office for the Environment, Biocided & Plant Protection Products Section - CH
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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the revised assessment of the ADME data for indolylbutyric acid (IBA), in order to conclude on tissue distribution, metabolites formation, accumulation potential and toxicokinetic (TK) parameters (e.g., Cmax, Tmax, T 1/2, AUC).**	**Indolylbutyric acid has high oral absorption (>80%), no potential for bioaccumulation and is expected to have limited tissue distribution in humans. *In vitro* metabolism was assessed, whereas TK parameters were not determined. Overall, it was considered that no further data is needed.**
Experts' consultation 2.2 **Experts to discuss the phototoxicity and photomutagenicity potential of IBA (being a UVB absorber).**	**Data gap.** **Since indolylbutyric acid has a maximum absorption just at the edge of the critical range, it should be tested for its phototoxicity potential, according to OECD 432 (2019) including amiodarone as validated positive control for UVB absorbers.** **A scientific justification for the lack of photomutagenicity should be provided since no validated test is available.**
Experts' consultation 2.3 **Experts to discuss the short-term toxicity of IBA, taking into account:** **- the revised assessment of the**	**In the oral 28-day study, the LOAEL is 1000 mg/kg bw per day (based on altered hematological and urinalysis parameters, and spots on the lung of females).** **The NOAEL in the 90-day rat is 100 mg/kg bw per day based on effects observed at the LOAEL (300 mg/kg bw per day) including**

Subject	Conclusions Pesticide Peer Review Meeting
90-day oral rat study; - the proposed waiving for the 90-day dog study; - the proposed waiving for other routes of administration than oral.	- increased salivation in M/F - decreased BWG in M - decreased urinary pH in M - increased absolute and relative kidney weight in F - increased absolute and relative liver weight in F - stomach acanthosis in F - liver periacinar hypertrophy in M. Waiving of the 90-day dog study is agreed based on the natural presence of IBA and IAA (natural occurring plant hormones and metabolism of tryptophane in animals) and the endogenous levels in humans including pregnant women (from epidemiological studies). Waiving for the repeated dose toxicity study via dermal exposure is agreed based on the lack of systemic effects in the acute dermal toxicity study as well as absence of mortality, considering also the low dermal absorption value. Waiving for the repeated dose toxicity study via inhalation exposure is agreed due to the low vapour pressure and the lack of particles/droplets formation during application.
Experts' consultation 2.4 Experts to discuss the proposed waiving for long term/carcinogenicity data, considering the available mechanistic data (showing activation of the AhR *in vitro*).	Waiving for the long-term/carcinogenicity study is agreed based on absence of structural alerts from *in silico* predictions, natural presence of IBA and IAA (natural occurring plant hormones and metabolism of tryptophane in animals), the endogenous levels in humans including pregnant women (from epidemiological studies), lack of adverse effects (pre-neoplastic) in repeated dose toxicity studies, absence of activation by IBA of the AhR receptor in human liver cells together with considerations on the limited human exposure from the use on ornamentals in greenhouse. Open point: The RMS is requested to provide a more detailed assessment of the *in silico* approach (including an assessment of the applicability domain of the prediction) and to consider whether a read-across approach could be included to further support the waiving.
Experts' consultation 2.5	The parental NOAEL is 100 mg/kg bw per day based on increased incidence of salivation, decreased food consumption and body weight gain during lactation.

Subject	Conclusions Pesticide Peer Review Meeting
Experts to discuss the reproductive toxicity potential of IBA, and the relevant NOAELs, based on: - the revised assessment of the combined 90-day/reproductive toxicity study with IBA - the available data for the metabolite IAA.	The reproductive NOAEL is 100 mg/kg bw per day based on increase number of dead pups at birth and decreased number of implantation sites. The NOAEL for the offspring is 100 mg/kg bw per day based on decreased number of total live pups (related to decreased number of implantation sites) and based on deaths observed in pups during first days of lactation. According to Regulation (EC) No 1272/2008, the criteria for classification of indolylbutyric acid as Repr. 2, H361f may be met, based on the evidence of impaired fertility and the effects on reproductive parameters. Open point: The RMS is invited to submit a proposal for harmonised classification and labelling (CLH dossier) according to the Regulation (EC) No 1272/2008 to ECHA.
Experts' consultation 2.6 Experts' to discuss the developmental toxicity of IBA and the relevant NOAELs based on available studies with IBA and weight of evidence consideration with IAA.	The maternal NOAEL in rat is 300 mg/kg bw per day based on decreased body weight gain. The developmental NOAEL in rat is 100 mg/kg bw per day based on increased early resorptions. The maternal NOAEL in rabbit is 80 mg/kg bw per day based on decreased body weight gain and decreased food consumption. The developmental LOAEL in rabbit is 25 mg/kg bw per day based on malformations (spina bifida and filamentous tail) as well as increased skeletal variations and abortions at higher doses. According to Regulation (EC) No 1272/2008, the criteria for classification of indolylbutyric acid as Repr. 2, H361d may be met based on the evidence for effects on development. Open point: The RMS is invited to submit a proposal for harmonised classification and labelling (CLH dossier) according to the Regulation (EC) No 1272/2008 to ECHA.
Experts' consultation 2.7 Experts to discuss the evidence for neurotocity and developmental neurotoxicity for IBA and IAA.	There is no concern in relation to the neurotoxic potential of IBA. Further neurotoxicity testing is not required.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.8 Experts to discuss the immunotoxicity potential of IBA.	There is no evidence from available repeated dose and reproductive toxicity studies with IBA indicating that indolylbutyric acid may have immunotoxic properties. Further investigation on immunotoxic potential of IBA is not required.
Experts' consultation 2.9 Experts to discuss the ED potential for IBA.	T-modality Scenario 1a of the ECHA-EFSA ED Guidance is applicable and the ED criteria for T-modality are not met. EAS-modalities Scenario 2a(ii) of the ECHA-EFSA ED Guidance is applicable and the ED criteria for the EAS-modalities are not met. **Post-meeting note:** It is noted that the aromatase assay was not conducted according to the OPPTS 890.1200 (US EPA, 2009) as required by the testing strategy as per the ECHA-EFSA ED Guidance.
Experts' consultation 2.10 Experts to discuss the derivation of toxicological reference values (ADI, ARfD, AOEL and AAOEL) for IBA.	The toxicological reference values are: -ADI and AOEL: 0.025 mg/kg bw per day based on the LOAEL from the rabbit developmental toxicity study of 25 mg/kg bw per day. UF of 1000. -ARfD and AAOEL: 0.025 mg/kg bw per day based on the LOAEL from the rabbit developmental toxicity study of 25 mg/kg bw per day applying an overall UF of 1000. The additional UF of 10 accounts for the use of a LOAEL and limitations in the data set.
Experts' consultation 2.11 Experts to discuss dermal absorption and non-dietary exposure estimate for operator (appropriateness of the mixing/loading scenario considered and potential inhalation exposure) and for resident/by-stander (exposure to vapours).	Dermal absorption: The agreed dermal absorption value is 5.9% for IBA in 'Rhizopon AA Powder 2%'. Non-dietary exposure: The agreed estimated operator exposure without PPE is below the AOEL. The agreed estimated resident exposure is below the AOEL for both adult and children. The absence of potential worker exposure was agreed. Open point:

Subject	Conclusions Pesticide Peer Review Meeting
	The RMS is requested to provide revised exposure estimates for acute exposure of operators and bystanders. For bystanders (adult and children), only calculations of the Saturated Vapour Concentration are requested.
Experts' consultation 2.12 MS experts to discuss whether the available information is sufficient to conclude on the risk from the formulation(s) for representative use(s). The discussion should cover both the acute and long-term assessments. If data for the PPP are lacking, MS experts to discuss the ecotoxicological profile of each individual component other than the active substance.	Regarding the components contained in the formulation for the representative uses ('Rhizopon AA powder 2%'), sufficient information was available for all components. A proposal for harmonised classification of a component as Carcinogenic category 2 and STOT RE 1 (H372 - lungs and inhalation) has been submitted to ECHA. Pending the finalisation of the proposal for the harmonised classification for this component by ECHA, a concern over long-term toxicity and carcinogenicity by inhalation is identified for one of the components in this formulation. In addition, further assessment may be required to determine whether a higher category (Carcinogenic category 1B or 1A) for this component should be applied. Open point The RMS to integrate the outcome of the discussion in the revised RAR.

REPORT OF PESTICIDES PEER REVIEW TC 125

PROTHIOCONAZOLE – AIR III **Rapporteur Member State: PL**

2. Mammalian toxicity

Date: 30 January 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS Poland	E.V.A. - PL
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS Czechia	National Institute of Public Health - CZ
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Denmark	Danish Environmental Protection Agency - DK
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Expert nominated by MS Finland	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Netherlands	Ctgb - NL
National Expert nominated by MS Slovenia	National Institute of Public Health - SI
Observer	Danish Environmental Protection Agency - DK

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
New experts' consultation point 2.17 proposed by EFSA for completeness of discussion **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.**	**Regarding the co-formulants contained in the formulation for representative uses Aviator EC 225, based on the available information, sufficient toxicological data were available for the majority of them. However, for some co-formulant(s) there was insufficient information on genotoxicity, general toxicity, reproductive toxicity, and developmental toxicity. Therefore it is not possible to conclude whether there is an impact on the toxicity/classification and safety of the proposed formulation.** **Regarding the co-formulants contained in the formulation for representative uses Redigo FS 100, based on the available information, sufficient toxicological data were available for the majority of them. However, for some co-formulant(s) there was insufficient information on genotoxicity, general toxicity, reproductive toxicity, and developmental toxicity. Therefore it is not possible to conclude whether there is an impact on the toxicity/classification and safety of the proposed formulation.** **Open point (for all co-formulants in the representative formulations):** **RMS to complete the assessment of the toxicological profile of the co-formulants and report it in a revised RAR (Vol. 4) to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term toxicity of the chemically identified co-formulants, including mixtures, if any.** **The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion, and referred to the safety of the co-formulant per se as well as in relation to the concentrations in the PPPs.**

REPORT OF PESTICIDES PEER REVIEW TC 126

***Bacillus subtilis* strain RTI477 – NAS 1107** **Rapporteur Member State: NL**

6. Microorganisms-mammalian toxicity

Date: 1 February 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS Netherlands	Ctgb - NL
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS Belgium	Belgian Federal Public Service (FPS) Public Health, Food Chain Safety and Environment - BE
National Expert nominated by MS Belgium	Sciensano - BE
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
Observer	Federal Food Safety and Veterinary Office FSVO - CH
Observer	Ctgb - NL

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Discussion points/Outcome

6. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 **Experts to discuss the (geno)toxicological assessment of the metabolites for *B. subtilis* RTI477, and the possible need for risk assessment.**	***Bacillus subtilis* RTI477 has the QPS status. The qualification for absence of toxigenic potential was concluded on the basis of a negative Vero cell assay confirming the lack of cytotoxicity (in line with the EFSA FEEDAP guidance 2018) combined with an analysis of the whole genome sequencing data (as performed by the applicant).** **On basis of the available information and provided that low levels and low exposure are sufficiently demonstrated, the risk for human health due to the secondary metabolites produced after application (considering the representative use) by *B. subtilis* RTI477 could be expected to be low.** **Open point:** **RMS to include the new information highlighted for surfactin C (Santana Vieira Santos, 2018; and info from ECHA notification) in the revised RAR.** **Data gap:** **With regard to human exposure to the product (before application), it should be analytically demonstrated that surfactin C and subtilisin are not present in the technical material of *Bacillus subtilis* RTI477 (or below the threshold for classification as sensitiser for subtilisin).**
Experts' consultation 6.2	**Although the clearance was not investigated in the acute oral toxicity, pathogenicity and infectivity study with *Bacillus subtilis* RTI477, it can be concluded on the basis of the available**

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss on the acute oral toxicity, pathogenicity and infectiveness of *B. subtilis* RTI477 and the RMS proposal to waive the study on the grounds of *B. subtilis* being used as a feed additive.	information that this microorganism is not infectious or pathogenic, and no further investigations on acute oral pathogenicity and infectivity are required.
Experts' consultation 6.3 Experts to discuss the acute inhalation study on toxicity, pathogenicity and infectiveness of *B. subtilis* RTI477 based on additional tabulated results/assessment provided in the revised DAR.	The clearance was sufficiently investigated in the acute inhalation study on toxicity, pathogenicity and infectivity of *B. subtilis* RTI477, and the microorganism can be concluded as not infective after intratracheal administration.
Experts' consultation 6.4 Experts to discuss the acute intravenous study on toxicity, pathogenicity and infectiveness of *B. subtilis* RTI477 based on the revised assessment in the DAR.	The clearance was sufficiently investigated in the acute intravenous study on toxicity, pathogenicity and infectivity of *B. subtilis* RTI477, and the microorganism can be concluded as not infective after injection.
Experts' consultation 6.5 Experts to discuss the assessment of the genotoxicity studies provided for *Bacillus subtilis* strain RTI477.	The Ames test performed with *Bacillus subtilis* RTI477 is considered supportive. As there is no indication from public literature that B. subtilis strains can produce genotoxic metabolites, no further data are required. Bacillus subtilis RTI477 is concluded unlikely to be genotoxic.
Experts' consultation 0.1 Experts to discuss the contribution of the co-	Based on the available information, it is possible to conclude that the majority of the co-formulants is not expected to impact on the toxicity/classification and safety of the formulation F4034-5.

Subject	Conclusions Pesticides Peer Review Meeting
formulants to the toxicity profile of the *B. subtilis* strain RTI477.	**Open point:** **RMS is requested to integrate the additional information on the different co-formulants and their toxicological profile (on the basis of the discussion), and the outcome of the assessment in a revised RAR (Vol.4 FMC confidential).**

REPORT OF PESTICIDES PEER REVIEW TC 126

***Bacillus velezensis* strain RTI301 – NAS 1107** **Rapporteur Member State: NL**

6. Microorganisms - mammalian toxicity

Date: 1 February 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS Netherlands	Ctgb - NL
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS Belgium	Belgian Federal Public Service (FPS) Public Health, Food Chain Safety and Environment - BE
National Expert nominated by MS Belgium	Sciensano - BE
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
Observer	Federal Food Safety and Veterinary Office FSVO - CH
Observer	Ctgb - NL

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Discussion points/Outcome

6. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 **Experts to discuss the toxicological assessment of the metabolites for *Bacillus velezensis* strain RTI301, and the possible need for risk assessment.**	***Bacillus velezensis* RTI301 has the QPS status. The qualification for absence of toxigenic potential was concluded on the basis of a negative Vero cell assay confirming the lack of cytotoxicity (in line with the EFSA FEEDAP guidance 2018) combined with an analysis of the whole genome sequencing data (as performed by the applicant).** **On basis of the available information and provided that low levels and low exposure are sufficiently demonstrated, the risk for human health due to the secondary metabolites produced after application (considering the representative use) by *B. velezensis* RTI301 could be expected to be low.** **Open point:** **RMS to include the new information highlighted for surfactin C (Santana Vieira Santos, 2018; and info from ECHA notification) in the revised RAR.** **Data gap:** **With regard to human exposure to the product (before application), it should be analytically demonstrated that surfactin C and subtilisin are not present in the technical material of *Bacillus velezensis* RTI301 (or below the threshold for classification as sensitiser for subtilisin).**
Experts' consultation 6.2	**In the acute studies investigating the toxicity, pathogenicity and infectivity of *Bacillus velezensis* RTI301 (after oral or intratracheal administration), the**

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the acute studies on toxicity, pathogenicity and infectiveness, *Bacillus velezensis* strain RTI301 based on the newly provided study (by injection) and additional tabulated results provided in the revised DAR.	clearance has been sufficiently demonstrated and there is no evidence that the micro-organism may cause toxicity, pathogenicity or infectivity. **Open point** For the acute intratracheal study with *B. velezensis* RTI301, RMS to add information in the revised DAR on the limit of detection, and to clarify whether the CFUs at days 85/86 were below the LoD.
Experts' consultation 6.3 Experts to discuss the assessment of the genotoxicity studies provided for *Bacillus velezensis* strain RTI301.	The Ames test performed with *Bacillus velezensis* RTI301 is considered supportive. As there is no indication from public literature that *B. velezensis* strains can produce genotoxic metabolites, no further data are required. *Bacillus velezensis* RTI301 is concluded unlikely to be genotoxic.
Experts' consultation 0.1 Experts to discuss the contribution of the co-formulants to the toxicological profile of *Bacillus velezensis* strain RTI301.	Regarding the co-formulants contained in the formulation used for representative uses (F4034-5), based on the available information, sufficient toxicological data were available for the majority of the components. However, for some co-formulant(s), due to insufficient information on genotoxicity and long term toxicity, it is not possible to conclude whether there is an impact on the toxicity/ classification and safety of the formulation F4034-5. **Open point** RMS is requested to integrate the additional information on the different co-formulants and their toxicological profile (on the basis of the discussion), and the outcome of the assessment in a revised RAR (Vol.4 FMC confidential).

REPORT OF PESTICIDES PEER REVIEW TC 126

***PHTHORIMAEA OPERCULELLA* GRANULOVIRUS – NAS 1107** **Rapporteur Member State: NL**

6. Microorganisms-mammalian toxicity

Date: 1 February 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS Netherlands	Ctgb - NL
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS Belgium	Belgian Federal Public Service (FPS) Public Health, Food Chain Safety and Environment - BE
National Expert nominated by MS Belgium	Sciensano - BE
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
Observer	Federal Food Safety and Veterinary Office FSVO - CH
Observer	Ctgb - NL

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Discussion points/Outcome

6. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 6.1 **- To discuss the relevance of the available information on the general biology of baculoviruses (e.g. life cycle/mode of action) for the (vertebrate) mammalian risk assessment; this should consider any other relevant information, such as the use of baculoviruses as gene therapy vectors.** **- To discuss if the available literature on baculoviruses (on general biology, discussed as above described, and on putative effects on human health), the available experimental studies and the medical data provided, are sufficient to conclude on the toxicological assessment of PhopGV (isolate V65). The discussion should also**	**Based on up-to-date information on Baculoviruses (including biological properties, specificity to target organism, lack of infectivity, pathogenicity and toxicity for mammalians or the production of any metabolites or toxins) and in line with Commission Regulation (EU) 2022/1438 that refers to Baculoviruses as low risk active substances, there are no safety concerns for humans by the Baculovirus *Phthorimaea operculella*.** **No acute toxicity was observed in studies on the product (acute dermal test, skin sensitisation, inhalation test, eye irritation test).** **Open point:** **RMS to confirm the source/analysis of the most recent WGS data confirming the identity of *Phthorimaea operculella* GV in [redacted], 2023.**

Subject	Conclusions Pesticides Peer Review Meeting
address the possibility to use experimental studies on baculoviruses other than PhopGV (isolate V65) taking into account up-to-date information on its identity.	
Experts' consultation 0.0 (added by EFSA after column 4) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation TUTAVIR used for representative uses, based on the available information sufficient toxicological data were available for all components and it is not expected that they impact on the toxicity/classification and safety of the proposed formulation. Open point The RMS to check the toxicological assessments available under the other EU regulatory frameworks for some co-formulants and to integrate the additional information, as well as the outcome of the discussion in a revised RAR (vol.4).

REPORT OF PESTICIDES PEER REVIEW TC 126

***Pythium oligandrum* strain B301 – NAS 1107** **Rapporteur Member State: BE**

6. Microorganisms-mammalian toxicity

Date: 1 February 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS Belgium	Belgian Federal Public Service (FPS) Public Health, Food Chain Safety and Environment - BE
National Expert nominated by RMS Belgium	Sciensano - BE
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Netherlands	Ctgb - NL
Observer	Federal Food Safety and Veterinary Office FSVO - CH
Observer	Ctgb - NL

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Discussion points/Outcome

6. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 6.1 **Experts to discuss in an experts' meeting the relevance of the macroscopic findings (i.e., adhesions/ nodules) observed in the acute intraperitoneal toxicity study.**	**The provided acute intraperitoneal toxicity study in the rat does not raise concerns as regards the systemic pathogenicity and infectivity of *Pythium oligandrum* strain B301; macroscopic findings observed in both treated groups (given autoclaved and non-autoclaved test substance) are likely compatible with a local effect related to the injection procedure.**
Experts' consultation 6.2 **Infectivity/ pathogenicity potential of *Pythium oligandrum* B301 to be discussed by the experts, taking into account the deficiencies of the available toxicity studies.**	**The available acute studies on *Pythium oligandrum* strain B301 are considered adequate and do not demonstrate that it is infective or pathogenic, despite it can grow at human body temperature.**
Experts' consultation 6.3 **Experts to discuss the revised assessment of the secondary metabolites of *Pythium oligandrum* strain B301.**	**Based on the available information (whole genome sequence (WGS) and pilot batch analysis confirming the lack of secondary metabolites of concern, and literature data), no concern is identified for *Pythium oligandrum* strain B301.** **A data gap is identified for an updated literature review for potentially active metabolites.**

Subject	Conclusions Pesticide Peer Review Meeting
	For reasons of potential relevance (and related uncertainties), tryptamine should be specified in the microbial pest control agent (MPCA) (should be below the LOQ as applied in the pilot batch analysis).
New expert consultation point 6.4 proposed by EFSA for completeness of discussion: **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the preparation with respect to the acute toxicity (including irritation and sensitisation), pathogenicity and infectiveness. For the endpoints not addressed by the preparation data, MS experts to discuss the toxicological profile of each individual component other than the active substance considering i.a. genotoxicity, short- and long-term toxicity including carcinogenicity.**	**Regarding the co-formulant(s) in the formulation proposed for representative uses '17PYO1B', based on the available information, sufficient toxicological data are available to conclude that it is not expected to impact on the toxicity/classification and safety of this formulation.**

REPORT OF PESTICIDES PEER REVIEW TC 125

FORMETANATE – AIR III **Rapporteur Member State: ES**

2. Mammalian toxicity

Date: 30 January 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS Spain	Ministerio de Sanidad - ES
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS Czechia	National Institute of Public Health - CZ
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Denmark	Danish Environmental Protection Agency - DK
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Expert nominated by MS Finland	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Netherlands	Ctgb - NL
National Expert nominated by MS Poland	E.V.A. - PL
National Expert nominated by MS Slovenia	National Institute of Public Health - SI
Observer	Danish Environmental Protection Agency - DK

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues

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discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.13 proposed by EFSA **MS experts to discuss the BMD analysis of ChE inhibition data in the comparative cholinesterase assay and agree on the reference values of the AS.**	**The agreed reference values are:** **ADI: 0.00005 mg/kg bw per day** **ARfD: 0.00005 mg/kg bw** **AOEL: 0.00005 mg/kg bw per day** **AAOEL: 0.00005 mg/kg bw** **based on the BMDL10 for AChE inhibition in rat neonatal brain (0.016 mg/kg bw) derived from the comparative cholinesterase assay and applying an UF of 300 (standard UF of 100 plus an extra UF of 3 due to the lack of DNT study).** **Open points:** **1) RMS to include BMD analysis in the revised RAR;** **2) RMS to update non dietary exposure and risk assessment by using the newly agreed reference values.**
Experts' consultation 2.14 proposed by EFSA **MS experts to discuss the toxicological profile of metabolites.**	**The following conclusions were drawn regarding the metabolites discussed:** **3-FAMPC (3-formylamidophenyl-N-methylcarbamate) (residue)** **In the absence of experimental data and reliable QSAR analyses, and not being a major rat metabolite, data gaps were set for both genotoxicity (mutagenicity and chromosome abberations) and general toxicity.** **3-HPDMF (N'-(3-hydroxyphenyl)-N,N-dimethylformamidine hydrochloride) (residue)**

Subject	Conclusions Pesticides Peer Review Meeting
	Being a major rat metabolite, the Toxicological Reference Values (TRVs) of formetanate can apply. **3-HF (3'-Hydroxyformanilide) (residue)** **Being a major rat metabolite, the TRVs of formetanate can apply.** **3-APMC (3-Aminophenyl methylcarbamate) (residue)** **In the absence of experimental data and reliable QSAR analyses, and not being a major rat metabolite, data gaps were set for both genotoxicity (mutagenicity and chromosome abberations) and general toxicity.** **3-Acetamidophenol (residue)** **Being a major rat metabolite, the TRVs of formetanate can apply.** **3-aminophenol (3-AP) (GW>0.75 µg/L)** **In the absence of experimental data available in the dossier, data gaps were set for both genotoxicity (mutagenicity and chromosome abberations) and general toxicity.**

REPORT OF PESTICIDES PEER REVIEW

TC 124 and TC 125

DAMINOZIDE – AIR III **Rapporteur Member State: CZ**

2. Mammalian toxicity

Date: 30 January 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS Czechia	National Institute of Public Health - CZ
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Germany	Federal Environmental Agency (UBA) - DE
National Expert nominated by MS Denmark	Danish Environmental Protection Agency - DK
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Expert nominated by MS Finland	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS France	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Netherlands	Ctgb - NL
National Expert nominated by MS Poland	E.V.A. - PL
National Expert nominated by MS Slovenia	National Institute of Public Health -SI

Status	Name of institution / attendee
National Expert nominated by MS Slovenia	GEEST s.p. Visoko, Slovenia on behalf of Slovenian Compentent Authority - SI
Observer	Swiss Federal Office for the Environment, Biocided & Plant Protection Products Section - CH
Observer	Danish Environmental Protection Agency - DK
Observer	Finnish Safety and Chemicals Agency (Tukes) - FI
Observer	Ctgb - NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.22 **MSs experts to discuss in an expert meeting the ED potential of the substance daminozide, in view of the newly submitted data.**	**For the ED-potential of daminozide, all experts agreed as follows:** **For T-modality: Scenario 1a applies, ED criteria are not met because there is no T-mediated pattern of adversity in a complete dataset.** **For EAS-modalities:** **After the ED clock stop level 2 and 3 studies (OECD TG 458 AR STTA assays, OECD TG 456 H295R Steroidogenesis Assay, OPPTS 890.1200 Aromatase assay, and OECD TG 441 Hershberger Assay, OECD 455 ER transactivation assay), were made available and are acceptable and negative. Therefore, the dataset for the EAS-modalities is considered complete and the applicable scenario is Scenario 2a (ii): ED criteria not met because no endocrine activity has been observed for the EAS modalities.** **Open point:** **RMS to revise the Vol. 1, specifically on page 237 in Vol. 1 2023-12-14, to delete the sentence: „*Changes in endpoints sensitive to but not diagnostic of T-mediated adversity were not regarded as relevant for ED assessment*" and include the following: *Considering the dataset as a whole the effects in other endpoints sensitive to but not diagnostic of endocrine adversity and or complementary were considered no T-mediated considering the overall WoE. In particular, among others, increase on numbers of embryonic or foetal deaths and viable foetuses and fetal development (i.e. reduced foetal weight and consequent increases in skeletal variationin rabbits; increase incidence of anomalies) and other was considered secondary to over maternal toxicity; liver histopathological changes in rats and mice and changes in pituitary were considered no T-mediated considering the overall WoE.*** **Open point:**

Subject	Conclusions Pesticides Peer Review Meeting
	RMS to include this in the revised RAR Vol. 1 as part of the WoE assessment for the EAS mediated adversities the following agreed statement: Overall, the RMS considered that there is no pattern of EAS-mediated adversity. The potential adverse effects were isolated, found only in aging animals in carcinogenicity studies (in addition NTP carcinogenicity study is of low reliability). Nevertheless, the EAS-mediated adversity was not sufficiently investigated.
New experts' consultation point 2.23 proposed by EFSA for completeness of discussion: MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance. ALAR 85 SG	Regarding the co-formulants contained in the formulation ALAR 85 SG sufficient toxicological data were available for the majority of them. However, for some co-formulant(s) there was insufficient information on genotoxicity, short and long-term toxicity, reproductive and developmental toxicity. Therefore, it is not possible to conclude whether there is an impact on the toxicity/ classification and safety of the proposed formulation. Open point: RMS to check the levels of co-formulants in the formulation ALAR 85 SG; the RMS to integrate the assessment of co-formulants, as needed, in a revised RAR, vol. 4.
New experts' consultation point 2.23 proposed by EFSA for completeness of discussion: MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute,	Regarding the co-formulants contained in the formulation Dazide Enhance sufficient toxicological data were available for the majority of them. However, for some co-formulants(s)there was insufficient information on the genotoxicity, short and long-term toxicity, reproductive and developmental toxicity. Therefore, it is not possible to conclude whether there is an impact on the toxicity/ classification and safety of the proposed formulation. Open point: RMS to check the levels of co-formulants in the formulation Dazide Enhance; the RMS to integrate the assessment of co-formulants, as needed, in a revised RAR, vol. 4.

Subject	Conclusions Pesticides Peer Review Meeting
genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance. Dazide Enhance	

REPORT OF PESTICIDES PEER REVIEW TC 125

GIBBERELLINS – AIR IV **Rapporteur Member State: SI**

2. Mammalian toxicity

Date: 30 January 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS Slovenia	National Institute of Public Health - SI
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS Czechia	National Institute of Public Health - CZ
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Denmark	Danish Environmental Protection Agency - DK
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Expert nominated by MS Finland	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Netherlands	Ctgb - NL
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discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
New experts' consultation point 2.7 identified after the ED clock stop: **Experts to rediscuss the Toxicological Reference Values (TRVs) in view of the RMS recalculations of the doses of the 2-generation reproductive toxicity study for GA 4/7.**	As the substance is naturally occurring and the long-term toxicity has been considered sufficiently addressed, a total uncertainty factor (UF) of 300 is considered sufficient to cover the use of LOAEL for the derivation of the toxicological reference values. The **Acceptable Daily Intake (ADI)** is 0.33 mg/kg bw per day based on the LOAEL of 100 mg/kg bw per day from the developmental study in rabbit and applying a total UF of 300. The **Acceptable Operator Exposure Level (AOEL)** is 0.09 mg/kg bw per day based on the LOAEL of 100 mg/kg bw per day from the developmental study in rabbit, corrected for oral absorption of 26% and applying a total UF of 300. The **Acute Reference Dose (ARfD)** is 0.33 mg/kg bw based on the LOAEL of 100 mg/kg bw per day from the developmental study in rabbits and applying a total UF of 300. The **Acute Operator Exposure Level (AAOEL)** is 0.09 mg/kg bw based on the LOAEL of 100 mg/kg bw per day from the developmental study in rabbit, corrected for oral absorption of 26% and applying a total UF of 300. **Open point** RMS to provide revised non-dietary exposure estimates (for operators, workers, residents and bystanders) with the agreed (A)AOEL in a revised RAR.
New experts' consultation point 2.8 proposed by EFSA for completeness of discussion	Based on the available information, the co-formulant(s) in the formulation for representative uses 'Novagib' are not expected to impact the toxicity/classification and safety of the formulation. **Open point** RMS to include the assessment of the co-formulant(s) in the final RAR Vol.4.

Subject	Conclusions Pesticides Peer Review Meeting
MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	

REPORT OF PESTICIDES PEER REVIEW TC 125

GIBBERELLIC ACID – AIR IV **Rapporteur Member State: SI**

2. Mammalian toxicity

Date: 30 January 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS Slovenia	National Institute of Public Health - SI
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS Czechia	National Institute of Public Health - CZ
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Denmark	Danish Environmental Protection Agency - DK
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Expert nominated by MS Finland	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Netherlands	Ctgb - NL
National Expert nominated by MS Poland	E.V.A. - PL
Observer	Danish Environmental Protection Agency - DK

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
New experts' consultation point 2.10 proposed by EFSA for completeness of discussion MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulants contained in the formulation used for representative uses ('Progibb 40 SG'), based on the available information, sufficient toxicological data were available for all components and it is not expected that they impact on the toxicity/classification and safety of the formulation for representative uses.

REPORT OF PESTICIDES PEER REVIEW

TC 124 AND TC 125

BENSULFURON-METHYL – AIR IV **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 30 January 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Czechia	National Institute of Public Health - CZ
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Germany	Federal Environmental Agency (UBA) - DE
National Expert nominated by MS Denmark	Danish Environmental Protection Agency - DK
National Expert nominated by MS Finland	Finnish Safety and Chemicals Agency (Tukes) - FI
National Expert nominated by MS France	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail - FR
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Experts nominated by MS Netherlands	Ctgb - NL
National Expert nominated by MS Poland	E.V.A. - PL
National Expert nominated by MS Slovenia	GEEST s.p. Visoko, Slovenia on behalf of Slovenian Compentent Authority - SI

Status	Name of institution / attendee
National Expert nominated by MS Slovenia	National Institute of Public Health - SI
Observer	Danish Environmental Protection Agency - DK
Observer	Swiss Federal Office for the Environment, Biocided & Plant Protection Products Section - CH
Observer	Finnish Safety and Chemicals Agency (Tukes) - FI

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

Please note that information part of this report may have been masked by EFSA in accordance with Article 63 of Regulation (EC) No 1107/2009 as well as EFSA's Practical Arrangements concerning confidentiality in accordance with Articles 7 and 16 of Regulation (EC) No 1107/2009, or EFSA's Practical Arrangements concerning transparency and confidentiality as a consequence of confidentiality requests submitted by the applicant on application dossiers for pesticides active substances or Maximum Residue Levels, respectively. Please note that information disclosed in this report is without prejudice to pre-existing intellectual property rights and data exclusivity clauses set out in Union law, and particularly in Article 62 of Regulation (EC) No 1107/2009.

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the oral absorption value for Bensulfuron methyl, taking into account the additional tabulated results for cannulated and non-cannulated animals separately to determine the fraction that is absorbed via oral route vs fraction excreted via bile.**	**Based on radioactivity retrieved from urine and cage wash in non-cannulated rats, oral absorption of bensulfuron-methyl is 60% of administered dose.**
Experts' consultation 2.2 **Experts to discuss the phototoxicity potential of bensulfuron-methyl considering the available phototoxicity study performed with UV wavelength above 320 nm while BSM is also absorbing UVB at wavelength of 290 nm.**	**The available phototoxicity study does not cover the more relevant wavelengths for UVB absorbers such as bensulfuron-methyl.** **A data gap is set for testing the substance at relevant wavelength.**
Experts' consultation 2.3	**In the 90-day oral toxicity study in rats, the NOAEL is confirmed at 93 mg/kg bw per day based on haematological effects (reduced**

Subject	Conclusions Pesticide Peer Review Meeting
Experts to discuss the short-term toxicity studies for bensulfuron-methyl, taking into account the additional tabulated results for the relevant toxicological studies (90-day rat study by [redacted] 1986; 90-day mice study by [redacted] 1984; 90-day dog study by [redacted] 1986 and 1-year dog study ([redacted], 1986)) and the revised assessment in the RAR.	number of erythrocytes, haemoglobin concentration and haematocrit) observed in males at 475 mg/kg bw per day. In the 90-day, oral toxicity study in mice, the NOAEL is lowered to 38.9 mg/kg bw per day based on the liver effects (increased liver weight and histopathology – centrilobular swelling of hepatocytes) observed at 132 mg/kg bw per day. In the 90-day, oral toxicity study in dogs, the NOAEL is confirmed at 32 mg/kg bw per day based on reduced food efficiency and liver toxicity (clinical chemistry changes - ALP and ALT, increased liver weight, and microscopic findings - centrilobular hepatocellular swelling, individual hepatocyte necrosis, bile stasis and gallbladder calculi) observed at 341 mg/kg bw per day. In the 1-year, oral toxicity study in dogs, the NOAEL is confirmed at 19.9 mg/kg bw per day, based on liver toxicity: increased liver weight, microscopic (biliary canaliculi: brown pigment) and clinical chemistry findings (increased ALT and ALP) observed at 222.6 mg/kg bw per day.
Experts' consultation 2.4 To discuss if the aneugenic potential of bensulfuron methyl has been sufficiently addressed, taking into account the available data package (results and acceptability of the different studies).	Bensulfuron-methyl in unlikely to be mutagenic, clastogenic or aneugenic. The *in vitro* evidence is sufficient to conclude on its aneugenicity potential.
Experts' consultation 2.5 Experts to discuss the long-term toxicity and carcinogenicity study in rats, including the setting of the NOAELs (for systemic toxicity and carcinogenicity), taking into account the additional tables for clinical chemistry and haematology parameters,	In the 2-year toxicity study in rats, the systemic chronic NOAEL is confirmed at 30 mg/kg bw per day based on reduced body weight and bw gain, haematological changes (reduced haemoglobin concentration) and liver toxicity (microscopical findings - centrilobular hepatocellular hypertrophy and increased incidence of focal fatty changes) observed at 309 mg/kg bw per day. The carcinogenic NOAEL is 309 mg/kg bw per day, the highest dose tested.

Subject	Conclusions Pesticide Peer Review Meeting
as well as further description of the liver effects.	
Experts' consultation 2.6 Experts to discuss findings (particularly clinical pathology data, kidneys and liver histopathological neoplastic and non-neoplastic changes, etc.) in the long-term toxicity and carcinogenicity study in mice by [redacted], 1985, and their impact on the study NOAELs.	In the 2-year toxicity and carcinogenicity study in mice, the NOAEL is confirmed at 226 mg/kg bw per day, based on liver toxicity (increased weight, chemical chemistry – increased AST activity and microscopical findings – centrilobular hepatocellular swelling) observed at the top dose level of 455 mg/kg bw per day. The carcinogenic NOAEL is 455 mg/kg bw per day, the highest dose tested. Open point: RMS to include the BMD calculations discussed during the meeting in a revised RAR.
Experts' consultation 2.7 Experts to discuss and agree on the rat developmental NOAEL from the developmental toxicity study by [redacted], 1999.	In the developmental toxicity study in rats, the maternal NOAEL is confirmed at 2000 mg/kg bw per day, the highest dose tested. The developmental NOAEL is lowered to 50 mg/kg bw per day, based on increased incidences of foetuses with variations per litter, i.e. partially or unossified hyoid and extra rib ossification centre observed at 500 mg/kg bw per day. Open point: RMS to provide in a revised RAR correct calculations of the incidences of developmental effects expressed as percentage on a litter basis.
Experts' consultation 2.8 Experts to discuss the outcome of the developmental toxicity study in rabbits, taking into account the historical control data and the revised assessment.	In the developmental toxicity study in rabbits the maternal NOAEL is 300 mg/kg bw per day, based on decreased body weights and food consumption, and on the occurrence of spontaneous deaths observed at 1500 mg/kg bw per day; the developmental NOAEL is 300 mg/kg bw per day, based on increased total resorptions and reduced foetal weights (>10%) observed at 1500 mg/kg bw per day.
Experts' consultation 2.9 Experts to discuss ED potential of bensulfuron-	*T-modality* There is no evidence of a pattern of T-mediated adversity in the available and complete dataset consisting of studies of different duration conducted in mice, rats and dogs. Scenario 1a of the

Subject	Conclusions Pesticide Peer Review Meeting
methyl in an experts' meeting.	EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and the ED criteria for T-modality are not met. ***EAS-modalities*** There is no evidence of EAS-related endocrine activity/adversity in the available dataset. Scenario 2a (ii) of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and the ED criteria for EAS-modalities are not met. **Open point:** RMS to revise the RAR in accordance with the outcome of the peer review meeting discussion.
Experts' consultation 2.10 Experts to discuss the toxicological assessment of the following groundwater metabolites and specifically the genotoxicity and general toxicity of: • IN-R9419 • IN-J0290 • IN-5297 • IN-DIR84 • IN-DAT97 (The groundwater metabolites to be discussed might vary pending confirmation of their predicted levels from the new e-fate studies)	For the following metabolites found in GW and in residues, the following conclusions were agreed: • IR-R9419: o As GW metabolite: in the absence of experimental data, data gap for chromosome aberration (covering clastogenicity and aneugenicity) o As residue metabolite: considering the structural similarity with the parent, read across is considered acceptable for both genotoxicity and general toxicity and reference values of the parent might apply. • IN-J0290: o As GW and/or residue metabolite: data gap for chromosome aberration (covering clastogenicity and aneugenicity) and general toxicity. • IN-N5297: o As GW metabolite: data gap for genotoxicity (mutagenicity, clastogenicity and aneugenicity) and general toxicity. o As residue metabolite: data gap for chromosome aberration (clastogenicity and aneugenicity) and general toxicity (mutagenicity was considered covered by the neg. Prediction by QSAR analysis). • IN-DIR84: o as GW metabolite: data gap for genotoxicity (mutagenicity, clastogenicity and aneugenicity) and general toxicity. o As residue metabolite: data gap for chromosome aberration (clastogenicity and aneugenicity) and

Subject	Conclusions Pesticide Peer Review Meeting
	general toxicity. Mutagenicity was considered covered by the neg. prediction by QSAR analysis. • IN-DAT97: o GW metabolite only: data gap for genotoxicity (mutagenicity, clastogenicity and aneugenicity) and general toxicity.
Experts' consultation 2.11 Experts to discuss the genotoxicity and/or general toxicity of the following residue metabolites: IN-J0290, IN-R9419, IN-DIR84, Didesmethyl bensulfuron-methyl, IN-H9235, IN-B6895, IN-5297, IN-F7880, IN-78184, IN-N8989.	For conclusions on metabolites IN-5297, IN-R9419, IN-J0290 and IN-DIR84 as metabolites found in residues and GW see 2.10. For the following metabolites found in residues, the following conclusions were agreed: • IN-B6895 (homosaccharin): data gap for chromosome aberration and general toxicity. • IN-H9235 glucose conjugate: read across to IN-J0290 for gene mutation based on structural similarity, and data gap for chromosome aberration and general toxicity. • IN-F7880: being a major rat metabolite, reference values of the parent might apply. • IN-78184: data gap for genotoxicity (all endpoints) and general toxicity. • Di-desmethyl bensulfuron-mehtyl: read across to the parent for gene mutation based on structural similarity; data gap for chromosomal aberration and general toxicity. • IN-N8989: data gap for chromosome aberration and general toxicity.
Experts' consultation 2.12 Experts need to agree on the toxicological end points for assessment of risk following long-term dietary exposure – ADI (acceptable daily intake), and acute dietary exposure – ARfD (acute reference dose), as well as toxicological end points for assessment of occupational, bystander and resident risks (A)AOEL (acceptable operator exposure level)	The agreed reference values are: • ADI: 0.2 mg/kg bw per day based on the NOAEL of 19.9 mg/kg bw per day for increased liver weights accompanied by microscopic findings (biliary canaliculi: brown pigment) and statistically significant increased alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activity in the 1-year study in dogs: UF of 100 • No ARfD set as bensulfuron-methyl is not acutely toxic. • AOEL: 0.12 mg/kg bw per day based on the NOAEL of 19.9 mg/kg bw per day from the 1-year oral toxicity study in dogs, applying an UF of 100 and correction for limited oral absorption of 60%. • No AAOEL allocated as bensulfuron-methyl is not acutely toxic.

Subject	Conclusions Pesticide Peer Review Meeting
including the correction factor for oral absorption.	
Experts' consultation 2.13 Experts to discuss the non-dietary exposure estimates, including worker exposure for the representative use on rice and the re-entry in flooded rice field.	For the representative use on rice, the relevant scenario for the worker re-entering the field for inspection activities should include exposure estimates from exposure to dry residues (on treated crops) and exposure from the re-entry in flooded rice fields. Open point: RMS to calculate the worker exposure for inspection in rice crops, summing the potential exposure to dry residues and the exposure by walking into the flooded paddy field (with the agreed parameters and relevant application rates).
Experts' consultation 2.14 (set by EFSA after column 4 step) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	Regarding the co-formulant(s) contained in the formulation used for representative uses (Londax 60 BF), sufficient toxicological data were available for the majority of them. However, for [redacted], due to insufficient information on the grade used, it is not possible to conclude whether [redacted] impact on the toxicity (genotoxicity and general toxicity)/classification and safety of the proposed formulation. In addition, for a co-formulant, some concerns are present in relation to the possible adverse effects via inhalation.

REPORT OF PESTICIDES PEER REVIEW

TC 124 AND TC 125

MEPIQUAT CHLORIDE – AIR IV **Rapporteur Member State: FI**

2. Mammalian toxicity

Date: 30 January 2024

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by RMS Finland	Finnish Safety and Chemicals Agency (Tukes) - FI
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Czechia	National Institute of Public Health - CZ
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Germany	Federal Environmental Agency (UBA) - DE
National Expert nominated by MS Denmark	Danish Environmental Protection Agency - DK
National Expert nominated by MS France	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail - FR
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Experts nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Netherlands	Ctgb - NL
National Expert nominated by MS Poland	E.V.A. - PL
National Expert nominated by MS Slovenia	GEEST s.p. Visoko, Slovenia on behalf of Slovenian Compentent Authority - SI

Status	Name of institution / attendee
National Expert nominated by MS Slovenia	National Institute of Public Health - SI
Observer	Danish Environmental Protection Agency - DK
Observer	Swiss Federal Office for the Environment, Biocided & Plant Protection Products Section - CH
Observer	Finnish Safety and Chemicals Agency (Tukes) - FI

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.13 identified after the ED clock stop: **MSs experts to discuss the overall conclusion of the endocrine disruption (ED) assessment in an experts' meeting.** **The discussion should also cover the adequacy and the outcome of the developmental neurotoxicity (DNT) study in view of the new consideration provided by the applicant and the newly available in vitro measurement (ToxCast).**	***EAS-modalities*** **There is no evidence of EAS-related endocrine activity/adversity in the available dataset. Scenario 2a (ii) of the ECHA EFSA ED Guidance (ECHA-EFSA, 2018) is applicable and the ED criteria for the EAS-modalities are not met.** ***T-modality*** **There is no evidence of a pattern of T-mediated adversity in the available and complete dataset consisting of studies of different duration conducted in mice, rats and dogs. Scenario 1a of the ECHA-EFSA ED Guidance is applicable and the ED criteria for T-modality are not met.** **DNT study** **The dose selection of the DNT study is adequate and sufficient to investigate DNT endpoints. The NOAEL for developmental neurotoxicity is 30 mg/kg bw per day based on a decreased thickness of the corpus callosum in both male and female pups at post-natal day (PND) 22 and 62 at the top dose of 60 mg/kg bw per day (LOAEL), in the absence of maternal toxicity.** **Open point:** **RMS to revise the RAR in accordance with the outcome of the peer review meeting discussion.**
Experts' consultation 2.14 identified after the ED clock stop: **MSs experts to discuss the potential impact of the ECHA RAC Opinion (2021),**	**In March 2020, at the Pesticides Peer Review Experts meeting 25, all the the toxicological reference values (TRVs) for mepiquat chloride were set on the basis of hydrocephaly at the lowest dose of 50 mg/kg bw per day (LOAEL) in the prenatal developmental toxicity study in Himalayan rabbits via oral administration (gavage).**

Subject	Conclusions Pesticides Peer Review Meeting
adopted during the ED clock stop, on the risk assessment for the substance mepiquat chloride.	In 2021, ECHA RAC concluded on no classification of mepiquat chloride for STOT SE 2 or Repr. 2. The evidence from the rabbit developmental toxicity study was considered as not sufficiently strong to trigger classification as Cat 2 Reproductive toxicant. Regarding the potential impact of the RAC Opinion, the MS experts stressed that hazard-based classification and risk assessment are two independent processes, and that a toxicological study not triggering classification by RAC could still be used for establishing a point of departure for risk assessment. Nonetheless, the MS experts re-examined the rabbit developmental toxicity study, and expressed uncertainty as to whether the few cases of hydrocephaly were treatment-related, when considering the litter as the statistical unit, and the incidence of hydrocephaly still within historical control data. The DNT study was therefore selected as the critical study for setting the (A)AOEL and ARfD and the previously proposed TRVs were revised as follows: AOEL (Acceptable Operator Exposure level) is 0.23 mg/kg bw per day based on the NOAEL of 30 mg/kg bw per day for pups‘ lethality in the DNT study, applying a standard uncertainty factor (UF) of 100 and correcting for 77% oral absorption. Acute AOEL (AAOEL) is 0.23 mg/kg bw, based on the NOAEL of 30 mg/kg bw per day for pups‘ lethality in the DNT study, applying a standard UF of 100 and correcting for 77% oral absorption. ARfD (Acute Reference Dose) is 0.3 mg/kg bw based on the NOAEL of 30 mg/kg bw per day for pups‘ lethality in the DNT study, applying a standard UF of 100. ADI (Acceptable Daily Intake) is 0.065 mg/kg bw per day based on the LOAEL of 13 mg/kg bw per day for decreased body weight and body weight gain in the 2-year rat study and an UF of 200 (100 for intra- and inter-individual variability and 2 for the extrapolation of the NOAEL from the LOAEL). Open point RMS to modify in RAR Vol. 1 and LoEP the classification proposal of Repr.2. Open point RMS to correct the values in the RAR for the litter incidence (i.e. 0, 1.0, 0.0, 1.0 at 0, 50, 100 and 150 mg/kg bw per day) in the rabbit prenatal developmental toxicity study.

Subject	Conclusions Pesticides Peer Review Meeting
	Open point RMS to revise the non-dietary exposure assessment based on the newly agreed TRV values. **Open point** As regards the critical effects in the 2-year rat study chosen for setting the ADI, please indicate that those refer to both decreased body weight and decreased body weight gain. This should be corrected in Vol 1, Vol 3 and the LoEP, where „decreased bw changes" is instead reported.
Experts' consultation 2.15 identified after the ED clock stop: MSs experts to discuss the outcome of the reproductive/developmental toxicity study (OECD TG 421) and its implications on the toxicological endpoints and human health (including NOAEL/LOAEL values).	For the new OECD TG 421-compliant reproductive/developmental toxicity study the agreed NOAELs are: NOAEL for reproductive toxicity: 135 mg/kg bw per day, for decreased mean implantation sites and decreased live born pups parental NOAEL (systemic): 115/134 mg/kg bw per day (M/F) for decreased body weight, decreased body weight gain and decreased food consumption in F0 NOAEL for postnatal toxicity: 135 / 146 mg/kg bw per day (M/F) for decreased mean pup body weight and decreased pup body weight gain. The NOAELs from the OECD 421 study are either higher or in the same order of magnitude of those in the 2-generation study. They have no impact on the toxicological endpoints and TRVs for mepiquat chloride. Based on the 2-generation toxicity study, the agreed relevant reproductive NOAEL and the relevant offspring NOAEL are 155 mg/kg bw per day. The relevant parental NOAEL is 52 mg/kg bw per day. **Open point** RMS to include in a revised RAR Vol. 1 and Vol. 3 B6 the agreed NOAEL for reproductive toxicity in the OECD TG 421 (135 mg/kg/day based on decreased mean implantation site and decreased live born pups).
New experts' consultation point 2.16 proposed by EFSA for completeness of discussion: MS experts to discuss whether the available information is sufficient to characterise the full	Due to the nature of the co-formulant present in the representative formulation, the assessment of its toxicological profile is not needed. However, since the formulation contains two active substances, an additive risk assessment is needed. However, no additional concerns were identified for co-formulants. **Open point:**

Subject	Conclusions Pesticides Peer Review Meeting
toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	**RMS to ensure that the RAR reflects the availability and outcome for the additive risk assessment for the two active substances.**

REPORT OF PESTICIDES PEER REVIEW

TC 118 and TC 119

CHLOROTOLURON – AIR III **Rapporteur Member State: BG**

2. Mammalian toxicity

Date: 17 November 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by RMS BG	Risk Assessment Center on Food Chain - BG
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (Bfr) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS EL	BENAKI PHYTOPATHOLOGICAL INSTITUTE - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Experts nominated by RMS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS HR	Institute for Medical Research and Occupational Health - HR
National Expert nominated by MS HU	National Food Chain Safety Office (NEBIH) - HU
National Experts nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Expert nominated by MS NL	Ctgb - NL
Observer (CH)	FSVO - CH

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Discussion points/Outcome

2. Mammalian toxicity

Please note that information part of this report may have been masked by EFSA in accordance with Article 63 of Regulation (EC) No 1107/2009 as well as EFSA's Practical Arrangements concerning confidentiality in accordance with Articles 7 and 16 of Regulation (EC) No 1107/2009, or EFSA's Practical Arrangements concerning transparency and confidentiality as a consequence of confidentiality requests submitted by the applicant on application dossiers for pesticides active substances or Maximum Residue Levels, respectively. Please note that information disclosed in this report is without prejudice to pre-existing intellectual property rights and data exclusivity clauses set out in Union law, and particularly in Article 62 of Regulation (EC) No 1107/2009.

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the ADME studies for chlorotoluron (including the final report of the pharmacokinetics study in rats) in relationship with: - the setting of an oral absorption value for chlorotoluron to be applied for the derivation of the (A)AOEL; - the residue definition for the monitoring of (human) body fluids (urine, blood): which metabolites should be included, at which time point they should be analysed and if validated analytical methods are available.	For chlorotoluron, an oral absorption value ≥ 80% is applicable, considering the entero-hepatic circulation of the compound after oral absorption. Regarding the proposed residue definition, major metabolites should be included with chlorotoluron (i.e. CTU benzyl alcohol, desmethyl CTU benzoic acid, and CTU benzoic acid). **Open point** RMS to indicate in a revised RAR if validated analytical methods are available for the metabolites included in the residue definition (CTU, CTU benzyl alcohol, desmethyl CTU benzoic acid and CTU benzoic acid) (with a cross-reference to their assessment in section B.5).
Experts' consultation 2.2 Experts to discuss the results of *in vitro* comparative metabolism (tested species and possible unique human metabolite desmethyl-CTU).	Based on a newly available *in vitro* comparative metabolism study presenting some limitations (e.g. rabbit metabolism not investigated), the metabolite R17 (desmethyl CTU) is identified as a disproportionate human metabolite of chlorotoluron (present at a level 4 times higher in human than in rat microsome). See also experts' consultation 2.12 where its toxicological profile is discussed.
Experts' consultation 2.3	In the 90-day rat study (pre-guideline), a LOAEL was identified at 52.7 mg/kg bw per day (low dose tested) based on decreased red blood cells in

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the NOAELs in the 90-day rat and dog studies.	females, increased relative liver weight in males, congestion and dark discolouration of the spleen and liver in males. In the 90-day dog study (pre-guideline), a LOAEL of 21.5 mg/kg bw per day (low dose tested) was identified based on decreased red blood cells in females, and haemosiderosis in the liver and spleen.
Experts' consultation 2.4 Genotoxicity potential of chlorotoluron to be discussed by the experts, considering the available data (*in vitro* tests and literature data) together with the additional *in vivo/in vitro* tests provided during the stop-clock.	Based on the new genotoxicity studies with a recent batch of technical CTU, it can be concluded that CTU is unlikely to be genotoxic since no mutagenic, clastogenic or aneugenic potential has been detected. **Open point** RMS to clarify/check if the *in vivo* Nucleus anomaly test in Chinese hamsters (1982) and the Dominant lethal assay mentioned by the applicant during the commenting period were in the dossier. If yes, their assessment should also be included in the revised RAR.
Experts' consultation 2.5 Experts to discuss the long-term mouse study including: - the setting of the NOAEL for chronic toxicity, considering the revised assessment provided by the RMS; - the setting of the NOAEL for carcinogenicity, considering the available mechanistic data (on kidney tumors in male mice).	In the 2-yr mouse study with chlorotoluron, the NOAEL for chronic toxicity is 100 ppm (low dose) based on increased albumin level in males, while the NOAEL for carcinogenicity is 500 ppm (mid dose) based on increased incidences of tumours in kidney, liver and Harderian gland. Mechanistic studies (with limitations) were not considered sufficient to support the non-relevance of renal tumours to humans. **Open point** RMS is requested to check the dose conversion for the 2-yr mouse study in the different parts of the RAR: for the low dose, 11.2 is mentioned in Vol.1 for males while 11.4 is mentioned in Vol.3 B.6. Furthermore, a new table 5.5.1-1 has been included in the revised RAR with Test article intake for different time points during the study, and the reported value (11.0 at wk 52 or 8.2 at wk 101) is not corresponding to the reported values in the text.
Experts' consultation 2.6 Experts to discuss the rat long term toxicity of chlorotoluron (relevant systemic NOAEL and carcinogenicity NOAEL), considering the assessment of the second long term rat study in the revised RAR.	For the first 2-year rat study, the NOAEL for systemic toxicity is 100 ppm (low dose) based on decreased body weight and mean food consumption at 500 ppm (in both sexes). The NOAEL for carcinogenicity is 2500 ppm (top dose) in the absence of treatment-related oncogenic findings. For the second 2-year rat study, the proposed NOAEL for carcinogenicity and systemic toxicity is 200 ppm (low dose) based on the limited available assessment. **Open point** RMS is requested to check the dose levels as expressed in mg/kg bw per day in the first 2-yr rat study and to revise the table of organ weight at terminal sacrifice (Table CA 5.5.2-4) and the table of Microscopic findings (CA 5.5.2-4) since some results seems incorrectly reported.

Subject	Conclusions Pesticides Peer Review Meeting
	Open point RMS to provide additional tabulated summaries in the revised RAR for the second 2-yr rat study, in order to allow a transparent assessment for findings other than tumours to support the derivation of the NOAEL for systemic toxicity, as well as for body weight values to support the conclusion on the MTD.
Experts' consultation 2.7 Experts to discuss the revised assessment of the 2-generation rat study.	For the 2-generation rat study with chlorotoluron, the parental NOAEL is 300 ppm based on reduced body weight and increased spleen weight (F2 females); the offspring NOAEL is 1000 ppm based on reduced body weight and decreased exploratory locomotion pattern in F2 pups; the NOAEL for reproductive parameters 1000 ppm based on the decreased number of implantation sites. On the basis of the information as currently reported in the RAR, considering the distribution of the litter/pup mortality across all groups, it is not possible to identify a treatment related effect, however uncertainty in the reliability and conclusions of the study is acknowledged. The recommended OECD TG 443 study (see EC 2.10 below) would be expected to provide more reliable information on reproductive toxicity and neurotoxicity in the sensitive population. **Open point** For the rat multigeneration study, RMS is requested to provide in a revised RAR more details about the conversion of the doses in ppm into mg/kg bw per day, including the mean value for the period 1 to 8 weeks of the premating period. **Open point** For the rat multigeneration study, RMS is requested to provide in a revised RAR an updated tabulated summary for the body weight values (Table 5.6.1-4) including F1 and providing the % change vs controls (rather than vs the low dose group). **Open point** For the high mortality observed in the litters of the rat multigeneration study, RMS is requested to include in the revised RAR a new Table 5.6.1-1 reporting litter mortality in details, including clearly the number of dead pups per litter and per group. Also the RMS is requested to verify if historical control data are reported in the dossier, and amend the revised RAR with this information if available.
Experts' consultation 2.8 Experts to discuss the revised assessment of the rat developmental toxicity study (and	For the rat developmental toxicity study, the maternal NOAEL 21 mg/kg bw per day (low dose) based on spleen weight increase and haematological changes at the mid dose; the developmental NOAEL is 470 mg/kg bw per day (high dose) in the absence of treatment-related adverse effects.

Subject	Conclusions Pesticides Peer Review Meeting
range-finding study), including setting of the relevant developmental and maternal NOAELs.	**Open point** RMS to check whether a correction has been applied to the low dose level, considering that there was a lack of stability of the test substance after storage (-21%) at the low dose, and, in the case this was not done, to correct it accordingly.
Experts' consultation 2.9 Experts to discuss the revised assessment of the developmental rabbit toxicity studies (with setting of maternal and developmental NOAELs), including consideration of the additional studies provided for the characterization of the maternal toxicity in rabbits.	For the **first rabbit** developmental toxicity study (with Himalayan rabbits), the maternal NOAEL is 140 mg/kg bw per day based on decreased body weight and food consumption at 630 mg/kg bw per day (top dose); the developmental NOAEL is 12 mg/kg bw per day based on foetal malformations at 140 mg/kg bw per day (mid dose). For the **second rabbit** developmental toxicity study (with Chinchilla rabbits), the maternal NOAEL is 450 mg/kg bw per day (top dose); the developmental NOAEL is 50 mg/kg bw per day based on post implantation losses, as supported by BMD analysis. The additional study investigating maternal toxicity in rabbits (New Zealand White) and not developmental toxicity, was concluded as not impacting on the developmental and maternal toxicity results with other strains of rabbits (Chinchilla and Himalayan).
Experts' consultation 2.10 Experts to discuss the ED potential of chlorotoluron on the basis of the assessment according to the ECHA/EFSA GD, taking into account new available data providing during the clock-stop.	**T modality** There is no evidence of a pattern of T-mediated adversity in an incomplete dataset. Since some changes in T4 and TSH were observed in the male and female peripubertal studies **Scenario 2a(i)** of the EFSA/ECHA ED Guidance is applicable. **EAS-modalities** A pattern of EAS-mediated adversities was not observed in an incomplete dataset. **Scenario 2a(iii)** of the EFSA/ECHA ED Guidance is applicable. Overall, based on the limited reliability of the available dataset and on the necessity of having additional data to conclude on the EATS modalities, a study in line with OECD TG 443, with the inclusion of the F2 generation and of T mediated endpoints measured in the sensitive population (i.e. THs, TSH and thyroid histopathology in dams, foetuses GD20 and pups on PND 4 and 21), is recommended.
Experts' consultation 2.11 Experts to discuss the toxicological relevance of the groundwater metabolite CTU benzoic acid.	For the groundwater metabolite CTU benzoic acid, it can be concluded that it has no genotoxic potential, but the toxicological relevance cannot be excluded since it has not been demonstrated as not sharing the reproductive toxicity and carcinogenic properties of chlorotoluron (classified Repro cat 2 and Carc cat 2). For the metabolite CTU benzoic acid found in Residues, the toxicological reference values of chlorotoluron can be applied for the consumer's risk assessment.
Experts' consultation 2.12	For the metabolites

Subject	Conclusions Pesticides Peer Review Meeting
Experts to discuss the profile of the following metabolites, for their genotoxicity and general toxicity (whether they share the same toxicological profile as the parent CTU and their relative potency or if separate toxicological reference values need to be derived): 1) desmethyl-CTU (CGA 16339) 2) didesmethyl-CTU (CGA 16340) 3) CTU benzoic acid (CGA 15140) 4) desmethyl-CTU benzoic acid (CGA 15139) 5) didesmethyl-CTU benzoic acid (CGA 14119) 6) CTU benzyl alcohol (CGA 18029) 7) desmethyl CTU benzyl alcohol (CGA 16342) 8) didesmethyl CTU benzyl alcohol (CGA 25932) 9) cysteine conjugate of desmethyl CTU 10) cysteine conjugate of didesmethyl CTU 11) N-formyl CTU benzoic acid	• desmethyl-CTU (CGA 16339), • didesmethyl-CTU (CGA 16340), • CTU benzoic acid (CGA 15140), • desmethyl-CTU benzoic acid (CGA 15139), • didesmethyl-CTU benzoic acid (CGA 14119), • CTU benzyl alcohol (CGA 18029), • desmethyl CTU benzyl alcohol (CGA 16342), • didesmethyl CTU benzyl alcohol (CGA 25932), the available experimental data, QSAR analyses, grouping and read across approaches did allow to conclude that they were unlikely to be genotoxic and that the toxicological reference values of chlorotoluron were also applicable. For the metabolites • cysteine conjugate of desmethyl CTU, • cysteine conjugate of didesmethyl CTU, • N-formyl CTU benzoic acid, based on the available data (QSAR predictions for bacterial mutagenicity negative), their genotoxic potential (clastogenicity and aneugenicity) and general toxicity profile cannot be concluded. **Open point** RMS is requested to present in a revised RAR the outcome of the QSAR analyses available for the metabolite **didesmethyl-CTU (CGA 16340)** in order to clarify that the positive predictions are of no concern considering the applicability domain. **Open point** RMS is requested to provide in the revised RAR an assessment of the *in vivo* micronucleus test with the metabolite **desmethyl-CTU benzoic acid (CGA 15139)** ('Nucleus anomaly tests in somatic interphase nuclei') since this test was mentioned in the reporting table (see data requirement in comment 2(188)).
Experts' consultation 2.13 Experts to discuss the derivation of the toxicological reference values: ADI, ARfD, AOEL and AAOEL.	Considering the limitations in the available studies (e.g. 90-day dog study, rat multigeneration study), the lack of assessment of some studies (e.g. the second 2-year rat study), and the recommendation to provide an additional OECD TG 443 study to finalise the ED assessment, it was agreed to postpone the discussion on the toxicological reference values applicable to chlorotoluron.
Experts' consultation 2.14 Experts to discuss the dermal absorption values for the	The dermal absorption values for Chlorotoluron 700 SC are 10% for the concentrate (700 g/L) and 11% for the dilution (12.5 g/L). No pro-rata correction is needed for higher dilutions.

Subject	Conclusions Pesticides Peer Review Meeting
representative use (winter and spring cereals) of the product Tolurex 700 SC, including consideration of the need of pro-rata correction for the highest dilution (4.5 g/L). It is noted that EFSA GD 2012 was applicable when dossier was submitted, but EFSA GD 2017 should also be used in order to agree on DA values that could potentially be used at MS level.	
Experts' consultation 2.15 proposed by EFSA MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	As only the acute toxicity profile of the co-formulants in Chlorotoluron 700 SC has been considered, no conclusion on the overall safety of the co-formulants can be drawn. **Open point:** RMS is requested to complete the assessment of the toxicological profile of the co-formulants in Chlorotoluron 700 SC and report it in the revised RAR (vol. 4) to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures. The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion, and referred to the safety of the co-formulant per se as well as in relation to the concentrations in the PPP. A disclaimer should be included for all evaluations, indicating the limitations of the database as to the reliance of the existing evaluations.

REPORT OF PESTICIDES PEER REVIEW

TC 118 and TC 119

CYPRODINIL – AIR III after ED clock stop **Rapporteur Member State: FR**

2. Mammalian toxicity

Date: 17 November 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by RMS BG	Risk Assessment Center on Food Chain - BG
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (Bfr) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS EL	BENAKI PHYTOPATHOLOGICAL INSTITUTE - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Experts nominated by RMS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS HR	Institute for Medical Research and Occupational Health - HR
National Expert nominated by MS HU	National Food Chain Safety Office (NEBIH) - HU
National Experts nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Expert nominated by MS NL	Ctgb - NL
Observer (CH)	FSVO - CH

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.17 **MSs experts to discuss the applicant position on the reliability of balano-preputial separation assessment and the acceptability of the of the 2-generation toxicity study (OECD TG 416).**	**The rationale** **Based on the statistical significance of the observed dose-effect and on the reliability of the concurrent control, a treatment related adverse effect can be considered for the balano-preputial separation (BPS) and the results should be considered reliable.** **Conclusion** **There is a statistically significant, treatment-related effect in BPS in the reproductive 2-genaration rat study (OECD TG 416). The effect starts at 1400 ppm (mean +2.3 days) and has a high magnitude at 4200 ppm (mean +6.3 days). Such effect should be considered in the overall EAS-assessment of cyprodinil.**
Experts' consultation 2.18 **MSs experts to discuss at the experts' consultation meeting the ED potential properties regarding the EATS-modalities including in the overall weight of evidence the new studies/data made available during the regulatory stop-of-the-clock period.**	**T-modality** **T-mediated ED effects were evaluated considering the new studies submitted. T-mediated endocrine activity was observed in the new studies, i.e inhibition of NIS, inhibition of DIO3 and inhibition of IYD lead to the conclusion that a pattern of adversity and an endocrine MoA can be expected (scenario 1b).** **T-mediated effects are considered inconclusive in align with the current dataset.** **EAS-modalities** **A pattern of EAS-mediated adversity i.e. increased age at balano-preputial separation and decreased AGDI in F1 and F2 males and**

Subject	Conclusions Pesticides Peer Review Meeting
	females, has been observed for cyprodinil in a sufficiently investigated dataset. Effect on parameters considered sensitive to but not diagnostic of i.e. increased number of ovarian follicles, decreased number of implantation scars, also corroborated the pattern observed. The observed pattern of EAS-mediated adversity suggests an anti-androgenic mode of action (MoA) without excluding other potentially relevant MoAs, i.e. estrogenic and aromatase inhibition. This is substantiated by the results of the OECD TG 456 study i.e. positive for induction of E2 synthesis and weak positive for decrease of testosterone synthesis, as well as OECD TG 441 study where an anti-androgenic effect cannot be excluded. Cyprodinil met the ED criteria for EAS-modalities according to scenario 1b of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018). Open points: 1. RMS to change the RAR the 2-generation effect of AGDI treatment-retaled from mid-dose (instead of confined to the top dose). RMS to include the OECD TG 456 steroidogenesis assay conclusion according to the current TG in a revised RAR
Experts' consultation 2.19 MSs experts to discuss at the experts' consultation meeting the reproductive/offspring NOAELs/LOAELs of the new 2-generation toxicity study (OECD TG 416) and the impact on the current reproductive /offspring NOAELs/LOAELs.	New 2-gen toxicity study in Wistar rats: • parental NOAEL: 1400 ppm (equivalent to 77 mg/kg/bw per day) based on decreased bw/bwg, as well as increased liver weight observed at 4200 ppm (equivalent to 269 mg/kg bw per day). • offspring and reproductive NOAEL: 420 ppm (equivalent to 23 mg/kg bw per day) based on delayed sexual maturation (increased age at balanopreputial separation in males and decrease in anogenital distance in both sexes) observed at the dose level of 1400 ppm (equivalent to 77 mg/kg bw per day) onwards. Overall, the TRVs for cyprodinil are not impacted by the new 2-generation study. Open point: the RMS to revise the LoEPs updating the NOAELs in line with the peer review meeting discussion. RMS also to amend parental and reproductive NOAEL (74 and not 71 mg/kg bw per day) for the Khalil (1993) study in RAR (pag.135).

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.20 identified by EFSA following ED clock stop **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.**	**Open point (applicable to all co-formulants):** **RMS to complete the assessment of the toxicological profile of the co-formulants and report it in the revised RAR (Vol. 4) to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures.** **The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion, and referred to the safety of the co-formulant per se as well as in relation to the concentrations in the PPPs.** **A disclaimer should be included for all evaluations, indicating the limitations of the database as to the reliance of the existing evaluations.** **Post-meeting note (November 2023):** **After internal discussion on the proposal presented by the RMS (data gap for applicant), EFSA reported that the same approach used in other previous and similar cases should be kept also for cyprodinil.** **Therefore, although the proposal from the RMS is appropriate, the open point for RMS is maintaned.**

REPORT OF PESTICIDES PEER REVIEW

TC 118 and TC 119

FENOXAPROP-P – AIR III after ED clock stop **Rapporteur Member State: AT**

2. Mammalian toxicity

Date: 17 November 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by RMS BG	Risk Assessment Center on Food Chain - BG
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (Bfr) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS EL	BENAKI PHYTOPATHOLOGICAL INSTITUTE - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Experts nominated by RMS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS HR	Institute for Medical Research and Occupational Health - HR
National Expert nominated by MS HU	National Food Chain Safety Office (NEBIH) - HU
National Experts nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Expert nominated by MS NL	Ctgb - NL
Observer (CH)	FSVO - CH

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Discussion points/Outcome

2. Mammalian toxicity

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.17 **The A modality, including the outcome of the Hershberger assay, the proposed MOA and the human relevance should be discussed. Discussion should include a reassessment of the WOE analysis and the impact of lack of a level 5 study (OECD TG 443 with the inclusion of the 1b generation) which should have been conducted in line with the EFSA-ECHA ED GD. Because of this, the WOE should also include in the analysis any effect observed in the dataset for sensitive endpoints.** **The analysis of the non-human relevance of the MOA as proposed by the applicant should therefore considered the weakness of lack of ED hazard investigation because A mediated sensitive endpoints were not measured in the dataset for**	**For the EAS-modalities, following the 30-month regulatory stop-of-the clock, data on endocrine activity were provided and positive outcome for the endocrine activity was reported in the Hershberger assay. However, level 5 studies were not conducted and assessment of the lines of evidence of adversity (for EAS mediated and EAS sensitive endpoints) was done with the inclusion of the positive outcome for endocrine activity in the weight of evidence (WoE) analysis.** **Based on the WoE and uncertainty analysis it was concluded that the ED criteria for the A-modality are met and that a pattern of A mediated adversity exists and it is substantiated by evidence of changes observed in prostate, epididymis and testes weights in the F2 population in the 2-generation toxicity study.** **Scenario 2b of the ECHA/EFSA ED Guidance is applicable and ED criteria are considered met for the A modality.** **Open point for EFSA:** **To reflect in the EFSA conclusion that a higher level of uncertainty was considered to conclude on the ED assessment for the substance fenoxaprop-P-ethyl due to the lack of level 5 study as recommended in the testing strategy in the ECHA/EFSA ED Guidance and in the previous PREV 07.** **The mode of action (MoA) proposed by the applicant (enhanced hepatic clearance of testosterone) is theoretically plausible but is not empirically supported; moreover, based on the *in vitro* metabolism data, the exclusion of human relevance for the proposed MoA is not possible (experts' consultation 2.18).**

Subject	Conclusions Pesticides Peer Review Meeting
the A modality. The absence of these data avoids clarifying the current uncertainties for the MoA. The WOE analysis should also address the S modality.	The available experimental data on fenoxaprop-ethyl or fenoxaprop-P-ethyl do currently not indicate any concern for hyperdeoxycorticosteronism or endocrine disruption of the S-modality (experts' consultation 2.19). Based on the results reported in the publication by *Ji et al., 2020*[3], there is no convincing evidence that the endogenous metabolites are involved in the anti-androgenic effects observed in the Hershberger assay conducted with the active substance (experts' consultation 2.20). For completeness the following points were also tackled during the meeting. - For E and S-modalities: scenario 1a is applicable and ED criteria are not met. For T-modality: scenario 2aii is applicable and ED criteria are not met.
Experts' consultation 2.18 The appropriateness of the *in vitro*/*in vivo* metabolism studies should be discussed. The relevance of the studies in the MOA analysis, including the human relevance should be discussed.	See conclusion under experts' consultation 2.17 above.
Experts' consultation 2.19 The S modality to be discussed at the expert consultation meeting. Discussion should include the impact of the available in vitro evidence for the assessment of the S modality.	See conclusion under experts' consultation 2.17 above.
Experts' consultation 2.20	See conclusion under experts' consultation 2.17 above.

[3] Ji, C., Song, Q., Chen, Y., Zhou, Z., Wang, P., Liu, J., ... & Zhao, M. (2020). The potential endocrine disruption of pesticide transformation products (TPs): The blind spot of pesticide risk assessment. Environment international, 137, 105490.

Subject	Conclusions Pesticides Peer Review Meeting
See comment 3; the uncertainty analysis performed as part of the ED assessment should include also the available evidence from endogenous metabolites.	
Experts' consultation 2.21 identified by EFSA following ED clock stop MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	**Data gap (Puma S 69 EW, FPP+MPR EW 144 (69+75 g/L)):** Overall, no concerns are raised on the toxicological profile of the co-formulants present in this formulation, except for the co-formulant [redacted] for which the known composition is incomplete, the CAS number not available and repeated-dose toxicity data are missing. All experts also agreed that the presence of [redacted] at the concentration calculated by the RMS would result in classifying the whole formulation as a Skin Sensitiser 1A. Regarding the formulation "Fenoxaprop-P-Ethyl 69 G/L EW", no concern was raised on the toxicological profile of the co-formulants, except for the co-formulant [redacted] on which information with respect to short- and long-term toxicity is missing. MSs having toxicological information on this co-formulant will provide it to the RMS. Open point for the RMS to complete the assessment for this co-formulant or data gap in case this information is not provided.

REPORT OF PESTICIDES PEER REVIEW TC 120

ACETOCHLOR (MRL Art. 10) **EMS: ES**

2. Mammalian toxicity

Date: 22 November 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (Bfr) - DE
National Expert nominated by EMS ES	University of Granada/Spanish Agency of Food Safety and Nutrition Scientific Committee - ES
National Expert nominated by EMS ES	University of Valencia/Spanish Agency of Food Safety and Nutrition Scientific Committee
National Expert nominated by EMS NL	Ctgb - NL
Observer	Ctgb - NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the ED potential of acetochlor**	**There is no evidence of a pattern of EATS-mediated adversities in a sufficiently investigated dataset.** **Scenario 1a of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and the ED criteria for EATS-modalities are not met.** **Open point:** **EMS to include the EFSA ED assessment in the ER.**
Experts' consultation 2.2 **Experts to discuss the derivation of the toxicological reference values of acetochlor, taking into account:** **- the conclusion on its ED potential and related critical NOAEL,** **- the BMD analysis for the long term mouse study (related to the ADI),** **- the acute effects observed in the rat acute neurotoxicity study vs the rabbit developmental toxicity studies (related to the ARfD)**	**The Acceptable Daily Intake (ADI) for acetochlor is 0.0036 mg/kg bw per day, based on the 78-week mouse study, and applying an increased uncertainty factor of 300 due to the use of a LOAEL.** **This LOAEL was identified for the occurrence of tubular basophilia (first step of nephrotoxicity) accompanied by an increased kidney weight at the low dose. The BMD analysis for these findings did not allow further refinement.** **The Acute Reference Dose (ARfD) for acetochlor is 1 mg/kg bw per day, based on the rabbit developmental toxicity study, applying a standard uncertainty factor of 100.** **Open point** **EMS is requested to include further details of the BMD analysis, as discussed during the experts' meeting, in the revised ER.**

Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.3 **Experts to discuss the genotoxicity assessment of the two metabolites t-sulfinyllactic acid and 1-hydroxyethyl s-oxanilic acid (currently based on QSAR and read across)**	**For the metabolites A (tert-sulfinyllactic acid) and B (1-hydroxyethyl sec-oxanilic acid), taking into account the results of the QSAR analysis, the incomplete read-across analysis and considering that aneugenicity has not been assessed for some of the metabolites used for read-across, their genotoxicity potential (aneugenicity and clastogenicity endoints) cannot be concluded.**

REPORT OF PESTICIDES PEER REVIEW TC 120

ETHIPROLE (MRL Art. 10) **EMS: NL**

2. Mammalian toxicity

Date: 22 November 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Expert nominated by MS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (Bfr) - DE
National Expert nominated by EMS ES	University of Granada/Spanish Agency of Food Safety and Nutrition Scientific Committee - ES
National Expert nominated by EMS ES	University of Valencia/Spanish Agency of Food Safety and Nutrition Scientific Committee
National Expert nominated by EMS NL	Ctgb - NL
Observer	Ctgb - NL

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[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the new IVCM study in relationship with identification of unique human metabolites, and comparison of rat versus mouse as possible support of bone marrow exposure (apparently demonstrated in rats)**	**Based on the new *in vitro* comparative metabolism study, presenting minor deviations compared to the approach recommended, but considered acceptable, there is no unique human metabolite of ethiprole.** **Considering the lines of evidence regarding bone marrow exposure, there is sufficient evidence of target organ exposure in the *in vivo* micronucleus test.** **Open point** **EMS to include in the description of the new *in vitro* comparative metabolism study [redacted] information regarding the deviations from the approach recommended in the EFSA Scientific Opinion (EFSA, 2021).**
Experts' consultation 2.2 **Experts to discuss the NOAELs in the 90-day and 1-year dog studies, considering the additional tabulated results and the adversity of the changes in AP levels, prostate weight, acceptability of TSH/T3/T4 levels, organ weight**	**For the 90-day dog study, the NOAEL is 1 mg/kg bw per day based on decreased body weight gain, accompanied by lower thymus weight.** **For the 1-year dog study, the NOAEL is 0.22 mg/kg bw per day based on relative liver weight increase in females.** **For the new 90-day rat study, the NOAEL is 0.62 mg/kg bw per day based on liver effects in males (hepatocyte hypertrophy) and thyroid effects in males and females (follicular hypertrophy).** **Open point**

Subject	Conclusions Pesticides Peer Review Meeting
changes in females, thymus changes. Please also consider the new 90-day rat study if NOAEL is agreed.	EMS to revise the different sections of the ER regarding the 90-day and 1-year dog studies, to be in line with the conclusion reached at the peer review meeting.
Experts' consultation 2.3 Experts to discuss the NOAELs for the long term studies in rats and mice, considering potential carcinogenic effects of ethiprole, including : - subcutaneous lipomas in male rats, - ovarian sex cord tumours in female rats, - hepatocellular adenomas in male rats and female mice, - thyroid adenomas in female rats (including considerations of new data on thyroid mode of action and ED assessment). (including discussion and proposal for CMR classification if appropriate)	The following NOAELs have been set for the long term studies in rats and mice. Rat chronic/carcinogenicity study: The NOAEL for systemic toxicity is 0.85 mg/kg bw per day based on increased body weight gain, effects on prothrombin times (increase in males, decrease in females), changes in clinical chemistry (decreased bilirubin), changes in urinalysis parameters (higher pH), effects on thyroid hormone levels (increased TSH, decreased T4 in F), increase in thyroid and liver weights, follicular cell hypertrophy and colloid mineralisation of the thyroid. The NOAEL for carcinogenicity is 4.4 mg/kg bw per day, based on follicular cell adenoma in thyroid (M/F), liver adenomas in males, ovarian sex cord stromal tumours in females, benign subcutaneous lipomas in males. Mouse carcinogenicity study: The NOAEL for systemic toxicity is 26 mg/kg bw per day, based on liver weight increase and associated pathology. The NOAEL for carcinogenicity is 36 mg/kg bw per day, based on an increase of liver adenomas in females. Regarding the available tumour data, the hepatocellular adenomas and thyroid tumours were considered not relevant for humans. The human relevance of the subcutaneous lipomas and ovarian sex cord stromal tumours was considered not clear. Altogether, the tumours findings were considered to not warrant classification.
Experts' consultation 2.4 Experts to discuss the revised assessment of the rat 2-generation toxicity study, considering the additional historical control data (for the post-implantation loss).	The NOAELs for the rat 2-generation study were set as follows: - Parental NOAEL: 0.7 mg/kg bw per day based on increased liver weight (absolute and relative; F0 and F1 females) and decreased pituitary weight (F1). - Offspring NOAEL: 4.8 mg/kg bw per day based on reductions in pup body weight during lactation and organ weight changes in the liver, brain, spleen, kidney and thymus. - Reproductive NOAEL: 32 mg/kg bw per day (top dose). It was concluded that the post-implantation loss effects are not treatment-related.

Subject	Conclusions Pesticides Peer Review Meeting
	Open point: **RMS to bring summary descriptions in the ER in line with the detailed assessments in appendix (regarding adverse findings for NOAEL setting).**
Experts' consultation 2.5 **Experts to discuss the NOAELs in the rat developmental toxicity study**	**For the rat developmental toxicity study, the maternal NOAEL is 3 mg/kg bw per day based on liver weight increase; the developmental NOAEL is 10 mg/kg bw per day based on higher incidence of foetuses with enlarged thymus, ossification retardation and short 13th rib(s).**
Experts' consultation 2.6 **Experts to discuss the NOAELs in the rabbit developmental toxicity study**	**For the rabbit developmental toxicity study the maternal NOAEL was set at 0.5 mg/kg bw per day based on body weight loss and reduced food intake, and the developmental NOAEL was set at 0.5 mg/kg bw per day based on incomplete ossification (of pubis, metacarpal and/or middle phalanges).**
Experts' consultation 2.7 **Experts to discuss the DNT potential of ethiprole on the basis of the available data (including effects on TH in rats vs mice DNT studies)**	**With regard to the DNT potential of ethiprole, a reliable DNT study is lacking. The margin of safety for thyroid effects and neurotoxic effects resulting from the use of the NOAEL from the 1-year dog study for the risk assessment are considered sufficient, and no further investigation of DNT is required at this stage.**
Experts' consultation 2.8 **Experts to discuss the ED potential of ethiprole**	**T-modality** **A pattern of T-mediated adversity i.e. increased weight and follicular cell hypertrophy was observed in rats in studies conducted following different dose regimes and time length. The modes of action (MoA) proposed by the EMS is dealing with CAR/PXR induction as molecular initiating events (MIEs). Other MIE (TPO and NIS inhibition) were investigated and negative.** **The dataset includes supporting evidence of endocrine activity i.e., decrease serum T4 and increase of TSH in short-term toxicity studies in rat. Although there is no information on nuclear receptor activation, there is evidence of induction of phase I and II liver enzymes and circumstantial evidence of increased hepatic clearance of thyroid hormones due to upregulation of UDP-GT in rats. However, the *in vitro* comparative enzyme assay submitted to demonstrate the non-human relevance of the effect is not sufficient to dismiss a thyroid effect of ethiprole in humans.** **Scenario 1b of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and the ED criteria for T-modality are met for ethiprole.**

Subject	Conclusions Pesticides Peer Review Meeting
	The proposing NOAEL for thyroid effects is 1 mg/kg bw per day based on the thyroid follicular hypertrophy observed at 3-5 mg/kg bw per day in the carcinogenicity study in rats (by diet). **EAS-modality** **Based on a complete ED dataset with no observed EAS-adversity, it was concluded that EAS criteria are not met for ethiprole, in a scenario 1a of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018).** **Open point:** **EMS to correct the evaluation report (ER) regarding impact of the increase adrenal weight in the 28-day rat study.**
Experts' consultation 2.9 **Experts to discuss the genotoxicity and general toxicity profile of the metabolites Ethiprole–sulfone RPA097973 and Ethiprole-amide RPA112916**	**The metabolite ethiprole-amide RPA112916 (M05) is considered unlikely to be genotoxic and of similar potency as or lower potency than ethiprole. RPA112916 (M05) is therefore considered covered by the toxicological profile of the parent, and the reference values of the parent are also applicable to RPA112916 (M05).** **The metabolite ethiprole-sulfone RPA097973 (M01) is considered a major rat metabolite when also considering downstream metabolites. RPA097973 (M01) is therefore considered covered by the genotoxicity and general toxicity profile of the parent, and the reference values of the parent are also applicable to RPA097973 (M01).**
Experts' consultation 2.10 **Experts to discuss the setting of the ADI and ARfD for ethiprole**	**The Acceptable Daily Intake (ADI) for ethiprole is 0.002 mg/kg bw per day based on the 1-yr dog study (increased relative liver weight) and applying a standard uncertainty factor of 100.** **The Acute Reference Dose (ARfD) for ethiprole is 0.005 mg/kg bw based on the rabbit developmental toxicity study (decreased body weight during gestation days 6-8) and applying a standard uncertainty factor of 100.**

REPORT OF PESTICIDES PEER REVIEW

TC 118 and TC 119

FLUDIOXONIL – AIR III after ED clock stop **Rapporteur Member State: FR**

2. Mammalian toxicity

Date: 17 November 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by RMS BG	Risk Assessment Center on Food Chain - BG
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (Bfr) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS EL	BENAKI PHYTOPATHOLOGICAL INSTITUTE - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Experts nominated by RMS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS HR	Institute for Medical Research and Occupational Health - HR
National Expert nominated by MS HU	National Food Chain Safety Office (NEBIH) - HU
National Experts nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
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Observer (CH)	FSVO - CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.16 (Point 1). MSs experts to discuss at the experts' consultation meeting: 1. the endocrine disruption (ED) potential properties regarding the oestrogen, androgen, thyroid, and steroidogenesis (EATS)-modalities including in the overall weight of evidence the new studies/data made available during the regulatory stop-of-the-clock period. The assessment should follow the ECHA/EFSA ED Guidance decision tree starting from the identification of EATS mediated adversity (if any), followed by the assessment of endocrine activity and overall conclusion thereof.	**T-modality** There is no evidence of a pattern of T-mediated adversity in the available and complete dataset consisting of studies of different duration conducted in mice, rats and dogs. Scenario 1a of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and the ED criteria for the T-modality are not met. **EAS-modalities** A pattern of EAS-mediated adversity i.e., increased age at balano-preputial separation (BPS) in F1 generation, decreased ano-genital distance index (AGDI) in F1a males and increased mean length of the oestrus cycles in F1 animals, has been observed for fludioxonil in a sufficiently investigated dataset (OECD TG 416 according to the last protocol is available). Effects on parameters considered ‚*sensitive to but not diagnostic of EAS*' i.e. increased number of ovarian follicles, decreased number of implantation scars, decreased number of born pups, decreased post-implantation loss, also corroborated the pattern observed. The observed pattern of EAS-mediated adversity suggests an anti-androgenic mode of action (MoA), though other MoAs affecting steroidogenesis and/or estrogenic pathways cannot be completely excluded based on the empirical evidence. The dataset includes supporting evidence of endocrine activity from the Androgen Receptor TransActivation (ARTA) assay i.e. AR antagonism (OECD TG 458), steroidogenesis assay i.e. decreased T and increased E2 (OECD TG 456) and from the Hershberger assay i.e. equivocal anti-androgenic effect (OECD TG 441). In addition, literature studies are also supporting the evidence of a weak antagonism of the androgen receptor (AR) (*Scholze et al.,*

Subject	Conclusions Pesticides Peer Review Meeting
In presenting the data the following points should be specifically addressed: - 1a. the applicant position on the reliability of Balano-Preputial Separation assessment and the acceptability of the 2-generation toxicity study (OECD TG 416) - 1b. the reliability of the historical control data (HCD) provided on Balano-Preputial Separation (PPS), anogenital distance (AGD) and ovary follicles count parameters measured in the 2-generation toxicity study (OECD TG 416) - 1c. the outcomes and the reliabilities of the steroidogenesis, aromatase and Hershberger assays, including the interpretation of the total weight of all Accessory Sex Organ.	*2020*[3]) and weak ERalpha antagonism (e.g. Yeast Estrogen Screen (YES) assay, ERalpha CALUX, Schlotz et al. 2017[4]). Fludioxonil met the ED criteria for the EAS-modalities according to scenario 1b of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018). Open point: The RMS is kindly asked to revise the RAR Vol.1 and Vol. 3B6 to be aligned with the conclusion of the Pesticide Peer review meeting.
Experts' consultation 2.16 (Point 2) MSs experts to discuss at the experts' consultation meeting: 2. the outcome of the 2-generation toxicity study in rats (OECD TG 416), the reproductive/offspring	The offspring and reproductive NOAELs were 1000 ppm (equivalent to 58 mg/kg bw per day) based on delayed sexual maturation in males i.e. clear dose-related relationship for increased delay in BPS initiated at 3000 ppm and with large magnitude at 7000 ppm. The parental NOAEL was 3000 ppm (equivalent to 175 mg/kg bw per day) based on decreased body weight and body weight gains in F0 and F1 and increased liver weight observed at 7000 ppm (415 mg/kg bw per day). Open point:

[3] Scholze, M., Taxvig, C., Kortenkamp, A., Boberg, J., Christiansen, S., Svingen, T., ... & Vinggaard, A. M. (2020). Quantitative in vitro to in vivo extrapolation (QIVIVE) for predicting reduced anogenital distance produced by anti-androgenic pesticides in a rodent model for male reproductive disorders. Environmental health perspectives, 128(11), 117005.
[4] Schlotz, N., Kim, G. J., Jäger, S., Günther, S., & Lamy, E. (2017). In vitro observations and in silico predictions of xenoestrogen mixture effects in T47D-based receptor transactivation and proliferation assays. Toxicology in Vitro, 45, 146-157.

Subject	Conclusions Pesticides Peer Review Meeting
NOAELs/LOAELs and the implication of this study on the toxicological endpoints and human health risk assessment.	RMS to revise the LoEPs updating the NOAELs (parental, offspring and reproductive) in line with the peer review meeting discussion. **Toxicological Reference Values (TRVs)** Overall, the TRVs (ADI, AOEL, AAOEL and ARfD) are not impacted by the newly submitted 2-generation toxicity study. The lowest NOAEL for the ED endpoint is 1000 ppm (equivalent to 58 mg/kg bw per day) based on delayed BPS. Therefore, the TRVs are considered covering the endocrine effects.
Experts' consultation 2.17 Experts to discuss the negligible exposure assessment, if required, for the representative uses of fludioxonil.	Not discussed. Since the applicant provided a negligible exposure assessment for a use that was not part of the representative uses submitted for EU renewal, this could not be further considered for the peer review. As clarified by the European Commission, for the assessment of negligible exposure, the representative uses (GAPs) should not be changed i.e. the applicant/RMS should consider negligible exposure for the representative use(s) only.
New experts' consultation 2.18 MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	**Open point (applicable to all co-formulants):** RMS to complete the assessment of the toxicological profile of the co-formulants and report it in the revised RAR (Vol. 4) to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term toxicity of the chemically identified co-formulants, including mixtures. The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion, and referred to the safety of the co-formulant per se as well as in relation to the concentrations in the PPP. A disclaimer should be included for all evaluations, indicating the limitations of the database as to the reliance of the existing evaluations. **Post-meeting note (November 2023):** After internal discussion on the proposal presented by the RMS (data gap for applicant), EFSA reported that the same approach used in other previous and similar cases should be kept also for fludioxonil. Therefore, although the proposal from the RMS is appropriate, the open point for RMS is maintained.

REPORT OF PESTICIDES PEER REVIEW TC 119

ACETAMIPRID – Art. 31 mandate **Rapporteur Member State: NA**

2. Mammalian toxicity

Date: 17 November 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Experts nominated by MS AT	Austrian Agency for Food and Health Safety - AT
National Expert nominated by RMS BG	Risk Assessment Center on Food Chain - BG
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (Bfr) - DE
National Experts nominated by RMS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS HR	Institute for Medical Research and Occupational Health - HR
National Expert nominated by MS HU	National Food Chain Safety Office (NEBIH) - HU
Observer (CH)	FSVO - CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the tociological properties of IM-2-1 metabolite of acetamiprid**	**Based on the available genotoxicity studies (Ames test, in vitro micronucleus test, mouse lymphoma assay) it was concluded that IM-2-1 metabolite is unlikely to be genotoxic.** **Based on the available evidence (i.e., IM-2-1 metabolite is a major rat metabolite; structural similarities IM-2-1 and parent; the available 28-day rat study on IM-2-1 does not allow to conclude on a different toxicological qualitative or quantitative profile of the metabolite compared to parent), all experts agreed that the toxicological profile of IM-2-1 is considered as covered by parent and the same reference values (ADI and ARfD) of the parent should apply to the metabolite.**

REPORT OF PESTICIDES PEER REVIEW

TC 118 and TC 119

CARBENDAZIM AND THIOPHANATE-METHYL – Art. 43 mandate

Rapporteur Member State: DE (Carbendazim) and SE (thiophanate-methyl)

2. Mammalian toxicity

Date: 17 November 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Experts nominated by RMS AT	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by RMS BG	Risk Assessment Center on Food Chain - BG
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (Bfr) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS EL	BENAKI PHYTOPATHOLOGICAL INSTITUTE - EL
National Expert nominated by MS ES	Ministerio de Sanidad - ES
National Experts nominated by RMS FR	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Expert nominated by MS HR	Institute for Medical Research and Occupational Health - HR
National Expert nominated by MS HU	National Food Chain Safety Office (NEBIH) - HU
National Experts nominated by MS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Expert nominated by MS NL	Ctgb - NL

Status	Name of institution / attendee
Observer (CH)	FSVO - CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the endocrine disruption (ED) potential of carbendazim and thiophanate-methyl and whether they meet the scientific criteria for the determination of endocrine disrupting properties as laid down in Commission Regulation (EU) 2018/605.** **See Terms of Reference in the mandate.**	***Thiophanate-methyl*** **Thyroid (T)-modality** **A pattern of T-mediated adversity (i.e., increased thyroid weight and histopathological findings) was observed across multiple species (i.e. dog and rat) and studies conducted following different dose regimes.** **The modes of action (MoA) proposed are dealing with 1) thyroperoxidase (TPO) inhibition and 2) CAR/PXR induction as molecular initiating events (MIEs). The dataset includes supporting evidence of endocrine activity i.e., decreased TPO activity in tissue-based cell-free assays and in the guaiacol assay, decreased serum T4 and T3 levels in short- and long-term toxicity studies in rat, dog, and mice, and increased serum TSH levels in rat and mouse in short- and long-term studies. Although there is no information on nuclear receptor activation and there is no experimental evidence on additional MIEs directly acting on thyroid, there is circumstantial evidence of increased hepatic clearance of thyroid hormones due to upregulation of UDP-GT.** **Therefore, Scenario 1b of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and the ED criteria for T-modality are met.** **Oestrogen, androgen and steroidogenesis (EAS)-modalities**

Subject	Conclusions Pesticides Peer Review Meeting
	No evidence of EAS-mediated adversity was observed in an incomplete dataset (no OECD TG 416 and/or TG 443 is available). **The E-modality is concluded to be sufficiently investigated because a level 2 study i.e. ToxCast ER predictive model is available and negative. Scenario 2a(ii) of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and the ED criteria for E-modality are not met.** **For the A and S modalities, the dataset is incomplete for both adversity and activity. Scenario 2a (iii) of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and further data should be generated before a firm conclusion can be drawn on A and S modalities:** • **OECD TG 456 (H295R Steroidogenesis Assay);** • **OPPTS 890.1200 (Aromatase assay);** • **OECD TG 458 (Androgen Receptor Mediated Stably Transfected Transcriptional Activation (AR STTA) assays);** **OECD TG 441 (Hershberger Assay) in case OECD TG 456 and 458 and OPPTS 890.1200 are negative;** **If the above tests are negative, thiophanate-methyl will not meet the ED criteria for the AS modalities. However, in case of positive result/s based on the above tests for at least one modality, additional testing is needed: OECD TG 443 (with the inclusion of cohort 1B).** **<u>Toxicological reference values (TRVs)</u>** **The No Observed Adverse Effect Level (NOAEL) for T-mediated effect is 14.6 mg/kg bw per day and is based on a 2-generation toxicity study in rat (ID:12), which is also covering the effects in the sensitive populations.** **Considering that the effects observed for the T-modality are mainly based on enzymatic mechanisms, and therefore a monotonic dose response relationship is expected, the current ADI and ARfD are covering the identified endocrine disrupting properties of the substance and are considered sufficiently protective for consumers.** **Post-meeting note (23 Nov 2023):** **For the EAS-modalities scenario 2a(ii) is applicable for the E-modality (ED criteria not met), while for the A and S modalities scenario 2a(iii) is applicable (further data to be generated to allow conclusion). Therefore, a**

Subject	Conclusions Pesticides Peer Review Meeting
	residual uncertainty remains for the A and S modalities concerning the ED properties of thiophanate-methyl. **However, no additional uncertainty factor (UF) is considered necessary to cover this uncertainty based on lack of adversity in the available dataset for the *in vivo* endpoints that are expected to be sensitive to perturbations on the A and S modalities. In addition, the available information on the endocrine activity for the A and S modalities from the ToxCast database is not showing any concern.** ***Carbendazim*** **T-modality** **There is no evidence of a pattern of T-mediated adversity in the available and complete dataset. Scenario 1a of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and the ED criteria for the T-modality are not met for the substance carbendazim.** **EAS-modalities** **The overall weight of evidence (WoE) may be indicative of a perturbation of the hypothalamic pituitary gonadal (HPG) axis in the male rats. The likely mode of action (MoA) is dealing with the properties of carbendazim to interact with b-tubulin and thus, a non-endocrine mediated MoA is most likely. This is substantiated by lack of clear evidence of endocrine activity, lack of effect in female animals for which endpoints sensitive to perturbation of the HPG axis are known (e.g. changes in oestrous cyclicity), lack of evidence of effects in other than testes endocrine sensitive organs.** **Therefore, although a detailed MoA analysis cannot be performed for carbendazim, it is likely that the substance is acting as a direct testicular toxicant possibly acting on dividing spermatocytes and on Sertoli cells. The limited evidence reported on endocrine activity was considered as likely secondary to the primary effect observed on the testes.** **Scenario 1a of the EFSA/ECHA ED guidance (ECHA-EFSA, 2018) is applicable and the ED criteria for EAS-modalities are not met for the substance carbendazim.** **Toxicological reference values (TRVs)**

Subject	Conclusions Pesticides Peer Review Meeting
	Carbendazim in not an endocrine disruptor; no further considerations are needed on the impact of the ED assessment on the current TRVs.
Experts' consultation 2.2 Experts to discuss the toxicological reference values for carbendazim and thiophanate-methyl. In case carbendazim and/or thiophanate-methyl would be recognised as endocrine disruptor(s): • to consider whether the toxicological reference values for consumer risk assessment (ADI, ARfD) derived by EFSA in 2021[3] for the active substance(s) cover the identified endocrine disrupting properties of the substance(s) and are still sufficiently protective for consumers; • to derive toxicological reference values for consumer risk assessment (ADI, ARfD), should the ones proposed by EFSA in 2021 not be considered protective. See Terms of Reference in the mandate.	See conclusions reported under the previous experts' consultation point above.

[3] EFSA (European Food Safety Authority), 2021. Reasoned opinion on the toxicological properties and maximum residue levels (MRLs) for the benzimidazole substances carbendazim and thiophanate-methyl. EFSA Journal 2021;19(7):6773, 66 pp. doi:10.2903/j.efsa.2021.6773

REPORT OF PESTICIDES PEER REVIEW

WRITTEN PROCEDURE (follow up to the Pesticide Peer Review TC 99 from March 2023)

FLUFENACET – AIR III **Rapporteur Member State: PL**

2. Mammalian toxicity

Date: Written procedure from 13/10 to 24/10

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Estonian Agricultural Board	EE
Tragsatec on behalf of Ministerio de Sanidad (MISAN)	ES
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
E-V-A Sp. z o.o.	PL
Observer (1)	AT

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.17 (Follow up to the discussions held at the Pesticides Peer Review TC 99 on 29 March 2023) **MSs experts to discuss the outcome of the T-modality in an experts' meeting.**	During the previous peer review consultation (in May 2019), ED criteria for the T-modality were considered not met with evidence of a pattern of T-mediated adversity (i.e. changes in thyroid histopathology) and activity (i.e. changes in THs) mostly confined to or above the MTD. The newly provided studies confirmed a test-item related perturbation of the HPT axis with evidence at doses below the MTD. Although induction of liver enzymes, with increase in the clearance of THs could be considered as a plausible MoA, there is no evidence that this MoA is not human relevant. In addition, other MIEs, except for deiodinase (DIO) inhibition (which was positive), were not investigated and therefore could not be excluded. The DNT study is also considered as positive and of concern because flufenacet is negative in a battery of in vitro DNT test and therefore a thyroid mediated mode of action on the observed DNT effects cannot be excluded. On these bases, the experts at the peer review meeting agreed that the previous conclusion on T-modality could not be retained and flufenacet is considered to meet the ED criteria for T-modality. The RMS disagrees with the conclusion reached at the peer review meeting. **Follow-up written procedure (October 2023):** The ED assessment for humans for flufenacet was re-discussed in September 2023 by the ED working group (WG) as the CTA study available in the RAR and considered by the RMS and co-RMS was not discussed by the ED WG and/or during the previous Pesticides Peer Review Experts' TC 99. Taking into account the relevance of the CTA study to conclude on the T-modality, EFSA wanted to discuss this study with the ED WG in order to have a complete assessment.

Subject	Conclusions Pesticide Peer Review Meeting
	The new ED WG advice (from September 2023) includes now the assessment of the CTA study, including the re-analyses of the T3 and T4 by LC/MS-MS. The September ED WG advice is confirming the previous conclusion of the Pesticides Peer Review Experts' TC 99, that the substance is an ED and criteria are met for the T modality. A written procedure in October 2023 was launched on the conclusion of the September ED WG and the MS experts were in agreement with the conclusion of the ED WG. **Open point to the RMS:** to include in the revised RAR (in accordance with the Art 56 of the PPP Regulation) the CTA study.

REPORT OF PESTICIDE PEER REVIEW TC 114

PYRIMETHANIL– AIR III **Rapporteur Member State: CZ**

2. Mammalian toxicity

Date: 08 September 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff member	EFSA
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Belgium (2)	Federal Public Service Health, Food Chain Safety and Environment - BE
National Experts nominated by RMS Czech Republic	The National Institute of Public Health - CZ
National Experts nominated by MS Germany (2)	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain (2)	Ministerio de Sanidad - ES
National Experts nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Netherlands	Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) - NL
Observers	Federal Food Safety and Veterinary Office (FSVO) - CH
	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT

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discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.14 identified following ED clock stop: **Experts to discuss the effect of pyrimethanil on the T-modality.** **The discussion should consider also the potential effects in the most sensitive population (i.e. pregnant dams, pups) and consider the findings in the new EOGRT study as part of the WoE. The discussion should include evaluation of the adversity, including the assessment of thyroid mediated endpoints for the definition of adversity in pregnant dams and pups, possible perturbation of the HPT axis in pregnant dams, and relationships to changes in brain weight in all populations. In order to conclude on any possible effects on the T-modality (e.g. consequences of perturbation on brain development). The full database should be considered in the WoE.**	***T-modality:*** **criteria are not met for the T-modality based on lack of a clear pattern of T-mediated adversity in a complete dataset; in line with the ECHA/EFSA ED guidance (2018), scenario 1a is applicable.** **The effects observed in the EOGRT study are not suggestive of a perturbation of the HPT axis of sufficient magnitude to induce the DNT effects observed in cohorts 2A and 2B.** **This conclusion is in line with the EFSA ED WG Advice.** **For completeness of discussion the following was also agreed for** ***EAS-modalities*:** **criteria are not met for the EAS-modalities based on lack of EAS-mediated adversities in a complete dataset; in line with the ECHA/EFSA ED guidance (2018) scenario 1a is applicable.** **Open point** **The RMS to update the ED assessment on T-modality in a revised RAR in accordance with the discussion at the peer review experts' meeting.**

Subject	Conclusions Pesticide Peer Review Meeting
New experts' consultation point 2.15 proposed by EFSA for completeness of discussion **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.**	**Open point (applicable to all co-formulants):** **RMS to complete the assessment of the toxicological profile of the co-formulants and report it in the revised RAR (vol. 4) at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures.**
New experts' consultation 2.16 identified following ED clock stop: **Experts to discuss the impact of the newly submitted OECD 443 study on** **• NOAEL** **• toxicological reference values**	**The new extended one generation reproductive toxicity study (EOGRTS) has been considered more appropriate than the 2-generation study set the overall:** **• Parental NOAEL: 1500 ppm (corresponding to 140 mg/kg bw per day) based on:** **o statistically significant (>10%) ↓ in BW/BW gain (in F0 and F1 1B females, i.e. parental animals, ↓ BW during gestation and lactation and ↓ BWG during premating period and gestation; in F0 and F1 1B males ↓ BWG during certain study periods; in F1 1A and F1 2A animals ↓ BW/BWG during certain study periods);** **o statistically significant (>10%) ↓ in food consumption (in F0 and F1 1B females during gestation and lactation; in F1 1B males and F1 1A animals during certain study periods);** **o statistically significant (>15%) ↑ in absolute and relative liver weight in F0 males;** **o histopathological findings in liver, thyroid and pituitary (↑ incidence of hepatocyte centrilobular hypertrophy – minimal/mild in F0 and F1 1A animals; increased ↑ of follicular cell hypertrophy in thyroid – minimal/mild in F0 and F1 1A animals; ↑ incidence of vacuolation and hypertrophy of pituitary pars distalis – minimal/mild in F0 and F1 1A males);**

Subject	Conclusions Pesticide Peer Review Meeting
	• Offspring NOAEL: 1500 ppm (corresponding to 140 mg/kg bw per day) based on: o Statistically significant ↓ in BW development in F1 as well as F2 pups of both sexes. • reproductive NOAEL: 1500 ppm (corresponding to 140 mg/kg bw per day) based on statistically significant ↓ mean number of implantation sites/dam and subsequently ↓ mean number of delivered and live born pups/dam in F1 1B as well as F0 females. The DNT NOAEL is 1500 ppm (equivalent to approximately 140 mg/kg bw per day) based on: • statistically significant ↓ in absolute brain weights in females and statistically significant decrease in thickness of left and right hippocampus in males and non-statistically significant decrease in corpus callosum thickness (about 13%) in females. • statistically significant ↓ in startle amplitude in high dose females in block 1 cohort 2A on PND 24. The agreed reference values are: • ADI=0.013 mg/kg bw per day based on the 2-year rat; UF=100 • ARfD=1.0 mg/kg bw based on the acute neurotoxicity rat • AOEL=0.3 mg/kg bw per day based on the dog 1 yr study; UF=100 (previous agreed AOEL was 0.18 mg/kg bw per day based on 2-gen. repr. tox. study; UF=100) • AAOEL=1.0 mg/kg bw based on acute neurotoxicity study Open point: RMS to review the non-dietary exposure (NDE) estimations based on the revised AOEL.

REPORT OF PESTICIDE PEER REVIEW TC 114

DINOTEFURAN – MRL Art.10 Rapporteur Member State: PT

4. Mammalian toxicity

Date: 08 September 2023

Post meeting note: September 2025

List of participants:

Status	**Name of institution/attendee**
EFSA statutory staff member	EFSA
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Belgium (2)	Federal Public Service Health, Food Chain Safety and Environment - BE
National Experts nominated by MS Germany (3)	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Ireland	Department of Agriculture, Food and the Marine of Ireland – IE
National Experts nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Lithuania	The State Plant Service under the Ministry of Agriculture - LT
National Experts nominated by MS Netherlands	Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) - NL
Observers	Federal Food Safety and Veterinary Office (FSVO) - CH

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2,] EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues

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discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.2 MSs experts to discuss the (geno)toxicity profile of dinotefuran metabolites 1-methyl-3-(tetrahydro-3-furylmethyl) urea (UF) and 1-methyl-3-(tetrahydro-3-furylmethyl) guanidium dihydrogen (DN) in an experts' meeting.	1-methyl-3-(tetrahydro-3-furylmethyl) urea (UF) and 1-methyl-3-(tetrahydro-3-furylmethyl) guanidium dihydrogen (DN) were considered as covered by the toxicity profile of the parent compound since they were found , in significant amount (e.g. > 10%), in several tissues in rat metabolism study. Available experimental data do not underline any concern for the investigated endpoints. **Post meeting note (Sept 2025):** As part of the PRM TC 187 preparation (residues section), EFSA reviewed the available data related to metabolites UF and DN in both the Evaluation Report prepared by EMS PT and in the Original Study Report for ADME study submitted by the applicant. During this review, EFSA noted that the percentages of metabolite UF detected in the gastrointestinal tract (>29%), stomach (20%) and prostate (17%) and of the metabolite DN detected in liver (> 18%) and kidney (> 10%) represent the percentages of the total radioactivity detected in the tissues and not the percentages of the administered dose of dinotefuran as discussed at PRM TC 114 in Sept 2023 and reported in the related meeting report. These tissue values are much lower than 10% of the administered dinotefuran dose (see **Table 1** and **Table 2** for UF and DN, respectively) which is the cut-off typically applied to consider a metabolite as present in significant amount in rat metabolism study. As a result, UF and DN cannot be considered major metabolites in rats. Consequently, the conclusion previously reached that the two metabolites are covered by the toxicity profile of the parent compound is not valid and based on the available information, it cannot be concluded whether the toxicological reference values (TRVs) of the parent compound are applicable to them. Additional data should be requested to cover the toxicological

<table>
<tr><th>Subject</th><th>Conclusions Pesticide Peer Review Meeting</th></tr>
<tr><td></td><td>profile of metabolites, and the stop of the clock cannot be restarted.

Table 1 - Comparison of values % of total radioactivity detected in sample and % of total radioactivity administered UF. Ranged values are min and max values from the different groups (low single and repeated dose and high single dose) tested in the ADME study.
<table>
<tr><th>TISSUE</th><th>% of total radioactivity detected in sample</th><th>% of total radioactivity administered</th></tr>
<tr><td>GASTROINTESTINAL TRACT</td><td>Ranged from 0.00-29.5</td><td>Ranged from 0.00-0.42</td></tr>
<tr><td>STOMACH*</td><td>19.9</td><td>0.336</td></tr>
<tr><td>PROSTATE*</td><td>17.2</td><td>0.010</td></tr>
</table>
*single value from high dose group only.

Table 2 - Comparison of values % of total radioactivity detected in sample and % of total radioactivity administered DN. Ranged values are min and max values from the different groups (low single and repeated dose and high single dose) tested in the ADME study.
<table>
<tr><th>TISSUE</th><th>% of total radioactivity detected in sample</th><th>% of total radioactivity administered</th></tr>
<tr><td>LIVER</td><td>Ranged from 2.65-18.4</td><td>Ranged from 0.00-0.60</td></tr>
<tr><td>KIDNEY</td><td>Ranged from 0.00-10.8</td><td>Ranged from 0.00-0.07</td></tr>
</table></td></tr>
<tr><td>Experts’ consultation 2.3

MSs experts to discuss the ADI and ARfD, the critical endpoints and the use of additional (if needed) uncertainty factors of dinotefuran.</td><td>The ADI is 0.22 mg/kg bw per day based on the NOAEL of 22 mg/kg bw per day derived from the oral dietary 52-week study conducted in dogs and applying an uncertainty factor of 100.

The ARfD is 1.25 mg/kg bw based on the NOAEL of 125 mg/kg derived from the oral developmental toxicity study in rabbits and applying an uncertainty factor of 100.

The reference values were based on the data available in the Evaluation Report (ER) at the time of discussion.

In vitro comparative metabolism and phototoxicity studies were not provided; however, this was considered not impacting the risk assessment for the substance dinotefuran.

A discrepancy was observed in the ARfD setting vs. biocidal assessment.

It is noted that a renewal procedure is ongoing under the biocidal regulatory framework and some values may be reviewed based on new submitted data.</td></tr>
</table>

Subject	Conclusions Pesticide Peer Review Meeting
	Open point: The EMS to provide further detail on the discussion on the palatability issue and its impact on the setting of toxicological reference values. The EMS to check the availability of some toxicological studies not reported in the current version of the ER but assessed under other regulatory framework.

REPORT OF PESTICIDES PEER REVIEW TC 114

FORMETANATE – AIR III **Rapporteur Member State: ES**

2. Mammalian toxicity

Date: 08 September 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff member	EFSA
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Belgium (2)	Federal Public Service Health, Food Chain Safety and Environment - BE
National Experts nominated by MS Czech Republic	The National Institute of Public Health - CZ
National Experts nominated by MS Germany (2)	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by RMS Spain (2)	Ministerio de Sanidad - ES
National Experts nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Netherlands	Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) - NL
Observers	Federal Food Safety and Veterinary Office (FSVO) - CH
	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT

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Discussion points/Outcome

2. Mammalian toxicity

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.12 proposed by EFSA **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.**	**Open point (applicable to all co-formulants):** **RMS to complete the assessment of the toxicological profile of the co-formulants and report it in the revised RAR (vol. 4) at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures.**

REPORT OF PESTICIDES PEER REVIEW TC 114

ELEMENTAL IRON – NAS **Rapporteur Member State: AT**

2. Mammalian toxicity

Date: 08 September 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff member	EFSA
National Experts nominated by RMS Austria (3)	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Belgium (2)	Federal Public Service Health, Food Chain Safety and Environment - BE
National Experts nominated by MS Czech Republic (2)	The National Institute of Public Health - CZ
National Experts nominated by MS Germany (3)	German Federal Institute for Risk Assessment (BfR) – DE German Environment Agency (UBA) - DE
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain	National Institute for Agricultural and food research and technology (INIA) - ES
National Experts nominated by MS France	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Experts nominated by MS Ireland	Department of Agriculture, Food and the Marine of Ireland – IE
National Experts nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Lithuania	The State Plant Service under the Ministry of Agriculture - LT
National Experts nominated by MS Netherlands (2)	Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) - NL
National Experts nominated by MS Slovenia	National Institute of Public Health - SI
Observer	Federal Food Safety and Veterinary Office (FSVO) - CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the bioavailability of elemental iron (Fe0) in an experts' meeting.**	**In line with previous EFSA conclusions on other iron salts [3,4,5] and taking into account the low toxicity of elemental iron, an oral absorption value of 50% was agreed.** **Open point:** **The RMS to better elucidate the discussion on oral absorption/bioavailability in the DAR Vol.1, Vol. 3B6 and List of Endpoints (LoEP) in line with the discussion at the peer review experts' meeting.**
Experts' consultation 2.2 **MSs experts to discuss the genotoxic potential/exposure to elemental iron in an experts' meeting.**	**Elemental iron is unlikely to be genotoxic based on a Weight of evidence (WoE) approach.** **This is in line with previous genotoxicity assessment on other iron salts [3,4,5] where no concerns were identified.** **Open point** **The RMS to update the DAR Vol.1, Vol. 3B6 and List of Endpoints (LoEP) in line with the discussion at the peer review experts' meeting.**

[3] EFSA (European Food Safety Authority), 2012. Conclusion on the peer review of the pesticide risk assessment of the active substance iron sulfate. *EFSA Journal* 2012, 10(1):2521, 48 pp. https://doi.org/10.2903/j.efsa.2012.2521;

[4] EFSA (European Food Safety Authority), 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance ferric phosphate. *EFSA Journal* 2015, 13(1):3973, 50 pp. https://doi.org/10.2903/j.efsa.2015.3973;

[5] EFSA (European Food Safety Authority), 2020. Conclusion on the peer review of the pesticide risk assessment of the active substance ferric pyrophosphate. *EFSA Journal* 2020, 18(1):5986, 18 pp. https://doi.org/10.2903/j.efsa.2020.5986.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.3 MSs experts to discuss the NOAELs/LOAELs or threshold values for elemental iron in an experts' meeting.	No experimental studies were available with the substance elemental iron. For short-term studies, the study by Zhu et al. 2016[6] (supporting), was considered as not relevant for setting NOAELs. A waiver for long-term, carcinogenicity, reproductive toxicity and neurotoxicity studies was agreed. This is in line with the waiver accepted for the ED assessment of this substance (see experts' consultation point 2.4). Overall, although no toxicological data are available to assess the toxicological profile of elemental iron, this does not appear scientifically necessary considering the lack of concerns in the available scientific publications and that it is not expected that the use of elemental iron as a plant protection product will pose a risk when comparing to the use of iron as food supplement and food additive.[7,8,9,10,11]
Experts' consultation 2.4 Experts to discuss the waiving proposed for the ED assessment.	A waiver for the ED assessment of elemental iron in line with the EFSA/ECHA ED guidance (2018) was agreed.
Experts' consultation 2.5 MSs experts to discuss the setting of reference values or ADI/ARfD/AOEL in an experts' meeting.	Considering the low toxicological profile of elemental iron, the use of a semi-quantitative exposure assessment was agreed. This is based on the following reference values: - ADI=0.8 mg/kg bw per day based on permitted tolerable maximum daily intake (PMTDI) set by JEFCA.[12] - AOEL=0.4 mg/kg bw per day based on the PMTDI set by JEFCA and considering the 50% oral absorption value (see experts' consultation point 2.1).

[6] Zhu Q, Qian Y, Yang Y, Wu W, Xie J, Wei D. Effects of carbonyl iron powder on iron deficiency anemia and its subchronic toxicity. J Food Drug Anal. 2016 Oct;24(4):746-753. https://doi.org/10.1016/j.jfda.2016.04.003. Epub 2016 Jun 2. PMID: 28911612; PMCID: PMC9337281.

[7] EFSA Panel on Food Additives and Nutrient Sources (ANS), 2010. Scientific Opinion on the safety of ferrous ammonium phosphate as a source of iron added for nutritional purposes to foods for the general population (including food supplements) and to foods for particular nutritional uses. *EFSA Journal* 2010; 8(5):1584, 26 pp. https://doi.org/10.2903/j.efsa.2010.1584.

[8] EFSA (European Food Safety Authority), 2009. Ferrous phosphate added for nutritional purposes to food supplements. Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food. *EFSA Journal* 2009 951, 1-13.

[9] JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2010. Safety evaluation of certain food additives. Prepared by the 71st meeting of the JECFA. WHO Food Additives Series 62, 57 117.

[10] JECFA, 1983. Iron: Provisional maximum tolerable daily intake for man. WHO Food Additive Series 18.

[11] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009. Scientific Opinion on the substantiation of a health claim related to Iron and necessary for the cognitive development of children pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2009; 7(11):1360.

[12] https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/2859 [accessed in September 2023]

Subject	Conclusions Pesticide Peer Review Meeting
	The ARfD is considered not needed based on low acute toxicity of iron (LD_{50} > 50 g/kg) and the toxicological profile of iron mainly based on the mild effects observed in gastrointestinal tract which are not considered relevant for acute intake. **The conclusion reached for elemental iron is in line with the EFSA conclusions on other iron salts.** **Open point:** **The RMS to update the DAR Vol.1, Vol. 3B6 and List of Endpoints (LoEP) in line with the discussion at the peer review experts meeting.**
Experts' consultation 2.6 **MSs experts to discuss the operators, workers, bystanders and residents exposure in an experts' meeting.**	**The experts agreed with the input parameters in the EFSA calculator.** **Open point:** **the RMS to include new calculation using the agreed toxicological reference values (see experts' consultation point 2.5), and to include additional Risk Mitigation Measures (RMM) available in the used calculators as appropriate.**
Experts' consultation 2.7 proposed by EFSA **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.**	**Based on the available information at the date of the peer review meeting, all experts agreed that there is no concern for any co-formulants included in the formulation for representative uses.** **Open point:** **RMS to complete the assessment of the toxicological profile of the co-formulants and report it in the revised DAR Volume 4 to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures.** **The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion, and referred to the safety of the co-formulant per se as well as in relation to the concentrations in the PPP.**

REPORT OF PESTICIDE PEER REVIEW TC 114

CLOVE OIL – Amendment of approval conditions **Rapporteur Member State: MT**

2. Mammalian toxicity

Date: 08 September 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff member	EFSA
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Belgium (2)	Federal Public Service Health, Food Chain Safety and Environment - BE
National Experts nominated by MS Germany (4)	German Federal Institute for Risk Assessment (BfR) – DE
National Experts nominated by MS Denmark	Danish Environmental Protection Agency - DK
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Experts nominated by MS Ireland	Department of Agriculture, Food and the Marine of Ireland – IE
National Experts nominated by MS Lithuania	The State Plant Service under the Ministry of Agriculture - LT
National Experts nominated by RMS Malta	Benaki Phytopathological Institute – representing MT
National Experts nominated by MS Netherlands	Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) - NL
National Experts nominated by MS Slovenia	National Institute of Public Health - SI
Observer (3)	Federal Food Safety and Veterinary Office (FSVO) – CH
	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
	Malta Competition and Consumer Affairs Authority (MCCAA) - MT

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MS experts to discuss NDE of clove oil in an experts' meeting.**	**The operator exposure estimates are below the AOEL for the representative use of clove oil when using the EFSA calculator 2014 and considering the appropriate refinement for exposure to vapour only during mixing and loading (due to automatic drip irrigation in greenhouse).** **The worker dermal exposure estimates are below the AOEL for the exposure to soil residue. For the inhalation exposure, re-entry period of 24 h after application should be applied.** **The bystander and resident dermal exposure is not expected to occur. For the inhalation exposure, the conclusion is pending the outcome of the peer review experts' meeting in FATE.** **Open points:** **- RMS to provide operator exposure estimates for the task of mixing and loading considering the option of knapsack application in the EFSA calculator 2014.** **- RMS to update the RAR (Vol. 1, Vol. 3 CP and LoEP) with the final calculations/conclusions of non-dietary exposure estimates as agreed during the experts' meeting.**

REPORT OF PESTICIDES PEER REVIEW TC 114

1-METHYLCYCLOPROPENE – Amend of approval conditions **Rapporteur Member State: NL**

2. Mammalian toxicity

Date: 08 September 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff member	EFSA
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Belgium (2)	Federal Public Service Health, Food Chain Safety and Environment - BE
National Experts nominated by MS Germany (4)	German Federal Institute for Risk Assessment (BfR) – DE
National Experts nominated by MS Denmark	Danish Environmental Protection Agency - DK
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Experts nominated by MS Ireland	Department of Agriculture, Food and the Marine of Ireland – IE
National Experts nominated by MS Lithuania	The State Plant Service under the Ministry of Agriculture - LT
National Experts nominated by MS Malta	Benaki Phytopathological Institute – representing MT
National Experts nominated by RMS Netherlands	Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) - NL
National Experts nominated by MS Slovenia	National Institute of Public Health - SI
Observer (3)	Federal Food Safety and Veterinary Office (FSVO) – CH
	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
	Malta Competition and Consumer Affairs Authority (MCCAA) - MT

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[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MS experts to discuss the setting of reference values taking into account the available toxicity studies by inhalation and possible need for correction for inhalation absorption when deriving the AOEL and AAOEL.**	**Studies based on oral absorption are considered more accurate to determine the internal dose and derive an AOEL also in consideration of the fact that the 90-day study by inhalation presents some limitations.** **AOEL is set at 0.04 mg/kg bw per day based on rat 2-generation study and dog 90-day study with UF of 100 and no correction for oral absorption. The AOEL derived from the inhalation study (90-day inhalation study in rats with inhalation absorption of 66%) would result in the same value and is considered supportive.** **Previous agreed reference values (ADI=0.02 mg/kg bw per day, ARfD=0.12 mg/kg bw and AAOEL=0.12 mg/kg bw) are confirmed.** **Open Point: RMS to amend the List of Endpoints (LoEP) by including also the AOEL derived from the inhalation study as being supportive to the AOEL derived from the oral studies.**
Experts' consultation 2.2 **MS experts to discuss the waiving of long-term toxicity/carcinogenicity studies in an experts' meeting.**	**The waiving of long-term toxicity and carcinogenicity studies considered acceptable for the renewal of 1-MCP is considered also acceptable for the current application for amendment of approval conditions on the basis of:** • **No significant dietary exposure based on residues below LOQ;** • **No long-term occupational exposure;** • **No new toxicological information or regulatory appropriate endpoint to further inform the risk assessment would be gained from conducting these studies.** **The extra uncertainty factor of 2 to extrapolate from sub-chronic to chronic studies is considered appropriate for the derivation of the ADI.**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.3 MS experts to discuss non dietary exposure estimates for 1-MCP based on the available field studies.	Based on the EFSA model 2014[3] and on the results of a field study for the exposure by inhalation (KCP 7.2.1.2), the predicted exposure estimates for operators, worker, residents and bystanders are below the (A)AOEL. **Open point:** 1) RMS to check the justification for the lack of correction for the low recoveries for the results related to the operator (KCP 7.2.1.2) and add related information into the RAR. 2) RMS to include data of the different trials of the resident assessment in the RAR providing the underlying data to support why data from trial site 820 have been used for the assessment.
Experts' consultation 2.4 MS experts to discuss the appropriate dermal absorption value for the formulation AF-701.	For the concentrate of the formulation AF-701, the default dermal absorption value of 10% is applicable. For the in-use dilution (0.15 g/L), considering the physico-chemical properties of the substance (gaseous substance) and the fact that poor recoveries were obtained in the preliminary dermal absorption study (under occluded and unoccluded conditions) with the reference formulation AF-701 demonstrating the technical difficulties in testing the aqueous formulation, the dermal absorption value obtained with the formulation AF-600 (oil-based formulation) has been used, resulting in a dermal absorption value of 0.11% after pro-rata correction.

[3] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014; 12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

REPORT OF PESTICIDE PEER REVIEW TC 114

RIMSULFURON – AIR III mandated for ED assessment **Rapporteur Member State: SI**

2. Mammalian toxicity

Date: 08 September 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff member	EFSA
National Experts nominated by MS Austria (3)	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Belgium	Federal Public Service Health, Food Chain Safety and Environment - BE
National Experts nominated by MS Czech Republic (2)	The National Institute of Public Health - CZ
National Experts nominated by MS Germany (2)	German Federal Institute for Risk Assessment (BfR) – DE German Environment Agency (UBA) - DE
National Experts nominated by MS Spain	National Institute for Agricultural and food research and technology (INIA) - ES
National Experts nominated by MS France (2)	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) - FR
National Experts nominated by MS Ireland	Department of Agriculture, Food and the Marine of Ireland – IE
National Experts nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Lithuania	The State Plant Service under the Ministry of Agriculture - LT
National Experts nominated by MS Netherlands (2)	Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) - NL
National Experts nominated by RMS Slovenia	National Institute of Public Health - SI

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **The appropriateness of the testing strategy should be discussed in an expert consultation. The strategy proposed in the EFSA/ECHA ED GD could be not appropriate to investigate MoA dealing with impaired steroidogenesis when the pathway is mainly impacting progesterone and/or progesterone related metabolites. It is therefore necessary to discuss what would be the most appropriate testing strategy (including direct execution of the OECD TG 443) to address this uncertainty.**	***T-modality:*** **criteria are not met for the T-modality based on lack of a pattern of T-mediated adversity in a sufficiently investigated dataset; in line with the ECHA/EFSA ED guidance (2018), scenario 1a is applicable.** ***EAS-modalities:*** **No EAS-mediated adverse effects were observed based on an incomplete dataset. Additional testing is required to complete the current data package (scenario 2a(iii)):** • **A study in line with OECD TG 455 (ER binding and transactivation assay),** • **A study in line with OECD TG 458 (AR STTA assays),** • **A study in line with OECD TG 456 (H295R Steroidogenesis Assay)** • **A study in line with OPPTS 890.1200 (Aromatase assay)** • **A study in line with OECD TG 441 (Hershberger Assay) in case OECD TG 456, OECD TG 458 and OPPTS 890.1200 are negative** • **A study in line with OECD TG 440 (Uterothrophic assay) in case the OECD TG 455 is negative.** • **If the above studies are negative, the substance will not meet the ED criteria for EAS modalities (scenario 2a (ii)). However, in case of positive result/s based on the above tests for at least one modality, additional testing is needed (scenario 2a(i)):** • **i.e. extended one-generation (EOGRT) study with inclusion of the cohort 1a and 1b including the mating of cohort 1b to produce the F2 generation (OECD TG 443, Level 5).** **It is also recommended that applicant, while performing the OECD TG 456 (H295R Steroidogenesis Assay), should also include an**

Subject	Conclusions Pesticide Peer Review Meeting
	evaluation of progesterone/glucocorticoids pathways (Open point EFSA to provide a more definitive recommendation). **Post meeting note (Sept 2023):** **After careful consideration, EFSA concluded that in the OECD TG 456 (H295R Steroidogenesis Assay), only testosterone and oestradiol are validated endpoints (i.e., there are related acceptance criteria, like minimal production by control cells, minimal fold-changes in production by positive controls (prochloraz and forskolin), etc.), whereas no other hormones have been validated as readouts (including progesterone and glucocorticoids).** **Based on these additional considerations, EFSA is of the opinion that it should not be recommended to include evaluation of progesterone/glucocorticoids pathways in the OECD TG 456 study (H295R Steroidogenesis Assay).**

REPORT OF PESTICIDE PEER REVIEW TC 114

LENACIL – AIR III **Rapporteur Member State: BE**

2. Mammalian toxicity

Date: 08 September 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff member	EFSA
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by RMS Belgium (2)	Federal Public Service Health, Food Chain Safety and Environment - BE
National Experts nominated by MS Czech Republic	The National Institute of Public Health - CZ
National Experts nominated by MS Germany (2)	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by MS Spain (2)	Ministerio de Sanidad - ES
National Experts nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Netherlands	Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) - NL
Observers	Federal Food Safety and Veterinary Office (FSVO) - CH
	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT

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discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.11 (proposed by EFSA for completeness of discussion) **MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.**	**Open point (applicable to all co-formulants)** **RMS to complete the assessment of the toxicological profile of the co-formulants and include it in a revised RAR, at least as regards the acute toxicity, genotoxicity, short- and long-term toxicity and reproductive toxicity of the chemically identified co-formulants.** **A data gap for genotoxicity, short and long-term and reproductive toxicity was identified for [redacted], due to the lack of data.**

REPORT OF PESTICIDE PEER REVIEW TC 114

DICHLORPROP-P – AIR III mandated for ED re-assessment **Rapporteur Member State: IE**

2. Mammalian toxicity

Date: 08 September 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff member	EFSA
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Belgium (2)	Federal Public Service Health, Food Chain Safety and Environment - BE
National Experts nominated by MS Germany (3)	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS Greece	Benaki Phytopathological Institute - EL
National Experts nominated by RMS Ireland	Department of Agriculture, Food and the Marine of Ireland – IE
National Experts nominated by MS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS Lithuania	The State Plant Service under the Ministry of Agriculture - LT
National Experts nominated by MS Netherlands	Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) - NL
Observers	Federal Food Safety and Veterinary Office (FSVO) - CH

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[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation point proposed by EFSA as follow up from TC92 **Considering the new extended 1-generation study submitted during the ED clock-stop, experts to re-discuss the point of departure to be used in the risk assessment.**	**The majority of experts agreed with the NOAEL setting for the new 1-extended generation study as proposed by the RMS:** **Parental NOAEL: 500/325 ppm (35.9 mg/kg bw per day) based on decreased body weight gain and increased kidney weight.** **Reproductive performance NOAEL: 500/325 ppm (35.9 mg/kg bw per day) based on prolonged gestation and total litter loss.** **Offspring NOAEL: 500/325 ppm (35.9 mg/kg bw per day) based on decreased body weight.** **The experts agreed to keep reference values as agreed during previous peer review meetings by considering that the new 1-extended generation study does not challenge existing reference values.**

REPORT OF PESTICIDE PEER REVIEW TC 110

BUPROFEZIN – AIR IV **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 26 June 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS France	Agence Nationale Sécurité Sanitaire Alimentaire Nationale (ANSES) - FR
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) -DE
National Expert nominated by MS Germany	German Environment Agency (UBA) - DE
National Expert nominated by RMS Italy	International Centre for Pesticides and Health Risk Prevention (ICPS)
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Experts nominated by MS The Netherlands	Ctgb - NL
National Expert nominated by MS Sweden	Swedish Chemicals Agency - SE
National Expert nominated by MS Slovakia	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.6 Experts to discuss the NOAEL for pups in the preliminary dose finding and main developmental thyroid toxicity study, as well as the need for a DNT study on buprofezin.	***B.6.8.3.1/03 | 2011 | Buprofezin: Milk transfer and effect on the thyroid of suckling pups in rats by dietary administration to dams.*** The MS experts agreed that the study should not be used for risk assessment purposes since the study was considered as appropriate only for a qualitative evaluation of the transfer of buprofezin to milk. ***B.6.8.3.1/05 | 2015 | Buprofezin: Comparative thyroid assay in rats.*** The MS experts considered the study as reliable based on an appropriate methodology. The MS agreed on the following NOAEL for T-mediated effect in the different populations: Segment A (dams at GD 20 sampling): **80 mg/kg per day** based on increase TSH (+115%) and decreased T4 levels (-24%) and histopathology in thyroids (↑follicular cell height, ↓colloid area, ↑follicular hypertrophy) observed at 160 mg/kg bw per day. Segment C: **10 mg/kg bw per day** based on thyroid histopathology finding (↑follicular cell height, ↓colloid area, ↑follicular hypertrophy) at 80 mg/kg bw per day. Segment A foetuses (GD 20 foetuses): **10 mg/kg bw per day** based on increased TSH and increase thyroid weight from the dose of 80 mg/kg bw per day Segment B (PND 4): top-dose, **160 mg/kg bw per day**, based on no T-mediated effect observed in this population. Segment B (PND 21): **10 mg/kg bw per day**, based on thyroid weight and histopathological changes for which a pattern of dose-response was observed from 80 mg/kg bw per day, and TSH increase. As regards the lowest NOAEL/LOAEL for other toxicological effects than thyroid the MS experts agreed to set a LOAEL of **10 mg/kg bw per day for offspring** based on body weight and body weight gain (PND 0-7)

Subject	Conclusions Pesticide Peer Review Meeting
	reduction in Segment B PND 21 pups, starting at 10 mg/kg bw. The observed effect was considered adequate for setting NOAEL for systemic toxicity; however, the dose was considered to be below the MTD. ***B.6.8.3.1/07 | 1993 | Buprofezin: Peri- and Post-natal Developmental Study in Rat by the Dietary Route peri- and post- natal developmental study in the rat.*** The study is considered not acceptable and not useful in the weight of evidence of buprofezin as thyroid-disruptor chemical or to set NOAEL/LOAEL. **Open point 1** The RMS to include in a revised RAR Vol. 3 B.6 the revised assessment of the CTA study (***B.6.8.3.1/05)*** in line with the peer review meeting discussion and EFSA ED WG advice. **Open point 2** RMS to include the following study from US EPA dossier submitted by the applicant during the first clock stop in a revised RAR: • Study title: 'BUPROFEZIN: LACK OF NEURO-DEVELOPMENTALTOXICITY POTENTIAL IN RELATION TO THYROID STIMULATION' • Data requirement: OPPTS 870.6300, Developmental Neurotoxicity in Rat • Study Completion Date: October 21, 2002 • Reference from US EPA. The summary of the study and the RMS assessment should be included in the revised RAR.
Experts' consultation 2.7 Experts to discuss the endocrine disruption potential of buprofezin according to EFSA/ ECHA guidance.	Regarding T-modality: A clear pattern of T-mediated adversity is observed in a complete data set. The postulated Mode of Action (MOA) indicated CAR/PXR induction as the plausible Molecular Initiating Event (MIE) and phase I/II enzymes induction as the plausible key events (KE). All of the experts agreed that the ED criteria are met for T-modality. **Scenario 1b** was concluded. Regarding EAS modalities :

Subject	Conclusions Pesticide Peer Review Meeting
	All the experts agreed that the EAS-modality is sufficiently investigated and that there is no evidence for EAS-mediated adversity and EAS-mediated activity in the available dataset. **Scenario 1a** was concluded. <u>Open points</u> • **Open point 1** for the RMS to include the T-modality assessment accoding to the peer review meeting discussion, including reliability and detailed assessment of the CTA study and the [redacted] 1993 study (in Vol. 3 B.6) • **Open point 2** for the RMS to include the available ToxCast data (retrieved by the ED WG) for T MIEs. • **Open point 3** for the RMS to correct the sentence in Vol. 1 (in section 2.10.1.1.4 and 2.10.1.1.7 in ED assessment section) with regard to the lack of comparative *in vitro* assay for liver metabolism induction.
Expert consultation 2.8 Experts to discuss the reliability assessment of the thyroid comparative assay including HCD. Experts to conclude whether juvenile rats are more sensitive than adults in the comparative thyroid assay.	This experts' consultation was discussed together with experts' consultation 2.6.
Experts' consultation 2.9 Experts to discuss the setting of reference values, including ADI and ARfD.	The experts agreed on the following reference values: AOEL of 0.013 mg/kg bw per day based on the LOAEL of 10 mg/kg bw per day for offspring based on body weight and body weight gain (PND 0-7) reduction in the Comparative Thyroid Assay. Uncertainty factor (UF) of 100 plus additional UF of 3 because no identification of a NOAEL. Correction for oral absorption of 40%. ADI of 0.01 mg/kg bw per day based on the NOAEL of 0.9 mg/kg bw per day obtained in the rat 104-week study, based on increased incidence of eosinophilic foci of hepatocellular alteration in females and thyroid follicular cell hypertrophy in males (by using an uncertainty factor of 100). AAOEL of 0.04 mg/kg bw based on the NOAEL of 10 mg/kg bw per day based on subdue mood observed after one hour of treatment during the early part of week one in the 90-day dog study, by applying a standard uncertainty factor of 100 together with an adjustment factor to account for oral absorption of 40%. The AAOEL is also supported by the NOAEL of 10 mg/kg bw per day for thyroid mediated toxicity in pups in the CTA. ARfD of 0.1 mg/kg bw based on the NOAEL of 10 mg/kg bw per day based on subdue mood observed after one hour of treatment during the early part of week one in the 90-day dog study, by applying a standard uncertainty factor of 100. The ARfD is also supported by the NOAEL of 10 mg/kg bw per day for thyroid mediated toxicity in pups in the CTA.

Subject	Conclusions Pesticide Peer Review Meeting
New experts' consultation identified in May 2023 Experts to discuss if the DFR study from [redacted] 2010 is appropriate for refinement of worker exposure considering the intended use.	MS experts considered that the DT_{50} value of 9 days cannot be extrapolated to representative uses of buprofezin and the default DT_{50} should be used, since different crops and formulations were used in the studies and only one study is available in greenhouse. **Open point** RMS to provide revised worker exposure estimates for the representative use of buprofezin (ornamentals indoor), taking into account the outcome of the experts' consultation.

REPORT OF PESTICIDE PEER REVIEW TC 110

DELTAMETHRIN – AIR III **Rapporteur Member State: AT**

2. Mammalian toxicity

Date: 26 June 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Experts nominated by RMS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS France	Agence Nationale Sécurité Sanitaire Alimentaire Nationale (ANSES) - FR
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) -DE
National Expert nominated by MS Germany	German Environment Agency (UBA) - DE
National Experts nominated by MS Spain	Ministerio de Sanidad - ES
National Experts nominated by MS The Netherlands	Ctgb - NL
National Expert nominated by MS Sweden	Swedish Chemicals Agency - SE
National Expert nominated by MS Slovakia	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MS experts to discuss the NOAEL of the 13 week feeding study in dogs in an experts' meeting, including the BMD analysis.**	**The 90-day study in dogs (Report No. A98072) is considered supplementary because of the limitations observed (e.g., wide span of animal age, randomisation per group unclear, etc.).** **This study is therefore not suitable for setting toxicological reference values (TRVs) and sufficient information to derive TRVs is available from other studies.** **Open point: RMS to amend the figures related to the outcome of the applicant's BMD analysis of liquid faeces.** **Open point: RMS to include the BMD analysis provided by EFSA as an Annex in the revised RAR.**
Experts' consultation 2.2 **MS experts to discuss the NOAEL of the one year study in dogs ([redacted], 1993) in an experts' meeting.**	**The NOAEL of the one year study in dogs (Report No. A70808) is 1 mg/kg bw per day, based on clinical signs (unsteadiness of the gait, chewing/scratching of the extremities, tremor, splayed limbs/digits) and liquid faeces observed in females at 10 mg/kg bw per day.**
Experts' consultation 2.3 **MS experts to discuss the issue of proof of bone**	**Systemic toxicity (one death) and acute signs of toxicity observed in all animals (e.g. piloerection, hyperactivity and locomotor disorders) are considered suitable evidence the bone marrow was exposed to deltamethrin in the *in vivo* micronucleus (MN) test in mice (Report No. A41868).**

Subject	Conclusions Pesticide Peer Review Meeting
marrow exposure in the micronucleus test.	
Experts' consultation 2.4 MS experts to discuss the NOAEL of the 2-year feeding study in rats ([redacted], 1980) in an experts' meeting.	In the 2-year study in rats (Report No. A20243): • the increased incidence of testicular interstitial cell adenomas observed in males at top dose (50 ppm dietary level, corresponding to 2.1 mg/kg bw per day) compared to control group 1 is considered spontaneous and unrelated to the administration of the test substance. Similar incidence was observed in control group 2, it is a common finding in ageing rats, and the effect was not reproduced in the other 2-year study in rats where higher dose levels were used; • the increased incidence of axonal degeneration observed at 18-month interim sacrifice but not at termination is likely artifactual and not related to treatment. No treatment-related changes in the peripheral nerves were seen in the 13-week neurotoxicity study, where an adequate histopathological approach was applied. In the absence of any effect, the: NOAEL for systemic toxicity and carcinogenicity is the top dose of 50 ppm (corresponding to 2.1 and 2.8 mg/kg bw per day in males and females, respectively).
Experts' consultation 2.5 MS experts to discuss the reproductive toxicity assessment in an experts' meeting.	The 2-generation reproductive toxicity study in rats (Report No. A70863) is considered acceptable for the assessment of the reproductive toxicity of deltamethrin, as the study is compliant with an old version of the OECD test guideline 416. Some missing information, i.e. those on sexual maturation, can be provided for by the rat DNT study.
Experts' consultation 2.6 MS experts to discuss and agree on the NOAEL of the 2-generation rat study ([redacted], 1992) in an experts' meeting.	In the rat 2-generation study (Report No. A70863): • the reproductive NOAEL is 320 ppm (equivalent to 18.3 mg/kg bw/day, lowest dosage range), as deltamethrin did not affect mating performance or fertility • the parental NOAEL is 80 ppm (approximately 4.2 mg/kg bw/day, lowest dosage range) based on reductions in body weight and gastric erosion at 320 ppm • the offspring NOAEL is 80 ppm (approximately 7.6 mg/kg bw/day according to the intake in week 1 of pre-mating in the P1 parents) based on pup deaths and reduced body weights at 320 ppm
Experts' consultation 2.7	In the developmental toxicity study in rats (Report No: A20968):

Subject	Conclusions Pesticide Peer Review Meeting
MS experts to discuss the NOAEL of the developmental toxicity study in rats ([redacted], 1978) in an experts' meeting (although it is recognized this study has not been used for the risk assessment).	• the maternal NOAEL is 2.5 mg/kg bw per day based on reduced body weight gain and clinical signs (salivation); • the developmental NOAEL, in the absence of any effect, is the highest tested dose of 5 mg/kg bw per day.
Experts' consultation 2.8 MS experts to discuss the findings of the acute neurotoxicity study by [redacted] 1998 and the NOAEL for neuropathy in an experts' meeting.	The acute neurotoxicity study in rats (Report No. A74318) is considered supplementary due to some deviations (e.g. lack of data on food consumption and no neuropathological evaluation on samples from nervous tissues from low and intermediate dose groups). The NOAELs of the study are: • NOAEL for general toxicity and reversible neurotoxicity is 5 mg/kg bw, based on a range of clinical signs including salivation, soiled fur and impaired mobility at 15 mg/kg bw. • NOAEL for neuropathy is 50 mg/kg bw, the top dose tested. • The overall study NOAEL is 5 mg/kg bw/day based on clinical signs (salivation, soiled fur and impaired mobility at 15 mg/kg bw).
Experts' consultation 2.9 MS experts to discuss the ED properties of deltamethrin in an expert meeting.	***T-modality*** T-mediated parameters have been sufficiently investigated. There is no evidence for a pattern of T-mediated adversity and T-mediated activity in the available dataset. Scenario 1a of the EFSA/ECHA ED guidance is applicable. The ED criteria for T-modality are not met. ***EAS-modalities*** Considering that no EAS-mediated adverse effects were observed based on an incomplete data set, additional testing is required to complete the current data package: • A study in line with OECD TG 456 (H295R Steroidogenesis Assay) • A study in line with OECD TG 458 (AR STTA assays); In the case OECD TG 456 and 458 and OPPTS 890.1200 are negative, an In vivo Hershberger Assay OECD TG 441 should be performed.

Subject	Conclusions Pesticide Peer Review Meeting
	If the above tests are negative, deltamethrin will not meet ED criteria for EAS modalities. However, in case of positive result/s based on the above tests for at least one modality, additional testing is needed: • **OECD TG 443 (extended one-generation study) including the mating of cohort 1b to produce the F2 generation and including measurement in F1 generation of thyroid hormones on PND 4 and PND 22 and TSH measurement on PND 22.** **As part of the testing strategy an updated literature search according to Appendix F of the ED EFSA/ECHA Guidance should be provided during the regulatory stop-of-the-clock.** **Open points:** • **the RMS to update the ED assessment in Vol. 1 including in the testing strategy the OECD TG 443 as Level 5 including the mating of cohort 1b to produce the F2 generation** • **the RMS to revise the sentence in the RAR VOL. 1 at p. 222 and replace it with the following one: *No T mediated endpoints i.e. thyroid histopathology or thyroid weight were measured in the OECD TG 426 for deltamethrin* .** • **the RMS is asked to provide the list of additional literature studies identified by the Swedish Authority (in charge of the biocidal assessment of the substance) that may be relevant for the assessment of ED properties of DLM.**
Experts' consultation 2.10 **MS experts to discuss in an experts' meeting if bone marrow can be considered sufficiently exposed to the metabolite Becisthemic acid in the micronucleus test in mice ([redacted], 1997b).**	**In the *in vivo* micronucleus test conducted in mice with metabolite Becisthemic acid (Report No. 374/050), the bone marrow has been considered as sufficiently exposed based on decreased PCE/NCE ratio and evidence of clinical signs. See also metabolite discussion under Experts' consultation 2.12.**
Experts' consultation 2.11	**In the immunotoxicity study (Report No. SA 10360):**

Subject	Conclusions Pesticide Peer Review Meeting
MS experts to discuss the NOAEL of the immunotoxicity study ([redacted], 2012) in an experts' meeting.	• the NOAEL for general toxicity is 100ppm (8.3 mg/kg bw per day); • the NOAEL for immunotoxicity is confirmed at 600ppm (48.3 mg/kg BW per day), since no immunotoxic effects were noted in deltamethrin treated animals.
Experts' consultation 2.12 MS experts to discuss the toxicity of Deltamethrin's metabolites and isomers in an experts' meeting.	***Alpha-R isomer of Deltamethrin (M01)*** The grouping with the parent compound was accepted. The metabolite is considered unlikely to be genotoxic based on the read-across (structural similarity and multi-QSAR analyses) with the parent for which experimental genotoxicity data are available. The reference values of the parent applied. ***Trans-isomer of Deltamethrin (M02)*** The grouping with the parent was accepted. The metabolite is considered unlikely to be genotoxic based on the read-across (structural similarity and multi-QSAR analyses) with the parent for which experimental genotoxicity data are available. The reference values of the parent applied. ***Becisthemic acid (Br2CA) (M10)*** The metabolite is considered unlikely to be genotoxic based on experimental genotoxicity data available : negative Ames test and *in vivo* MN test, with evidence of bone marrow exposure (refer to experts' consultation 2.10). The metabolite was found in rat urine in the range of 2-12% (and above 10% for females only). Although the metabolite is not a major rat metabolite in males, by considering the amount found in females urine (above 10%) and considering that the metabolite is expected to be qualitatively different from the parent i.e. the metabolite does not share the same toxophore identified for pyrethroids, the reference values of the parent can be applied since this would represent a worst-case. ***3-phenoxybenzaldehyde (M32)*** Experimental data on genotoxicity exist under other dossiers (e.g., including alpha-cypermethrin, cypermethrin, not an exhaustive list), and these should be prioritised vs. the Q(SAR) analyses.

Subject	Conclusions Pesticide Peer Review Meeting
	A data gap is identified for available experimental data from other dossiers. ***3-Phenoxybenzoic acid (PBA) (M39)*** **The metabolite is considered unlikely to be genotoxic based on the information reported in the *EFSA PPR Panel Scientific opinion on toxicity of pyrethroid common metabolites* (EFSA PPR Panel, 2022[3]). It is acknowledged that not all the experimental data evaluated, and peer reviewed in the EFSA PPR Panel scientific opinion, were available to the applicant and to the RMS.** **With regard the general toxicity, the conclusion reached by the EFSA PPR panel was considered as applicable for PBA (M39): the metabolite has different qualitative (no neurotoxic mechanism) and quantitative (higher NOAELs) toxicity compared to the parent pyrethroid compounds; ADI of 0.1 mg/kg bw per day and ARfD of 1 mg/kg bw.** ***4'-OH-mPB-acid (M49)*** **The metabolite is considered unlikely to be genotoxic based on the information reported in the *EFSA PPR Panel Scientific opinion on toxicity of pyrethroid common metabolites* (EFSA PPR Panel, 2022[4]). It is acknowledged that not all the experimental data evaluated, and peer reviewed in the EFSA PPR Panel scientific opinion, were available to the applicant and to the RMS.** **With regard the general toxicity, the conclusion reached by the EFSA PPR panel was considered as applicable for PBA: the metabolite has different qualitative (no neurotoxic mechanism) and quantitative (higher NOAELs) toxicity compared to the parent pyrethroid compounds; ADI of 0.1 mg/kg bw per day and ARfD of 1 mg/kg bw** **Open point: the RMS is asked to include the consideration reported in the Scientific opinion on toxicity of pyrethroid common metabolites (EFSA Journal 2022;20(10):7582) with regard to metabolites M39 and M49.** ***3-Phenoxybenzaldehyde cyanohydrin (3-PBC)*** **No gene mutation is observed for this metabolite 3-PBC based on a negative Ames Test. No additional experimental genotoxicity data**

[3] EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), Hernandez-Jerez, AF, Adriaanse, P, Aldrich, A, Berny, P, Duquesne, S, Focks, A, Marinovich, M, Millet, M, Pelkonen, O, Pieper, S, Tiktak, A, Topping, CJ, Widenfalk, A, Wilks, M, Wolterink, G, Binaglia, M, Chiusolo, A, Serafimova, R, Terron, A and Coja, T, 2022. Scientific opinion on toxicity of pyrethroid common metabolites. EFSA Journal 2022; 20(10):7582, 31 pp. https://doi.org/10.2903/j.efsa.2022.7582

[4] EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), Hernandez-Jerez, AF, Adriaanse, P, Aldrich, A, Berny, P, Duquesne, S, Focks, A, Marinovich, M, Millet, M, Pelkonen, O, Pieper, S, Tiktak, A, Topping, CJ, Widenfalk, A, Wilks, M, Wolterink, G, Binaglia, M, Chiusolo, A, Serafimova, R, Terron, A and Coja, T, 2022. Scientific opinion on toxicity of pyrethroid common metabolites. EFSA Journal 2022; 20(10):7582, 31 pp. https://doi.org/10.2903/j.efsa.2022.7582

Subject	Conclusions Pesticide Peer Review Meeting
	were submitted to address the other genotoxicity endpoints and address the genotoxicity potential of 3-PBC. No grouping was proposed. Data gaps (to be confirmed by residues experts) for genotoxicity (chromosomal aberration) and general toxicity. ***Post-meeting note*:** Please refer to the report of the Pesticide Peer Review TC 112 (27 June 2023) where the following was agreed: *data gap: Further data to address the toxicity of 3-phenoxy benzaldehyde cyanohydrin, i.e. at least sufficient data to conclude on genotoxicity should be provided.* *Trans-Becisthemic acid (M15)* The grouping with metabolite M10 was accepted. The metabolite is unlikely to be genotoxic based on read-across (structural similarity and multi-QSAR analyses) with M10 metabolite for which experimental data are available. For general toxicity for M15 the same conclusion as M10 should be applied being M15 an isomer of M10. ***Additional metabolites (for which only genotoxicity data was requested by residues):*** *4`-OH-deltamethrin + alpha-S isomer (M04)* The grouping with the parent was not accepted. The assessment of genotoxicity is inconclusive based on lack of data and not acceptance of the grouping proposed by the applicant due to additional positive predictions identified in the Q(SAR) analyses. *Deltamethrin-amide + alpha-S isomer (M08)* The grouping with the parent was accepted. The metabolite is considered unlikely to be genotoxic based on the read-across (structural similarity and multi-QSAR analyses) with the parent for which experimental genotoxicity data are available. *cis-CH2OH-cis-Br2CA (M16)* The grouping with metabolite M10 was accepted. The metabolite is considered unlikely to be genotoxic based on the read-across (structural similarity and multi-QSAR analyses) with M10 for which experimental genotoxicity data are available.

Subject	Conclusions Pesticide Peer Review Meeting
	Br2CA conjugate(s) (M14) **The grouping with metabolite M10 was accepted.** **No additional alerts were identified in Q(SAR) analyses compared to the source compound M10.** ***Cis-COOH-cis-Br2CA (M21)*** **The grouping with M10 was not accepted.** **The assessment of genotoxicity is inconclusive based on lack of data and not acceptance of the grouping proposed by the applicant due to additional positive predictions identified in the Q(SAR) analyses.** ***Trans-COOH-cis-Br2CA (M23)*** **The grouping with M10 was not accepted.** **The assessment of genotoxicity is inconclusive based on lack of data and not acceptance of the grouping proposed by the applicant due to additional positive predictions identified in the Q(SAR) analyses.** ***trans-COOH-cis-CH2OH-cis-Br2CA (M25)*** **The grouping with M10 was not accepted.** **The assessment of genotoxicity is inconclusive based on lack of data and not acceptance of the grouping proposed by the applicant due to additional positive predictions identified in the Q(SAR) analyses.** ***mPB-alcohol (M34)*** **The grouping with metabolites M39 and M49 was accepted.** **The metabolite is considered unlikely to be genotoxic based on the read-across (structural similarity and multi-QSAR analyses) with M39 and M49 for which experimental data are available in the EFSA PPR Panel scientific opinion (*EFSA PPR Panel 2022)*** ***4'-OH-mPB-alcohol (M37)*** **The grouping with metabolites M39 and M49 was accepted.** **The metabolite is considered unlikely to be genotoxic based on the read-across (structural similarity and multi-QSAR analyses) with M39 and M49 for which experimental data are available in the EFSA PPR Panel scientific opinion (*EFSA PPR Panel 2022).***

Subject	Conclusions Pesticide Peer Review Meeting
	mPB-amide (M55) **The grouping with M39 and M49 was not accepted.** **The assessment of genotoxicity is inconclusive based on lack of data and not acceptance of the grouping proposed by the applicant due to additional positive predictions identified in the Q(SAR) analyses.** ***Metabolites not discussed during the PRM TC 110*** **(not found in residue trials):** • **M03, M05, M06, M11, M19, M18, M41.**
Experts' consultation 2.13 **MS Experts' to discuss reference values in an Experts' meeting.**	**The agreed reference values are:** • **ADI=0.0025 mg/kg bw per day based on the NOAEL of 0.25 mg/kg bw per day from [redacted] 2019 study (for effects observed at 0.5 mg/kg bw per day: increased startle responses in males and impaired learning and memory in males and females); standard UF of 100.** • **ARfD=0.0025 mg/kg bw based on the NOAEL of 0.25 mg/kg bw per day from [redacted] 2019 study (for effects observed at 0.5 mg/kg bw per day: increased startle responses in males, impaired learning and memory and decreased BW in males and females); standard UF of 100.** • **AOEL=0.0019 mg/kg bw derived from the ADI of 0.0025 mg/kg bw per day with a correction of oral absorption of 0.75 (oral absorption=75%); standard UF of 100.** • **AAOEL=0.0019 mg/kg bw derived from the ARfD of 0.0025 mg/kg bw with a correction for oral absorption of 0.75 (oral absorption=75%); standard UF of 100.** **Open point:** **RMS to update the RAR on the basis of these agreed reference values (i.e. Vol. 1, LoEP and the different Vol. 3)** **Open point:** **RMS to provide revised exposure estimates with the agreed endpoints, considering the models available at the time of dossier submission. It is also recommended to use the EFSA model (preferably from EFSA guidance 2022, covering also indoor uses) for completeness and possible consideration at MS level for national authorisations. However, if the estimates with the EFSA model are above the (A)AOEL, both the new and old calculations (before implementation of EFSA model) should be reported.**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.14 **MS experts to discuss dermal absorption values for Deltamethrin (Meghmani and Sapec) in an experts' meeting.**	**The agreed dermal absorption values for the different formulations are:** • **Decis EW 15 (Bayer)** **Based on EFSA GD 2012:** • **concentrate (15 g/L): 7 % (excluding cell H19);** • **dilution (0.05 g/L): 11 % (all cells or excluding H08);** • **dilution (0.005 g/L): 14 %** **Bases on EFSA GD 2017 (including all cells):** • **concentrate (15 g/L): 6.8 %;** • **dilution (0.05 g/L): 9.3 %** • **dilution (0.005 g/L): 11 %** • **Deltamethrin 25 EC (Sapec)** **Based on EFSA GD 2017:** **- concentrate: 25 % (default value)** **- dilution: 70 % (default value)** **Based on EFSA GD 2012:** **- concentrate: 10 % (default value)** **- dilution: 10 % (default value)** • **Deltamethrin 2.5 % EC (Meghmani)** **Based on EFSA GD 2012 and 2017:** **- concentrate (25 g/L): 6 %** **- dilution (8.33 g/L): 8 %** **- dilution (0.0125 g/L): 10 % (default value from EFSA GD 2012) or 70 % (default value from EFSA GD 2017).** **Open point** **RMS to include these revised considerations of the dermal absorption studies in a revised RAR.**

Subject	Conclusions Pesticide Peer Review Meeting
New Experts' consultation 2.15 proposed by EFSA MS to discuss the DNT assessment (plus PBPK model).	Based on all the available evidence included in the RAR by RMS and in the EFSA IATA OECD Case Study 362, deltamethrin active substance may pose a concern for DNT in humans. Overall, on a weight of evidence approach, the NOAEL of 0.25 mg/kg bw day should be considered as sufficiently protective for DNT related hazards. This is mainly based on the assessment as provided in the AOP informed IATA OECD Case Study 362 and considering DNT endpoints of regulatory relevance (increased startle responses from the dose of 0.5 mg/kg bw day in males and impaired learning and memory from the dose of 0.5 mg/kg bw day in males and females from [redacted] 2019 study) Open point: RMS to include the endorsement of the OECD DNT IATA and its final conclusions by the Peer Review Meeting in the revised RAR. Open point: RMS to include the UA summary done by the EFSA IATA WG of the PBK analysis, as reported in the advice provided by the EFSA WG, in the revised RAR.
New Experts' consultation 2.16 proposed by EFSA MS experts to discuss the toxicological profile of co-formulants.	No concern is raised on any of the co-formulants present in the three formulations for the representative uses. Open point: RMS to include the assessment of the co-formulants present in the three formulations in the respective revised volumes 4.

REPORT OF PESTICIDE PEER REVIEW TC 110

DINOTEFURAN – MRL ART. 10 **Rapporteur Member State: PT**

2. Mammalian toxicity

Date: 26 June 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Experts nominated by MS Austria (2)	Austrian Agency for Health and Food Safety (AGES) - AT
National Experts nominated by MS Germany (2)	German Federal Institute for Risk Assessment (BfR) - DE
National Experts nominated by MS Netherlands	Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)- NL
National Experts nominated by MS Slovak Republic	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the ED potential of dinotefuran (including discussion on the testing strategy and the completeness of the data set) in an experts' meeting.**	***T-modality*** **T-mediated parameters have been sufficiently investigated.** **There is no evidence for a pattern of T-mediated adversity in the available dataset.** **Scenario 1a of the EFSA/ECHA ED guidance is applicable and the ED criteria for T-modality are not met.** ***EAS-modalities*** **EAS-mediated parameters have been sufficiently investigated.** **There is no evidence for a pattern of EAS-mediated adversity in the available dataset.** **Scenario 1a of the EFSA/ECHA ED guidance is applicable and the ED criteria for EAS-modalities are not met.** **Open points for the EMS concerning the ED assessment:** • **The EMS is asked to include in the ER the ED assessment for T and EAS modalities in line with the template for the ED assessments (Appendix I, in the administrative guidance for peer review of pesticide active substances[3]); a revision of the Lines of Evidence tables on T and EAS modalities should also be included as requested in the template. The EFSA ED assessment attached to the current report could be used and fulfilled for the part not included i.e. lines of evidence table.** • **The EMS is asked to update the Appendix E, including the ID matrix of all the studies considered in the ED assessment. ToxCast data should also be included and detail on which ToxCast assays**

[3] European Food Safety Authority 2019. Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances, EFSA supporting publication 2019: 16(4): EN-1612. 49 pp. doi: 10.2903/sp.efsa.2019.EN-1612

Subject	Conclusions Pesticide Peer Review Meeting
	are available for the substance under assessment should be reported and each ToxCast assay should be accompanied by an ID number • For the T-modality, for the 104-wk toxicity study in rat the EMS is asked to: o The EMS should correctly report the in the ER the information on the HCD (discrepancies exist between the excel table included as part of the study IIA 5.5.1-01 and what is reported in the ER at p. 193); the following should therefore be specified: the n. of studies on which the HCD are based, the time period covered, the testing facility, the strain of the tested species and the n. of animals. **Open point for EFSA:** • EFSA to revise the EFSA ED assessment and separate the finalisation on T-modality from an extra paragraph on the c-cell and parathyroid findings. • For the T-modality, for the 104-wk toxicity study in rat further details on the HCD should be included in the revised EFSA-ED assessment: incidence of C-cell adenoma in terminal animals while checking if there is any incidence at interim kills and decedents. • For the assessment of the EAS-modalities EFSA to check whether in the 2-gen toxicity study in rats, the assessment of ovary histopathology and sperm parameters for the P and F1 generations, at low and mid dose groups, is included in the EFSA ED assessment in accordance with the third amendment of the ER . If not included, this has to be reported in the revised EFSA ED assessment.

REPORT OF PESTICIDE PEER REVIEW TC 110

QUINOLIN-8-OL (8-HYDROXYQUINOLINE) – AIR IV **Rapporteur Member State: ES**

2. Mammalian toxicity

Date: 26 June 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
National Experts nominated by RMS Spain	Ministerio de Sanidad - ES
National Experts nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) - AT
National Expert nominated by MS France	Agence Nationale Sécurité Sanitaire Alimentaire Nationale (ANSES) - FR
National Experts nominated by MS Germany	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS Germany	German Environment Agency (UBA) - DE
National Experts nominated by MS Italy	UNIMI/ICPS - IT
National Expert nominated by MS The Netherlands	Ctgb - NL
National Expert nominated by MS Slovakia	National Reference Laboratory for Pesticides, University of Veterinary Medicine and Pharmacy in Košice - SK
National Expert nominated by MS Sweden	Swedish Chemicals Agency - SE

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the results of comparative in vitro metabolism for 8-hydroxyquinoline, including unique human metabolites and relevance of tested species.**	**Considering the limitations identified in the study, a data gap is set for a new interspecies comparative *in vitro* metabolism study, including the four representative species (rat, dog, rabbit and human material), performed with primary hepatocytes and identifying all unique human metabolites or disproportionate human metabolites present above 5%.**
Experts' consultation 2.2 **Experts to discuss the findings in the 90-day dog study (clinical chemistry, thyroid, spleen) and the setting of the NOAEL.**	**In the 90-day dog study, the NOAEL is 10 mg/kg bw per day, based on increased relative thyroid with parathyroid weight.**
Experts' consultation 2.3 **Phototoxic and photo-mutagenic (-carcinogenic) potential of 8-HQ to be discussed by the experts.**	**Quinolin-8-ol is phototoxic *in vitro*.** **A formal data gap is identified for photomutagenicity since, according to the Regulation (283/2012), photomutagenicity should be addressed for phototoxic substances. However, it is acknowledged that there is currently no validated test guideline or guidance that can be suggested to address this endpoint.**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.4 **Experts to discuss the genotoxic potential of 8-HQ, taking into account the positive results for mutagenicity and clastogenicity *in vitro*, and the available *in vivo* studies.**	**Quinolin-8-ol was demonstrated to be clastogenic *in vitro*.** **No conclusion could be reached over the gene mutation potential of quinolin-8-ol *in vitro*.** **The clastogenic and aneugenic potential could not be concluded based on the available *in vivo* studies.** **Accordingly, the genotoxic potential of quinolin-8-ol is inconclusive.** **Open point** **RMS to revise the RAR detailing the acceptability of each of the genotoxicity studies, taking into account the meeting discussion for this experts' consultation.**
Experts' consultation 2.5 **Experts to discuss the relevant NOAELs for long term toxicity in rats, mice (and dogs).**	**In the 2-year rat study, the NOAEL for toxicity is 73 mg/kg bw per day, based on reduced body weight, body weight gain and feed consumption, atrophy of splenic follicles and pituitary angiectasis observed at 143 mg/kg bw per day; the carcinogenicity NOAEL is the highest dose tested of 143 mg/kg bw per day.** **In the 2-year study in mice, the NOAEL for chronic toxicity is 217 mg/kg bw per day based on reduced body weight, body weight gain and food consumption, lung epithelial hyperplasia and pituitary gland dilation; the carcinogenic NOAEL is the high dose of 396 mg/kg bw per day based on the absence of carcinogenic effects.** **Both studies are considered supplementary. Considering their significant limitations to address chronic toxicity (only 2 dose levels tested, lack of haematological, clinical chemistry, urinalysis and organ weights data), an additional UF could be considered when setting toxicological reference values to account for these limitations.**
Experts' consultation 2.6 **Experts to discuss the NOAELs in the multigeneration rat study.**	**In the two-generation reproduction toxicity study in rats, the parental NOAEL is 98.32 mg/kg bw per day based on reduced body weight gain and food consumption, increased spleen weight and decreased prostate weight at 282.8 mg/kg bw per day.** **The reproductive and offspring toxicity LOAELs are 98.43 mg/kg bw per day, based on reduced litter size and mean number of viable pups at birth at this low dose level.**
Experts' consultation 2.7	**Regarding developmental toxicity studies in rats and rabbits the following NOAELs were agreed:**

Subject	Conclusions Pesticide Peer Review Meeting
Experts to discuss the developmental toxicity studies in rats and rabbits, taking into account the additional data and revised assessment.	In rats, the maternal LOAEL is 100 mg/kg bw per day (the lowest dose tested) based on reduced body weight. The developmental LOAEL is 100 mg/kg bw per day, based on increased number of skeletal retardations (in sternebrae), reduced number of foetal ossification centers and reduced placental weight. In rabbits, the maternal NOAEL is 5 mg/kg bw per day based on the clinical signs reported in dams (nervous system excitation after dosing followed by lethargy). The developmental LOAEL is 5 mg/kg bw per day based on the increased number of foetuses with skeletal retardations.
Experts' consultation 2.8 Experts to discuss the available assessment of the ED potential of 8-hydroxyquinoline and the possible need of additional test(s).	***T-modality*** T-mediated parameters have been sufficiently investigated. There is no evidence for a pattern of T-mediated adversity in the available dataset. Some active hits were observed in the assays available in ToxCast database (i.e. thyroid hormone receptor antagonistic activity and TPO inhibition); however, they were regarded as unlikely to be selective and overall, there is no T-mediated endocrine activity. Scenario 1a of the EFSA/ECHA ED guidance is applicable. The ED criteria for T-modality are not met. ***EAS-modalities*** EAS-modalities have been sufficiently investigated. No evidence for EAS-mediated adversities and EAS-mediated activities in the available dataset. Scenario 1a of the EFSA/ECHA ED guidance is applicable. The ED criteria for EAS-modalities are not met. Open points: - RMS to check whether the count of primordial follicles was executed in the OECD TG 416; if not, these should be listed in the list of parameters not investigated and reported as a deviation from the OECD TG study protocol. - RMS to update in the revised RAR Vol.1 the endpoints VO and BPS, measured in the 2-gen toxicity study in rats, referring to them as „EATS-mediated parameters“ and not as „sensitive to but not diagnostic of“ - RMS to report the conclusion agreed during the peer review meeting in the revised RAR vol. 1 ED assessment section.
Experts' consultation 2.9	Toxicological reference values (ADI, AOEL, ARfD and AAOEL) cannot be established for quinolin-8-ol since its genotoxicity

Subject	Conclusions Pesticide Peer Review Meeting
Experts to discuss the derivation of toxicological reference values (ADI, ARfD, AOEL and AAOEL) for 8-hydroxyquinoline, including - considerations of the use of oral absorption vs bioavailability for the (A)AOEL derivation; - possible read-across between 8HQ and 8HQS (since operators will be exposed to 8HQS during mixing/loading).	potential is inconclusive (with regards to gene mutation, clastogenicity and aneugenicity).
Experts' consultation 2.10 Dermal absorption values for 8-HQ to be discussed by the experts, taking into account the new dermal absorption study ([redacted] 2020).	Dermal absorption of the formulation for the representative uses is 0.97% for the concentrate and 42% for the in-use dilution.
Experts' consultation 2.11 Experts to discuss the non-dietary exposure estimates for operators, workers, residents and bystanders, for the representative use of Beltanol by drip irrigation in permanent greenhouses. The discussion should take into account: - the need to identify a negligible exposure due to the harmonised classification of 8-HQ as	For the Tier I assessment, the representative use of drip irrigation in greenhouses is not fully represented in the available models. Consequently, the use of validated models for greenhouse uses (with application by spraying) can be considered as providing worst-case estimates for operators, workers, bystanders and residents. For the Tier II assessment, the submitted field study shows several limitations and it is considered only as supportive evidence.

Subject	Conclusions Pesticide Peer Review Meeting
Repr. 1B (including MoE considerations); - a first tier approach with available models and ad hoc considerations; - a second tier assessment based on a field study with experimental measurements of operators, workers, bystanders and residents' exposure for the representative use of Beltanol.	
Experts' consultation 2.11 (added by EFSA after column 4 step) MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation for representative uses with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	No concern is raised with regard to [redacted] co-formulan[redacted]level in the formulation, except for [redacted] toxicological properties already identified – Skin Corr Cat. 1A). Open Point: RMS to integrate the given toxicological information on [redacted]co-formulan[redacted]in vol. 4 of a revised RAR (C.1.3, detailed composition of the preparation (summary table), proposal to include the full data as an appendix of Vol.4).

REPORT OF PESTICIDE PEER REVIEW TC 106

BUPROFEZIN – AIR IV **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 26 May 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Expert nominated by RMS CZ	The National Institute of Public Health - CZ
National Experts nominated by RMS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES)- AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency - DK
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	CTGB - NL
Observer	Swiss Federal Office for the Environment - CH
Hearing expert	Claudia Bolognesi - IT

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the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss residue definition for body fluids and tissues.**	**The most suitable residue definition for body fluids and tissues is buprofezin, BF-13, BF-23 and BF-28 based on the metabolites found in urine the ADME studies.** **Open point** **RMS (phys-chem) to consider if validated monitoring methods are available for the compounds included in the residue definition for monitoring in body fluids and tissues.**
Experts' consultation 2.2 **Experts to discuss:** • **the reliability of the Ames test by [redacted], 1998.** • **the reliability of the study by [redacted] 1983 (B.6.4.2/01).** **See 2(30), 2(31) and 2(32).** • **the reliability of the study by [redacted]. (2006b).**	**Ames test (B.6.4.1/02):** **All experts considered it as not acceptable as stand-alone test to address bacterial gene mutation of buprofezin based on significant deviations.** ***In vitro* chromosome aberration study (B.6.4.1/08)** **All experts considered it as acceptable with limitations based on minor deviations identified.** ***In vivo* micronucleus study (B.6.4.2/01):** **The majority of experts considered it as acceptable with limitations based on minor deviations identified.** ***In vivo* micronucleus study (B.6.4.2/02):** **All the experts considered the study as inconclusive since it is not interpretable.**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.3 Experts to discuss the genotoxic potential of buprofezin.	The majority of MS experts agreed with the RMS and the cross-crotting Working group (ccWG) on genotoxicity to consider buprofezin unlikely to be genotoxic based on available experimental data.
Experts' consultation 2.4 Experts to discuss the NOAEL for carcinogenicity in the study by [redacted] 1984 considering liver neoplasms.	<u>24-Month mouse study (B.6.5/03):</u> Experts agreed to set the NOAEL for carcinogenicity at 200 ppm in females (89 mg/kg bw per day) based on increase incidence of liver tumours in females at 2000 and 5000 ppm. <u>2-year rat carcinogenicity study (B.6.5/02):</u> Experts agreed to set the NOAEL for carcinogenicity at 2000 ppm, the highest dose since no treatment-related tumours were observed up to the highest dose level tested.
Experts' consultation 2.5 Experts to discuss the developmental NOAEL in the rabbit developmental toxicity studies.	The slight majority of the experts agreed with the proposal to set the NOAEL for developmental toxicity at 50 mg/kg bw per day based on increased incidence of enlarged aortic arch at 250 mg/kg bw per day. The RMS did not agree.
Experts' consultation 2.6 Experts to discuss the NOAEL for pups in the preliminary dose finding and main developmental thyroid toxicity study, as well as the need for a DNT study on buprofezin.	Point postponed to June experts' peer review meeting.
Experts' consultation 2.7 Experts to discuss the endocrine disruption potential of buprofezin	Point postponed to June experts' peer review meeting.

Subject	Conclusions Pesticide Peer Review Meeting
according to EFSA/ ECHA guidance.	
Expert consultation 2.8 Experts to discuss the reliability assessment of the thyroid comparative assay including HCD. Experts to conclude whether juvenile rats are more sensitive than adults in the comparative thyroid assay.	Point postponed to June experts' peer review meeting.
Experts' consultation 2.9 Experts to discuss the setting of reference values, including ADI and ARfD.	Point postponed to June experts' peer review meeting.
Experts' consultation 2.10 Experts to discuss the approaches used for non-dietary exposure estimates for greenhouse uses.	**Dermal absorption:** Experts confirmed dermal absorption values of 0.75% for the concentrate (250 g a.s./L) and 5.6% for the dilution. **Operators:** Experts considered that based on the level of validation and time of dossier submission the Dutch Greenhouse model should be considered for the EFSA conclusion. For completness the last EFSA model (2022) should be presented. **Bystanders/residents:** As a first step, vapour exposure from the EFSA model 2014 should be provided since the applicant disagreed with the use of the last EFSA model (2022). For completnessthe 3 routes of exposure according to the EFSA model (2022) should be presented. **Open point (to be confirmed/finalised at the June experts' peer review meeting):**

Subject	Conclusions Pesticide Peer Review Meeting
	RMS to provide revised non-dietary exposure estimates with the agreed endpoints (dermal absorption and (A)AOEL), considering also: - for operators: as a first step, national validated models (e.g. Dutch Greenhouse model) should be used since the applicant disagreed with the use of the last EFSA model (2022). As a second step, if possible, the results with the last EFSA model (2022) should also be provided for completeness. - for bystanders/residents: as a first step, vapour exposure from the EFSA model 2014 should be provided since the applicant disagreed with the use of the last EFSA model (2022). For completness the 3 routes of exposure according to the EFSA model (2022) should be presented
Experts' consultation 2.11 Experts to discuss if the DFR study from [redacted], 2010 is appropriate for refinement of worker exposure considering the intended use.	Point postponed to June experts' peer review meeting: No final conclusion on worker exposure was drawn during the meeting in May 2023 since further details from the RMS are needed. An open point was set: Open point RMS to provide further details in a revised RAR as regards calculation of the DT50 value of 4.1 days. Open point (to be confirmed/finalised at the June experts' peer review meeting): RMS to provide revised worker exposure estimates for the representative use of buprofezin, considering - the available model(s) for greenhouse uses at the time of dossier submission (e.g., EFSA 2014 includes estimates for workers in greenhouses), as well as the EFSA model 2022 for completeness - the agreed endpoints (dermal absorption, (A)AOEL, and refined DT50 value) during the experts' meeting - considering also representative uses with one application only.
New experts' consultation point 2.12 proposed by EFSA for completeness of discussion MS experts to discuss whether the available	Open Point: RMS to integrate the substance identification and content in the formulation of the co-formulants in the revised RAR. RMS to assess the toxicological potential of the formulation for representative uses. If exhaustive information is not available on the formulation, RMS to report the assessment of the toxicological profile of the co-formulants in the revised RAR to enable an

Subject	Conclusions Pesticide Peer Review Meeting
information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures. The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion.

REPORT OF PESTICIDE PEER REVIEW TC 106

FENPROPIDIN – AIR III **Rapporteur Member State: CZ**

2. Mammalian toxicity

Date: 26 May 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Expert nominated by RMS CZ	The National Institute of Public Health - CZ
National Experts nominated by RMS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES)- AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency - DK
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	CTGB - NL
Observer	Swiss Federal Office for the Environment - CH

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discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation **The experts to discuss all the available data and study results for the relevant metabolites to conclude on the toxicity and genotoxic potential and the reference values to be applied, if needed - follow up of TC 92.**	**Genotoxicity endpoints prediction using two Q(SAR) models (Derek Nexus and Sarah Nexus) and read-across assessment were made available to EFSA, RMS and MSs in view of the TC 106 Peer Review Meeting. All experts agreed that the submitted Q(SAR) analyses and grouping approaches cover the data gap on genotoxicity identified in the TC 92, conclusion of the pesticide peer review meeting for each metabolite is reported below.** **For general toxicity, the agreement reached in previous TC 92 i.e. data gap (to be confirmed by residue/fate) for general toxicity endpoints for all metabolites except for CGA289267 (major rat metabolite, for which the toxicological reference value of fenpropidin are applicable), still remains.** **Group 1 – metabolites with parent** **For the metabolites mentioned below, grouping with the parent was proposed by the applicant for genotoxicity endpoints.** **CGA289263** **Negative Q(SAR)s predictions for mutagenicity and chromosome aberration. Extrapolation of data from genotoxicity studies conducted with the parent compound was applicable.** **The metabolite is unlikely to be genotoxic.** **CGA289268 – (M19; 4U)**

Subject	Conclusions Pesticide Peer Review Meeting
	Negative Q(SAR)s predictions for mutagenicity and chromosome aberration. Extrapolation of data from genotoxicity studies conducted with the parent compound was applicable. **The metabolite is unlikely to be genotoxic.** **CGA289268 glucose conjugate** **The CGA289268 glucose conjugate is equivalent to its respective aglycone CGA289268; therefore, the same conclusion applied.** **CGA289268 sulphate conjugate** **The CGA289268 sulphate conjugate is equivalent to its respective aglycone CGA289268; therefore, the same conclusion applied.** **CGA289265 (I6)** **Negative Q(SAR)s predictions for mutagenicity and chromosome aberration. Extrapolation of data from genotoxicity studies conducted with the parent compound was applicable.** **The metabolite is unlikely to be genotoxic.** **CGA289266 (I10)** **Negative Q(SAR)s predictions for mutagenicity and chromosome aberration. Extrapolation of data from genotoxicity studies conducted with the parent compound was applicable.** **The metabolite is unlikely to be genotoxic.** **Group 2- metabolites with CGA289267** **For the metabolites mentioned below, grouping with CGA289267 was proposed by the applicant for genotoxicity endpoints.** **CGA289267 (M20; 1U)** **The metabolite is unlikely to be genotoxic based on the available experimental data (supported by the fact that is a major rat metabolite).** **Acyl glycoside of dihydroxy CGA289267 and Hydroxy CGA289267** **Open point for EFSA: to check whether the OH location could be clarified for metabolites Acyl glycoside of dihydroxy CGA289267 and Hydroxy CGA289267.**

Subject	Conclusions Pesticide Peer Review Meeting
	Pending further clarification (on whether OH could be also present in the aromatic ring or not for metabolite Hydroxy CGA289267) experts agreed that for Acyl glycoside of dihydroxy CGA289267 the same conclusion reached for Hydroxy CGA289267 metabolite is applicable (a data gap for clastogencity and aneugenicity to be confirmed by residues). **Group 3 - metabolites with SYN550939** **For the metabolites mentioned below, grouping with SYN550939 (the salt of the sulphate form of SYN515213) was proposed by the applicant for genotoxicity endpoints.** **SYN515213** **Extrapolation of data from genotoxicity studies conducted with SYN550939 (the salt of the sulphate form of SYN515213) was applicable.** **SYN515213 is unlikely to be genotoxic. Such conclusion is also supported by structural similarity of SYN515213 with the parent compound.** **SYN515213 sulphate ester conjugate (M5)** **The same conclusions of SYN515213 applied also for the sulphate conjugate of SYN515213.** **Group 4 - metabolites with SYN515215** **For the metabolites mentioned below, grouping with SYN515215 was proposed by the applicant for genotoxicity endpoints.** **SYN515215 and its conjugates** **SYN515215 is unlikely to be genotoxic based on experimental data. The same applied to the sulphate form since it is considered equivalent to SYN515215.** **SYN515216** **Negative Q(SAR)s predictions for mutagenicity and chromosome aberration. Extrapolation of data from genotoxicity studies conducted with the SYN51521 was applicable.** **The metabolite is unlikely to be genotoxic.** **Group 7 - SYN522245 only**

Subject	Conclusions Pesticide Peer Review Meeting
	SYN522245 **Structural dissimilar from the parent and any other analogous. Data gap for genotoxicity *(data gap to be confirmed by residues*).** **Group 8 - metabolites with SYN552105** **For the metabolite mentioned below, grouping with SYN552105 was proposed by the applicant for genotoxicity endpoints.** **SYN522250 (I3)** **Open point for EFSA :** **to clarify with whether the metabolite SYN522250 is the one present in the crops and processed commodities. In case this is the metabolite identified then a concern for genotoxicity is highlighted.** ***Post-meeting notes on metabolites Acyl glycoside of dihydroxy CGA289267, Hydroxy CGA289267 and SYN522250:*** ***For the metabolite Hydroxy CGA289267, it was clarified that the structure reported for Hydroxy CGA289267 shows that the OH group can be located in the available positions between brackets. Therefore, based on this, the following decision applied : for mutagenicity the same conclusion as the CGA289267 applied to the hydroxy-CGA289267. However, experts acknowledged that for chromosomal aberration some uncertainties exists, and the grouping proposed by the applicant (based on equivalence to the aglycone CGA289267) cannot be accepted. The uncertainties identified are mainly related to the lack of Q(SAR) prediction for chromosomal aberration, preventing the experts to conclude on clastogenic/aneugenic potential of hydroxy- CGA289267 in comparison with the CGA289267 (data gap for clastogencity and aneugenicity, to be confirmed by residues).*** ***For metabolite Acyl glycoside of dihydroxy CGA289267 grouping proposed by the applicant (based on equivalence to the aglycone CGA289267) was not accepted. No Q(SAR) predictions were provided for this metabolite. Data gap for genotoxicity (to be confirmed by residues).*** ***For metabolite SYN522250, the possibility that the N-methylol group is an artifact of the analytical method, was discussed. It was confirmed that no further information or argumentations were given in the RAR Vol. 1, Vol. 3 CA B.7 and Vol. 3 CA B.5 on the probability that the metabolite SYN522250 is an artifact of***

Subject	Conclusions Pesticide Peer Review Meeting
	analytical method; the metabolite was considered by the applicant as a real metabolite in the residue studies where it appears. Therefore, considering the alerts (equivocal) for mutagenicity in Q(SAR) Derek (N-methylol group) the grouping with compound SYN552105 was not accepted and a concern for genotoxicity was identified for metabolite SYN522250. **Open point:** • **RMS to reflect the outcome of the Peer review meeting discussion in the revised RAR.** • **RMS to check whether the information reported in RAR Vol. 3 CA B.6 Table 6.8.1 – 11 is correct for metabolite SYN515214. In the table indicated, it is mentioned that there are experimental data available for this metabolite, this is not in line with the info reported in Table 6.8.1 – 2 where no experimental data were indicated to be available.** • **RMS to include in the revised RAR Vol. 3 CA B.6 Table 6.8.1-9 the information on QSAR prediction for metabolites SYN522249, SYN522248, SYN522250 (currently reported as „not included“).**

REPORT OF PESTICIDE PEER REVIEW TC 106

PYRETHRINS – AIR IV **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 26 May 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff members	EFSA
EU statutory staff representing EU Institutions, agencies or other bodies (other than EFSA)	ECHA
National Expert nominated by RMS CZ	The National Institute of Public Health - CZ
National Experts nominated by RMS IT	International Centre for Pesticides and Health Risk Prevention (ICPS) - IT
National Experts nominated by MS AT	Austrian Agency for Health and Food Safety (AGES)- AT
National Experts nominated by MS DE	German Federal Institute for Risk Assessment (BfR) - DE
National Expert nominated by MS DE	German Environment Agency (UBA) - DE
National Expert nominated by MS DK	Danish Environmental Protection Agency - DK
National Expert nominated by MS FR	French Agency for Food, Environmental and Occupational Health & Safety (ANSES) - FR
National Experts nominated by MS NL	CTGB - NL
Observer	Swiss Federal Office for the Environment - CH

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the oral absorption value in an experts' meeting.**	**Oral absorption of pyrethrins is 55%, based on the amounts recovered in urine and tissues within 72 hours in animals treated with the low dose (mean between males and females), acknowledging that bile excretion is expected to occur, but it was not investigated.**
Experts' consultation 2.2 **MSs experts to discuss the potential for bioaccumulation of pyrethrins in an experts' meeting.**	**Pyrethrins are unlikely to present bioaccumulation potential.**
Experts' consultation 2.3 **MSs experts to discuss the lack of metabolism investigations of the pentadienyl side chain moiety of pyrethrins and the relevance of the metabolism study performed on 4 different dosing formulations in an experts' meeting.**	**Metabolism of pyrethrin 1** **The available *in vivo* and *in vitro* data support that pyrethrin 1 splits to form chrysanthemic acid and pyrethrolone in the liver. However, the same systemic exposure (in terms of level and time) cannot be assumed to occur to the two parts of the molecule, since there is no data on the subsequent metabolism of the pyrethrolone moiety.** **The rat metabolism study investigating the impact of 4 different oral dosing formulations on the excretion pattern and the metabolic profile of Pyrethrin 1 is considered as supplementary due to the low number of animals investigated and its scope related to providing additional information.**

Subject	Conclusions Pesticide Peer Review Meeting
See also 2(7) See reporting table 2(6)	
Experts' consultation 2.4 Local and systemic effects observed in the 90-day inhalation study, as well as the dose-response analysis performed for the incidence of squamous metaplasia to be discussed at the Experts meeting.	In the rat 90-day inhalation toxicity study, the systemic NOAEC is 100 mg/m³ (equivalent to 20.57 mg/kg bw per day), based on anaemia. The NOAEC for local effects in the larynx (mucosal inflammation and squamous metaplasia) is 30 mg/m³.
Experts' consultation 2.5 MSs experts to discuss the genotoxicity potential of pyrethrins in an experts' meeting.	Pyrethrins are unlikely to be genotoxic.
Experts' consultation 2.6 MSs experts to discuss the relevance of carcinogenicity findings and respective NOAELs in the rat, 2-year and mouse, 18-month studies in an experts' meeting.	In the 2-year study in rats, the systemic NOAEL is 4.4 mg/kg bw per day based on thyroid hyperplasia in males; the carcinogenic NOAEL is 4.4 mg/kg bw per day based on increased incidence of benign liver tumours (hepatocellular adenomas) and benign thyroid tumours (thyroid follicular adenomas) not relevant to humans based on the mode of action (MoA). In the 18-month carcinogenicity study in mouse, the NOAEL is 13.8 mg/kg bw per day based on liver toxicity (increased weight, vacuolar fatty changes and discolouration). The carcinogenicity NOAEL is 686 mg/kg bw per day, the highest dose tested.
Experts' consultation 2.7 MSs experts to discuss the reliability of the 2-generation reproductive toxicity study, its outcome with regards to body weight and food consumption and	The 2-generation reproductive toxicity study is considered supplementary, due to the lack of effects at the high dose and the lack of investigations according to current standards. The parental and reproductive NOAELs are 200 mg/kg bw per day, the highest dose tested. The offspring's toxicity NOAEL is 5 mg/kg bw per day for reduced body weight.

Subject	Conclusions Pesticide Peer Review Meeting
respective NOAEL, and whether the study addresses the reproductive toxicity of pyrethrins in an experts' meeting.	
Experts' consultation 2.8 MSs experts to discuss the reliability and outcome of the rat developmental toxicity study in an experts' meeting.	In the developmental toxicity study in rats, the maternal and developmental toxicity NOAELs are 75 mg/kg bw per day, the highest dose tested. Open point: RMS to include details on the historical control data (HCD) provided (range and means, as the incidence should be compared to the mean HCD and not to the extremes of the distribution, whether within 5 years of the conduct of the study, from the performing laboratory).
Experts' consultation 2.9 MSs experts to discuss the reliability and outcome of the rabbit developmental toxicity study in an experts' meeting.	The rabbit developmental toxicity study is considered acceptable. The NOAEL for maternal toxicity is 25 mg/kg bw per day, based on reduced body weight and neurotoxicity, *i.e.,* excessive salivation and arched head. The NOAEL for developmental toxicity is the highest dose tested of 250 mg/kg bw per day. Open point: RMS to include details on the HCD provided (range and means, as the incidence should be compared to the mean HCD and not to the extremes of the distribution, whether within 5 years of the conduct of the study, from the performing laboratory).
Experts' consultation 2.10 MSs experts to discuss the acute and repeated-dose neurotoxicity endpoints in an experts' meeting.	In the acute neurotoxicity study in rats, the NOAEL is 20 mg/kg bw based on tremors in females, reduced rearing, ambulation, and fine movement in males at 63 mg/kg bw (LOAEL). Data gaps were identified for the repeated-dose neurotoxicity and developmental neurotoxicity (DNT) potential of pyrethrins. Provisional reference values can be set considering the uncertainties identified regarding neurotoxicity by applying an additional UF of 10.
Experts' consultation 2.11 MSs experts to discuss the ED potential of pyrethrins in an experts' meeting.	For concluding on the endocrine disruption (ED) potential of pyrethrins experts agreed that a stepwise approach, as per the standard testing strategy reported in EFSA/ECHA ED guidance, is the preferred option to minimize animals use. However, considering the deficiencies in the data package as in the case of pyrethrins, a level 5 study, *i.e.,* an Extended One Generation Reproductive Toxicity Study according to OECD TG 443, with the inclusion of an F2 generation is requested (Data requirement). The requested OECD TG 443 study should also cover: thyroid assessment, *i.e.,* thyroid histopathology, thyroid

Subject	Conclusions Pesticide Peer Review Meeting
	hormones (THs) and TSH in sensitive populations, *i.e.,* dams (at gestational day (GD) 21, lactational day (LD) 22), foetuses (GD21) and new-borns (postnatal day (PND) 4 and PND21), neurotoxicity assessment with the inclusion of a DNT cohort plus neurotoxicity assessment in the adults (F1 generation). The study should also include a proper selection of the doses to maximise the ability of the study to capture the different hazards (EAS mediated, reproductive toxicity, neurotoxicity and T-mediated hazard). **Open points:** **RMS to include in a revised RAR the summary table on thyroid findings presented during the peer review expert meeting, clarifying:** - **the timing at which the endpoints were measured for both F0 and pups.** - **the diagnosis for thyroid histopathology. Which should be in line with what is reported in the RAR (hypertrophy rather than hyperplasia) and discussed at the expert meeting.** **RMS to include the preliminary Comparative Thyroid Assay (CTA) in Volume 1 (under human health ED assessment) and Vol. 3- B.6 under the ED assessment.** **RMS to revise the ED assessment in Volume 1 in line with the EFSA/ECHA guidance (2018).**
Experts' consultation 2.12 **MSs experts to discuss the genotoxicity and general toxicity profile of the metabolites pyrethric acid, pyrethrolone and chrysanthemic acid derivatives (relevant to consumer exposure) in an experts' meeting.**	**For the metabolite dicarboxylic chrysanthemic acid, systemic toxicity and genotoxicity potential is covered by the toxicological profile of pyrethrins, since the metabolite is a major rat metabolite.** **For the other metabolites, the genotoxicity potential is inconclusive with respect to clastogenic and aneugenic potential. There is also no information on their relative systemic toxicity compared to that of pyrethrins.** **Data gaps depend on the outcome of the discussion held in the residues section.** **Open point:** **RMS to check the QSAR report submitted by the applicant for *in silico* analysis on the different components of pyrethrins (cinerin 1 and 2, jasmolin 1 and 2).**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.13 **MSs experts to discuss the setting of toxicological reference values, taking into consideration the agreed NOAELs and uncertainties identified in the dossier, including the additional data to be provided on the storage stability in vertebrate's diet, the validation of the analytical methods, as well as the acceptability/reliability of "outdated" toxicological studies.**	**Toxicological reference values are set provisionally for pyrethrins, by including an additional UF of 10, pending the outcome of a new OECD TG 443-compliant study requested to address the uncertainties identified regarding repeated neurotoxicity (see EC 2.10) and developmental neurotoxicity (see EC 2.11).** **The ADI is 0.004 mg/kg bw per day, based on the NOAEL of 4.4 mg/kg bw per day for thyroid hyperplasia in a 2-year rat study and applying an uncertainty factor (UF) of 1000.** **The ARfD is 0.02 mg/kg bw based on the NOAEL of 20 mg/kg bw for acute toxic and pharmacological responses including tremors, salivation and exaggerated startle response, and changes in motor activity measurements in an acute neurotoxicity study and applying an UF of 1000.** **The AOEL is 0.007 mg/kg bw per day, based on the NOAEL of 13.7 mg/kg bw per day for haematological changes and increased liver weight in the 1-year study in dogs. An UF of 1000 and oral absorption correction factor of 55% applied.** **The AAOEL is 0.011 mg/kg bw, based on the same basis as the ARfD, applying a 55% correction for oral absorption.** **Definitive reference values will be re-discussed, upon assessment of the Extended One Generation Reproductive Toxicity Study (OECD TG 443) including a DNT arm that has been requested following the human ED assessment for pyrethrins (see EC 2.11 for further details).** **Open point:** **RMS to provide revised non-dietary exposure estimates for pyrethrins considering:** **- the agreed systemic AOEL and AAOEL (to be compared to systemic exposure estimates from the calculators)** **- minimum volume of water of 100L/ha for GAP uses 6-7 and 300 L/ha for GAP uses 1-5** **- concerning the lack of applicability of the EFSA calculator for the low application rates (<1.5 kg a.s./ha), EFSA would rather support the view that valid exposure estimates are only provided for tractor-mounted application in low crops.** **- for the worker, EFSA's view is that the consideration of 10 days re-entry interval for ornamentals is unlikely to be applicable under real agricultural practices (this calculation of safe re-entry interval is nevertheless provided in the EFSA calculator 2022 for information purpose for risk managers and national authorities' considerations)** **- for indoor uses:**

Subject	Conclusions Pesticide Peer Review Meeting
	- EFSA calculator 2014 is not applicable (only for worker exposure after fogging applications) - SEGM is not a EU validated model, a nationally validated model at the time of dossier submission (e.g., Dutch greenhouse) should have been preferably used at the time of dossier submission - EFSA calculator 2022 could be used for completeness since it is the only EU model for greenhouses uses (acknowledging that it was implemented after dossier submission of pyrethrins).
New experts' consultation point 2.14 proposed by EFSA for completeness of discussion MS experts to discuss whether the available information is sufficient to characterise the full toxicological profile of the formulation(s) for representative use(s) with respect to the acute, genotoxicity, short- and long-term toxicity. If certain endpoints are not covered, MS experts to discuss the toxicological profile of each individual component other than the active substance.	No concern is raised from the co-formulants present in the pyrethrins formulation. Open point: RMS to include the co-formulants' assessment in the RAR.

REPORT OF PESTICIDE PEER REVIEW TC 100

MEPANIPYRIM – AIR III, re-assessment of ED following mandate

Rapporteur Member State: BE

2. Mammalian toxicity

Date: 21 April 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff	EFSA
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) (AT)
National Expert nominated by MS Belgium - RMS	Belgian Federal Public Service (FPS) Health, Food Chain and Environment (BE)
National Expert nominated by MS Belgium - RMS	Sciensano (BE)
National Expert nominated by MS Germany	German Federal Institute for Risk Assessment (DE)
National Expert nominated by MS Greece - RMS	BENAKI PHYTOPATHOLOGICAL INSTITUTE (BPI) (EL)
National Expert nominated by MS Italy - RMS	International Centre for Pesticides and Health Risk Prevention (IT)
National Expert nominated by MS Finland - RMS	Finnish Safety and Chemicals Agency (FI)
National Expert nominated by MS Poland - RMS	E-V-A Sp. z o.o. (PL)
Observer	Austrian Agency for Health and Food Safety (AGES) (AT)

MEETING MINUTES – 21 April 2023
Pesticide Peer Review TC 100
Mepanipyrim

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.12 **Experts to discuss the conclusion of the endocrine disruption (ED) assessment for thyroid (T)-modality, considering the quality, the results and uncertainties of the new evidence provided in the revised RAR.**	**ED criteria for the T modality are not met and scenario 1a of the ECHA-EFDA ED (2018) guidance is applied.**
Experts' consultation 2.13 **Experts to discuss the revised ED assessment considering the outstanding data still remained following EFSA's request for additional information to complete the ED data package and leaving the data requirement still not resolved after the ED regulatory stop of the clock.** **It is noted that the Applicant has not**	**For the EAS-modalities, following the 30 month regulatory stop of the clock, data on endocrine activity were provided and endocrine activity was reported in the steroidogenesis assay. Level 5 studies were however not conducted and a line of evidence of adversity (for EAS mediated and EAS sensitive endpoints) was done with the inclusion of the positive endocrine activity outcome in the weight of evidence (WoE) analysis.** **Based on the WoE and uncertainty analysis it was concluded that the ED criteria for the EAS-modalities were met and that a pattern of EAS mediated adversity exists and substantiated by evidence of changes in uterus, oestrus cyclicity, testicular histopathology and weight, ovary weight and histopathology, and prostate weight. Scenario 2b of the ECHA-EFSA ED guidance is applicable.** **Open point for RMS:** **RMS to update the RAR in line with the discussions of the meeting.**

Subject	Conclusions Pesticide Peer Review Meeting
completed the ED assessment in line with the testing strategy as proposed by EFSA in accordance with the EFSA/ECHA ED guidance in order to fulfil the data requirement and complete the data package for the EAS-modalities with a view to allow a robust conclusion to be drawn. In the absence of a full data package and/or proper justification for the lack of data, it is proposed hold a discussion of all the available results collectively at a Pesticide Peer Review experts' Meeting on ED with a view to establish an overall conclusion whether the approval criteria according to point 3.6.5 of Annex II of Regulation (EC) No 1107/2009 on the endocrine disruption potential in line with Commission Regulation (EU) No 2018/605 are met, and to allow agreement on the level and extent of any remaining uncertainties.	**Open point for EFSA:** EFSA to consider whether the assessment of the pattern of adversity is leading to possibly different NOAEL/LOAEL for reproductive and developmental endpoints. **Open point for EFSA:** EFSA to include a summary table in the Advice of the EFSA ED Working Group (WG) reporting the "sensitive to but not diagnostic of endpoints".

REPORT OF PESTICIDE PEER REVIEW TC 100

PHENMEDIPHAM – AIR III, re-assessment of ED following mandate

Rapporteur Member State: FI

2. Mammalian toxicity

Date: 21 April 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff	EFSA
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) (AT)
National Expert nominated by MS Belgium - RMS	Belgian Federal Public Service (FPS) Health, Food Chain and Environment (BE)
National Expert nominated by MS Belgium - RMS	Sciensano (BE)
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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.17 **MSs experts to discuss the acceptability of the androgen receptor transactivation assay, OECD TG 458, and the weight of evidence regarding androgen activity in an experts' meeting.**	**All the experts agreed that the objections raised by the RMS concerning the dose selection in the AR STTA (Stably transfected human androgen receptor transcriptional activation) assay are considered justified and the study should be considered as not acceptable.** **Overall, for androgen activity, considering the lack of activity in the ToxCast Pathway AR model (Level 2), and the negative Hershberger assay (Level 3), it is not expected that a higher test concentration in the AR STTA assay would change the outcome.** **In addition to this, a level 5 study was made available (see experts' consultation 2.19).**
Experts' consultation 2.18 **MSs experts to discuss the outcome of the steroidogenesis study (OECD TG 456) according to the revised interpretation criteria (2022) in an experts' meeting.**	**All experts agreed that the study provides some evidence indicative of induction of E2 synthesis. All the experts agreed that the study is equivocal in accordance with the new release of the OECD TG 456 (June 2022) and applying the decision matrix of the updated guidance, a third confirmatory run would have been needed. This uncertainty should be considered in the uncertainty analysis and in the WoE for the endocrine activity.**
Experts' consultation 2.19 **MSs experts to discuss the outcome of the extended one-generation reproductive**	**Extended one-generation reproductive toxicity (EOGRT):** **The changes observed in F1 generation Cohort 1A in the newly submitted OECD TG 443 are not treatment related but rather of spontaneous background pathology. The following uncertainties have been identified:**

Subject	Conclusions Pesticide Peer Review Meeting
toxicity (EOGRT) study in rats and its implications on the toxicological endpoints and human health and ecotoxicological risk assessment in an experts' meeting.	▪ evaluation of a 2nd generation in the OECD TG 443 is lacking. *EFSA/ECHA ED Guidance* recommends continuing with an assessment of the second generation to allow the exposure of the offspring during all vulnerable periods of development and to detect late effects becoming manifest after weaning in relation to reproductive function (but later ones);
In particular with regards to changes observed in testes, effects on estrogen-sensitive tissues (mammary gland, gynaecomastia) and estrogen-dependent tumour formation and its implications on the toxicological endpoints and human health and ecotoxicological risk assessment in an experts meeting.	▪ effects were observed in a unique population (in a population exposed during foetal and peri-post natal period until sexual maturation), where these changes (testicular degeneration/atrophy) are considered unlikely to be endocrine-mediated. In the INHAND publication, the testicular degeneration/atrophy is classified as background incidental finding. The same population has not been investigated in other studies, therefore the uncertainty remains with regard to the reproducibility of the effect. However, A-mediated endpoints (i.e. AGD) sensitive to exposure during the fetal period, were not affected by treatment.
It is recommended a submission by RMS to ECHA of an update of the CLH report by including the results of the new EOGRTS study (2022) and its possible impact on the reproductive toxicity hazard assessment.	<u>The following NOAELs were set for the EOGRT study:</u> NOAEL parental: 15 mg/kg bw per day based on hemosiderin pigment deposition in kidney and spleen of F0 males and on hematological findings observed in F0 males from 60 mg/kg bw per day; NOAEL reproductive toxicity: > 200 mg/kg bw per day (highest dose tested); NOAEL offspring : 15 mg/kg bw per day based on hemosiderin pigment deposition in kidney in F1 males and spleen in F1 females and hematological findings observed in F1 males starting from 60 mg/kg bw/day. NOAEL developmental was not derived since no developmental endpoints were measured (a second-generation is not included in the study). Other changes, observed in the original dataset, were considered unlikely treatment related and/or not endocrine-mediated Open points: The RMS to update the RAR LoEPs with the NOAELs values agreed. The RMS to check the implication for the risk assessment of the active substance based on the new NOAELs agreed. Open point (EFSA):

Subject	Conclusions Pesticide Peer Review Meeting
	to provide the detail of the reference *Vidal et al. 2018*[3] mentioned in the ED WG advice to the RMS and the RMS to report this in a revised RAR.
Experts' consultation 2.20 MSs experts to discuss the updated weight of evidence for a potential ED regarding T-modality in an experts' meeting in the light of the new data made available during the clock stop. In particular taking into consideration the newly submitted ToxCast data on TPO and respective WoE presented by the RMS in an experts meeting.	The result of the high throughput screening /HTS) *in vitro* assays available in ToxCast do not change the conclusion reached in 2019 for Human Health on T-modality. The dataset is considered as sufficiently investigated, no T-mediated adversity and activity has been observed in the available studies. Phenmedipham does not met the criteria for T-modality. All the experts agreed. Open point: the RMS to include an evaluation of the ToxCast assays (15 assays related to the thyroid activity of phenmedipham) in the MamTox section of a revised RAR Vol. 1 and 3CA B.6.
Experts' consultation 2.21 MSs experts to discuss the weight of evidence for a potential ED regarding EAS-modalities in an experts' meeting.	All the experts agreed that the EAS-modality is sufficiently investigated, without evidence of a pattern of EAS-mediated adversity and/or activity. All the experts agreed that the ED criteria for EAS-modalities are not met. Open point: The RMS to revise the RAR including the outcome of the peer review meeting discussion.

3 Vidal, J. D., Wood, C. E., Colman, K., Whitney, K. M., & Creasy, D. M. (2018). Reproductive system and mammary gland. In Toxicologic Pathology (pp. 889-1020). CRC Press

REPORT OF PESTICIDE PEER REVIEW TC 100

ZOXAMIDE – Art.10 of REG. (EC) No 396/2005

EMS: LV

2. Mammalian toxicity

Date: 21 April 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff	EFSA
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) (AT)
National Expert nominated by MS Belgium - RMS	Belgian Federal Public Service (FPS) Health, Food Chain and Environment (BE)
National Expert nominated by MS Belgium - RMS	Sciensano (BE)
National Expert nominated by MS Germany	German Federal Institute for Risk Assessment (DE)
National Expert nominated by MS Greece - RMS	BENAKI PHYTOPATHOLOGICAL INSTITUTE (BPI) (EL)
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National Expert nominated by MS Poland - RMS	E-V-A Sp. z o.o. (PL)
Observer	Austrian Agency for Health and Food Safety (AGES) (AT)

MEETING MINUTES – 21 April 2023
Pesticide Peer Review TC 100
Zoxamide

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the (geno)toxicity profile of zoxamide metabolites RH-141452, RH-141455, RH150721, RH-129151, RH-24549, RH-141288 in an experts' meeting.**	**The ADI of RH-141452 is covered by the ADI of the parent zoxamide. If needed, and ADI of 0.54 mg/kg bw per day can apply to the metabolite, based on the NOAEL of 538 mg/kg bw per day, the highest dose tested in a 90-day toxicity study in rats, and adverse effects observed in a 14-day dose range-finding study in rats at 1268 mg/kg bw per day, and applying an uncertainty factor (UF) of 1000, including an additional UF of 10 for the limited data base available on the metabolite, in particular the lack of studies on dogs, the most sensitive species to zoxamide toxicity.** **The ADI established for RH-142452 applies to the metabolite RH-24549.** **The ADI of RH-141455 is 0.3 mg/kg bw per day based on the NOAEL of 368 mg/kg bw per day for reduced body weight gain in males in the 14-day study and applying an UF of 1000; the ADI is supported by the LOAEL of 924 mg/kg bw per day in the 90-day study and applying an additional UF of 3 to account for the LOAEL.** **Open point for the EMS to include the summary tables of male body weight gains in the 14-day study (Table 9, D:1-D:14) and in the 90-day study (Table 19, D:1-D:90) in a revised ER.** **The ADI of RH-150721 is 0.04 mg/kg bw per day based on the NOAEL of 44 mg/kg bw per day for reduced body weight gain in the 90-day study in rats and applying an UF of 1000.** **The ARfD of RH-150721 is 0.22 mg/kg bw based on the LOAEL of 66 mg/kg bw per day for reduced body weight gain in the first**

Subject	Conclusions Pesticide Peer Review Meeting
	days of dosing in a 14-day study in female rats and applying an UF of 300. **The ADI and ARfD established for RH-150721 apply to the metabolite RH-129151.** **The toxicity profile of metabolite RH-141288 is covered by the ADI set for the parent zoxamide.**

REPORT OF PESTICIDE PEER REVIEW TC 100

PARAFFIN OIL CAS 8042-47-5 – AIR IV **Rapporteur Member State: EL**

2. Mammalian toxicity

Date: 21 April 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff	EFSA
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) (AT)
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the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the oral absorption value relevant to the paraffin oil under review in an experts' meeting.**	**No pivotal studies are available on paraffin oil CAS No 8042-47-5, and it was agreed that studies on substances fulfilling predefined criteria (surrogate substances) can be used for the assessment of this active substance.** **The oral absorption value of 25% was agreed for paraffin oil CAS No 8042-47-5, based on data on oral absorption in the rat of n-alkanes and cycloalkanes (C26-C29, the most representative for this active substance).**
Experts' consultation 2.2 **MSs experts to discuss the relevance of the histopathological findings observed in the short term oral toxicity study in Fischer rat (KCA 5.3.2/13) in an experts' meeting.**	**The accumulation and vacuolation of macrophages in the small intestine of rats given mineral hydrocarbon substances were considered a treatment-related physiological response consequent to oil material absorption and accumulation following oral intake; not being associated with other intestinal changes (e.g., inflammation) they are considered not adverse. Microscopic findings in the kidneys and heart are of unclear treatment relationship, since sporadic, compatible with background conditions, not statistically significant, and not reproduced in another comparable more robust short term toxicity study in Fischer rats-study (KCA 5.3.2/15).** **These findings observed in the short term oral toxicity study in Fischer rats (KCA 5.3.2/13) were therefore not considered relevant to set the NOAEL.** **Further discussion on this study in EC 2.3.**
Experts' consultation 2.3 **MSs experts to discuss the relevance of the microscopic**	**Oral/dietary short-term studies** **Mineral Oil Saturated Hydrocarbons (MOSH) treatment-related microscopic changes were observed in the liver and mesenteric lymph node (MNL) of Fischer rats from several short-term studies.**

Subject	Conclusions Pesticide Peer Review Meeting
findings observed in the liver, mesenteric lymph nodes and gastro-intestinal tract, spleen, bone marrow and lungs in short term toxicity studies with paraffin oil in an experts' meeting.	Liver findings were considered adverse based on their histopathological characteristics (granulomas or microgranulomas with necrotic cells, lymphocytic infiltration and fibrosis). MNL findings were considered an adaptive physiological consequence to MOSH deposition and not adverse, based on their histopathological characteristics (discrete accumulations of macrophages, sinus histiocytosis), lack of progression to adverse lesions and lack of effect on the immune function. Small intestine, kidney and heart findings observed in one study were considered not adverse or of uncertain relationship to treatment and therefore not relevant to set the NOAEL (see EC 2.2). NOAEL in Fischer rat was agreed at 22 mg/kg bw per day, based on increased incidence of liver microgranulomas; the LOAEL was set at 222 mg/kg bw per day (based on the short-term oral toxicity study in rats (KCA 5.3.2/10-experiment 1)). **Open point:** the RMS to indicate that the experiment 2 of the short-term oral toxicity study in rats (KCA 5.3.2/10) is under revision; if a revised version is published on time, this will also be reported in the revised RAR. **Relevance of Fischer rat MOSH-related liver findings to humans** Adverse findings in the liver from Fischer rats following short term oral exposure to MOSH are of doubtful relevance to humans. The accumulation of mineral oils in human liver following dietary intake is associated to lipogranulomas, morphologically distinct from the microgranulomas observed in Fischer rats and lacking relevant inflammatory component. Moreover, human lipogranulomas are largely asymptomatic, not progressing over years and not associated with abnormalities of clinical relevance. Clinical trials using MOSH as placebo are available (Olshansky et al, 2020 and Ridker et al, 2022), however MOSH effects in humans are of unclear relevance at this stage. **Open point:** the RMS to include a summary and assessment two publications on clinical trials using MOSH as placebo in a revised RAR: 1. Olshansky et al, 2020 https://doi.org/10.1093/eurheartj/suaa117 2. Ridker, et al, 2022 https://doi.org/10.1161/circulationaha.122.059410

Subject	Conclusions Pesticide Peer Review Meeting
	Short-term inhalation studies NOAEC was agreed at 500 mg/m³ based on the increased severity and diffuse distribution of alveolar macrophages and multifocal granulomatous pneumonia at 1500 mg/m³ (based on the short term inhalation study KCA 5.3.3/09). The MAK value established by the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area was set at 5 mg/m³ based on a 2-year study (see EC point 2.6). **Short-term dermal toxicity** NOAEL for local effects) was agreed <125 mg/kg bw per day (adjusted for 60% paraffin content to 75 mg/kg bw per day) based on skin irritation (based on a 13-week study) NOAEL for systemic effects was agreed at 500 mg/kg bw per day (adjusted for 60% paraffin content to 300 mg/kg bw per day), based on a decrease in bodyweight slightly exceeding 10% at 2000 mg/kg bw per day (based on a 13-week study).
Experts' consultation 2.4 MSs experts to discuss the genotoxic potential of paraffin oil (CAS 8042-47-5) in an experts' meeting.	No genotoxicity studies on paraffin oil (CAS No 8042-47-5) are available. Genotoxicity was assessed and agreed in a WoE approach taking into account the summaries of studies used for REACH registration, information from published literature on surrogate substances and QSAR analyses. The majority of experts agreed that an uncertainty is present regarding aneugenicity. **Data gap**: the uncertainty for aneugenicity should be addressed, e.g. by an in vitro micronucleus test.
Experts' consultation 2.5 MSs experts to discuss the outcome of the 2-year dietary rat studies (KCA 5.5/01 and KCA 5.5/02) in an experts' meeting.	NOAELs in Fischer rat for the two available long-term toxicity and carcinogenicity studies on surrogate substances were agreed for both general toxicity and carcinogenicity as follows: 1200 mg/kg bw per day (top dose, study KCA 5.5/01); 1941/2291 mg/kg bw per day in males and females respectively (top dose, study KCA 5.5/02) Noteworthy, in these studies no adverse liver findings (i.e. dose related granulomas) were seen; and not adverse MLN histiocytosis was noted. No long term-carcinogenicity study on MOSH by oral/dietary route in mice was provided. It was agreed to waive for the carcinogenicity study in mice considering that white mineral oils can be concluded as not carcinogenic based on the absence of long-term

Subject	Conclusions Pesticide Peer Review Meeting
	toxicity/carcinogenicity by MOSH in rats (exposed via the oral and inhalation route) and in mice (via the dermal and inhalation route), the absence of any evidence of cancer in humans despite the long-term use of highly purified white mineral oils in medicine and cosmetics, and the negative human epidemiology study on kerosene.
Experts' consultation 2.6 MSs experts to discuss the long-term toxicity and carcinogenicity by inhalation in an experts' meeting.	NOAEC was derived considering two long-term toxicity and carcinogenicity studies in multiple species with surrogate substances (study KCA 5.5/07 and study KCA 5.5/04), and based on lung microgranulomas observed in SD rats and dogs at a respirable aerosol concentration of 100 mg/m³. Therefore, NOAEC were agreed as follows: NOAEC for rat and dog at 5 mg/m³ (oil microgranulomas in lungs at 100 mg/m³); NOAEC for mouse and gerbil at: 100 mg/m³ (top dose tested; study KCA 5.5/07); NOAEC for mouse, hamster and rabbit: 100 mg/m³ (top dose tested, study KCA 5.5/04). MAK Value A MAK value of 5 mg/m³ R (respirable fraction) has been established by the German Commission for the Investigation of Health Hazards of Chemical Compounds for pharmaceutical white oil based on the lung critical effect (microgranulomas in one long-term study with rats and dogs at a respirable aerosol concentration of 100 mg/m³ with a NOAEC of 5 mg/m³ in the study KCA 5.5/07), see EC point 2.4.
Experts' consultation 2.7 MSs experts to discuss the (need of deriving) an ADI and AOEL in an experts' meeting.	ADI, ARfD: It was agreed that an ADI and an ARfD are not triggered based on the toxicological profile of MOSH. MOSH-related adverse liver findings were observed upon short-term oral administration in Fischer rats; no progression of liver findings was noted in this rat strain upon long term administration up to 1941/2291 mg/kg bw per day (males and females respectively); no similar findings were observed in other tested species; these findings are of doubtful relevance to humans (see EC 2.7) AOEC An AOEC was agreed at 5 mg/m³ (MAK value) based on local adverse effects in the lungs following short-term and long-term inhalation exposure to MOSH in rat and dog.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.8 NEW **Dermal absorption**	**It was agreed to use the default dermal absorption values of 25% and 70% for the concentrate and dilution, respectively, as proposed in the EFSA Guidance (2017) for the EC formulations.** **Open point:** **RMS to provide revised non-dietary exposure estimates comparing the MAK values to the predicted air concentration caused by product application, and considering also the following recommendations.** **For the product BCP405D-CCL742:** - **Table 6.4-1: the application rate in the GAP table should not be adjusted for lower purity, instead the volume of the product applied, not part of the GAP table, should be amended.** - **For manual upward spraying: please clarify if dense foliage is considered** **For the product NEU1130 IEW:** - **For the GH uses, it is suggested to use also the EFSA GD 2022 (since it is the only EU validated model)** - **For manual upward spraying: please clarify if dense foliage is considered** - **For ornamentals: upward spraying should also be considered** - **Note that non-professional operators are not covered by professional knapsack** **For the product PARAFFIN OIL 79% EC:** - **For manual upward spraying: please clarify if dense foliage is considered** - **Note that non-professional operators are not covered by professional knapsack**
Experts' consultation 2.9 NEW **[redacted] as impurities**	**[redacted] may be present as impurities in paraffin oil at a maximum level of [redacted] (based on the EU Pharmacopeia).** **In the context of NDE, a Margin of Exposure approach was used (based on EFSA SC, 2005 https://doi.org/10.2903/j.efsa.2005.282) and EFSA SC, 2012 https://doi.org/10.2903/j.efsa.2012.2578)** **Comparing the exposure estimates for the highest AR with the BMDL10 ([redacted]) the corresponding Margin of Exposure (MoE) is higher than 10,000 and would indicate a low concern for human health.**

Subject	Conclusions Pesticide Peer Review Meeting
	Please refer to Residue section for further discussion on [redacted] maximum content in paraffin oil (CAS No 8042-47-5)
Experts' consultation 2.10 NEW ED	A waiver of the ED assessment for the EATS-modalities has been agreed based on the overall weight-of-evidence. Conduction of additional mammalian toxicity studies is not considered necessary based on lack of toxicological concern in all available studies on surrogate substances and due to the knowledge on its toxicological properties, in line with EFSA/ECHA guidance. Open points - The RMS is asked to provide further details on which endocrine organs was examined in the public literature studies mentioned to support the waiving. The exact references should be included. - The RMS is asked to check that enough details on QSAR analysis i.e. methods and results and acceptability of the models are included in the RAR. - Any other uses (e.g., cosmetic and drugs) for which there is no report of endocrine disturbance. - The RMS to include the update ED assessment in the Vol. 1 rather than in Vol. 3.
Experts' consultation 2.11 proposed by EFSA for completeness of discussion. NEW Experts to discuss the toxicological profile of the co-formulants.	Open point: RMS to integrate the substance identification and content in the formulation on the co-formulants in the revised RAR (if needed, case by case). RMS to assess the toxicological potential of the formulation for representative uses. If exhaustive info is not available on the formulation, based on the discussion during the experts meeting, RMS to report the assessment of the toxicological profile of the co-formulants in the revised RAR to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures. The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion.

REPORT OF PESTICIDE PEER REVIEW TC 100

PICLORAM – AIR III **Rapporteur Member State: PL**

2. Mammalian toxicity

Date: 21 April 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff	EFSA
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) (AT)
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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Member States experts to discuss the results of the *in vitro* comparative metabolism study (CA 6.1.4/1) in an experts' meeting.**	**Although presenting limitations, the *in vitro* comparative metabolism study can be considered acceptable and shows that picloram is not metabolised by rat, rabbit or human liver microsomes; no specific human metabolite have been identified.**
Experts' consultation 2.2 **Member States experts to discuss the NOAEL of the 90-day toxicity study in rats (CA 6.3.2/3) in an experts' meeting.**	**The agreed NOAEL of the 90-day toxicity study in rats is 150 mg/kg bw per day, based on significantly increase in relative liver weight (≥10% over controls) associated with very slight/slight histopathological changes (increased size of hepatocytes often accompanied by altered tinctorial properties, centrilobular).**
Experts' consultation 2.3 **Member States experts to discuss the NOAEL of the the 6-month toxicity study in dogs (B.6.3.2/1) in an experts' meeting.**	**The 6-month study in dogs is considered supplemental and not suitable for setting a NOAEL (being the 1-year study considered more appropriate). Changes in relative liver weight at 175 mg/kg bw per day are in line with those seen the 1-year study; liver weight changes observed at 7 and 35 mg/kg bw per day are considered transient/incidental.** **Open point: RMS to include in the updated RAR the individual values for liver weight for the 6-month study in dogs.**
Experts' consultation 2.4	**The 90-day study in mice is considered supplemental (some limitations have been observed, including the selection of doses).**

Subject	Conclusions Pesticide Peer Review Meeting
Member States experts to discuss the NOAEL of the 90-day toxicity study in mice (CA 6.3.2/4) in an experts' meeting.	A LOAEL of 1000 mg/kg bw per day is agreed on the basis of effects on liver weight increase (i.e. statistically significant increase in absolute liver weights, increased in relative liver weight >10%) and associated histopathology (i.e. changing in the staining properties of hepatocytes in different areas of the hepatic lobules likely due to vacuolation of cells near the portal triads, with the cells in the region of the central veins having cytoplasm that was slightly basophilic and of a ground-glass appearance).
Experts' consultation 2.5 Member States experts to discuss the systemic and carcinogenicity NOAELs of the 2-year chronic toxicity/carcinogenicity study in rats (CA 6.5/1) in an experts' meeting. In addition, MS experts to discuss the biological significance of adenocarcinoma of the pars distalis of the pituitary observed in females.	The agreed systemic NOAEL of the long term toxicity/carcinogenicity study in rats is 20 mg/kg bw per day on the basis of liver effects (i.e. increased size of the hepatocytes often accompanied by centrilobular altered tinctorial properties and bile duct hyperplasia in males). Adenocarcinoma of the pars distalis of the pituitary observed in females is considered not treatment-related since also not observed in the other study where higher dose levels were used. In the absence of treatment-related carcinogenicity findings, the agreed carcinogenicity NOAEL is 200 mg/kg bw per day (top dose).
Experts' consultation 2.6 Member States experts to discuss the systemic and carcinogenicity NOAELs of the 2-year chronic toxicity/carcinogenicity study in rats (CA 6.5/2) in an experts' meeting.	The long term toxicity/carcinogenicity study in rats is considered supplemental/additional, since testing just 2 dose levels higher than the ones used in the previous 2-year study. The agreed systemic LOAEL is 250 mg/kg bw per day on the basis of exacerbation of chronic progressive glomerulonephropathy in males.
Experts' consultation 2.7 Member States experts to discuss the systemic and carcinogenicity NOAELs of the chronic toxicity/carcinogenicity study in mice (CA 6.5/3) in an experts' meeting.	The statistically significant slight increase in kidney weight observed in the 2-year chronic toxicity/carcinogenicity study in mice is not associated with histopathological correlates; in addition, tubular degeneration/regeneration (unilateral or bilateral) noted in the kidneys of males and females from all groups, including controls, is considered compatible with an age-related condition in the mouse (the different distribution across groups is considered incidental). The agreed systemic and carcinogenicity NOAEL is 1000 mg/kg bw per day.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.8 **Member States experts to discuss and agree the developmental NOAEL of the teratogenicity studies in rats (CA 6.6.2/1-study 1 and CA 6.6.2/2-study 2) in an experts' meeting.**	**Developmental study in rats (study 1): maternal NOAEL agreed at 500 mg/kg bw per day of picloram K salt (corresponding to 430 mg/kg bw per day of picloram acid), based on excessive salivation at the top dose; in the absence of findings, the agreed developmental NOAEL is the top dose of 1000 mg/kg bw per day of picloram K salt (corresponding to 860 mg/kg bw per day of picloram acid).** **Developmental study in rats (study 2): the agreed maternal NOAEL is 500 mg/kg bw per day of picloram TIPA (corresponding to 280 mg/kg bw per day of picloram acid), based on excessive salivation and significantly reduced weight gain and food consumption at the top dose level; the agreed developmental NOAEL is 500 mg/kg bw per day of picloram TIPA (corresponding to 280 mg/kg bw per day of picloram acid) on the basis of distended lateral ventricles of the brain, exencephaly and open eye.**
Experts' consultation 2.9 **Member States experts to discuss and agree the developmental NOAEL of the developmental toxicity studies in rabbits (CA 6.6.2/3-study 1 and CA 6.6.2/4-study 2) in an experts' meeting.**	**Developmental study in rabbit (study 1):** **Maternal NOAEL agreed at 40 mg/kg bw per day of picloram acid equivalent based on the initial weight loss and overall reduced weight gain seen at dose levels of ≥200 mg/kg bw per day.** **Developmental NOAEL agreed at 200 mg/kg bw per day of picloram acid equivalent on the basis of forelimb flexure observed at the high dose.** **Developmental study in rabbit (study 2):** **Maternal NOAEL agreed at 54 mg/kg bw per day of picloram TIPA (corresponding to 30 mg/kg bw per day picloram acid) on the basis of bodyweight effects.** **Developmental NOAEL is agreed at 538 mg/kg bw per day of picloram TIPA (corresponding to 300 mg/kg bw per day of picloram acid) on the basis of the abormalities observed (i.e. persistent aortic arch and retrooesophageal right subclavian artery and missing cartilage rings in the trachea of one animal) and in the absence of robust HCD.**
Experts' consultation 2.10 **Member States experts to discuss the endocrine disruptive potential of picloram in an experts' meeting.**	**T-modality is sufficiently investigated and that there is no evidence for T-mediated adversity and T-mediated activity in the available dataset. Scenario 1a was concluded.** **No EAS-mediated adverse effects were observed based on an incomplete data set. Additional testing is required to complete the current data package:**

Subject	Conclusions Pesticide Peer Review Meeting
	A study in line with OECD TG 456 (H295R Steroidogenesis Assay) A study in line with OECD TG 458 (AR STTA assays); OPPTS 890.1200 (Aromatase assay) A study in line with OECD TG 441 (Hershberger Assay) in case OECD TG 456, OECD TG 458 and OPPTS 890.1200 are negative. If the above tests are negative, the substance will not meet ED criteria for EAS modalities. However, in case of positive result/s based on the above tests for at least one modality, additional testing is needed: i.e. extended one-generation study with inclusion of the cohort 1a and 1b including the mating of cohort 1b to produce the F2 generation (OECD TG 443, Level 5)
Experts' consultation 2.11 Member States experts to discuss metabolites (4-amino-2,3,5-trichloropyridine (PYR) and on 4-amino-3, 5-dichloro-6-hydroxypicolinic acid (6-OH)) in an experts' meeting.	For the 2 metabolites found in residues (4-amino-2,3,5-trichloropyridine and 4-amino-3,5-dichloro-6-hydroxypicolinic acid), in the absence of experimental data, the lack of coverage in ADME studies with the parent and considering the insufficient information to support the reliability of the available QSAR predictions, a data gap was agreed (to be confirmed by residues).
Experts' consultation 2.12 Member States experts to discuss and agree reference values (expressed as picloram acid) in an experts' meeting.	Agreed reference values: • ADI = 0.2 mg/kg bw day based on histopathological findings in the liver (slightly increased size and altered tinctorial properties of centrilobular hepatocytes and bile duct hyperplasia observed in the 2-year rat study (Landry 1986); UF of 100 • ARfD = 0.3 mg/kg bw based on maternal toxicity (body weight changes) observed in the developmental toxicity study in rabbits (Vedula, 1992); UF of 100 • AOEL = 0.3 mg/kg bw per day based on maternal toxicity (body weight changes) observed in the developmental toxicity study in rabbits (Vedula, 1992); UF of 100 • AAOEL = 0.3 mg/kg bw based on maternal toxicity (body weight changes) observed in the developmental toxicity study in rabbits (Vedula, 1992); UF of 100
Experts' consultation 2.13	For picloram in the SL formulation GF-224, the default values from the EFSA GD 2017 for SL formulation (i.e. 10% for concentrate and 50% for dilution) should be used for the risk assessment (since

Subject	Conclusions Pesticide Peer Review Meeting
Member States experts to discuss dermal absorption values for picloram.	they are exceeded by corrected values from experimental in vivo data with rats). **Open point:** RMS to provide revised calculations of dermal absorption in the revised RAR, based on the in vivo study with rats and in accordance with the EFSA GD on Dermal absorption 2012 and 2017. **Open point:** RMS to provide revised non-dietary exposure estimates (including values for potential exposure) considering the agreed AOEL, AAOEL and dermal absorption values for picloram acid (10% for the concentrate and 50% for the dilution), and following the EFSA Guidance 2014. Since the technical specification and reference values are for picloram acid, the exposure estimates should also be estimated as picloram acid.
New experts' consultation point 2.14 proposed by EFSA for completeness of discussion Member States experts to discuss the toxicological profile of co-formulants	**Open point:** RMS to integrate the substance identification and content in the formulation on the co-formulant in the revised RAR (if needed, case by case). RMS to assess the toxicological potential of the formulation for representative uses. If exhaustive info is not available on the formulation, based on the discussion during the experts meeting, RMS to report the assessment of the toxicological profile of the co-formulants in the revised RAR to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures. The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion.

REPORT OF PESTICIDE PEER REVIEW TC 100

PENOXSULAM – AIR IV **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 21 April 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff	EFSA
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) (AT)
National Expert nominated by MS Belgium - RMS	Belgian Federal Public Service (FPS) Health, Food Chain and Environment (BE)
National Expert nominated by MS Belgium - RMS	Sciensano (BE)
National Expert nominated by MS Germany	German Federal Institute for Risk Assessment (DE)
National Expert nominated by MS Greece - RMS	BENAKI PHYTOPATHOLOGICAL INSTITUTE (BPI) (EL)
National Expert nominated by MS Italy - RMS	International Centre for Pesticides and Health Risk Prevention (IT)
National Expert nominated by MS Finland - RMS	Finnish Safety and Chemicals Agency (FI)
National Expert nominated by MS Poland - RMS	E-V-A Sp. z o.o. (PL)
Observer	Austrian Agency for Health and Food Safety (AGES) (AT)

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by

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the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the NOAEL setting considering liver findings observed in the 28-day mice study (CA 5.3.1 / 3).**	**Experts' consultation fulfilled.** **All MS experts agreed with the proposal of the RMS to change the NOAEL of the 28-day mice study from 10 mg/kg bw per day to 100 mg/kg bw per day since the relative liver weight change observed at 100 mg/kg per day was not accompanied by histopathology and not considered adverse (below the threshold of 15% difference as compared to the controls) in the 28-day mice study.**
Experts' consultation 2.2 **Experts to discuss the NOAEL setting in the 90-day dog study (CA 5.3.2 / 4) by considering:** **- adversity of liver findings**	**Experts' consultation fulfilled.** **All MS experts agreed with the proposal of the RMS to set the NOAEL at 0.045% (18 mg/kg bw per day) based on renal findings (multifocal hyperplasia of the pelvic epithelium and crystals in the renal pelvis and collecting dusts) in both male and female dogs in the 90-day dog study.**
Experts' consultation 2.3 **Experts to discuss the NOAEL setting in the 13-week mice study (CA 5.3.2 / 6) by considering:** **- adversity of liver findings**	**Experts' consultation fulfilled.** **All the MS experts agreed with the RMS proposal to set the NOAEL at 100 mg/kg bw per day NOAEL based on increases in liver weight correlated with histopathological centrilobular hepatocellular hypertrophy and kidney findings in the 13-week mice study.**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.4 **Experts to discuss the NOAEL setting in the 90-day Fisher rat study (CA 5.3.2 / 1) by considering:** - **changes in prothrombin and platelet counts**	**Experts' consultation fulfilled.** **All the MS experts agreed with the RMS proposal of 50 mg/kg bw per day as a NOAEL based on decreased body weight gain, feed consumption in males, perineal soiling and 20% increase in liver weights in males at 250 mg/kg bw/day in the 90-day Fisher rat study.** **An open point was set for the RMS to check other coagulation related parameters (e.g., APTT and fibrinogen) to have the complete picure on changes on coagulation.**
Experts' consultation 2.5 **Experts to discuss the NOAEL setting in the 90-day Wistar rat study (5.3.2 / 3) by considering:** - **liver findings adversity** - **cholesterol findings adversity**	**Experts' consultation fulfilled.** **MS experts have agreed to maintain a NOAEL of at 50 mg/kg bw per day since the statistically significant increases in cholesterol levels seen in mid (around 20%) and high dose (around 30%) male rats were not associated with changes in other markers of liver damage (e.g. transaminases), nor with other variations in the lipid profile (e.g triglycerides) in the 90-day Wistar rat study. The finding was considered treatment related, but its adversity remains unclear.**
Experts' consultation 2.6 **Experts to discuss the NOAEL setting in the 1-year dog study (CA 5.3.2 / 5) by considering:** - **AP activity adversity**	**Experts' consultation fulfilled.** **In the 1-year dog study MS experts agreed with the RMS to set a NOAEL of 0.045% (14.7 mg/kg bw per day) for males based on kidney findings, and 0.15% (44.8 mg/kg bw/day) for females based on the lack of clearly adverse treatment-related effects.**
Experts' consultation 2.7 **Experts to discuss the NOAEL for long-term toxicity and carcinogenicity in the 2-year F334 rat study (CA 5.5 / 1), considering:** – **Adversity of liver findings** – **Cholesterol findings**	**Experts' consultation fulfilled.** **The majority of MS experts including the RMS agreed to set the systemic LOAEL at 5 mg/kg bw per day based on liver weight changes (above 15%) and increased cholesterol levels.** **Regarding carcinogenicity, the majority of MS experts consider that NOAEL should be set at the top dose level of 250 mg/kg per day (no indication of carcinogenic potential up to highest dose tested).** **EFSA encourages the RMS to submit a CLH proposal to ECHA for discussing harmonised classification and labelling.**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.8 Experts to discuss the endocrine disruption potential of penoxsulam.	**Experts' consultation fulfilled.** Based on the Weight of Evidence (WoE) which showed that T-mediated parameters were sufficiently investigated (weight and histology of thyroid parameters), and a pattern of adversity for T-modality was not consistently observed, all experts agreed that the ED criteria are not met for the T-modality according to Scenario 1a. Moreover, based on the WoE which indicated that there was no consistent evidence of adversity (two-generation reproductive toxicity study (OECD TG 416)) or activity following exposure with penoxsulam in EAS-related parameters, all experts agreed that the ED criteria are not met for the EAS-modality, according to Scenario 1a. An open point was set for EFSA to check ToxCast for the updated results.
Experts' consultation 2.9 Experts to discuss the toxicological profile of metabolites – 5-OH-XDE-638, – BSA – X740591 – BST – BSTCA	**Experts' consultation fulfilled.** **5-OH-XDE-638** Genotoxicity: Unlikely to be genotoxic (based on experimental data). General toxicity: covered by parent (based on structural similarities). **BSA** Genotoxicity: inconclusive. QSAR analysis did not suggest genotoxicity, however it is considered inconclusive given limited details available. General toxicity: inconclusive (further data would be needed). **X740591** Genotoxicity: unlikely to be genotoxic based on structural similarities compared to 5-OH penoxsulam (as well as to the parent) General toxicity: covered by parent (based on structural similarities) **BST** Genotoxicity: Unlikely to be genotoxic (based on experimental data). General toxicity: inconclusive (further data would be needed). **BSTCA** Genotoxicity: Unlikely to be genotoxic (based on experimental data). General toxicity: inconclusive (further data would be needed).

Subject	Conclusions Pesticide Peer Review Meeting
	2-amino-TP **Genotoxicity: inconclusive. QSAR analysis suggested genotoxicity, however it is considered inconclusive given limited details available.** **General toxicity: inconclusive (further data would be needed).**
Experts' consultation 2.10 **Experts to discuss the setting of reference values for penoxsulam.**	**Experts' consultation fulfilled.** **The agreed ADI of 0.016 mg/kg bw per day is based on the agreed LOAEL from chronic studies (5 mg/kg bw per day), established from the 2-year rat study chronic toxicity/carcinogenicity and with the application of the standard uncertainty factor of 100 plus an additional UF of 3 to be added considering the (low) severity of the observed effects (liver changes) at the LOAEL setting.** **ArfD and AAOEL are not triggered based on the toxicological profile of the substance.** **An AOEL of 0.15 mg/kg bw per day was established based on the lowest NOAEL (15 mg/kg bw/day) from the 1-year dog dietary study (critical effect was multifocal hyperplasia of the pelvic epithelium of males) with the application of an UF of 100.** **An open point was set for the RMS to recalculate consumer risk assessment based on the new ADI.**
New experts' consultation point 2.11 proposed by EFSA for completeness of discussion **MS experts to discuss the toxicological profile of co-formulants**	**Experts' consultation fulfilled.** **EFSA presented to MS experts non-exhaustive information collected for the co-formulant used in the formulation for the representative uses (GF-1076). No further discussion took place during the expert meeting.** **An open point was set for the RMS to integrate the substance identification and content in the formulation on the co-formulants in the revised RAR (if needed, case by case).** **RMS to assess the toxicological potential of the formulation for representative uses. If exhaustive info is not available on the formulation, based on the discussion during the experts meeting, RMS to report the assessment of the toxicological profile of the co-formulants in the revised RAR to enable an independent hazard identification and characterisation at least as regards the acute toxicity, genotoxicity, short- and long- term of the chemically identified co-formulants, including mixtures. The conclusion of the RMS should be presented clearly, separately from the applicant's conclusion.**

REPORT OF PESTICIDE PEER REVIEW TC 100

CHLORFENAPYR – Art.43 of REG. (EC) No 396/2005 (non-approved a.s.)

Rapporteur Member State: NA

2. Mammalian toxicity

Date: 21 April 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff	EFSA
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) (AT)
National Expert nominated by MS Belgium - RMS	Belgian Federal Public Service (FPS) Health, Food Chain and Environment (BE)
National Expert nominated by MS Belgium - RMS	Sciensano (BE)
National Expert nominated by MS Germany	German Federal Institute for Risk Assessment (DE)
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National Expert nominated by MS Italy - RMS	International Centre for Pesticides and Health Risk Prevention (IT)
National Expert nominated by MS Finland - RMS	Finnish Safety and Chemicals Agency (FI)
National Expert nominated by MS Poland - RMS	E-V-A Sp. z o.o. (PL)
Observer	Austrian Agency for Health and Food Safety (AGES) (AT)

MEETING MINUTES – 21 April 2023
Pesticide Peer Review TC 100
Chlorfenapyr

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the genotoxicity profile of chlorfenapyr according to current standards in an experts' meeting.**	**Chlorfenapyr is unlikely to be mutagenic or clastogenic. There is uncertainty regarding the aneugenicity potential of chlorfenapyr.**
Experts' consultation 2.2 **MSs experts to discuss the quality of the toxicological reference values (TRVs) for chlorfenapyr set at EU level and of those established by JMPR, considering the completeness of the set of toxicological studies used to derive the TRVs, as to assess if it would be acceptable according to the current standards. In case deficiencies are identified, these should be highlighted along with the resulting uncertainties.**	**The ADI and ARfD of chlorfenapyr are 0.028 mg/kg bw (per day) based the NOAEL of 2.8 mg/kg bw per day for on decreases in body weight gain and vacuolation of the white matter of the brain at 16.6 mg/kg bw per day in an 18-month mouse study.** **The ADI is supported by the 2-year toxicity and carcinogenicity study in rats and the 1-year neurotoxicity study in rats.** **The ARfD is supported by the pharmacological study (acute study) in mouse.** **These values are considered appropriate by the experts, even if data gaps and uncertainties were identified when the data set is compared with current standards.**

REPORT OF PESTICIDE PEER REVIEW TC 100

DICOFOL – Art.43 of REG. (EC) No 396/2005 (non-approved a.s.)

Rapporteur Member State: NA

2. Mammalian toxicity

Date: 21 April 2023

List of participants:

Status	Name of institution / attendee
EFSA statutory staff	EFSA
National Expert nominated by MS Austria	Austrian Agency for Health and Food Safety (AGES) (AT)
National Expert nominated by MS Belgium - RMS	Belgian Federal Public Service (FPS) Health, Food Chain and Environment (BE)
National Expert nominated by MS Belgium - RMS	Sciensano (BE)
National Expert nominated by MS Germany	German Federal Institute for Risk Assessment (DE)
National Expert nominated by MS Greece - RMS	BENAKI PHYTOPATHOLOGICAL INSTITUTE (BPI) (EL)
National Expert nominated by MS Italy - RMS	International Centre for Pesticides and Health Risk Prevention (IT)
National Expert nominated by MS Finland - RMS	Finnish Safety and Chemicals Agency (FI)
National Expert nominated by MS Poland - RMS	E-V-A Sp. z o.o. (PL)
Observer	Austrian Agency for Health and Food Safety (AGES) (AT)

MEETING MINUTES – 21 April 2023
Pesticide Peer Review TC 100
Dicofol

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the genotoxicity profile of dicofol according to current standards in an experts' meeting.**	**The available data package is insufficient to conclude on the genotoxicity potential of dicofol with regards to gene mutation and aneugenicity.**
Experts' consultation 2.2 **MSs experts to discuss the quality of the toxicological reference values (TRVs) for dicofol set at EU level and of those established by JMPR, considering the completeness of the set of toxicological studies used to derive the TRVs, as to assess if it would be acceptable according to the current standards. In case deficiencies are identified, these should be highlighted along with the resulting uncertainties.**	**There are too many uncertainties in the dataset available, in particular the genotoxicity potential of dicofol cannot be concluded and the ED potential is of concern. Therefore, TRVs cannot be proposed and it is not considered adequate to add an UF to the existing TRVs.**

REPORT OF PESTICIDE PEER REVIEW TC 99

METRIBUZIN – AIR III **Rapporteur Member State: EE**

2. Mammalian toxicity

Date: 29 March 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Estonian Agricultural Board	EE
Tragsatec on behalf of Ministerio de Sanidad (MISAN)	ES
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
E-V-A Sp. z o.o.	PL
Observer (1)	AT

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.13 **The potential of metribuzin to disrupt the T-modality will be discussed at the peer review expert consultation. Data provided during the 3 months stop of the clock (Comparative in vitro liver induction study, Dose Range finding in SD rat to support the Comparative Thyroid Assay (CTA) study, the CTA study in SD rat and a 4 weeks tox study by oral (dietary) route in rat study) will be discussed for their reliability and relevance and evidence will be included in the overall weight of evidence (WOE) to conclude if criteria for the T modality are met for the a.s. metribuzin. The overall analysis of the WOE will be based on all available evidence in the dataset of studies**	**The T-mediated parameters are sufficiently investigated in line with the EFSA/ECHA ED guidance.** **The Comparative Thyroid Assay (CTA) study, submitted during the stop-of-the-clock period, is confirming the concern that metribuzin is a thyroid disrupting chemical (TDC) and when considering the full dataset there is evidence of adversity.** **The new *in vitro* comparative UGT assay does not provide sufficient evidence to conclude on the human relevance of the Mode of Action (MoA). Several uncertainties and limitations in the *in vitro* comparative study were identified. Moreover, the available information on endocrine activity, including information on Molecular Initiating Events (MIEs) i.e. TPO, NIS, CAR/PXR, DIO inhibition, are not sufficient to conclude on the MoA for metribuzin. Phase II enzyme induction is a plausible MoA at high doses in the rat; however, this is not considered sufficient to explain changes in T4 at low doses possibly occurring as consequence of different MoA.** **All experts agreed that the criteria for T-modality are met for metribuzin.**

Subject	Conclusions Pesticide Peer Review Meeting
conducted with metribuzin.	
Experts' consultation 2.14 The reliability of the grading system applied in the CTA DRF and CTA studies will be discussed at the expert meeting	The scoring system applied in the CTA study was considered adequate. The CTA used a pre-defined scoring to describe in more details the diagnosis of thyroid follicular cell hypertrophy, including consideration on follicular cell height, presence of vacuoles and changes in colloidal area.

REPORT OF PESTICIDE PEER REVIEW TC 99

FLUFENACET – AIR III **Rapporteur Member State: PL**

2. Mammalian toxicity

Date: 29 March 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Estonian Agricultural Board	EE
Tragsatec on behalf of Ministerio de Sanidad (MISAN)	ES
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
E-V-A Sp. z o.o.	PL
Observer (1)	AT

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.15 **MSs experts to discuss the NOAEL of the oral reproduction/developmental toxicity screening study (B.6.8.3) to be discussed in an experts' meeting.**	**In the OECD TG 421 oral reproduction/developmental toxicity screening study:** - **the NOAEL (systemic) is 100 ppm based on adverse effects on hematological parameters observed at 500 ppm in F0 males and females rats.** - **the NOAEL (reproductive) is 500 ppm (the highest dose tested).** - **The NOAEL (neonatal and developmental) for F1 animal is 500 ppm (the highest dose tested).** **In the context of the endocrine disruptors (EDs) assessment, the top dose of 500 ppm is considered as the maximum tolerated dose (MTD) (mainly based on haematological changes) and adequate for the assessment of the ED properties of the substance.**
Experts' consultation 2.16 **MSs experts to discuss the testing strategy and completeness of the data set provided to address the ED potential of flufenacet in an experts' meeting.**	**E and S modalities were assessed in the newly submitted studies and neither adversity, nor endocrine activity were observed in a complete dataset.** **OECD TG 441 (Hershberger study) was positive and flufenacet is considered anti-androgenic.** **Although the conduction of the OECD TG 443 still remains the preferred option (in line with the EFSA/ECHA ED GD), A-mediated endpoints i.e. AGD, nipple retention, PPS, genital abnormalities, testes, seminal vesicles and epididymes weight and histopathology (including staging) and seminology have been all investigated in the newly submitted studies; therefore, the dataset is considered sufficient to conclude on the A modality.**

Subject	Conclusions Pesticide Peer Review Meeting
	Overall, there is no evidence of adversity for the A modality and therefore scenario 1a is applicable and criteria for EAS-modality are not met. **With regard to experts' consultation point 2.19, the effect observed in the DNT study (i.e. increase in time at preputial separation at the two highest doses of 100 and 500 ppm) was considered of limited magnitude and, in isolation, as not sufficient to conclude on a pattern of A-mediated adversity.** **With regard to experts' consultation point 2.20, cystic hyperplasia is a common spontaneous finding in older rats defined by actively proliferating endometrial glands with cystic dilatation. The effect was observed in the presence of a decrease in body weight gain (BWG) of 15% from the affected intermediate dose of 400 ppm where haematological changes were also observed. Although an effect on the uterus caused by estrogen dominance, there were no additional changes attributable to the E modality in the dataset and therefore the observed effect in the rat 2-year study was not considered sufficient evidence of disruption of the E modality.** **Open points:** • **RMS to include in the RAR a conclusion on the positive anti androgenic effect observed in the OECD TG 441.** • **RMS to include the outcome of the FSH and LH gene expression in the weight of evidence for EAS endocrine activity.** • **RMS to correct in the RAR the OECD TG 421 indicated as level 5 instead as level 4.**
Experts' consultation 2.17 **MSs experts to discuss the outcome of the T-modality in an experts meeting.**	**During the previous peer review consultation (in May 2019), ED criteria for the T-modality were considered not met with evidence of a pattern of T-mediated adversity (i.e. changes in thyroid histopathology) and activity (i.e. changes in THs) mostly confined to or above the MTD. The newly provided studies confirmed a test-item related perturbation of the HPT axis with evidence at doses below the MTD.** **Although induction of liver enzymes, with increase in the clearance of THs could be considered as a plausible MoA, there is no evidence that this MoA is not human relevant. In addition, other MIEs, except for deiodinase (DIO) inhibition (which was positive), were not investigated and therefore could not be excluded. The DNT study is also considered as positive and of concern because flufenacet is negative in a battery of in vitro DNT test and therefore a thyroid mediated mode of action on the observed DNT effects cannot be excluded.**

Subject	Conclusions Pesticide Peer Review Meeting
	On these bases, the experts at the peer review meeting agreed that the previous conclusion on T-modality could not be retained and flufenacet is considered to meet the ED criteria for T-modality. The RMS disagrees with the conclusion reached at the peer review meeting.
Experts' consultation 2.18 **MSs experts to discuss the A-modality from the outcome of the Hershberger, ToxCast and male pubertal rats' studies in an experts' meeting.**	***See conclusion of the pesticide peer review meeting under experts' consultation 2.16***
Experts' consultation 2.19 **MSs experts to discuss the EAS-mediated adversity observed in the DNT study in an experts' meeting.**	***See conclusion of the pesticide peer review meeting under experts' consultation 2.16***
Experts' consultation 2.20 **MSs experts to discuss the EAS-mediated adversity observed in the 2-year rat study in an experts' meeting.**	***See conclusion of the pesticide peer review meeting under experts' consultation 2.16***
Experts' consultation 2.21 **MSs experts to discuss the relevant scenario applying to flufenacet ED assessment and overall conclusion of the ED assessment in an experts' meeting.**	***See conclusion of the pesticide peer review meeting under experts' consultation 2.16***

REPORT OF PESTICIDE PEER REVIEW TC 98

FENARIMOL – Art.43 of REG. (EC) No 396/2005 (non-approved a.s.)

Rapporteur Member State: N/A

2. Mammalian toxicity

Date: 29 March 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Food and Health Safety	AT
German Federal Institute for Risk Assessment	DE
Tragsatec on behalf of Ministerio de Sanidad (MISAN)	ES
French Agency for Food, Environmental, Occupational Health & Safety (ANSES)	FR
Ctgb	NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 MSs experts to discuss the genotoxicity profile of fenarimol according to current standards in an experts' meeting.	There are too many uncertainties in the dataset available and the genotoxicity potential of fenarimol cannot be concluded (for gene mutation, clastogenicity and aneugenicity).
Experts' consultation 2.2 MSs experts to discuss the quality of the toxicological reference values (TRVs) for fenarimol proposed at EU level and of those established by JMPR, considering the completeness of the set of toxicological studies used to derive the TRVs, as to assess if it would be acceptable according to the current standards. In case deficiencies are identified, these should be highlighted along with the resulting uncertainties.	Considering the lack of conclusion on the genotoxicity potential of fenarimol and uncertainties identified in the dataset, TRVs cannot be proposed.
Experts' consultation 2.3 MSs experts to discuss potential endocrine-mediated	With the data available it can be concluded that fenarimol should be considered an endocrine disruptor according to current

Subject	Conclusions Pesticide Peer Review Meeting
reduction of fertility and adverse effects on parturition.	standards, at least with adverse effects on male fertility through an aromatase inhibition MoA.

REPORT OF PESTICIDE PEER REVIEW TC 98

ENDOSULFAN – Art.43 of REG. (EC) No 396/2005 (non-approved a.s.)

Rapporteur Member State: N/A

2. Mammalian toxicity

Date: 29 March 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Food and Health Safety	AT
German Federal Institute for Risk Assessment	DE
Tragsatec on behalf of Ministerio de Sanidad (MISAN)	ES
French Agency for Food, Environmental, Occupational Health & Safety (ANSES)	FR
Ctgb	NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the genotoxicity profile of endosulfan according to current standards in an experts' meeting.**	**The standard test battery is not available for endosulfan, the genotoxicity profile of endosulfan is unclear and no conclusion can be drawn on its genotoxicity potential.**
Experts' consultation 2.2 **MSs experts to discuss the quality of the toxicological reference values (TRVs) for endosulfan set at EU level and of those established by JMPR, considering the completeness of the set of toxicological studies used to derive the TRVs, as to assess if it would be acceptable according to the current standards. In case deficiencies are identified, these should be highlighted along with the resulting uncertainties.**	**Considering the lack of conclusion on the genotoxicity potential of endosulfan and uncertainties identified in the dataset, TRVs cannot be proposed.**

REPORT OF PESTICIDE PEER REVIEW TC 98

DIAZINON – Art.43 of REG. (EC) No 396/2005 (non-approved a.s.)

Rapporteur Member State: N/A

2. Mammalian toxicity

Date: 29 March 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Food and Health Safety	AT
German Federal Institute for Risk Assessment	DE
Tragsatec on behalf of Ministerio de Sanidad (MISAN)	ES
French Agency for Food, Environmental, Occupational Health & Safety (ANSES)	FR
Ctgb	NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 MSs experts to discuss the genotoxicity profile of diazinon according to current standards in an experts' meeting.	Considering the limitations and uncertainties identified in all genotoxicity studies, the genotoxicity potential cannot be fully ruled out for diazinon when considering current standards.
Experts' consultation 2.2 MSs experts to discuss the quality of the toxicological reference values (TRVs) for diazinon set at EU level and of those established by JMPR, considering the completeness of the set of toxicological studies used to derive the TRVs, as to assess if it would be acceptable according to the current standards. In case deficiencies are identified, these should be highlighted along with the resulting uncertainties.	The toxicological reference values established in 2006 cannot be confirmed due to the inconclusive genotoxicity potential of diazinon, and other uncertainties identified, such as missing developmental neurotoxicity study that is critical to the risk assessment of organophosphate pesticides.

REPORT OF PESTICIDE PEER REVIEW TC 98

PYDIFLUMETOFEN – mandate, NAS 1107 **Rapporteur Member State: FR**

2. Mammalian toxicity

Date: 29 March 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Food and Health Safety	AT
German Federal Institute for Risk Assessment	DE
Tragsatec on behalf of Ministerio de Sanidad (MISAN)	ES
French Agency for Food, Environmental, Occupational Health & Safety (ANSES)	FR
Ctgb	NL
Hearing experts (2)	IT

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Genotoxicity and general toxicity profile (including possible derivation of ADI/ARfD) of the metabolite 2,4,6-trichlorophenol to be discussed by the experts.**	**The results of gene mutation studies in bacteria, cultured mammalian cells and Big Blue transgenic rats indicate that 2,4,6-TCP does not induce gene mutations. Other *in vitro* data and limited *in vivo* data show that 2,4,6-TCP has the potential to induce structural chromosome aberrations and/or aneugenic effects. No robust in vivo study on the induction of chromosome aberrations and/or aneugenicity by 2,4,6-TCP is available.** **Data gap** **A combined *in vivo* Comet/micronucleus assay (conducted according to the OECD TG 489/474) should be performed with the metabolite 2,4,6-TCP.**
Experts' consultation 2.2 **Genotoxicity and general toxicity profile (including possible derivation of ADI/ARfD) of the metabolite SYN547891 to be discussed by the experts.**	**For the metabolite SYN547891, the available QSAR and read-across analysis indicate a low probability of a genotoxic potential.** **If reference values would be required for consumer risk assessment a formal assessment for general toxicity should be provided (e.g. by following ECHA framework on read-across).**
Experts' consultation 2.3 **Experts to discuss the toxicological relevance of the theoretical impurities [redacted] and**	**For the theoretical impurities [redacted] and [redacted] a robust assessment of the toxicological profile (genotoxicity and general toxicity) has not been provided and therefore their toxicological relevance cannot be concluded (data gap).**

Subject	Conclusions Pesticide Peer Review Meeting
[redacted] based on the available QSAR analysis for genotoxicity. It is noted that these three impurities were not found at levels [redacted] LOQ (~[redacted]/kg) in the 5 batches from [redacted]. [redacted] was found at [redacted]g/kg.	For the theoretical impurity [redacted] data are missing to clarify the presence of this impurity in the 5-batch analysis, and if present, to further clarify the assessment of its toxicological relevance (data gap).

REPORT OF PESTICIDE PEER REVIEW TC 97

AZOCYCLOTIN – Art.43 of REG. (EC) No 396/2005 (non-approved a.s.)

2. Mammalian toxicity

Date: 19 January 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
German Federal Institute for Risk Assessment (BfR)	DE
Ctgb	NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the genotoxicity profile of azocyclotin according to current standards in an experts' meeting.**	**Although the overall outcome of the various tests is negative or equivocal, the quality of the available studies and reporting is not sufficient to conclude on the genotoxicity potential of azocyclotin according to current standards.**
Experts' consultation 2.2 **MSs experts to discuss the setting of the ADI and ARfD for azocyclotin in an experts' meeting.**	**Since the genotoxicity potential of azocyclotin is inconclusive, toxicological reference values could not be established. In addition, data gaps and critical uncertainties were identified in the available data, that would not allow to perform an up-to-date risk assessment.**

REPORT OF PESTICIDE PEER REVIEW TC 97

CYHEXATIN – Art.43 of REG. (EC) No 396/2005 (non-approved a.s.)

2. Mammalian toxicity

Date: 19 January 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
German Federal Institute for Risk Assessment (BfR)	DE
Ctgb	NL

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the genotoxicity profile of cyhexatin according to current standards in an experts' meeting.**	**Cyhexatin is unlikely to have clastogenic or aneugenic potential, however, its mutagenic potential is inconclusive due to positive results seen *in vitro* that were not followed up *in vivo*.**
Experts' consultation 2.2 **MSs experts to discuss the setting of the ADI and ARfD for cyhexatin in an experts' meeting.**	**Since the genotoxicity potential of cyhexatin is inconclusive, toxicological reference values could not be established. In addition, data gaps and critical uncertainties were identified in the available data, that would not allow to perform an up-to-date risk assessment.**

REPORT OF PESTICIDE PEER REVIEW TC 92

FENPROPIDIN – AIR III **Rapporteur Member State: CZ**

2. Mammalian toxicity

Date: 18 January 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Central Institute for Supervising and Testing in Agriculture	CZ
National Institute of Public Health	CZ
Federal Institute for Risk Assessment (BfR)	DE
INIA	ES
Ministerio de Sanidad	ES
Tragsatec	ES
ANSES	FR
Department Agriculture Food and the Marine Ireland	IE
State Plant protection Service	LV
Ctgb	NL
Hearing expert	ES
Observers (2)	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 To discuss the results from the *in vitro* metabolism study and to conclude on the need to obtain further data.	The comparative *in vitro* metabolism study has been considered unreliable based on the limitation of the study (e.g. metabolic competence of human hepatocytes was not demonstrated in the test conducted with the positive control) . A new comparative *in vitro* metabolism study including as test species the ones used in the toxicological studies (i.e. rats, dogs, mice, rabbits) has to be provided (data gap). The experts suggested the new study to be conducted in accordance with the indications of the EFSA Scientific Opinion (EFSA, 2021).
Experts' consultation 2.2 The experts will discuss the results of the oral 90-day study in mice to establish the NOAEL.	The LOAEL of the oral 90-day study in mice is 625 ppm (<>58 mg/kg bw per day in males and 87 mg/kg bw per day in females) based on the non-statistically significant decrease of body weight gain (BWG) and on the statistically significant decrease in body weight observed in females at 1250 ppm. Open points: - The RMS to include tabulated data on the histological effects observed in liver in the 90-day toxicity study in mice. - The RMS to include tabulated data on the body weight and BWG. - The RMS to report a justification on the fact that thymus weight has been weighted whereas is written in the deviation that it was not.
Experts' consultation 2.3	The NOAEL for the 1-year study in dog is 5 mg/kg bw per day based on demyelination of spinal cord, hind limb paresis, lens cataracts and liver toxicity (i.e., increased liver weight by more than 20% in males, increased

Subject	Conclusions Pesticide Peer Review Meeting
The experts will discuss the results of the 1-year oral dog study to establish the NOAEL.	alkaline phosphatase level in both sexes, and hepatocyte hypertrophy in all animals) observed at 20 mg/kg bw per day.
Experts' consultation 2.4 To discuss the results of the 28-day-oral-dietary study in rat and establish the NOAEL.	The NOAEL for the 28-day toxicity study in rats is 200 ppm <> 20.1 mg/kg bw per day in males and 19.9 mg/kg bw per day in females, based on increase alanine aminotransferases (ALT) values in males and increased incidence of foam cells in lungs in females, observed at 1000 ppm.
Experts' consultation 2.5 The experts will discuss the results of the rat carcinogenicity study to establish the NOAEL and the relevance of the findings reported.	The NOAEL (carcinogenic) for the 2-year toxicity study in rat is 250 ppm <> 8.53 mg/ kg bw per day in males and 11.83 mg/kg bw per day in females, the highest dose tested. The increased incidence of pancreatic islet cell adenoma in males at top-dose was considered as not treatment-related based on the provided historical control data and on the acknowledge that the effect is frequently reported as spontaneous finding in the strain tested. The NOAEL (systemic) is 50 ppm <> 2.27 mg/kg bw per day in females, based on decrease of absolute body weight in females at 250 ppm. Open point: RMS to include in the revised RAR table presented during the experts' meeting on the incidence of pancreatic cell tumour.
Experts' consultation 2.6 The experts will discuss the results of the mice carcinogenicity study to establish the local NOAEL and the relevance of the findings reported.	The local NOAEL for the 18-months toxicity study in mouse is 30 ppm <> 4.12 mg/kg bw per day in males and 5.47 mg/kg bw per day in females, based on the hyperkeratosis in the oesophagus and stomach observed at 100 ppm in both sexes. NOAEL (systemic) is 300 ppm <> 41.9 mg/kg bw per day in males and 51.7 mg/kg bw/day in females based on effects on body weights, body weight gain, food consumption and increased males mortality. NOAEL (carcinogenic) is 1000 ppm <> 143.8 mg/ kg bw per day in males and 166.1 mg/kg bw per day in females, the highest dose tested.
Experts' consultation 2.7 The experts will discuss the available data for the assessment of the endocrine disruption potential of fenpropidin.	T-modality: All experts agreed that: the database for T-modality is considered complete and there is no evidence of a T-mediated pattern of adversity. ED criteria for T-modality are not met (i.e. Scenario 1a ECHA/EFSA GD is applied). EAS-modalities: All experts agreed that: the database for EAS-modality is complete and there is no evidence of a EAS-mediated pattern of adversity. ED criteria for EAS-modalities are not met (i.e. Scenario 1a ECHA/EFSA GD is applied).

Subject	Conclusions Pesticide Peer Review Meeting
	Open Point: RMS is kindly asked to include in a revised RAR the data presented at the expert meeting and consider the discussions at the meeting. In particular: all parameters used for the assessment of the sperm (also negative) and the data on sperm analysis should be contextualized in the WoE with testis histopathology and organ weights data. The table summarising the sexual maturation endpoints should include the BW at the initiation and at the end of the processes (preputial separation and vaginal opening). HCD and its assessment for the reported parameters should be clarified in the RAR (specify the metric used). The WoE conclusion should be aligned with the conclusion in the Peer Review report (i.e dataset is considered complete). Open point to EFSA: EFSA to check if the ED assessment in Vol 1 is complete and in line with EFSA template.
Experts' consultation 2.8 The experts will discuss all the available data and study results for the relevant metabolites to conclude on the toxicity and genotoxic potential and the reference values to be applied, if needed.	Overall, the methodological approach proposed by the RMS (grouping based on structural similarity to the parent) as well as the related scientific justifications (e.g. based on decreased logP) are not robust enough to support the similarity of the metabolites with the parent compound for both genotoxicity and general toxicity. Only one QSAR model (derek nexus) was used for systemic toxicity endpoints but no genotoxicity endpoint predictions were included. Experts noted that for an adequate and reliable QSAR analysis, two independent QSAR models i.e., one expert rule-based and a statistical model, should be used. QSAR analyses for genotoxicity and using two independent models are missing (data gap to be confirmed by residues). **CGA289263** Data addressing genotoxicity endpoints (i.e. gene mutation, clastogenicity/aneugenicity) and general toxicity endpoints are missing (data gap to be confirmed by residues/fate). The toxicological reference values of the parent are not applicable. **CGA289267** The metabolite is unlikely to be genotoxic based on the available experimental data (supported by the fact that is a major rat metabolite). Being a major rat metabolite, the general toxicity is covered by the parent compound. The reference value of the parent can apply to the metabolite (if needed). **CGA289268** Data addressing genotoxicity endpoints (i.e. gene mutation, clastogenicity/aneugenicity) and general toxicity endpoints are missing (data gap to be confirmed by residues/fate). The toxicological reference values of the parent are not applicable. **SYN515213**

Subject	Conclusions Pesticide Peer Review Meeting
	Data addressing genotoxicity endpoints (i.e. gene mutation, clastogenicity/aneugenicity) and general toxicity endpoints are missing (**data gap to be confirmed by residues**). The toxicological reference values of the parent are not applicable. **No further discussion took place on the following metabolites:** - **CGA289268 sulphate** - **CGA289268 glucose conjugate** - **SYN515215 (7U) conjugates (sulphate ester)** - **SYN 515216 (9U)** - **SYN522250 (I3)** - **CGA289265(I6)** - **SYN522245 (I9)** - **CGA289266(I10)** - **SYN 515213 sulphate ester conjugate (M5)** - **Acyl glycoside of dihydroxy CGA289267** - **Hydroxy CGA289267** - **I1** - **I2** - **I5** - **I8** - **I16a** **Genotoxicity and general toxicity data are missing (data gap to be confirmed by residue/fate).** No specific discussion took place on **SYN515215 (7U).** According to the RMS, available experimental data do not raised concern for genotoxicity (gene mutation, aneugenicity/ clastogenicity). Data addressing general toxicity endpoints are missing **(data gap to be confirmed by residue/fate).** **Open point:** The RMS to clarify the labelling of all metabolites in the revised RAR.
Experts' consultation 2.9 The experts will discuss the available toxicological data and all the reference values will be derived and agreed.	**The acceptable daily intake (ADI)** is **0.01 mg/kg bw per day** based on the NOAEL of 2.27 mg/kg bw per day from a 2-year rat toxicity study and applying an uncertainty factor (UF) of 200. **The acceptable operator exposure level (AOEL)** is **0.025 mg/kg bw per day**, based on the NOAEL of 5 mg/kg bw per day from the 1-year toxicity study in dog and applying an UF of 200. No correction for oral absorption is required (oral absorption > 80%).

Subject	Conclusions Pesticide Peer Review Meeting
	The additional UF of 2, considered in the derivation of ADI and AOEL, was applied to account for uncertainties in the database (i.e lack of a reliable comparative in vitro metabolism study) associated with potential concerns for human metabolism). The acute reference dose (ARfD) is 0.05 mg/kg bw based on the local NOAEL of 5.4 mg/kg bw per day derived from the 28-day toxicity study in rats and applying a standard uncertainty factor of 100. No correction for oral absorption is required (oral absorption > 80%). The acute AOEL (AAOEL) is 0.05 mg/kg bw based on the same point of departure used for setting the ARfD and applying a standard uncertainty factor of 100. Pending the discussion at TC 94 on fate and behaviour and at TC 96 on residues, and in the absence of toxicological studies to characterise the hazard of the two enantiomers of fenpropidin, all experts agreed that the additional factor of 2 could be considered in the exposure considerations of residents and workers since they are exposed after application. Whereas, operators and bystanders, exposed during mixing-loading and during application, are considered exposed to the racemic mixture only. **Open point:** The RMS to clearly report in Vol. 3ca B6, under each toxicity study, the conclusion on the NOAELs and the basis for their derivation. This has to be checked and aligned to the other sections (including Vol. 1 and LoEPs). Moreover, in the LoEPs the NOAEL should be reported in mg/kg bw per day and not only in ppm. **Open point:** RMS to provide an amendment of the RAR Vol. 1 to reflect the agreed toxicological reference values and related results of non-dietary exposure estimates.
Expert consultation 2.10 The experts will discuss the non-dietary exposure calculation for the active substance.	Based on the new *in vitro* dermal absorption study with the formulation for the representative uses, the agreed dermal absorption values to be applied for the non-dietary exposure estimates are 18% for the low application rate and 13% for the high application rate. For the worker, the submitted dislodgeable foliar residue studies were not considered appropriate for refinement of the exposure estimates (not sufficiently representative of the supported uses on cereals) and the default DFR and DT_{50} values will be used. For the residents and bystanders, the agreed maximum air concentration value of 1.66 µg/m³ (to be used in the EFSA model calculations) resulted from a specific field study, with a correction to cover the higher application rate from the representative uses.

Subject	Conclusions Pesticide Peer Review Meeting
	Open point: RMS to provide the Excel table (BfR) as support for the derivation of the dermal absorption values in line with EFSA guidance 2017. **Open point:** RMS to provide revised non-dietary exposure estimates with the agreed endpoints from the experts' discussions, including available risk mitigation measures as appropriate (e.g. for residents and bystanders).
Expert consultation 2.11 New experts' consultation point added by EFSA for completeness of discussion. Experts to discuss the toxicological profile of the co-formulants included in formulation and of the relevant impurities identified in the technical material.	**Co-formulants:** The co-formulants added in the formulation for representative uses do not contribute to the toxicity of the product containing fenpropidin. **Open point:** The RMS is requested to check the correct CAS No. for the co-formulants added in the formulation for representative uses. **Open point:** The RMS is asked to integrate substance identification and available toxicological information on co-formulants included in the formulation for representative uses. **Relevant impurities:** CGA 289273, is a toxicologically relevant impurity based on the hazard classification (Repr. 1b); however, it is of no concern at the proposed level in the reference specification.

REPORT OF PESTICIDE PEER REVIEW TC 92

MECOPROP-P – AIR III (ED re-assessment) **Rapporteur Member State: IE**

2. Mammalian toxicity

Date: 18 January 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Central Institute for Supervising and Testing in Agriculture	CZ
National Institute of Public Health	CZ
Federal Institute for Risk Assessment (BfR)	DE
National Institute for Agricultural and food research and technology (INIA)	ES
Ministerio de Sanidad	ES
Tragsatec	ES
Department Agriculture Food and the Marine Ireland, Pesticides Registration & Control Division	IE
State Plant protection Service	LV
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
Observers (2)	CH

In accordance with EFSA's Policy on Independence[1] and the Decision of the Executive Director on Competing Interest Management[2], EFSA screened the Annual Declarations of Interest filled out by the participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

Please note that information part of this report may have been masked by EFSA in accordance with Article 63 of Regulation (EC) No 1107/2009 as well as EFSA's Practical Arrangements concerning confidentiality in accordance with Articles 7 and 16 of Regulation (EC) No 1107/2009, or EFSA's Practical Arrangements concerning transparency and confidentiality as a consequence of confidentiality requests submitted by the applicant on application dossiers for pesticides active substances or Maximum Residue Levels, respectively. Please note that information disclosed in this report is without prejudice to pre-existing intellectual property rights and data exclusivity clauses set out in Union law, and particularly in Article 62 of Regulation (EC) No 1107/2009.

Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the outcome of the OECD TG 456 (H295R Steroidogenesis assay) in an experts' meeting.**	**All experts agreed that:** **-The updated OECD TG 456 (2022) should be used for assessing the results of the steroidogenesis study submitted.** **-In the steroidogenesis assay, mecoprop-P is a weak positive for estradiol induction and inconclusive for testosterone.**
Experts' consultation 2.2 **MSs experts to discuss the outcome of the extended one-generation reproductive toxicity (EOGRT) study in rats in an experts' meeting.**	**In the new EOGRT study submitted, the parental, reproductive and offspring NOAELs are 500/325 ppm corresponding to 24.3-33.7 mg/kg bw per day based on increased kidney weight (parents), low number of implantations for F1 Cohort 1B females and resultant F2 litter size in the second generation (reproductive toxicity) and decreased offspring body weight (offspring toxicity) at 1200/780 ppm (corresponding to 59.5-80.8 mg/kg bw per day).** **Open point: RMS to check the implications in the LoEP and human health and ecotox risk assessment of the new 443 study provided and include it in the revised RAR, in particular review the LoEP.**
Experts' consultation 2.3 **MSs experts to discuss the WoE for a potential ED of**	**For T-modality:** **All experts agreed that when integrating and weighting the results of the new OECD TG 443 study submitted in the WoE for T-modality, there is no pattern of adversity for the T modality and ED criteria were not met for the T modality. Scenario 1 a apply. This is in line with the former conclusion on T modality held in the peer review meeting PREV 10 on July 2019.**

Subject	Conclusions Pesticide Peer Review Meeting
the EAS modalities in an experts' meeting.	**For EAS-modalities:** **All experts agreed that when integrating and weighting the results of the new OECD TG 443 study submitted in the WoE for EAS-modalities, there is no pattern of adversity for the EAS-modalities and ED criteria were not met for the EAS modalities. Scenario 1 a apply.**

REPORT OF PESTICIDE PEER REVIEW TC 92

DICHLORPROP-P – AIR III (mandated for ED re-assessment) **Rapporteur Member State: IE**

2. Mammalian toxicity

Date: 18 January 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Central Institute for Supervising and Testing in Agriculture	CZ
National Institute of Public Health	CZ
Federal Institute for Risk Assessment (BfR)	DE
INIA	ES
Ministerio de Sanidad	ES
Tragsatec	ES
ANSES	FR
Department Agriculture Food and the Marine Ireland	IE
State Plant protection Service	LV
Ctgb	NL
Hearing expert	ES
Observers (2)	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.10 **The study *Van den Berg KJ, van Raaij JA, Bragt PC, Notten WR. Arch Toxicol. 1991;65(1):15-9. "Interactions of halogenated industrial chemicals with transthyretin and effects on thyroid hormone levels in vivo"*, should be discussed and included in the uncertainty analysis.**	**The study retrived from open literature (*Van den Berg KJ, van Raaij JA, Bragt PC, Notten WR. Arch Toxicol. 1991;65(1):15-9. "Interactions of halogenated industrial chemicals with transthyretin and effects on thyroid hormone levels in vivo"* was discussed and considered not reliable with several limitations.** **Conclusion** **Because of the several limitations the study was considered not reliable and not impacting the final conclusions on the T-modality.** **Open point to RMS to include the study in the ED weight of evidence (WoE) in Vol 1.**
Experts' consultation 2.11 **The outcome of the EOGRT study should be discussed to address EATS mediated and EATS sensitive endpoints as well as the impact of the new study on the overall NOAEL for reproductive toxicity endpoints.**	**The newly submitted OECD TG 443 was discussed during the meeting. Discussion was focus on the EATS mediated and sensitive endpoints to conclude on the ED properties of the active substance.** **Conclusion** **It was concluded that there is no evidence of a pattern of an EATS mediated adversity in a complete dataset and that scenario 1a of the EFSA/ECHA ED guidance document applies. ED criteria are not met for the EATS-modalities.**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.12 **The assessment of the OECD TG 456 in line with the updated interpretative guidance should be presented and discussed.**	**The outcome of the newly submitted OECD TD 456 (steroidogenesis assay) was discussed in view of the updated interpretative criteria issue by the OECD in 2022.** **It was concluded that, based on the new criteria, the outcome of the study should be considered negative and there is no effect on estradiol and testosterone measured levels.**

REPORT OF PESTICIDE PEER REVIEW TC 92

BIPHENYL-2-OL (2-PHENYLPHENOL) – AIR IV

Rapporteur Member State: ES

2. Mammalian toxicity

Date: 18 January 2023

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Central Institute for Supervising and Testing in Agriculture	CZ
National Institute of Public Health	CZ
Federal Institute for Risk Assessment (BfR)	DE
INIA	ES
Ministerio de Sanidad	ES
Tragsatec	ES
ANSES	FR
Department Agriculture Food and the Marine Ireland	IE
State Plant protection Service	LV
Ctgb	NL
Hearing expert	ES
Observers (2)	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the toxicological equivalence of 2-phenylphenol (=ortho-phenylphenol, OPP) and its sodium salt, i.e. sodium biphenyl-2-olate (sodium ortho-phenylphenol, SOPP) and the possible extrapolation of results where/if needed (see also developmental effects in mice in SOPP versus OPP by considering also the meta-study provided by [redacted] 2013).**	**Under physiological conditions 2-phenylphenol (=ortho-phenylphenol, biphenyl-2-ol, OPP) and its sodium salt, i.e. sodium biphenyl-2-olate (sodium ortho-phenylphenol, SOPP) are chemically equivalent, and their systemic toxicity is assumed to be similar.** **Extrapolation of data and NOAELs from toxicity studies with OPP to SOPP is concluded as applicable.**
Experts' consultation 2.2 **MS experts to discuss and agree on the oral absorption value and toxicokinetic (TK) data in an experts' meeting.**	**The oral absorption values for OPP and SOPP are set at 100% given the rapid and significant recovery of both substances (or metabolites) after 24 hours of exposure to OPP or SOPP in multiple studies.** **A data gap was agreed for oral toxicokinetic (TK) data with OPP.**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.3 **MS experts to discuss the possible need of an *in vitro* comparative metabolism study.**	**A data gap was agreed for an *in vitro* comparative metabolism study with OPP, in line with the data requirements laid down in Regulation (EC) No 283/2013.**
Experts' consultation 2.4 **MS experts to discuss if the data requirements for short-term toxicity are considered fulfilled for short term toxicity studies in consideration of the fact that many studies are considered supportive. In addition, MS experts to discuss and agree on the NOAEL of the 1-year study in the dog (Vol.3 CA, B.6.3.2-03, 1990) by taking into consideration emesis and effects on body weight and finally agree the overall short-term NOAEL.**	**Even though all short-term studies were only rated as supportive, the short-term toxicity data requirement was concluded as fulfilled, based on the large number of studies available in the dossier also including two studies considered as the most reliable ones, that overall showed consistent results with those from long-term studies.** **Regarding the dog 1-year study (Vol.3 CA, B.6.3.2-03, 1990), the LOCAL NOAEL is 100 mg/kg bw per day, based on emesis at 300 mg/kg bw per day. A SYSTEMIC NOAEL is not set due to the unknown level of dog systemic exposure as a result of emesis.** **For OPP: the relevant oral short-term NOAEL is 285 mg/kg bw per day, based on the increase of mitotic activity and hyperplasia of bladder urothelium in male rats after 13 weeks of treatment with 568 mg/kg bw per day (LOAEL).** **For SOPP: the relevant oral short-term NOAEL is 322 mg/kg bw per day as extrapolated from OPP, based on the molecular weight adjustment.** **For OPP: the relevant dermal systemic short-term NOAEL is 1000 mg/kg bw per day, based on the absence of effects at the highest dose tested (21-day dermal study in rats).** **For OPP: the dermal local NOAEL is 100 mg/kg bw per day, based on the irritation and associated histopathology on skin at 500 mg/kg bw per day.** **Open point:** **RMS to update the relevant short-term NOAELs for OPP and SOPP both in the RAR and LoEP.**
Experts' consultation 2.5 **Genotoxicity profile of 2-phenylphenol (and possible read across with SOPP) to be discussed by the experts,**	**Based on the weight of the evidence, OPP is considered unlikely to be genotoxic.** **Given the chemical equivalence of OPP and SOPP in solution, no genotoxicity potential is expected for SOPP.**

Subject	Conclusions Pesticide Peer Review Meeting
considering the newly available data (Ames test and *in vitro* micronucleaus test) and the (revised) assessment of the literature data, considering also the recommendations from the EFSA Scientific Committee on the genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Journal 2011;9(9):2379).	
Experts' consultation 2.6 MS experts to discuss the results (haematology, clinical chemistry, urinalysis, histopathological findings and the incidences of cataracts) and NOAELs of the 2-year toxicity study in rats (Vol.3 CA B.6.5-02, 1996). In addition, experts should also discuss the available evidence also from other rat carcinogenicity studies of possible urinary bladder tumours formation by considering mode of action information and possible human relevance. It is noted that the CLH process for 2-phenylphenol is running in parallel and RMS's proposal for classification of 2-phenylphenol as Carc. 2 H351 is therefore pending ECHA outcome.	For OPP, based on the 2-year toxicity study in rats (Vol.3 CA B.6.5-02, 1996), the relevant systemic NOAEL is 39 mg/kg bw per day, based on structural alterations in the urinary bladder (hyperplasia) of male rats at 200 mg/kg bw per day (= LOAEL); the relevant NOAEL for carcinogenicity is 39 mg/kg bw per day, based on neoplasms in the urinary bladder in males at 200 mg/kg bw per day. The bladder carcinogenicity is relevant to humans and classification as Carc. 2 (H351) is supported by ECHA. For SOPP, both the systemic NOAEL and the NOAEL for carcinogenicity are 44 mg/kg bw per day, based on the extrapolation of the respective NOAELs from OPP and on molecular weight adjustment.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.7 **MS experts to discuss the relevance of testes weight changes in conjunction with histopathological findings in the 2-year dietary study in rats (Vol.3 CA B.6.5-02, 1996), in the 91-week dietary study in rats ([redacted], 1984), in the first 2-generation reproductive toxicity in rats (Vol.3 CA B.6.6.1-01, 1990) and in the second 2-generation reproductive toxicity study in rats (Vol.3 CA B.6.6.1-02, 1995).**	**The increased relative testis weight observed in the rat 2-year study and in the two 2-generation reproduction toxicity studies is not considered as biologically relevant since (i) no changes were concomitantly seen in the absolute testes weight; (ii) relative weight changes were not accompanied by treatment-related histopathological effects.**
Experts' consultation 2.8 **MS experts to discuss pelvis dilatation findings in both offspring and adults, increased incidences of calculi and haemorrhage in adults, the effects on testes particularly in F1 males and the NOAELs in the two-generation reproductive toxicity study in rat.**	**In a rat two-generation reproductive toxicity study, the renal pelvic dilatation observed in both offspring and adults is considered of doubtful relation to treatment and not adverse, given the lack of dose response (except for F2A pups ≥21 days), the inconsistency of findings across F1 and F2 generations, and the lack of repeatability of this effect in a subsequent 2-generation reproductive toxicity study by the same author.** **In adults, calculus and haemorrhage incidences were considered adverse and treatment-related but with no impact on the study systemic NOAEL of 35 mg/kg bw per day based on bladder histopathology.** **Relevant NOAELs for OPP:** **Parental NOAEL: 35 mg/kg bw per day, based on bladder histopathology.** **Reproductive NOAEL ≥457 mg/kg bw per day, no adverse effects.** **Offspring NOAEL: 92 mg/kg bw per day, based on decreased pup bodyweight in F1 and F2 generation at the high dose tested.** **Relevant NOAELs for SOPP: extrapolated from OPP and molecular weight adjustment:** **Parental NOAEL: 39.5 mg/kg bw per day** **Reproductive NOAEL: > 516. 4 mg/kg bw per day** **Offspring NOAEL: 104 mg/kg bw per day**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.9 **MS experts to discuss the incidences of resorptions and other study findings in the rabbit developmental study by considering also the re-evaluation of the study by [redacted] and [redacted], 2013.**	**OPP Maternal NOAEL: 100 mg/kg bw per day based on the decrease in body weight gains and the increase in mortality and renal tubular degeneration.** **OPP developmental NOAEL: 25 mg/kg bw per day based on the increased resorption and the decreased percent of live litter.** **SOPP maternal NOAEL: 112.8 mg/kg bw per day** **SOPP developmental NOAEL 28.2 mg/kg bw per day** **Both SOPP NOAELs are based on extrapolation of the OPP NOAELs and adjustment for molecular weight.** **Open point:** **RMS to update the RAR and the LoEP in relation to the developmental NOAEL for both OPP and SOPP.**
Experts' consultation 2.10 **MS experts to discuss the endocrine disrupting (ED) potential of 2-phenylphenol in an experts' meeting.**	**The thyroid (T)-modality was assessed in a complete dataset and no adversity was observed in several studies and species. Scenario 1a of the EFSA/ECHA ED guidance applies (no adversity in a complete dataset) and the ED criteria are not met for the T-modality.** **The oestrogen, androgen and steroidogenesis (EAS)-modalities were assessed in a non-complete dataset (lack of an updated level 5 study in line with the EFSA/ECHA ED guidance).** **A pattern of adversity was not evident for the EAS-modalities in a non-complete dataset but endocrine activity was observed. A mode of action (MoA) analysis is therefore necessary and additional information is needed to conclude on EAS-mediated adverse effects.** **Scenario 2a(i) of the EFSA/ECHA ED guidance applies (perform MoA analysis; additional information may be needed for the analysis).** **Data requirement:** **An OECD TG 443 study with the inclusion of the 2nd generation is requested.** **Open point:** **RMS to include the ToxCast oestrogen receptor (ER) and androgen models and their relative outcomes in a revised RAR**
Experts' consultation 2.11 **Experts to discuss the toxicological profile of the metabolites phenylhydroquinone (PHQ), phenylbenzoquinone (PBQ)**	**As regards the metabolites of OPP, the experts agreed that:** **- for PHQ, neither the genotoxicity potential nor the general toxicity assessment can be concluded (data gaps for both genotoxicity and general toxicity);** **- for PBQ, the genotoxicity potential cannot be concluded (data gap);** **- for 2-MBP, the genotoxicity potential cannot be concluded (data gap).**

Subject	Conclusions Pesticide Peer Review Meeting
and 2-methoxy biphenyl (2-MBP) (including genotoxicity and general toxicity).	
Experts' consultation 2.12 Setting of the toxicological reference values for 2-phenylphenol to be discussed by the experts.	The toxicological reference values for OPP and SOPP were agreed as follows: For OPP, the acceptable daily intake (ADI), (Acute)Acceptable Operator Exposure Level ((A)AOEL), and Acute Reference Dose (ARfD) are 0.25 mg/kg bw per day, based on the developmental NOAEL of 25 mg/kg bw per day for increased resorption from the rabbit developmental toxicity study and applying a standard uncertainty factor of 100. For SOPP, the ADI, (A)AOEL), and ARfD are 0.28 mg/kg bw per day, based on extrapolation of the NOAEL identified as point of departure for OPP, corrected for the different molecular weight, and applying a standard uncertainty factor of 100
Experts' consultation 2.13 Experts to discuss the exposure estimates for the representative use of drenching citrus, including - operators: exposure during mixing/loading (M/L) with the EFSA model; - workers: first tier model; second tier field study (with revised assessment) and exposure to the metabolite PHQ (found in the peel of citrus); - residents/bystander: exposure to vapour.	As regards non-dietary exposure estimates the experts concluded as follows: For operators, only exposure during mixing/loading will be considered (with the EFSA model) for an amount of 1 kg a.s. handled per day (to treat 120 tons fruit/day). For workers, a higher tier approach will be applied, considering the results of the field study during post-harvest activities at pear and citrus fruit packaging facilities, covering dermal and inhalation exposure. For residents and bystanders, only exposure to vapour is considered relevant and will be based on results from the field study for workers as EFSA default values do not apply to highly volatile compounds. Open point: RMS to provide revised non-dietary exposure estimates for operators, workers, bystanders and residents with the application of the new AOEL and AAOEL values: - operators: considering 1 kg a.s. handled per day, - workers: considering the max individual exposure for the different activities (pre-sorting, sorting and packaging),

Subject	Conclusions Pesticide Peer Review Meeting
	- bystanders and residents: using maximum air concentration values in the different areas of the study (pre-sorting, sorting and packaging) and a justification of their relevance for bystanders and residents, and considering also use of relevant percentiles if sufficient number of measurements has been provided.

REPORT OF PESTICIDE PEER REVIEW TC 84

GLYPHOSATE – AIR V

Rapporteur Member State: Assessment Group on Glyphosate (AGG) consisting of FR, HU, NL, SE

2. Mammalian toxicity (endocrine disruption (ED) properties)

Date: 02 December 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Public Service Health	BE
Federal Institute for Risk Assessment (BfR)	DE
Federal Environmental Agency (UBA)	DE
Ministry of Environment and Food of Denmark, Environmental Protection Agency	DK
TRAGSATEC	ES
Finnish Safety and Chemicals Agency (Tukes)	FI
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
National Food Chain Safety Office (NEBIH)	HU
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
Swedish Chemicals Agency (KemI)	SE
National Institute of Public Health	SI
External experts (2)	EFSA

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

participants invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

Discussion points/Outcome

2. Mammalian toxicity

Please note that information part of this report may have been masked by EFSA in accordance with Article 63 of Regulation (EC) No 1107/2009 as well as EFSA's Practical Arrangements concerning confidentiality in accordance with Articles 7 and 16 of Regulation (EC) No 1107/2009, or EFSA's Practical Arrangements concerning transparency and confidentiality as a consequence of confidentiality requests submitted by the applicant on application dossiers for pesticides active substances or Maximum Residue Levels, respectively. Please note that information disclosed in this report is without prejudice to pre-existing intellectual property rights and data exclusivity clauses set out in Union law, and particularly in Article 62 of Regulation (EC) No 1107/2009.
Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.23 MS experts to discuss the endocrine disruption (ED) potential of the active substance glyphosate and the toxicological relevance of the effects on oestrus cyclicity.	**Thyroid (T)-modality:** The dataset for the T-modality is considered sufficiently investigated for the active substance glyphosate. No T-mediated adversity and activity were observed in a sufficiently investigated dataset consisting of several studies of different duration and multiple doses administered in mouse, rat, rabbit and dog. **Oestrogen, androgen and steroidogenesis modalities (EAS)-modalities:** The dataset for the EAS-modalities is considered sufficiently investigated for the active substance glyphosate. There is no evidence of EAS-mediated adversity and activity in a sufficiently investigated dataset consisting of several studies of different duration and multiple doses administered in mouse, rat, rabbit and dog. It was concluded that the ED criteria according to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, are not met for the EAS- and T-modalities for the active substance glyphosate.
Experts' consultation 2.29 Experts to discuss:	The RMS provided updated information in the revised RAR for the reliability and relevance assessment of studies included in the ED properties assessment.

Subject	Conclusions Pesticide Peer Review Meeting
• The relevance and reliability of the available studies (both regulatory and from literature) and assessed parameters for their use in the weight of evidence for ED assessment; • The information that can be derived from the available studies based on: tested item, test system (including species, where necessary) study design and parameters assessed; • The weight of evidence for ED leading to the overall conclusion on whether the criteria as laid down in point 3.6.5 of Annex II to Regulation 1107/2009 are met.	The EFSA ED Working Group (WG) conducted an independent reliability and relevance assessment, and this was presented to the experts in the peer review meeting. When applying both approaches (by RMS and EFSA) for the quality assessment of the evidence in the public literature, there are no factual differences, and the results are in agreement when using the outcome of the studies in a weight of evidence (WoE) approach for the assessment of the ED properties of glyphosate active substance. It was however noted that the level of details for assessing the risk of bias of the endpoints measured in the public literature studies is different. During the discussion, EFSA informed the RMS and the MSs that the EFSA ED WG Weight of Evidence report will be published by EFSA as a supporting documentation to the regulatory assessment of the active substance glyphosate. As a matter of transparency and completeness and taking into account that many comments were received during the public consultation on the methods and results of this quality assessment, EFSA suggested the RMS to consider and make reference to the EFSA ED WG WoE report and related appendices in the revised RAR. **Open points** 1. RMS to revise the ED assessment and include the missing studies. 1.1. RMS to conduct the reliability and relevance and uncertainty analysis of the endpoints measured in the studies. 2. RMS to make a reference to the EFSA ED WG WoE report.

REPORT OF PESTICIDE PEER REVIEW TC 80

GLYPHOSATE – AIR V
Rapporteur Member State: Assessment Group on Glyphosate (AGG) consisting of FR, HU, NL, SE

2. Mammalian toxicity

Date: 25 November 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Sciensano - HRIA	BE
Federal Public Service Health	BE
Federal Institute for Risk Assessment (BfR)	DE
Ministry of Environment and Food of Denmark, Environmental Protection Agency	DK
TRAGSATEC	ES
Ministerio de Sanidad	ES
Finnish Safety and Chemicals Agency (Tukes)	FI
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
National Food Chain Safety Office (NEBIH)	HU
Pesticide Control Division, Department of Agriculture, Fisheries & Food	IE
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
Eko-Futura Sp. Z o.o. , an external unit of The Ministry of Agriculture and Rural Development	PL
Swedish Chemicals Agency (KemI)	SE
National Institute of Public Health	SI
External experts (11)	EFSA

Pesticide Peer Review TC 80 (14 – 25 November 2022)
Glyphosate

Institute	Member States Country code
Observer	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the **absorption, distribution, metabolism and excretion** of glyphosate acid in mammals and to agree on an overall oral absorption value. Toxicokinetic behaviour and **potential accumulation** of glyphosate in bone matrix should also be discussed.	The oral absorption value is 20% as proposed during the previous renewal assessment (EFSA, 2015[3]). The highest levels of glyphosate acid were measured in bone, followed by kidney and liver. There was no evidence of a potential for accumulation in animal tissues. **Open point:** RMS to provide a revised RAR reporting the agreement of the meeting.
Experts' consultation 2.2 Experts to discuss and agree on the overall no observed adverse effect levels (NOAELs) for **short-term toxicity studies** conducted in dogs, rats and mice.	The relevant short-term oral NOAEL in rats is 79 mg/kg bw per day derived from a 90-day repeated dose study (Report No. 434/016) and based on effects of caecum (i.e. mucosal atrophy) and increased alkaline phosphatase (ALP) reported at the lowest observable adverse effect level (LOAEL) of 730 mg/kg bw per day. This NOAEL also covers for other critical effects observed at higher doses, i.e., soft stool, diarrhoea, reduction in body weight gain and food consumption, and liver effects (increased weight, changes in blood chemistry).

[3] EFSA (European Food Safety Authority), 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA Journal 2015; 13(11):4302, 107 pp. doi:10.2903/j.efsa.2015.4302.

Subject	Conclusions Pesticide Peer Review Meeting
For findings on salivary glands, see also experts' consultation 2.15.	The relevant short-term oral NOAEL in mice is 1221 mg/kg bw per day derived from a 90-day repeated study (Report No. IET 94-0136) based on decreased food consumption, liver effects (blood chemistry), caecum (distension not accompanied by histopathological changes), and increased incidence of cystitis in the urinary bladder reported at the LOAEL of 6295 mg/kg bw per day. The relevant short-term oral NOAEL in dog is 53 mg/kg bw per day derived from a 90-day repeated toxicity study (Report No. 1816) and based on decreased food consumption, increased gamma-glutamyl transferase (GGT), increased ALP and bilirubin at the LOAEL of 252/253 mg/kg bw per day. The relevant short-term dermal NOAEL in rat (systemic) is 1000 mg/kg bw per day derived from 21-day studies (Report No. CTL/P/4985 and Report No. 7839). A LOAEL for local effects of 1000 mg/kg bw per day was derived from a 21-day study and based on the mild skin irritation observed at the only dose tested. The relevant short-term dermal NOAEL in rabbit (systemic) is 2000 mg/kg bw per day derived from 28-day studies (Report No. CTL/P/4985 and Report No. 7839). A NOAEL of 1000 mg/kg bw per day is set for local effects. **Open point:** RMS to correct the value on the increased bilirubin observed in male dogs in Table 6.3.26-5 (Report No. 1816).
Experts' consultation 2.3 Experts to discuss the impact of the following deviations for genotoxicity studies on glyphosate (major vs minor deviation): • Absence of metabolic activation in *in vitro* genotoxicity studies, given	The experts agreed that the absence of metabolic activation in *in vitro* genotoxicity studies, given the limited metabolism of glyphosate, is a minor deviation. The experts agreed that a lack of positive control data alone, where positive results are obtained, would not lead to a score of 3 "reliability insufficient or unreliable" (using the Klimisch score). The experts agreed that the lack of historical control data (HCD) alone, provided positive results are observed, would not lead to a reliability

Subject	Conclusions Pesticide Peer Review Meeting
the limited metabolism of glyphosate. • Lack of positive control data where positive results are observed. • Lack of historical control data, provided that the study includes proper concurrent negative control data without high variability.	score of 3 “reliability insufficient or unreliable” (using the Klimisch score).
Experts’ consultation 2.4 Experts to discuss the outcome of the RMS’ assessment of the data submitted following the data requirements set in the genotoxicity section of the reporting tables (Member States and Public) also taking into account the outcome of the ECHA RAC committee assessment.	This experts’ consultation point has been discussed under Experts’ consultation 2.2, 2.3, 2.4 identified following comments by public (see further down in this report).
Experts’ consultation 2.5 Experts to discuss the reliability and relevance of the bacterial gene mutation assay CA 5.4.1/012; Report no. RL3393/2007-2.0AM-B (2007).	This experts’ consultation point has been discussed under Experts’ consultation 2.2 identified following comments by public (see further down in this report).
Experts’ consultation 2.6 Experts to discuss the reliability and relevance of the bacterial gene mutation assay	This experts’ consultation point has been discussed under Experts’ consultation 2.2 identified following comments by public (see further down in this report).

Subject	Conclusions Pesticide Peer Review Meeting
CA 5.4.1/015; Report no. IET 94-0142 (1995).	
Experts' consultation 2.7 Experts to discuss the reliability and relevance of the bacterial gene mutation assay CA 5.4.1/018; Report no. 887-MUT.AMES (1993).	This experts' consultation point has been discussed under Experts' consultation 2.2 identified following comments by public (see further down in this report).
Experts' consultation 2.8 Experts to discuss the reliability and relevance of the *in vitro* chromosome aberration (CA) test (1998) CA 5.4.1/025.	This experts' consultation point has been discussed under Experts' consultation 2.3 identified following comments by public (see further down in this report).
Experts' consultation 2.9 Experts to discuss the reliability and relevance of the *in vitro* CA test, 1996, CA 5.4.1/026.	This experts' consultation point has been discussed under Experts' consultation 2.3 identified following comments by public (see further down in this report).
Experts' consultation 2.10 Experts to discuss the reliability and relevance of the *in vitro* CA test, 1995, CA 5.4.1/027.	This experts' consultation point has been discussed under Experts' consultation 2.3 identified following comments by public (see further down in this report).
Experts' consultation 2.11 Experts to discuss the reliability and relevance of the *in vitro* CA test, 1995, CA	This experts' consultation point has been discussed under Experts' consultation 2.3 identified following comments by public (see further down in this report).

Subject	Conclusions Pesticide Peer Review Meeting
5.4.1/028 (Report No. 141918).	
Experts' consultation 2.12 The reliability and relevance of the *in vitro* micronucleus (MN) test by Roustan, A. et al, 2014[4] to be discussed by the experts.	This experts' consultation point has been discussed under Experts' consultation 2.3 identified following comments by public (see further down in this report).
Experts' consultation 2.13 MSs experts to discuss the NOAEL from the 2-year rat study 2 (Report No. CTL/PR1111, 2001) in an experts' meeting.	The NOAEL of the 2-year rat study 2 (Report No. CTL/PR1111) is 121 mg/kg bw per day, based on decreased adrenal weight in females and increased ALP (>50% compared with controls) observed at 361 mg/kg bw per day.
Experts' consultation 2.14 MSs experts to discuss the NOAEL of the 2-year rat study 5 (Report No. 886.C.C-R, 1996) in an experts' meeting.	The NOAEL of the 2-year rat study 5 (Report No. 886.C.C-R) is 59.4 mg/kg bw per day, based on increased incidence of liver lesions (small livers, focal haemorrhage, small cyst and a pale and mottled appearance), lung lesions (increased incidence of emphysema, collapse, petechiae, ecchymoses), cataracts and increased ALP observed at 595.2 mg/kg bw per day. **Open point** The RMS is kindly asked to revise the RAR based on the outcome of the discussion.
Experts' consultation 2.15 MSs experts to discuss the relevance of the salivary gland findings observed in	The experts concluded that the salivary gland effects are likely to be a local effect. It was agreed to apply a margin of safety (MOS) approach based on a local effect. To this aim the local LOAEL of 100 mg/kg bw per day derived from the 2-year rat study 7 (Report No. 7867 from 1993) was compared with the acceptable daily intake (ADI) of 0.5 mg/kg bw per day, resulting in a MOS of 200. This margin was

[4] Roustan A, Aye M, De Meo M, Di Giorgio C. Genotoxicity of mixtures of glyphosate and atrazine and their environmental transformation products before and after photoactivation. Chemosphere. 2014 Aug;108:93-100. doi: 10.1016/j.chemosphere.2014.02.079. Epub 2014 Apr 12. PMID: 24875917

Subject	Conclusions Pesticide Peer Review Meeting
- Oral 90-day toxicity study in rats – study 6, Report No. 7136,1991; p. 106; - Oral 90-day toxicity in mice – study 1, Report No. IET 94-0136, 1995; p. 133; - 1-year rat study 6 (Report No. CTL/P/5143, 1996, p. 61); - 2-year rat study 7 (Report No. 7867, 1993, p. 84-85); - Parental toxicity in the 2-generation reproductive toxicity study in rat Report No. CHV 47/911129, 1992: p. 73 And referencing: - 8-week oral rat study of citric acid (B.6.8.2.2, Report No. WIL-50361, 2010, p. 326) in an experts' meeting.	considered sufficiently protective for local effects of glyphosate upon exposure at the ADI level. Overall, the experts concluded that the salivary gland effects are not relevant to derive toxicological reference values.
Experts' consultation 2.16 MSs experts to discuss the reliability of the 18-month mouse study 2 (Report No. Toxi: 1559.CARC-M, 2001, p. 111-121) in an experts' meeting.	In the 18-month mouse study 2 (Report No. Toxi: 1559.CARC-M), the NOAEL is revised at 149.7 mg/kg bw per day based on increased mortality and the increased incidence of stomach cysts at the top dose level of 1454 mg/kg bw per day. The study was assessed as reliable with restrictions. Open point RMS to include in the RAR more information regarding the distribution of ecto/endoparasites among controls and treated groups. Open point The RMS is kindly asked to revise the RAR based on the outcome of the discussion.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.17 MSs experts to discuss the potential for glyphosate to induce oxidative stress in an experts' meeting.	Glyphosate may induce oxidative stress, but increased oxidative stress was not consistently demonstrated in the available studies. Regarding epidemiological studies investigating oxidative stress endpoints, it was agreed that no conclusion can be drawn on the possible relationship between glyphosate exposure and changes in oxidative stress parameters on the basis of the limited database and outcome from human observational studies available. Overall, no clear conclusion can be reached. **Open point** New studies identified after the public consultation period (see experts' consultation 2.37) to be considered by the RMS in a revised RAR: • Robin Mesnage, Mariam Ibragim, Daniele Mandrioli, Laura Falcioni, Eva Tibaldi, Fiorella Belpoggi, Inger Brandsma, Emma Bourne, Emanuel Savage, Charles A Mein, Michael N Antoniou, Comparative Toxicogenomics of Glyphosate and Roundup Herbicides by Mammalian Stem Cell-Based Genotoxicity Assays and Molecular Profiling in Sprague-Dawley Rats, Toxicological Sciences, Volume 186, Issue 1, March 2022, Pages 83–101, https://doi.org/10.1093/toxsci/kfab143 **Open point** RMS to consider three epidemiological studies investigating oxidative stress in a revised RAR (new studies identified after the public consultation period, see experts' consultation 2.37): • Makris et al. 2022: Oxidative stress of glyphosate, AMPA and metabolites of pyrethroids and chlorpyrifos pesticides among primary school children in Cyprus. Environ Res 212, 113316. doi: 10.1016/j.envres.2022.113316. • Eaton et al. 2022: The association between urinary glyphosate and aminomethyl phosphonic acid with biomarkers of oxidative stress among pregnant women in the PROTECT birth cohort study. Ecotoxicology and Environmental Safety, 233, 113300. doi: 10.1016/j.ecoenv.2022.113300.

Subject	Conclusions Pesticide Peer Review Meeting
	• Sidthilaw et al. 2022: Effects of exposure to glyphosate on oxidative stress, inflammation, and lung function in maize farmers, Northern Thailand. BMC Public Health, 22, 1343. doi: 10.1186/s12889-022-13696-7.
Experts' consultation 2.18 MSs experts to discuss the NOAEL of the 2-year rat study 8 (Report No. MSL-10495, 1990) in an experts' meeting.	The NOAEL of the 2-year rat study 8 (Report No. MSL-10495) is 89 mg/kg bw per day based on stomach mucosal irritation observed at higher dose levels (362 mg/kg bw per day and higher).
Experts' consultation 2.19 MSs experts to discuss the weight of evidence on the relationship between glyphosate exposure and risk of lymphohematopoietic cancer (LHC), including non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (and other subtypes), multiple myeloma (MM), and leukemia from epidemiological studies and the outcome of the newly reported studies in an experts' meeting. Also taking into account the outcome of the ECHA RAC meeting and their opinion on classification.	The available epidemiological studies currently do not provide sufficient indication that glyphosate exposure is associated with any cancer-related health effect. **Open point** RMS to consider in a revised RAR the study by De Roos et al. 2022 identified after the public consultation period (see experts' consultation 2.37): Herbicide use in farming and other jobs in relation to non-Hodgkin's lymphoma (NHL) risk. Occupational and Environmental Medicine, 79(12), 795-806.
Experts' consultation 2.20 MS experts to discuss the relevance and reliability of all the available studies (both	All the experts agreed with the RMS on the relevance and reliability of all the available studies included in the revised RAR. These include both regulatory studies as well as the studies from the open literature including the parameters assessed and used in the weight of evidence for reproductive and developmental toxicity assessment. The experts

Subject	Conclusions Pesticide Peer Review Meeting
regulatory and from literature) and assessed parameters for their use in the weight of evidence for reproductive and developmental toxicity assessment. Also taking into account the outcome of the ECHA RAC meeting and their opinion on classification.	also agreed on the inclusion of the considerations made by the ECHA Risk Assessment Committee (RAC) meeting and of their opinion on the inclusion of this evidence for classification[5].
Experts' consultation 2.21 MS experts to discuss the human relevance and use of rabbit in the developmental toxicity assessment of glyphosate.	The human relevance of the effects observed in the rabbit developmental toxicity studies could not be dismissed for the derivation of the reference values for human risk assessment. An overall rabbit developmental NOAEL was set at 150 mg/kg per day based on increased incidence of post-implantation loss at 450 mg/kg bw per day and reduced foetal weight at 300 mg/kg bw per day in the study Report No. CHV 45 & 39 & 40/901303 (1991). An overall rabbit maternal NOAEL was set at 50 mg/kg bw per day based on reduced body weight gain (gestation day (GD) 7-19) by 24-29% in dams administered 200 mg/kg bw per day. Since gastrointestinal irritation is observed in several species, also following administration via diet, it is appropriate to set an acute reference dose (ARfD) based on a NOAEL for the most sensitive species. Using the developmental NOAEL set at 150 mg/kg bw per day in the rabbit developmental toxicity study (Report No. CHV 45 & 39 & 40/901303) as point of departure and a standard uncertainty factor of 100, results in an ARfD of 1.5 mg/kg bw which would also protect from the post-implantation loss observed in rabbits. All experts agreed that the rabbit developmental toxicity study (Report No. 434/020) is considered as supplementary information only because of the excessive mortality observed at the high dose, compromising the dose-response analysis. Open point

[5] ECHA RAC, 2022. Committee for Risk Assessment (RAC) Opinion proposing harmonised classification and labelling at EU level of glyphosate (ISO); N-(phosphonomethyl)glycine. Adopted on 30 May 2022.

Subject	Conclusions Pesticide Peer Review Meeting
	RMS to revise the reliability of the rabbit developmental toxicity study (Report No. 434/020) in a revised RAR.
Experts' consultation 2.22 MS experts to agree on values for NOAEL/LOAEL reproductive in the reproductive toxicity studies and agree on the overall NOAEL/LOAEL reproductive considering all comments/concerns raised during the commenting period. Reference is made to the following comments: - MS experts to discuss the reduced number of homogenisation resistant spermatid in cauda epididymis observed in F0 for the reproductive toxicity study B.6.6.1/01 (Report number 2060/0013). - MS experts to discuss the findings of increased large follicles and increased number of animals with irregular cycle observed in the reproductive toxicity study B.6.6.1/01 (2060/0013). - MS experts to discuss the toxicological significance of the ano-genital distance (AGD) values normalised to the cube root of pup weight	**Overall reproductive NOAEL** is 351 mg/kg bw per day, based on decrease in homogenisation resistant spermatid count in F0 males observed at limit dose in Report No. 2060/0013. **Overall NOAEL for offspring toxicity** is 293 mg/kg bw per day, based on reduced body weight observed at 985 mg/kg bw per day in Report No. CTL/P/6332. **Overall NOAEL/LOAEL for parental toxicity** is 417 mg/kg bw per day, based on increased liver and kidney weights at 2151 mg/kg bw per day observed in study Report No. IET 96-0031. **Open point** RMS to provide a revised RAR reporting the agreement of the meeting.

Subject	Conclusions Pesticide Peer Review Meeting
for the study B.6.6.1/001 (2060/0013). - MS experts to discuss the limitations of oestrus cyclicity assessments conducted in reproductive toxicity studies. MS experts to agree on values for NOAEL / LOAEL offspring in the reproductive toxicity studies and agree on the overall NOAEL/LOAEL offspring considering all comments/concerns raised during the commenting period. Reference is made to the following comments: - MS experts to discuss the setting of NOAEL offspring based on delayed preputial separation observed in F1 offspring for the reproductive toxicity study B.6.6.1/01 (2060/0013). - MS experts to discuss the setting of NOAEL offspring based on reduction in pup body weight observed in the reproductive toxicity studies. MS experts to agree on values for NOAEL / LOAEL parental in the reproductive toxicity studies and agree on the overall NOAEL/LOAEL parental considering all comments/concerns raised	

Subject	Conclusions Pesticide Peer Review Meeting
during the commenting period. See expert consultation 2.29 regarding the endocrine disruption (ED) assessment of glyphosate.	
Experts' consultation 2.23 MS experts to discuss the endocrine disruption (ED) potential of the active substance glyphosate and the toxicological relevance of the effects on estrus cyclicity.	*Please refer to the Pesticide Peer Review TC 84 Mammalian toxicology – Ecotoxicology joint ED session (1-2 December 2022)*
Experts' consultation 2.24 Experts to discuss the relevance and reliability of the available historical control data for developmental toxicity parameters and the impact on the assessment of developmental toxicity effects.	All experts agreed that historical control data (HCD) are correctly reported and contextualized in the revised RAR and there is no remaining concern.
Experts' consultation 2.25 Experts to discuss the setting of maternal and developmental NOAEL/LOAEL values in the rat developmental toxicity studies.	In the rat developmental toxicity studies, - the overall maternal NOAEL is 300 mg/kg bw per day based on the findings in study Report No. CHV 43 & 41/90716 (clinical signs, reduced bodyweight gain in dams) and Report No. IET 94-0152 (clinical signs) at 1000 mg/kg bw per day; - the overall developmental NOAEL is 300 mg/kg bw per day based on the findings in study Report No. CHV 43 & 41/90716 (reduced ossification, skeletal variations in foetuses) at 1000 mg/kg bw per day.

Subject	Conclusions Pesticide Peer Review Meeting
	Open point RMS to provide a revised assessment of the study Report No. CHV 43 & 41/90716 considering the body weight gain (BWG) change between gestation day (GD) 6 and GD 20.
Experts' consultation 2.26 Experts to discuss the assessment of the retro-oesophageal right subclavian artery also in the context of a non-monotonic dose-response (NMDR) effect.	The retro-oesophageal right subclavian artery finding is not treatment related and not consequent to a non-monotonic dose-response (NMDR).
Experts' consultation 2.27 Experts to discuss in an experts' meeting the neurotoxic potential of glyphosate by taking carefully into consideration all the available evidence from the applicants, literature and epidemiological studies in a weight of evidence approach. Particular consideration should be given to the discussion of the: • systemic NOAEL of the 90-day neurotoxicity study in rats Report No. 2060-0010, 2006; • possible effect of glyphosate on the concentrations of several neurotransmitters in various regions of the brain in rodents and relevance of the findings;	1) The NOAEL for systemic toxicity is 395 mg/kg bw per day in males, based on reduced body weight gain and food consumption in the 90-day neurotoxicity study in rat (Report No. 2060-0010); in the absence of neurotoxicity findings, the NOAEL for sub-chronic neurotoxicity is confirmed to be ≥ 1499 mg/kg bw per day in males. This is in line with the conclusion reached in Report No. CTL/P/4867 (additional 90-day neurotoxicity study in rats). 2) There is no sufficient evidence of an effect of glyphosate active substance and/or glyphosate-based herbicides (GBH) on neurotransmitters. 3) Limited data are available from *in vitro* and *in vivo* studies regarding the potential relationship between exposure to glyphosate and parkinsonism/Parkinson's disease; the integration of the epidemiological studies with the experimental evidence is not triggering a concern for parkinsonism. No relevant indication of neurodegenerative changes in the pivotal neurotoxicity studies conducted up to 1499 mg/kg bw per day was observed. 4) There is no sufficient evidence on the association between glyphosate exposure and autism spectrum disorder (ASD). 5) There is no sufficient evidence on the association between glyphosate exposure and amyotrophic lateral sclerosis (ALS); no relevant indication of neurodegenerative changes in the pivotal

Subject	Conclusions Pesticide Peer Review Meeting
• the possible relationship between long-term exposure to glyphosate and developing chronic and neurodegenerative diseases such as Parkinson's disease by taking into consideration all the available evidence and epidemiological studies; • potential relationship between autism spectrum disorder and exposure to glyphosate by taking into consideration all the available evidence and epidemiological studies; • potential relationship between amyotrophic lateral sclerosis and exposure to glyphosate by taking into consideration all the available evidence and epidemiological studies.	neurotoxicity studies conducted up to 1499 mg/kg bw per day was observed. 6) Developmental Neurotoxicity (DNT). A specific DNT study on glyphosate acid is not available. Some non-guideline studies on glyphosate and glyphosate-based herbicide (GBH) formulations indicated isolated DNT findings only observed with the GBH. It was noted that in a guideline DNT study, performed with the glyphosate trimesium, positive effects were reported. Overall (considering that glyphosate trimesium is not representing glyphosate from the qualitative toxicological profile perspective), based on the available data on glyphosate acid and GBH and on the fact that it is not possible to identify a pattern of effects suggesting DNT liabilities for glyphosate acid using the available dataset, it is considered that the current toxicological reference values (TRVs) are protective. The residual uncertainties (coming from the studies performed with GBH) are considered of having no impact on the TRVs. However, a data gap can be identified to further refine the toxicological profile and assessment of glyphosate acid for DNT endpoints. **Open point** RMS to include in the revised RAR an assessment of the following studies on DNT potential for glyphosate, identified after the public consultation (see experts' consultation 2.37): • Glyphosate Trimesium. Study type: developmental neurotoxicity study - rat; MRID 45539801 [6] • Luna et al., 2021: Glyphosate exposure induces synaptic impairment in hippocampal neurons and cognitive deficits in developing rats. Arch Toxicol 95(6):2137-2150 • Del Castilo et al. 2022: Lifelong exposure to a low-dose of the glyphosate-based herbicide RoundUp causes intestinal damage, gut dysbiosis, and behavioural changes in mice. Int J Mol Sci, 23(10):5583. • Ojiro et al., 2023: Comparison of the effect of glyphosate and glyphosate-based herbicide on hippocampal neurogenesis after developmental exposure in rats. Toxicol 483:153369

[6] U.S. EPA: Data evaluation Record. Glyphosate Trimesium. Study type: developmental neurotoxicity study - rat; MRID 45539801. 2005. Accessed from: https://www.regulations.gov/document/EPA-HQ-OPP-2016-0093-0183

Subject	Conclusions Pesticide Peer Review Meeting
	• US EPA ToxCast/Tox21 Dashboard[7] **Open point** RMS to include in the revised RAR an assessment of the following studies on neurotoxic potential for glyphosate, identified after the public consultation (see experts' consultation 2.37): • Moser et al., 2022: Glyphosate and neurological outcomes: a systematic literature review of animal studies. J Toxicol Environ Health, part B, 25(4):162-209. • Winstone et al., 2022: Glyphosate infiltrates the brain and increases pro-inflammatory cytokine TNFα: implications for neurodegenerative disorders. J of inflammation, 19:193.
Experts' consultation 2.28 Experts to discuss the relevance of inappropriate immunostimulation findings and the impact of this on the overall risk assessment (including a potential definition of a NOAEL).	No evidence of immunosuppression was reported in the available immunotoxicity study (Report No. WIL-50393) which is designed to investigate a suppression of the humoral immune response and no conclusions can be drawn on the toxicological relevance of the apparent increase in Total Spleen Activity IgM/potential immunostimulation by glyphosate. Based on this study, the agreed NOAEL is 1448 mg/kg bw per day (highest dose tested). **Open point** RMS to correct the measures used to assess the variability in the results from the study Report No. WIL-50393 in Table B.6.8.2.1-3 (to be presented as mean +/- standard error of the mean (SEM)).
Experts' consultation 2.29 Experts to discuss • The relevance and reliability of the available studies (both regulatory and from literature) and assessed parameters for their use in the weight of	*Please refer to the Pesticide Peer Review TC 84 Mammalian toxicology – Ecotoxicology joint ED session (1-2 December 2022)*

[7] Available at this link: https://comptox.epa.gov/dashboard/chemical/invitrodb/DTXSID1024122 [accessed in November 2022].

Subject	Conclusions Pesticide Peer Review Meeting
evidence for ED assessment; • The information that can be derived from the available studies based on: tested item, test system (including species, where necessary), study design and parameters assessed; • The weight of evidence for ED leading to the overall conclusion on whether the criteria as laid down in point 3.6.5 of Annex II to Regulation 1107/2009 are met.	
Experts' consultation 2.30 Experts to discuss the weight-of-evidence assessment of the available data regarding - the potential effect of glyphosate on the gut microbiota (in animals and humans) and possible consequences; - the potential impact of glyphosate on the health of livestock and pet animals. (it should be considered if this assessment would change the previous EFSA assessment of the impact of glyphosate on animal health (https://www.efsa.europa.eu/en/efsajournal/pub/5283)).	Studies on potential effects of glyphosate on the human and animal gut microbiome are not expected to impact the risk assessment, based on the current state of knowledge; the available data for the mammalian toxicity assessment were sufficiently protective for any health impact for livestock and pet animals (in line with the conclusions of the EFSA scientific report, 2018[8]). The impact of glyphosate on the microbiome was also discussed in the Pesticide Peer Review Experts' TC 82 on ecotoxicology (see Expert consultation point 5.1 identified following comments from the public) and similar conclusions were achieved. **Open point** RMS to include the assessment of 7 additional articles (identified after the public consultation, see also experts' consultation 2.37) in the revised RAR (see below): • Barnett JA, Bandy ML, Gibson DL (2022). Is the Use of Glyphosate in Modern Agriculture Resulting in Increased Neuropsychiatric Conditions Through Modulation of the Gut-brain-microbiome Axis?

[8] EFSA (European Food Safety Authority), 2018. Scientific Report on evaluation of the impact of glyphosate and its residues in feed on animal health. *EFSA Journal* 2018;16(5):5283, 22 pp. https://doi.org/10.2903/j.efsa.2018.5283

Subject	Conclusions Pesticide Peer Review Meeting
It is acknowledged that, due to the absence of validated guidelines and criteria to assess the impact of gut microbiome modifications on human health, the relevance of the related studies and reliability of the results may not be conclusive from a regulatory perspective. It is however noted that the ongoing gut microbiome research is expected to play a relevant role in regulatory science in the future, with potential implications for risk assessments and predictive risk models.	Front Nutr. 9: 827384. https://doi.org/10.3389%2Ffnut.2022.827384 • Del Castilo I, Neumann AS, Lemos FS, De Bastiani MA, Oliveira FL, Zimmer ER, Rêgo AM, Hardoim CCP, Antunes LCM, Lara FA (2022). Lifelong Exposure to a Low-Dose of the Glyphosate-Based Herbicide RoundUp® Causes Intestinal Damage, Gut Dysbiosis, and Behavioral Changes in Mice. Int. J. Mol. Sci. 23, 5583 https://doi.org/10.3390/ijms23105583 • Hu J, Lesseur C, Miao Y, Manservisi F, Panzacchi S, Mandrioli D, Belpoggi F, Chen J, Petrick L (2021). Low-dose exposure of glyphosate-based herbicides disrupt the urine metabolome and its interaction with gut microbiota. Sci Rep 11, 3265 https://doi.org/10.1038/s41598-021-82552-2 • Huch M, Stoll DA, Kulling SE, Souku ST (2022). Metabolism of glyphosate by the human fecal microbiota. Toxicology Letters, 358: 1-5 https://doi.org/10.1016/j.toxlet.2021.12.013 • Liu JB, Chen K, Li ZF, Wang ZY, Wang L. (2022). Glyphosate-induced gut microbiota dysbiosis facilitates male reproductive toxicity in rats. Sci Total Environ 20;805:150368. https://doi.org/10.1016/j.scitotenv.2021.150368 • Mesnage R, Calatayud M, Duysburgh C, Marzorati, M, Antoniou M (2022). Alterations in infant gut microbiome composition and metabolism after exposure to glyphosate and Roundup and/or a spore-based formulation using the SHIME technology. Gut Microbiome, 3, E6 https://doi.org/10.1017/gmb.2022.5 • Puigbò P, Leino LI, Rainio MJ, Saikkonen K, Saloniemi I, Helander M (2022). Does Glyphosate Affect the Human Microbiota? Life 2022, 12, 707 https://doi.org/10.3390/life12050707
Experts' consultation 2.31 Experts to discuss the toxicity profile of the following metabolites (other	AMPA (M02) The experts unanimously concluded that AMPA is unlikely to be genotoxic and that it has a similar toxicity profile as glyphosate. The majority of the experts agreed with the RMS' proposal to apply glyphosate's reference values to this metabolite.

Subject	Conclusions Pesticide Peer Review Meeting
metabolites could also be discussed depending on the outcome of the residues discussion: - general toxicity and genotoxicity data: AMPA, N-acetyl glyphosate, N-acetyl AMPA. - Genotoxicity data for: N-methyl AMPA, N-glyceryl AMPA, N-malonyl AMPA.	**N-methyl AMPA (M03)** The experts unanimously concluded that N-methyl AMPA is unlikely to be genotoxic. **Open point:** RMS to include the negative Ames test present in the confidential RAR also in the non-confidential RAR after asking for and getting the permission from the applicants. **N-acetyl glyphosate (M04)** The experts unanimously concluded that the genotoxicity of N-acetyl glyphosate was insufficiently investigated as far as aneugenicity is concerned (data gap), whereas general toxicity was sufficiently investigated. The data gap for aneugenicity is not critical because it involves a threshold mechanism. The metabolite does not appear to be of greater toxicity than glyphosate. The majority of the experts agreed with the RMS' proposal to apply glyphosate's reference values to this metabolite. **N-acetyl AMPA (M05)** The experts unanimously concluded that N-acetyl AMPA is unlikely to be genotoxic and that it has a similar toxicity profile as glyphosate. The majority of the experts agreed with the RMS' proposal to apply glyphosate's reference values to this metabolite. **N-glyceryl AMPA (M06)** The experts unanimously concluded that the available quantitative structure–activity relationship (QSAR) analysis does not raise concern for genotoxicity. Nevertheless, the QSAR analysis is not considered sufficiently reliable for the endpoints "clastogenicity/aneugenicity" and the experts agreed that an *in vitro* micronucleus (MN) test will be needed to address the metabolite's clastogenic/aneugenic potential (data gap). **N-malonyl AMPA (M07)** The experts unanimously concluded that the available QSAR analysis does not raise concern for genotoxicity. Nevertheless, the QSAR analysis is not considered sufficiently reliable for the endpoints "clastogenicity/aneugenicity" and the experts agreed that an *in vitro*

Subject	Conclusions Pesticide Peer Review Meeting
	MN test will be needed to address the metabolite's clastogenic/aneugenic potential (data gap). **Methylphosphonic acid (M08)** The experts unanimously concluded that the available QSAR analysis does not raise concern for genotoxicity. Nevertheless, the QSAR analysis is not considered sufficiently reliable for the endpoints "clastogenicity/aneugenicity" and the experts agreed that an *in vitro* MN test will be needed to address the metabolite's clastogenic/ aneugenic potential (data gap). **N-methyl glyphosate (M09)** The experts unanimously concluded that N-methyl glyphosate is unlikely to be genotoxic.
Experts' consultation 2.32 MS experts to discuss in an experts' meeting the case reports/literature studies and epidemiological data dealing with possible relationship between exposure to glyphosate and respiratory health issues. Classification as respiratory irritant of glyphosate is under the remit of ECHA, the applicants should refer to that process too.	Overall, there are no concerns regarding respiratory health effects (i.e., irritation and sensitisation) and glyphosate exposure. This is in line with the ECHA RAC assessment.
Experts' consultation 2.33 MS experts to discuss in an experts' meeting biomonitoring data and their relevance in relation to the reference values, ADME (adsorption-distribution-	The estimated human exposure levels to glyphosate (dietary or para-occupational) extrapolated from human biomonitoring data do not raise a concern for adults, children and/or operators. **Open point** RMS to update in a revised RAR the calculations based on biomonitoring data, including:

Subject	Conclusions Pesticide Peer Review Meeting
metabolism-excretion) data, and non-dietary exposure estimates.	- a comparison of the 95th percentile or maximum value (depending on the data available) for urinary glyphosate concentration with the acute acceptable operator exposure level (AAOEL)/ARfD as appropriate; - consideration of an oral absorption value of 1% for the data from dietary exposure, while 20% is still applicable for occupational exposure; - calculations for combined exposure with AMPA where available. **Open point** RMS to consider the additional studies evaluated by the EFSA WG for the revised calculations in the revised RAR (identified after the public consultation period, see experts' consultation 2.37): • Kougias et al., 2021: Risk Assessment of Glyphosate Exposures from Pilot Study with Simulated Heavy Residential Consumer Application of Roundup® using a Margin of Safety (MOS) Approach. Risk Analysis, 41(9), 1693-1715; doi:10.1111/ risa.13646 • Buekers et al., 2022a: Glyphosate and AMPA in Human Urine of HBM4EU Aligned Studies: Part A Children. Toxics, 10(8), 470. https://doi.org/10.3390/toxics10080470 • Buekers et al., 2022b:Glyphosate and AMPA in Human Urine of HBM4EU-Aligned Studies: Part B Adults. Toxics, 10(10), 552. https://doi.org/10.3390/toxics10100552 • NHANES, 2022 : National Health and Nutrition Examination Survey (NHANES), 2022 (weblink) (and Ospina M. et al, 2022: Exposure to Glyphosate in the United States: Data from the 2013–2014 National Health and Nutrition Examination Survey. Environment International, 107620. https://doi.org/10.1016/j.envint.2022.107620); • Connolly et al. 2022: A Human Biomonitoring Study Assessing Glyphosate and Aminomethylphosphonic Acid (AMPA) Exposures among Farm and Non-Farm Families. Toxics, 10(11), 690. DOI: 10.3390/toxics10110690

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.34 **Derivation of the toxicological reference values (ADI, ARfD, AOEL and AAOEL) to be discussed by the experts.**	**The acceptable daily intake (ADI) is 0.5 mg/kg bw per day based on the NOAEL of 53 mg/kg bw per day from a 90-day dog study, supported by the NOAEL of 59.4 mg/kg bw per day from a 2-year rat study and covering the NOAEL of 50 mg/kg bw per day for maternal toxicity in the rabbit developmental toxicity studies (for which human relevance was considered questionable).** **The acceptable operator exposure level (AOEL) is 0.1 mg/kg bw per day, based on the same considerations as for the ADI, and applying an additional correction for the limited oral absorption of 20%.** **The acute reference dose (ARfD) is 1.5 mg/kg bw based on the overall rabbit developmental NOAEL of 150 mg/kg bw per day and applying a standard uncertainty factor of 100.** **The acute AOEL (AAOEL) is 0.3 mg/kg bw based on the same point of departure as for setting the ARfD, and applying a standard uncertainty factor of 100 and a correction for the limited oral absorption of 20%.** **Open point** **RMS to clarify the NOAEL (value for the most sensitive sex) for the 2-year rat study (study 5; report No 886.C.C.-R of 1996) in a revised RAR.** **Open point** **RMS to communicate with the Residue section the agreed revised ADI (ARfD has not been changed with regard to the RMS proposal in the initial RAR 2021) for consumer risk assessment.** **Open point** **RMS to provide an amendment of the Section 2.6.10 of the RAR Vol. 1 to reflect the agreed toxicological reference values and related results of non-dietary exposure estimates.**
Experts' consultation 2.35	**Based on the *in vitro* dermal absorption study with human skin, the agreed dermal absorption values are**

Subject	Conclusions Pesticide Peer Review Meeting
Experts to discuss the dermal absorption values and the non-dietary exposure estimates for the representative uses of glyphosate.	- for the concentrate (360 g/L): 0.096% - for the dilution 1 (28.8 g/L): 0.23% - for the dilution 2 (2.4 g/L): 0.68% For the non-dietary exposure estimates, - for the workers re-entering the vegetable crops treated for cereal volunteers, the task of "inspection" is considered appropriate; - for the workers re-entering orchards and vineyards (for an exposure duration of 8h), the task of "inspection" is considered appropriate as well; - for the bystanders and residents' exposure estimates for the uses in orchards and vineyards, the scenario for cereals is applicable to provide appropriate spray drift values; - for the workers re-entering the vegetables after inter row application, the exposure estimates for the task "reaching, picking" are considered covered by the other uses on vegetables (with a maximum application rate of 2.16 kg as/ha); - for the use on railway tracks, it can be considered that there is no re-entry of workers; - for the uses on invasive species, the dermal absorption value of 0.23% can be used for the dilution in 5L water/ha. **Open point** RMS to provide the updated BfR template with the revised RAR, excluding the outliers for the *in vitro* dermal absorption study of glyphosate through human epidermis (Report No. JV2084-REG). **Open point** RMS to provide revised non-dietary exposure estimates (including for bystander children) for all representative uses with the agreed AOEL/ AAOEL, agreed dermal absorption values and agreed input parameters to be used in the EFSA calculator. RMS to report consistent numbers of the uses for clear reference to the GAP table. RMS to provide an overview table showing how scenarios can be grouped differently for all categories (Operators, Workers, Residents, Bystanders) and provide revised exposure estimates to demonstrate transparently which ones are the worst-case scenarios.

Subject	Conclusions Pesticide Peer Review Meeting
New experts' consultation point 2.36 proposed by EFSA for completeness of discussion (October 2022): **Experts to discuss the relevance of the identified impurities and the toxicological profile of the co-formulants.**	**Impurities:** **Four relevant impurities were identified in the reference specification.** **A data gap was identified for another impurity (of unclear toxicological relevance) that showed a potential for clastogenicity in an *in vitro* chromosome aberration study that was not followed up *in vivo*. This is a concern for the sources that contain this impurity in their reference specification.** **Open point for EFSA to identify in its conclusion to which sources this data gap is applicable.** **Co-formulants:** **All co-formulants have been discussed. All the MSs agreed that the available toxicological information is enough to conclude on their safety.** **However, EFSA noted that for one of them no repeated-dose toxicity data (e.g., over short and long-term) are available.** **Post-meeting note:** **EFSA is of the opinion that a data gap needs to be set to address potential issues upon repeated exposure.** **Open point** **RMS to integrate substance identification, content in the formulation, toxicological and ecotoxicological information on the co-formulants in the revised RAR.** **Post-meeting note:** **Open point** **The RMS is kindly requested to clarify the meaning of the function 'active' in the table on the composition on page 41 of Volume 4 (not for applicants). This is to avoid confusion with the function attributed to co-formulants as listed in Regulation (EU) 284/2013 (pages 11 and 12) and the function of glyphosate, as the only active substance in the formulation.**

Subject	Conclusions Pesticide Peer Review Meeting
New experts' consultation point 2.37 proposed by EFSA for completeness of discussion (October 2022): **Experts to consider some potentially relevant newly available publications arisen after the public consultation/reporting table stage.** **EFSA identified a number of publications that might be considered potentially relevant and therefore it was agreed to share these selected studies with MSs to allow a peer review and further consideration in the expert meetings.** **In particular, MS experts are asked to share their views whether these potentially relevant articles might be considered more critical or may alter the weight of evidence in the current assessment and to determine if any eventual follow up would be needed.**	**Formally, in line with the legislation, there is no legal obligation to consider newly available data submitted outside of the dedicated public and targeted consultations or after the deadline of the window for providing the additional information within the clock stop period, unless they constitute adverse data (cf Article 56 of Regulation (EC) No 1107/2009 regarding information on potentially harmful or unacceptable effects).** **For this reason, although a systematic review of the literature has not been carried out by EFSA or the RMS, EFSA has identified newly available papers on glyphosate even outside of the legal requirements and collected a list of studies as a result.** **Open point** **New studies identified after the public consultation on glyphosate to be considered for their potential relevance and impact on the overall risk assessment. See specific open points at expert consultation points 2.17, 2.19, 2.27, 2.30, 2.33.** **Additionally, the following studies should be considered further in a revised RAR:** - **Gerona et al., 2022: Glyphosate exposure in early pregnancy and reduced fetal growth: a prospective observational study of high-risk pregnancies. Environmental Health, 21(1), 1-12 doi: 10.1186/s12940-022-00906-3** - **Bai et al., 2022: Perinatal exposure to glyphosate-based herbicides impairs progeny health and placental angiogenesis by disturbing mitochondrial function. Environment International, 170, 107579 https://doi.org/10.1016/j.envint.2022.107579.**
Expert consultation points identified following comments by public	
Experts' consultation 2.1 identified following comments by public: **Experts to discuss the overall weight of evidence for genotoxicity on glyphosate**	**Glyphosate is unlikely to be genotoxic or mutagenic based on a weight of evidence approach.** **The formulation for the representative uses is unlikely to be genotoxic or mutagenic based on a weight of evidence approach.**

Subject	Conclusions Pesticide Peer Review Meeting
once the data requirements set have been addressed and discussed, and specific experts' consultations on specific endpoints (e.g. clastogenicity) and studies (e.g. Ames test) are fulfilled also taking into account the outcome of the ECHA RAC meeting and their opinion on classification.	
Experts' consultation 2.2 identified following comments by public: Experts to discuss the weight of evidence for gene mutation for glyphosate.	The following agreement was reached on acceptability for the following studies: • Report no. RL3393/2007-2.0AM-B (2007), CA 5.4.1/012 in RAR B.6.4.1.12. supportive based on relevance and reliability criteria: less relevant and reliable with restrictions. • Report no. IET 94-0142 (1995), CA 5.4.1/015 in RAR B.6.4.1.15. acceptable based on relevance and reliability criteria: relevant and reliable with restrictions. • Report no. 887-MUT.AMES (1993), CA 5.4.1/018 in RAR B.6.4.1.18. supportive based on relevance and reliability criteria: less relevant, reliable with restrictions. The following agreement was reached on the weight of evidence for gene mutation: Glyphosate does not have the potential to induce gene mutations based on a weight of evidence approach. The formulation for the representative uses does not have the potential to induce gene mutations based on a weight of evidence approach.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.3 identified following comments by public: **Experts to discuss the weight of evidence for clastogenicity and aneugenicity for glyphosate.**	**The following agreement was reached on acceptability for the following studies:** • **Report No. CTL/P/6050, CA 5.4.1/025 in RAR B.6.4.1.27 supportive based on relevance and reliability criteria: less relevant, reliable with restrictions.** • **Report No. 434/015, CA 5.4.1/026 in RAR B.6.4.1.28 supportive based on relevance and reliability criteria: less relevant, reliable with restrictions.** • **Report No. IET 94-0143, CA 5.4.1/027 in RAR B.6.4.1.29 acceptable based on relevance and reliability criteria: relevant and reliable with restrictions.** • **Report No. 141918, CA 5.4.1/028 in RAR B.6.4.1.30 Supportive based on relevance and reliability criteria: less relevant, reliable with restrictions.** • **Roustan, A. et al. 2014[9], RAR B.6.4.4.11 Not acceptable based on relevance and reliability criteria: less relevant, not reliable (lack of purity).** • **Report No. 830083, CA 5.4.2/016 in RAR B.6.4.2.17 Supplementary based on relevance and reliability criteria: less relevant, reliable with restrictions.** • **Report No. 300/3, CA 5.4.2/011 in RAR B.6.4.2.11 Not acceptable based on relevance and reliability criteria: less relevant, not reliable (lack of purity).** • **Report No. CTL/P/4954, CA 5.4.2/009 in RAR B.6.4.2.9 Acceptable based on relevance and reliability criteria: relevant and reliable with restrictions.** • **Report No. RF-G12.79/99, CA 5.4.2/008 in RAR B.6.4.2.8**

[9] Roustan, A., Aye, M., De Meo, M., & Di Giorgio, C. (2014). Genotoxicity of mixtures of glyphosate and atrazine and their environmental transformation products before and after photoactivation. Chemosphere, 108, 93-100.

Subject	Conclusions Pesticide Peer Review Meeting
	Supplementary based on relevance and reliability criteria: less relevant and reliable with restrictions. • Report No. 889-MUT.MN, CA 5.4.2/010 in RAR B.6.4.2.10 Acceptable based on relevance and reliability criteria: relevant and reliable with restrictions. • Report No.2060/014, CA 5.4.2/007 in RAR B.6.4.2.7 Supplementary based on relevance and reliability criteria: less relevant and reliable with restrictions. • Mañas, F. et al. 2009[10] in RAR B.6.4.4.35 *In vivo* micronucleus (MN) part, supplementary based on relevance and reliability criteria: less relevant and reliable with restrictions. • Ilyushina, N. et al. 2018b[11], CA 5.4/005 in RAR B.6.4.4.5 Not acceptable based on relevance and reliability criteria: relevant, reliability not assignable. • Paz-y-Mino et al., 2011[12] in RAR B.6.4.4.40. Not acceptable based on relevance and reliability criteria: less relevant, reliability not assignable. • Bolognesi et al., 2009[13] in RAR B.6.4.41. Supplementary based on relevance and reliability criteria: less relevant/reliable with several restrictions. Evidence of bone marrow exposure for all *in vivo* MN studies:

[10] Mañas, F., Peralta, L., Raviolo, J., Ovando, H. G., Weyers, A., Ugnia, L., ... & Gorla, N. (2009). Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests. Environmental toxicology and pharmacology, 28(1), 37-41.
[11] Ilyushina, N. A., Averianova, N., Masaltsev, G., & Revazova, Y. U. (2018). Comparative investigation of genotoxic activity of glyphosate technical products in the micronucleus test in vivo. Toksikologicheskiy vestnik, 151(4), 24-8.
[12] Paz-y-Miño, C., Muñoz, M. J., Maldonado, A., Valladares, C., Cumbal, N., Herrera, C., ... & López-Cortés, A. (2011). Baseline determination in social, health, and genetic areas in communities affected by glyphosate aerial spraying on the northeastern Ecuadorian border.
[13] Bolognesi, C., Carrasquilla, G., Volpi, S., Solomon, K. R., & Marshall, E. J. P. (2009). Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: association to occupational exposure to glyphosate. Journal of Toxicology and Environmental Health, Part A, 72(15-16), 986-997.

Subject	Conclusions Pesticide Peer Review Meeting
	It is concluded that glyphosate reaches the bone marrow in the available *in vivo* MN tests based on sufficient evidence. The following agreement was reached on the weight of evidence for chromosome aberration (clastogenicity/aneugenicity): Glyphosate is unlikely to be clastogenic or aneugenic based on a weight of evidence approach. The formulation for the representative uses is unlikely to be clastogenic or aneugenic based on a weight of evidence approach. **Open point** RMS to check the revised RAR regarding the cycle time as it seems to be a typo for the study CA 5.4.1/0025 (1998, Report No. CTL/P/6050) in RAR B.6.4.1.27. **Open point** RMS to assess the method of analysis used in the plasma analysis in the study CA 5.4.2/015 (Report No. 14613.402.078.14) in RAR B.6.4.2.15.
Experts' consultation 2.4 identified following comments by public: Experts to discuss the weight of evidence for DNA damage for glyphosate.	The following agreement was reached on acceptability for the following studies: • Mañas, T et al. 2013[14], CA 5.4/012 in RAR B.6.4.4.12 Supplementary based on the following relevance and reliability criteria: less relevant and reliable with restrictions. • Milic, M. et al. 2018[15], CA 5.3.1/010 in RAR B.6.4.4.14 Not acceptable based on the following relevance and reliability criteria: less relevant and not reliable.

[14] Mañas, Fernando Javier; Peralta, Laura; Ugnia, Laura; Weyers, Alicia; García Ovando, Hugo; et al.; 2013. Oxidative stress and comet assay in tissues of mice administered glyphosate and ampa in drinking water for 14 days; Sociedad Argentina de Genética; Journal of basic and applied genetics; 24; 2; 12-2013; 67-75

[15] Milić, M., Žunec, S., Micek, V., Kašuba, V., Mikolić, A., Tariba Lovaković, B., ... & Želježić, D. (2018). Oksidacijski stres, aktivnost kolinesteraza i primarna oštećenja u jetri, krvi i plazmi Wistar štakora nakon 28-dnevnog izlaganja glifosatu. Arhiv za higijenu rada i toksikologiju, 69(2), 154-168.

Subject	Conclusions Pesticide Peer Review Meeting
	• Paz-y-Mino et al., 2007[16], in RAR B.6.4.4.39 (discussed under experts' consultation 2.3. public). Not acceptable based on the following relevance and reliability criteria: less relevant, not reliable. • Koureas et al., 2014[17] in B.6.4.4.42 (discussed under experts' consultation 2.3. public). Supplementary based on the following relevance and reliability criteria: less relevant, reliable with restrictions. The following agreement was reached on the weight of evidence for DNA damage: Glyphosate may have the potential to induce DNA damage. The evidence is weak. Open point RMS to further clarify the information available on the toxicity of mice in other toxicity studies in the dossier to complement the assessment of Mañas, T et al. 2013, CA 5.4/012 in RAR B.6.4.4.12.
Experts' consultation 2.5 identified following comments by public: MSs experts to discuss the statistical analysis approach to be taken into account in carcinogenicity studies. MSs experts to discuss the use of HCD in the long- term/ carcinogenicity studies. MSs experts to discuss the appropriateness of the high	The methodology used by the RMS in the weight of evidence (WoE) assessment of the carcinogenic potential of glyphosate was agreed by all experts. Based on all the available evidence, the experts agreed that glyphosate is not considered carcinogenic in rats up to the highest dose level tested of 1214 mg/kg bw per day in males and 1498 mg/kg bw per day in females. The experts agreed that in the mouse studies no carcinogenic effects were seen up to 988 mg/kg bw per day in males and 1081 mg/kg bw per day in females. Open point

[16] Paz-y-Miño, C., Sánchez, M. E., Arévalo, M., Muñoz, M. J., Witte, T., De-la-Carrera, G. O., & Leone, P. E. (2007). Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate. Genetics and Molecular Biology, 30, 456-460.
[17] Koureas, M., Tsezou, A., Tsakalof, A., Orfanidou, T., & Hadjichristodoulou, C. (2014). Increased levels of oxidative DNA damage in pesticide sprayers in Thessaly Region (Greece). Implications of pesticide exposure. Science of the Total Environment, 496, 358-364.

Subject	Conclusions Pesticide Peer Review Meeting
doses used in the long- term/ carcinogenicity studies. MSs experts to discuss the relevance of the malignant lymphomas observed in male mice. MSs experts to discuss the relevance of the kidney tumours observed in male mice. MSs experts to discuss the relevance of the hemangiosarcomas observed in male and female mice. MSs experts to discuss the relevance of the skin keratoacanthomas observed in male mice. MSs experts to discuss the relevance of the skin basal cell tumours observed in male mice. MSs experts to discuss the relevance of the hepatocellular adenomas observed in male mice.	RMS to include the missing findings, WoE assessment and conclusion on the toxicological relevance of haemangiomas observed in female mice in a revised RAR. **Open point** RMS to revise the List of Endpoints (LoEP) regarding the carcinogenic potential of glyphosate in rats and mice.
Experts' consultation 2.6 identified following comments by public: MSs experts to discuss the outcome of the 2-year rat study 1 (Report No. 2060-0012) in an experts' meeting.	The NOAEL of the 2-year rat study 1 (Report No. 2060-0012) is 285.2 mg/kg bw per day, based on the increase in alkaline phosphatase, adipose infiltration of the bone marrow and kidney findings which are of equivocal relevance in both sexes, and the skin effects including areas of necrosis/giant cell reaction to keratin and keratoacanthoma observed in high dose males. **Open point** RMS to provide the incidences of adrenal adenomas, mammary gland adenocarcinomas, and combined adenocarcinomas and adenomas

Subject	Conclusions Pesticide Peer Review Meeting
	(which are reported in Portier, 2020[18]), and respective assessment in a revised RAR.
Experts' consultation 2.7 identified following comments by public: MS experts to discuss in an experts' meeting the epidemiological data dealing with possible relationship between exposure to glyphosate and reproductive toxicity, also taking into account the outcome of the ECHA RAC meeting and their opinion on classification.	No conclusion can be drawn on any potential causal association between glyphosate exposure and reproductive endpoints on the basis of the available epidemiological studies. Open point RMS to update the RAR by including the agreement of the meeting.
Experts' consultation 2.8 identified following comments by public: MS experts to discuss the possible relationship between exposure to glyphosate and non-Hodgkin's lymphoma in an experts' meeting by taking into consideration all the available literature and epidemiological data.	See expert's consultation 2.19

[18] Portier, C. J. (2020). A comprehensive analysis of the animal carcinogenicity data for glyphosate from chronic exposure rodent carcinogenicity studies. Environmental Health, 19(1), 1-17.

REPORT OF PESTICIDE PEER REVIEW TC 89

ZETA-CYPERMETHRIN – MRL Art. 12 **Evaluator Member State: AT**

2. Mammalian toxicity

Date: 8 September 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
National Institute of Public Health	CZ
Federal Institute for Risk Assessment (BfR)	DE
University of Veterinary Medicine and Pharmacy in Kosice	SK

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 MSs experts to discuss the similarity between cypermethrin and zeta-cypermethrin toxicokinetic properties and the need to provide zeta-cypermethrin ADME specific data (repeated dosing, distribution in tissues and testing of higher dose level were not provided for zeta-cypermethrin) in an experts' meeting.	**Addressed:** Toxicokinetic and physico-chemical parameters investigated with both cypermethrin and zeta-cypermethrin are comparable (oral absorption, excretion routes, metabolism). Missing information for zeta-cypermethrin (upon repeated or higher dose testing and distribution in organs and tissues) can be bridged between the two active substances.
Experts' consultation 2.2 MSs experts to discuss which metabolites should be considered major metabolites in rat (or other animal species) in an experts' meeting.	**Addressed:** Metabolites 4'-OH-phenoxybenzoic acid sulphate (M1), trans-DCVA-Glucuronide (M6) and trans-DCVA (M8) are major metabolites in rats. *In vitro* comparative metabolism study does not allow to conclude on the amount of each metabolites expected to be present *in vivo*.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.3 MSs experts to discuss the genotoxic potential of zeta-cypermethrin in an experts' meeting.	Addressed: Zeta-cypermethrin is unlikely to be genotoxic. This conclusion is partly bridged from cypermethrin (with regards to its aneugenic potential) and therefore the data gap set during the cypermethrin review is applicable to zeta-cypermethrin, this data gap does not impact on the derivation of the ADI and ARfD. Data gap: Further investigations of the relevance of micronuclei formation in blood (Vardavas *et al.*, 2016[3] with cypermethrin, Belgium, 2018[4]) and its possible link (causal or not) with inflammatory events needs to be provided - as was requested for cypermethrin (EFSA, 2018[5]).
Experts' consultation 2.4 MSs experts to discuss/agree on the data gap for the assessment of the ED potential of zeta-cypermethrin for human health in an experts' meeting.	Data gap: Insufficient data are available on zeta-cypermethrin to conduct an ED assessment. ED properties of zeta-cypermethrin can be bridged from cypermethrin. During the peer review of cypermethrin (EFSA, 2018), for which ED activity was demonstrated, a data gap for ED adversity was set. ED data conducted for cypermethrin were neither identified as the most critical studies nor led the ED assessment to an additional uncertainty factor for TRV setting of cypermethrin. Therefore, the impact of further ED assessment is considered low also regarding zeta-cypermethrin for setting toxicological reference values.
Experts' consultation 2.5 MSs experts to discuss the maternal NOAEL of the developmental toxicity study in rats (study 1) in an experts' meeting.	Addressed: In the developmental toxicity study in rats, the maternal NOAEL is 12.5 mg/kg bw per day, based on clinical signs of toxicity and transient effects on body weight gain and food consumption occurring at 25 mg/kg bw per day. The developmental toxicity NOAEL is 35 mg/kg bw per day, the highest dose tested, in the absence of developmental effects.

[3] Vardavas AI, Stivaktakis PD, Tzatzarakis MN, Fragkiadaki P, Vasilaki F, Tzardi M, Datseri G, Tsiaoussis J, Alegakis AK, Tsitsimpikou C, Rakitskii VN, Carvalho F, Tsatsakis AM. Long-term exposure to cypermethrin and piperonyl butoxide cause liver and kidney inflammation and induce genotoxicity in New Zealand white male rabbits. Food Chem Toxicol. 2016 Aug;94:250-9. doi: 10.1016/j.fct.2016.06.016. Epub 2016 Jun 16. PMID: 27321377.
[4] Belgium, 2018. Revised Renewal Assessment Report (RAR) on cypermethrin prepared by the rapporteur Member State Belgium in the framework of Regulation (EC) No 1107/2009, March 2018.
[5] EFSA, 2018. Conclusion on the peer review of the pesticide risk assessment of the activesubstance cypermethrin. EFSA Journal 2018;16(8):5402, 28 pp.https://doi.org/10.2903/j.efsa.2018.5402

Subject	Conclusions Pesticide Peer Review Meeting
	Open point: **The EMS is kindly requested to revise the C2 document, developmental toxicity in rats (study 1), Table C.2.6.1.2-3 on maternal body weight and Table C.2.6.1.2-4 on food consumption data according to the data presented during the meeting.**
Experts' consultation 2.6 **MSs experts to discuss the outcome of the acute neurotoxicity study in rats and classification proposal in an experts' meeting.**	**Addressed:** **In the acute neurotoxicity study in rats, the NOAEL is 10 mg/kg bw, based on clinical signs and functional observational battery (FOB) effects observed at 50 mg/kg bw.** **Regarding classification, it is noted that data on zeta-cypermethrin show higher acute toxicity [triggering for Acute Tox 3 (H301)] than for cypermethrin [classified as Acute Tox 4 (H302)].** **It is also noted that STOT-RE 2 (nervous system) may also be applicable to zeta-cypermethrin considering the bridging of the dog data with cypermethrin (no dog studies are available for zeta-cypermethrin); the same STOT-RE 2 classification may be considered appropriate applying the increased relative potency factor (2.5) for zeta-cypermethrin compared to cypermethrin.**
Experts' consultation 2.7 **MSs experts to discuss the outcome of the developmental neurotoxicity (DNT) study in rats (study 1, dose-range finding study) in an experts' meeting.**	**Addressed:** **No firm conclusion could be reached on the NOAEL of the preliminary DNT study since the motor activity findings on PND21 noted at all dose levels was non-statistically significant and with large variability, considering also information on concurrent controls and historical control data (HCD). It was not possible to confirm a treatment relationship of these findings.** **In the main DNT study, the offspring NOAEL of 0.15 mg/kg bw per day, based on decreased hindlimb grip strength in females at PND 60 and decreased motor activity in females on PND 17 at 125 ppm, i.e. 0.37 mg/kg bw per day. Offspring's exposure levels were calculated from the lactational transfer of 2.1% of the maternal dosing of 8.7 (NOAEL) and 21.4 (LOAEL) mg/kg bw per day during lactation and correction for the low purity of the tested material of 81.8%.**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.8 MSs experts to discuss the bridging between cypermethrin and zeta-cypermethrin toxicological properties and the setting of the ADI and ARfD for zeta-cypermethrin in an experts meeting.	Addressed: The ADI is 0.0015 mg/kg bw per day based on the offspring NOAEL of 0.15 mg/kg bw per day for decreased hindlimb grip strength in females at PND60 in a DNT study in rats with zeta-cypermethrin and applying an UF of 100. The ARfD is 0.0015 mg/kg bw based on the same NOAEL used to derive the ADI and applying an UF of 100.

REPORT OF PESTICIDE PEER REVIEW TC 89

TRICYCLAZOLE –ART.10 **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 8 September 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	*AT*
Central Institute for Supervising and Testing in Agriculture	CZ
National Institute of Public Health	CZ
Federal Institute for Risk Assessment (BfR)	DE
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
ASST Fatebenefratelli Sacco	IT
University of Veterinary Medicine and Pharmacy in Kosice	SK

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the NOAEL setting in the new 2-year rat study, the carcinogenic potential of tricyclazole, and the potential impact of the new 2-year rat study on the setting of the ADI.**	**New 2-year rat study (2020):** **The agreed non-neoplastic NOAEL is set at 126 ppm (approximately 5.90 mg/kg/day in males and 7.06 mg/kg/day in females) based on reduction of body weight gain observed in males and females at 400 ppm (approximately 18.25 mg/kg/day in males and 22.02 mg/kg/day in females), increase liver weight at 52 week at 400 ppm and effects on clinical chemistry (cholesterol level increase at the top dose).** **The agreed neoplastic NOAEL is set at 400 ppm (18.25 and 22.02mg/kg bw per day, the highest dose level tested). No carcinogenic potential is observed in rats. This is line with previous conclusion regarding mice where no carcinogenic potential was observed.** **The results of the new year rat study (2022) did not challenge the previous setting of reference values:** **ADI and ARfD of 0.05 mg/kg bw (per day) based on the NOAEL of 5 mg/kg bw in the rat developmental study.** **Open points:** **EMS to update the evaluation report considering the discussion held during the meeting to:** **1. include the relevance assessment of the Historical Control Data.**

Subject	Conclusions Pesticide Peer Review Meeting
	2. include in the Weight of Evidence (WoE) that no evidence on lipoma in the interim group and at other doses was observed. re-elaborate in the WoE considerations on preneoplastic findings and lack of pre neoplastic and neoplastic findings in the skin advising that this evidence should not be included in the WoE.
Experts' consultation 2.2 Experts to discuss the endocrine disruption potential of tricyclazole (human health only).	**T-modality** The data set for the T-modality was considered complete. Overall, no T-mediated adverse effects were observed in a sufficiently investigated dataset. The scenario 1a is applicable. The experts concluded that tricyclazole does not meet the ED criteria for the T-modalities in humans according to point 3.6.5 of Annex II of Regulation 1107/2009. **EAS-modality** The data set for the EAS-modality was considered complete. No evidence of a pattern of EAS-mediated adversity was observed in the dataset. The scenario 1a is applicable. The experts concluded that tricyclazole does not meet the ED criteria for the EAS-modalities in humans according to point 3.6.5 of Annex II of Regulation 1107/2009.

REPORT OF PESTICIDE PEER REVIEW TC 89

BIFENTHRIN – Bifenthrin – Art.43 of REG. (EC) No 396/2005 (non-approved a.s)

Rapporteur Member State: n/a

2. Mammalian toxicity

Date: 8 September 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
National Institute of Public Health	CZ
Federal Institute for Risk Assessment (BfR)	DE
University of Veterinary Medicine and Pharmacy in Kosice	SK

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 MSs experts to discuss the genotoxicity profile of bifenthrin according to current standards in an experts' meeting.	**Data gap:** An *in vitro* study covering mammalian gene mutation according to the most updated standard quality is not available; the *in vivo* MN study is lacking proof of bone marrow exposure. Overall, the data package available is considered obsolete. It is not possible to conclude on the genotoxicity potential of bifenthrin.
Experts' consultation 2.2 MSs experts to discuss the setting of the ADI and ARfD in an experts' meeting.	Toxicological reference values cannot be established for bifenthrin since genotoxicity could not be concluded, the data available was considered insufficient when compared to current standards, and uncertainty factors could not be established on the basis of deficiencies and uncertainties identified.

REPORT OF PESTICIDE PEER REVIEW TC 89

FAT DISTILLATION RESIDUES – AIR IV **Rapporteur Member State: CZ**

2. Mammalian toxicity

Date: 8 September 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Central Institute for Supervising and Testing in Agriculture	CZ
National Institute of Public Health	CZ
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
University of Veterinary Medicine and Pharmacy in Kosice	SK

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the proposed waiver for the endocrine disruption (ED) assessment.**	**Waiver of the ED assessment in line with the EFSA/ECHA (2018) ED Guidance was considered acceptable. This was mainly based on:** **1. The natural ocurrence of the fatty acids for which the impact of pesticide active substance exposure is considered negligible.** **2. Fat distillation residues contain predominantly palmitic and stearic acid (and their esters), which are not recognized as having ED properties as approved food additives.** **3. The pesticide mode of action, repellent (paste) applied on terminal sprouts or top whirls of seedlings, is considered of no/low concern for potential endocrine disruption.** **4. Negative outcome on endocrine activity based on supporting information from ToxCast (i.e. E, A models negative for palmitic, stearic and oleic acids; no evidence for S and T activity in ToxCast assays). Oleic acid, palmitic and stearic acids were not tested for steroidogenesis but were tested for aromatase activity.** **5. Similarity to other substances (fish oil and sheep fat) for which a waiver was applied.** **6. EFSA (EFSA, 2010 doi:10.2903/j.efsa.2010.1461)[3] opinion that setting of an ADI was considered not scientifically necessary and that fatty acids are included in Annex 4 of REACH regulation indicating low concern.**

[3] EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA); Scientific Opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol. EFSA Journal 2010; 8(3):1461. [107 pp.]. doi:10.2903/j.efsa.2010.1461

REPORT OF PESTICIDE PEER REVIEW TC 89

PIRIMICARB – Art.21 mandate **Rapporteur Member State: SE**

2. Mammalian toxicity

Date: 8 September 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
National Institute of Public Health	CZ
Federal Institute for Risk Assessment (BfR)	DE
Swedish Chemicals Agency (KemI)	SE
University of Veterinary Medicine and Pharmacy in Kosice	SK

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the setting of toxicological reference values for pirimicarb (TRVs) taking into account the revised assessment of the pup sensitivity to acetylcholinesterase (AChE) inhibition and the applicability of additional uncertainty factors.	The applicant provided additional data from the open literature to address the pup sensitivity to acetylcholinesterase inhibition. These data present deficiencies (e.g. limited reporting, limited samples size, pirimicarb not included, lack of appropriate comparative cholinesterase assay) and overall were considered supplementary and insufficient to justify the removal of the extra uncertainty factors (UF) previously set during the Pesticides Peer Review Experts' meeting 190 Session 2 (28 - 31 January 2019). The toxicological reference values are confirmed to be derived with extra uncertainty factors to take into consideration the lack of specific data on the sensitivity of pups to AChE inhibition: ADI and AOEL = 0.007 mg/kg bw per day, based on the NOAEL of 3.5 mg/kg bw per day from the 1-year dog study and UF of 500. ARfD and AAOEL = 0.01 mg/kg bw, based on the NOAEL of 10 mg/kg bw from the acute neurotoxicity study and UF of 1000.
Experts' consultation 2.2 Experts to discuss the toxicity profile of the following metabolites from residues:	For the metabolite R34885, the genotoxic profile (mutagenicity endpoint) cannot be concluded due to equivocal results in the provided Ames test. No data have been made available for general toxicity assessment.

Subject	Conclusions Pesticide Peer Review Meeting
R34885 R31680 R31805 R34865 R16210 R406405	The metabolite **R31680** is considered unlikely to be genotoxic, and confirmed to be of lower general toxicity than the parent compound. For the metabolite **R31805**, the new in vitro mammalian cell gene mutation test (negative), submitted instead of an in vivo Comet assay (as agreed during the renewal peer review) was considered insufficient to conclude on the genotoxicity potential of the metabolite. Toxicological reference values were conditionally derived during the previous expert meeting (Pesticides Peer Review Experts' meeting 190 (January 2019)), since they could only be applied once any genotoxic potential will be excluded. For the metabolite **R34865**, the new in vitro mammalian cell gene mutation test (negative), submitted instead of an in vivo Comet assay (as agreed during the renewal peer review) was considered insufficient to conclude on the genotoxicity potential of the metabolite. Toxicological reference values were conditionally derived during the previous expert meeting, since they could only be applied once any genotoxic potential will be excluded. For the metabolite **R16210**, as no data have been made available, both genotoxic and general toxicity assessment cannot be concluded. For the metabolite **R406405**, as no data have been made available and applicability of the read across for genotoxicity could not be agreed, both genotoxic and general toxicity assessment cannot be concluded.
Experts' consultation 2.3 Experts to discuss the non-dietary exposure assessment for the representative uses (existing uses from current approval[3] and uses submitted for renewal) of pirimicarb	**Toxicological endpoints:** The AOEL value of 0.007 mg/kg bw per day, and AAOEL value of 0.01 mg/kg bw have been confirmed (see Experts' consultation 2.1 above). For the dermal absorption, all values proposed by the RMS were confirmed, except for the representative use in sugar beet, where the pro-rata dermal absorption value of 15% (instead of 18%) should be applied for the in-use dilution. **Refinement of DFR (dislodgeable foliar residue) value for ornamentals and DT_{50} value for all uses:** Based on two dislodgeable foliar residue trials on indoor ornamentals, a DFR value of 1.74 µg/cm²/kg a.s./ha was agreed to be used in the non-dietary exposure estimates for the representative use on ornamentals;

[3] as detailed in Appendix II of the Review Report (SANCO/10529/05 – rev. 5)

Subject	Conclusions Pesticide Peer Review Meeting
	and a DT_{50} value of 4.65 days was agreed to be used in the non-dietary exposure estimates for all representative uses. **Operator:** For the existing uses from current approval as detailed in Appendix II of the Review Report (SANCO/10529/05 – rev. 5), the use of drift reduction nozzles, gloves and respiratory protective equipment is expected to be sufficient to reduce the exposure below the (A)AOEL. For the renewal uses, the same should be applied (if necessary) and the new EFSA model[4] (2022) should also be used (for completeness reason, in addition to the model used by the applicant) for indoor uses. **Workers:** For the existing uses from current approval as detailed in Appendix II of the Review Report (SANCO/10529/05 – rev. 5), the refined DT_{50} of 4.65 days is expected to be sufficient to reduce the exposure below the AOEL. For the renewal uses, the re-entry interval necessary to obtain an exposure below the AOEL for ornamentals will be indicated in the EFSA conclusion. **Bystanders and residents:** For the existing uses from current approval as detailed in Appendix II of the Review Report (SANCO/10529/05 – rev. 5), the refined DT_{50} of 4.65 days is expected to be sufficient to reduce the exposure below the (A)AOEL. For the renewal uses, exposure estimates are expected to be below the (A)AOEL with the default DT_{50} (which should still be applied in the revised calculations). **Open point:** RMS to amend the AAOEL value in Addendum Art. 21, B.6.8.1.4, p.113 (editorial). RMS to provide revised exposure estimates with the endpoints agreed during the expert meeting, for both existing uses (from current approval) and the uses submitted for the renewal, for all categories of the exposed population (operators, workers, residents and bystanders).

[4] EFSA (European Food Safety Authority), Charistou A, Coja T, Craig P, Hamey P, Martin S, Sanvido O, Chiusolo A, Colas M and Istace F, 2022. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. (https://doi.org/10.2903/j.efsa.2022.7032)

REPORT OF PESTICIDE PEER REVIEW TC 85

DITHIANON – MRL Art.12 **Rapporteur Member State: EL**

2. Mammalian toxicity

Date: 13 July 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Institute for Risk Assessment (BfR)	DE
Benaki Phytopathological Institute	EL
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
State Plant Service under the Ministry of Agriculture	LT
National Institute of Public Health	SI
Hearing expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the toxicological profile of 1,4-napthoquinone, including:** **- the phototoxicity potential of 1,4-napthoquinone** **- the genotoxicity potential of 1,4-napthoquinone** **- the setting of toxicological reference values (ADI, ARfD), the critical endpoints and the use of additional uncertainty factors**	**Phototoxicity** **No phototoxicity concern is highlighted in the available dataset for the metabolite 1,4-napthoquinone.** **Genotoxicity** **The substance 1,4-napthoquinone is equivocal *in vitro*. Further data would be needed to conclude *in vivo*.** **Data gap:** **the complete study report of the study included in the REACH registration dossier should be requested and assessed to allow a conclusion on the mutagenicity potential of 1,4-NQ. Pending the outcome of the detailed assessment of this second Ames test reported under REACH, further data may be needed as follow up in vivo mutagenicity testing.** **Setting of toxicological reference values (ADI, ARfD):** **it is noted that the applicability of the agreed reference values is pending the data gap on mutagenicity potential.** **The Acceptable Daily Intake (ADI) is 0.002 mg/kg per day, based on the NOAEL of 2 mg/kg bw per day for haematological changes and histopathological findings in the 28-day oral toxicity study in rats and applying an uncertainty factor of 1000 to cover for the intra and inter-species differences (10x10), and to account for the duration of exposure**

Subject	Conclusions Pesticide Peer Review Meeting
	(subacute to chronic) and the incomplete data package (covering other toxicity endpoints including immunotoxicity) (x10). The Acute Reference Dose (ARfD) is **0.03 mg/kg bw**, based on a NOAEL of 8 mg/kg bw per day for decreased body weight and body weight gain, clinical signs observed in the first week of the study in the 28-day oral toxicity study in rats and applying an uncertainty factor of 300 to cover for the intra and inter-species differences (10x10) and to account for the incomplete data package (x3). The experts agreed that setting an ARfD is appropriate because of the clinical signs observed in the toxicokinetic studies after single oral dose.
Experts' consultation 2.2 Experts to discuss the toxicological profile of o-phthalic acid, including - the setting of toxicological reference values (ADI, ARfD), the critical endpoints and the use of additional uncertainty factors	<u>Setting of toxicological reference values (ADI, ARfD):</u> The Acceptable Daily Intake (ADI) is **0.113 mg/kg bw per day**, based on a NOAEL of 113 mg/kg bw per day for histopathological findings in kidney in female rats in the 28-day oral toxicity study and applying an **uncertainty factor of 1000** to cover for the intra and inter-species difference (10x10) and to account for the duration of exposure (subacute to chronic) and the incomplete data package (x10). The Acute Reference Dose (ARfD) is **1.34 mg/kg bw**, based on a NOAEL of 402 mg/kg bw per day for decrease body weight gain in the first week of the study in the 28-day oral toxicity study in rats and applying an uncertainty factor of 300 to cover for the intra and inter-species differences (10x10) and to account for the incomplete data package (x3). Considering that no clear evidence of acute effect (no clinical signs observed) was reported and taking into account the uncertainty related to the lack of measurements (lack of body weight gain and body weight values) in the first hours/days (e.g. 24-48 hrs), the experts agreed that setting an ARfD at the dose selected is appropriate and sufficiently conservative.

REPORT OF PESTICIDE PEER REVIEW TC 85

SULFUR – AIR IV **Rapporteur Member State: FR**

2. Mammalian toxicity

Date: 13 July 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
Benaki Phytopathological Institute	GR
State Plant Service under the Ministry of Agriculture	LT
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
National Institute of Public Health	SI
Hearing experts	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **The need for a subchronic toxicity study by inhalation route is proposed to be discussed by the experts.**	**No repeated-dose inhalation toxicity study with sulfur is available in rodents. Although not mandatory for non-volatile chemicals, such a study can be requested if scientifically justified. For sulfur, some adverse respiratory effects have been described in rats upon acute inhalation. Respiratory changes have also been associated to sulfur- occupational exposure in human adults, and to sulfur environmental exposure in young children, even though the latter with some uncertainties. There is concern for potential exposure by inhalation, given the application of sulfur as a very fine powder/dust. On this ground, a new short term inhalation toxicity study in rodents is requested (data gap).**
Experts' consultation 2.2 **The assessment on the ED properties to be discussed by the experts.**	**A waiver for the ED assessment based on the EFSA/ECHA guidance is considered acceptable based on the available evidence, known biological and toxicological properties of sulfur and based on exposure consideration (the impact of the sulfur as PPP on the level of the endogenous level is considered unlikely to be relevant).**

REPORT OF PESTICIDE PEER REVIEW TC 78

DIMOXYSTROBIN – AIR III **Rapporteur Member State: HU**

2. Mammalian toxicity

Date: 10 June 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Institute for Risk Assessment (BfR)	DE
National Food Chain Safety Office, Directorate of Plant Protection, Soil Conservation and Agri-Environment	HU
External expert	IT

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Pesticide Peer Review TC 78 (10 June 2022) follow up meeting of TC 70 Dimoxystrobin

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the toxicological profile of metabolites for dimoxystrobin, including the updated QSAR assessment (Follow up discussion from TC 70 (January 2022) following updated RAR with revised assessment of the additional information submitted by the applicant during the clock stop). See revised RAR and Applicants overview of findings and relevant documents submitted during the clock stop.	QSAR models for mutagenicity predictions are considered reliable. Submitted QSAR models for chromosome damage (chromosome aberration and in vivo micronucleus) are considered not sufficiently reliable due to low performance, therefore, as a unique line of evidence (in the absence of experimental data as regards clastogenicity and aneugenicity for a metabolite within a group) it is not sufficient to conclude on clastogenicity/aneugenicity endpoints. Weight of evidence approach is applied by integrating lines of evidence (experimental data/QSAR/grouping and read-across): • <u>Group 1 : cleavage products:</u> - No experimental data as regards to aneugenicity are available for the metabolites of the group. - **505M01**: available data do not raise concern for genotoxicity (bacterial mutagenicity, mammalian cell mutagenicity and clastogenicity), however aneugenicity is not sufficiently addressed. - **505M80**: conjugate of 505M01 and the same conclusions apply. • <u>Group 2: hydroxylation products:</u> - Experimental data as regards to mutagenicity, clastogenicity and aneugenicity are available for the lead compound of the group. - **505M04** (lead compound): available data do not raise concern for genotoxicity (mutagenicity, clastogenicity and aneugenicity).

Subject	Conclusions Pesticide Peer Review Meeting
	- For the other metabolites of the group 2 (505M02, 03, 06, 47, 48, 49, 50, 51, 63, 78, 79, 82, 84, 86, 91, 93, 95, 107), the same conclusions as for 505M04 apply for genotoxicity assessment. • Group 3: carboxylation products - Experimental data as regards to mutagenicity, clastogenicity and aneugenicity are available for 505M08 and M09. - 505M08 and M09: available data do not raise concern for genotoxicity (mutagenicity, clastogenicity and aneugenicity). - For the other metabolite in the group 3 (505M81), it is a major rat metabolite covered by the toxicological profile of the parent. • Group 4: products with modifications at the side chain - No experimental data as regards to mutagenicity, clastogenicity and aneugenicity are available for the metabolites of the group. - 505M88: available data do not raise concern for genotoxicity (bacterial mutagenicity), however clastogenicity and aneugenicity are not sufficiently addressed. - For the other metabolites in the group 4 (505M89 and 505M94 (conjugates of 505M88)) the same conclusions as for 505M88 apply. • Group 5: hydroxylation and carboxylation products No experimental data as regards to aneugenicity and clastogenicity are available for the metabolites of the group. - 505M33: available data do not raise concern for genotoxicity (bacterial mutagenicity), however clastogenicity and aneugenicity are not sufficiently addressed. - For the other metabolite in group 5 (505M105 (conjugate of 505M76)), the same conclusions as for 505M33 apply. For the general toxicity of dimoxystrobin metabolites, the conclusions of the first peer review experts' meeting (TC 70) are still applicable. 505M108: available data do not raise concern for mutagenicity (bacterial mutagenicity), however the clastogenicity and aneugenicity are not sufficiently addressed. The metabolite was identified in IVCM (*in vitro* comparative metabolism), however it is not a unique human metabolite. **Open points:**

Pesticide Peer Review TC 78 (10 June 2022) follow up meeting of TC 70
Dimoxystrobin

Subject	Conclusions Pesticide Peer Review Meeting
	RMS to add the results from OECD Toolbox (profiling) in the revised RAR for the metabolites. RMS to update the List of Endpoints for metabolites.

REPORT OF PESTICIDE PEER REVIEW TC 73

QUARTZ SAND – AIR IV **Rapporteur Member State: LV**

2. Mammalian toxicity

Date: 29 April 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Institute for Risk Assessment (BfR)	DE
Ministry of Environment and Food of Denmark, Environmental Protection Agency	DK
Ministerio de Sanidad	ES
Benaki Phytopathological Institute	GR
State Plant Protection Service	LV

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the hazard-related to the maximum amount of crystalline silica particles with a size equal or below 10 µm in an Experts' meeting.	In quartz sand, the fraction of crystalline silica of toxicological concern refers to the 'respirable dust' consisting of particles with a diameter ≤ 10 µm. Consequently, it was unanimously agreed to lower - from 50 to 10 µm - the size of the crystalline silica particles that can be present in quartz sand with a maximum limit of 0.1% w/w.
Experts' consultation 2.2 Considering the data requirements for active substances (e.g. genotoxicity, carcinogenicity, etc), and the limited, if any, information/data in the RAR without providing a robust scientific justification for data waiving, the need for toxicological reference values and consequent risk assessment considerations (including dermal absorption, and inhalation exposure)	The limited toxicological dataset submitted does not support the derivation of any reference value (ADI, ARfD, (A)AOEL) for quartz sand. Nonetheless, the setting of reference values is not needed, due to the specific nature of the product formulation (ready-to-use paste) and the types of application (paintbrush or glove), which prevent inhalation exposure to quartz sand. **Open point:** RMS is kindly requested to present and assess the information available on SiO_2 that address the data requirements for active substances (as per Regulation (EU) 283/2013) including the literature published in the past 10 years, and to provide a more robust and elaborated scientific justification for data waiving in a revised RAR.

Subject	Conclusions Pesticide Peer Review Meeting
should be discussed in an Experts' meeting.	
Experts' consultation 2.3 Experts to discuss the ED properties of the active substance quartz sand.	A waiver for the ED assessment of quartz sand was unanimously agreed based on: -SiO_2 low systemic bioavailability after oral, dermal or inhalation exposure; - no evidence of effects on endocrine organs in the available short- and long-term toxicity studies including reproductive toxicity studies with amorphous SiO_2 -no evidence of endocrine activity based on the available in vitro HTS data on E, T and S modalities with SiO_2 - the authorised use of amorphous SiO_2 as a food additive (no ADI available). - the estimated negligible exposure deriving from the use of the PPP as a ready-to-use paste applied by brush painting on the trees as a repellent **Open point:** RMS is kindly requested to include in a revised RAR a robust justification (based on the above reasoning) for waiving additional data and conclude on the ED assessment of quartz sand.

REPORT OF PESTICIDE PEER REVIEW TC 73

UREA – AIR IV **Rapporteur Member State: EL**

2. Mammalian toxicity

Date: 29 April 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Institute for Risk Assessment (BfR)	DE
Ministerio de Sanidad	ES
Benaki Phytopathological Institute	GR
State Plant Protection Service	LV

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the genotoxic potential of urea during the experts' meeting. In particular, the relevance of *in vitro* and *in vivo* chromosomal aberration positive results in the process of urea-induced carcinogenicity should be discussed.	Urea has been tested for genotoxic potential and has shown no mutagenic effects in bacterial systems. Considering that the exposure to urea resulting from its use as a plant protection product would be very limited (see experts' consultation 2.3), experts concluded that despite the uncertainties related to the reliability of the database, urea is unlikely to pose any concern for genotoxicity or carcinogenicity potential.
Experts' consultation 2.2 Experts to discuss the ED potential of the active substance urea during the experts' meeting.	A waiver for the ED assessment based on the EFSA/ECHA guidance is considered acceptable based on the available evidence, known biological and toxicological properties of urea and based on exposure consideration (the impact of the urea as PPP on the level of the physiological endogenous level is considered unlikely to be relevant).

Pesticide Peer Review TC73 (27 – 29 April 2022)
Urea (AIR IV)

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.3 Experts to discuss the setting of reference values for urea during the experts' meeting.	All the experts support the position of the RMS that no reference values (i.e., ADI, ARfD, AOEL, AAOEL are needed for urea). Exposure to urea resulting from its use as a plant protection product would be very limited (see open point set to confirm it). **Open point:** The RMS is kindly requested to present a semi-quantitative risk assessment in the final revised RAR to confirm that exposure to urea resulting from its use as a plant protection product would be very limited. It is suggested to use the EFSA calculator for the exposure estimates. The exposure estimates should be compared to: 1) the estimated dose of low concern of 20 mg/kg bw per day indicated in the OECD SIDS report and derived from the study by Fleishman et al., 1981 2) the physiological range of urea excreted in urine.
Experts' consultation 2.4 Experts to discuss the non-dietary exposure risk assessment for operators, workers, bystanders, and residents for ENTOMELA 75 SL and AQUEOUS UREA.	Please refer to experts' consultation point 2.3.

REPORT OF PESTICIDE PEER REVIEW TC 73

(3E) 3-DECEN-2-ONE – NAS **Rapporteur Member State: NL**

2. Mammalian toxicity

Date: 29 April 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Institute for Risk Assessment (BfR)	DE
Ministerio de Sanidad	ES
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the newly submitted data for ADME and to conclude if the data provided are enough to evaluate the toxicokinetic profile and the systemic bioavailability of (3E)-3-dece-2-one.	All the experts agreed that the submitted ADME information (i.e., new *in vivo* metabolism study in rat, public literature data, read across to 4-phenyl-3-butene-2-one,) is sufficient to conclude on the toxicokinetic profile of (3E)-3-decen-2-one. Based on the results of the newly submitted *in vivo* metabolism study in rats, the oral systemic bioavailability of (3E)-3-dece-2-one is **approximately 91%.** **Open point:** The RMS is kindly requested to better reflect in a revised DAR the origin of the different values (91% vs. 18%) reported for the oral systemic bioavailability.
Experts' consultation 2.2 Experts to discuss the genotoxic potential of (3E)-3-decen-2-one (micronucleus test) and need for further genotoxicity study (comet	In the *in vivo* mouse micronucleus assay with (3E) 3-decen-2-one, the **bone marrow exposure** has been sufficiently demonstrated based on the clinical signs observed after the test substance administration in the assay, and toxicokinetic data in rats where systemic availability of (3E) 3-decen-2-one and/or its metabolites was demonstrated and supported by the expected high systemic bioavailability following an intraperitoneal route of administration in the *in vivo* micronucleus assay.

Subject	Conclusions Pesticide Peer Review Meeting
assay) for lungs (target organ).	The reasoning to select the tissues (duodenum, liver) for the ***in vivo*** comet assay was accepted. No investigation on the lung tissue was performed based on the irritative potential of the a.s. Overall, based on the weight of the evidence, (3E)-3-decen-2-one is considered **unlikely to be genotoxic.** **Open point:** RMS is kindly requested to provide a conversion of the dose levels in the *in vivo* micronucleus study (presented as 0.2, 0.5 and 1 MTD) in mg/kg bw per day in a revised DAR.
Experts' consultation 2.3 Experts to discuss the endocrine disrupting properties for (3E)-3-decen-2-one.	Waiver of the ED assessment in line with the EFSA/ECHA GD was considered acceptable. Additional data were submitted to the RMS outside the regulatory deadline and not reviewed in the context of the peer review process. These will be considered as a data gap in the outstanding issue section of the EFSA conclusion.
Experts' consultation 2.4 The toxicological profile of metabolites (2-decanone and 2-decanol) should be discussed in an expert meeting.	The metabolites 2-decanone and 2-decanol are considered to be of lower toxicity than (3E)-3-decen-2-one. **2-decanone** The toxicological profile of 2-decanone is covered by the parent compound (i.e. unlikely to be genotoxic and reference value of the parent can apply to the metabolite if needed). **2-decanol** The toxicological profile of 2-decanol is covered by the parent compound (i.e. unlikely to be genotoxic and reference value of the parent can apply to the metabolite if needed). **3-decen-2-ol (free and conjugated)** 3-decen-2-ol (free and conjugated) was identified as a major metabolite in plants in the new plants metabolism study submitted by the applicant during the peer review and discussed for the first time in the Residues

Subject	Conclusions Pesticide Peer Review Meeting
	Peer Review Meeting TC 76 (4-5 May 2022). A data gap for genotoxicity potential and general toxicity was identified. **Open point:** The RMS is kindly requested to list the endpoints investigated by the QSAR tools used for the analyses of the metabolites 2-decanone and 2-decanol in the revised DAR.
Experts' consultation 2.5 Experts to discuss the setting of toxicological reference values for (3E)-3-decen-2-one.	The Acceptable Daily Intake (ADI) is 0.5 mg/kg bw per day based on the maternal NOAEL of 300 mg/kg bw per day from the developmental toxicity study in rats and applying an uncertainty factor of 600 (subacute to chronic exposure extrapolation). The Acute Reference Dose (ARfD) is not required. The Acceptable Operator Exposure Concentration (AOEC) is 1.39 mg/m³ based on the NOAEC of 139 µg/L from the 5-day inhalation toxicity study in rats and applying an uncertainty factor of 100. It is noted that local effects (by inhalation) should be mitigated with the use of PPE/RPE as considered appropriate at Member State level. The Acceptable Operator Exposure Level (AOEL) is 0.27 mg/kg bw per day based on the NOAEC of 139 µg/L from the 5-day inhalation toxicity study in rats and applying an uncertainty factor of 100. The Acute Acceptable Operator Exposure Level (AAOEL) is 0.27 mg/kg bw/day, same as systemic AOEL, as the effects occurred within the 5 days of exposure.
Experts' consultation 2.6 Experts to discuss the exposure data for operators, workers and bystanders.	For operators, the model RISKOFDERM is applied for dermal exposure, while RPE are recommended due to lack of data on inhalation exposure of operators. For workers during crop inspection and removal of potatoes, air monitoring and residue data provide exposure estimates below the AOEL. This is for re-entry of limited duration; therefore, protective equipment should be implemented for longer exposure durations.

Subject	Conclusions Pesticide Peer Review Meeting
	For bystanders/residents, a buffer zone of 50 m around the storage facility is required to trigger exposure estimates below the AOEL. **Open point:** **RMS is kindly requested to provide revised operator exposure estimates with the RISKOFDERM model, by using higher percentile values (75th and 95th).** **Open point:** **RMS is kindly requested to provide revised worker exposure estimates (including combined dermal/inhalation exposure considering the second air monitoring study, max values where appropriate, and excluding exposure to metabolites) in a revised DAR.** **Open point:** **RMS is kindly requested to provide revised bystander/resident exposure estimates including also the exposure values at 50m from the storage facility.**

REPORT OF PESTICIDE PEER REVIEW TC 73

HYDROLYSED PROTEINS – AIR IV **Rapporteur Member State: ES**

2. Mammalian toxicity

Date: 29 April 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Institute for Risk Assessment (BfR)	DE
Ministerio de Sanidad	ES
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
New experts' consultation proposed by the RMS in the revised RAR (March 2022): **Experts to discuss the data waiving for acute inhalation toxicity of the active substance Hydrolysed proteins.**	**Hydrolysed protein is applied as a plant protection product by spraying, that is a condition requiring acute inhalation toxicity assessment according to Regulations (EU) No 283/2013 and No 284/2013.** **A data gap for inhalation toxicity has been agreed in the absence of an appropriate study, other data or a robust justification, for waiving an inhalation toxicity study, although the physico-chemical properties of the substance do not support inhalation systemic toxicity as a likely outcome.**
Experts' consultation 2.1 **Experts to discuss the ED potential of hydrolysed proteins in an experts' meeting.**	**A waiver for the ED assessment in line with the EFSA/ECHA GD was proposed and considered acceptable. This was mainly based on the physico-chemical properties, ADME properties and consolidated uses.**

Pesticide Peer Review TC73 (27 – 29 April 2022)
Hydrolysed proteins (AIR IV)

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.2 Experts to discuss the setting of reference values for Hydrolysed protein during the experts' meeting.	Reference values are not considered needed, because of the nature of this active substance (low concern).
Experts' consultation 2.3 Experts to discuss the non-dietary exposure risk assessment for operators, bystanders, and residents. The semi quantitative non-dietary exposure for the formulation ENTOMELA 50 SL (including a second active substance, urea) should also be discussed.	The non-dietary risk assessment is not required since the derivation of reference values is not triggered.
Experts' consultation 2.4 Experts to discuss the setting of default values for dermal absorption of the formulation ENTOMELA 50 SL.	The agreed dermal absorption values for ENTOMELA 50 SL are 10% for the concentrate and 50% for the diluted product.

REPORT OF PESTICIDE PEER REVIEW TC 70

RIMSULFURON – Ad-hoc mandate genotoxic potential of metabolite IN-E9260

Rapporteur Member State: SI

2. Mammalian toxicity

Date: 19 January 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
National Institute of Public Health	CZ
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Danish Environmental Protection Agency	DK
Finnish Safety and Chemicals Agency (Tukes)	FI
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
Benaki Phytopathological Institute (BPI)	GR
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EKO-FUTURA Sp. z oo	PL
National Institute of Public Health	SI
University of Veterinary Medicine and Pharmacy	SK
Hearing Expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MS experts to discuss the possibility to set reference values for IN-E9260 on the basis of the 4-week rat study.**	**The reference values of rimsulfuron can be applied also to its metabolite IN-E9260 in consideration of the amount found in urine (>10%) when adjusted for the absorbed dose (62%).**

REPORT OF PESTICIDE PEER REVIEW TC 70

DIMOXYSTROBIN – AIR III + MRL Art 10/12 conf data **Rapporteur Member State: HU**

2. Mammalian toxicity

Date: 19 January 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
National Institute of Public Health	CZ
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Danish Environmental Protection Agency	DK
Finnish Safety and Chemicals Agency (Tukes)	FI
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
Benaki Phytopathological Institute (BPI)	GR
National Food Chain Safety Office	HU
EKO-FUTURA Sp. z oo	PL
National Institute of Public Health	SI
University of Veterinary Medicine and Pharmacy	SK
Hearing Expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the toxicokinetics (ADME) of dimoxystrobin, including oral absorption.	Based on the comparative *in vitro* metabolism study and metabolism studies in rats, no human unique metabolites are identified for dimoxystrobin. Based on biokinetic study in mice, plasma levels demonstrate bone marrow exposure after oral administration of dimoxystrobin (2000 mg/kg bw) in the micronucleus study. Oral absorption of dimoxystrobin is 46%, based on biliary excretion in the rat metabolism study. **Open point:** RMS to provide a revised final RAR with harmonised coding for the metabolites throughout the mammalian toxicity section (and also harmonised with the other sections).
Experts' consultation 2.2 Experts to discuss the short-term toxicity NOAEL for dimoxystrobin, including the NOAEL for 90-day study in dog.	• Rat short-term NOAEL of 3 mg/kg bw per day is established based on clinical chemistry changes and increased thickness of duodenal mucosa in the 3-month study. • Mouse short-term LOAEL of 206 mg/kg bw per day is established based on decreased body weight gain in females in the 3-month study. • Dog short-term NOAEL of 6.1 mg/kg per day is established, based on impaired body weight change in the 3-month study. **Open point:** RMS to provide a final revised RAR with the agreed endpoints during the experts' meeting. RMS to include in the list of endpoints (LoEP) target organ/ critical effects and the relevant short-term NOAELs for each species.

Pesticide Peer Review TC 70 (17-19 January 2022)
Dimoxystrobin

Subject	Conclusions Pesticide Peer Review Meeting
Expert's consultation 2.3 Experts to discuss the genotoxicity potential for dimoxystrobin.	Dimoxystrobin was tested negative for gene mutations in bacterial and mammalian cells, *in vitro* chromosome aberrations and *in vivo* micronucleus tests in mice bone marrow, with proof of exposure. Based on this, dimoxystrobin is unlikely to be genotoxic.
Expert's consultation 2.4 Experts to discuss the long-term toxicity and carcinogenicity NOAELs.	**For the long-term toxicity studies in rat, the overall NOAEL** for systemic toxicity is established at 2 mg/kg bw per day based on the effects on testes (increased weight and incidence in Leydig cell cystic degeneration) and duodenal finding (single incidence and changes in ALP levels). **The overall NOAEL for carcinogenicity** is established at 6.9 mg/kg bw per day based on thyroid C-cell adenomas. **In mice, the NOAEL for long-term systemic toxicity** is established at 4 mg/kg bw per day, based on reduced body weight gain, increased ovary weights, and pathological changes in the duodenum. **Mice NOAEL for carcinogenicity** is established at 20 mg/kg bw per day based on increased incidences of duodenal adenomas and adenocarcinomas, as well as focal hyperplasia. Dimoxystrobin is classified as Carc. Cat.2 – H351. **Open point:** RMS to provide a final revised RAR with the agreed endpoints and considerations from the experts' meeting. RMS to include in the LoEP the relevant long-term and carcinogenicity NOAELs for each species.
Experts' consultation 2.5 Experts to discuss reproductive-developmental toxicity for dimoxystrobin, including evidence for RMS proposal for classification H362-"May cause harm to breast-fed children". It is noted that the public consultation on the CLH dossier was planned to be launched on 1 July 2019.	**Rat two-generation reproductive toxicity study:** • **Parental NOAEL** is established at 17 mg/kg bw per day based on reduced food consumption (FC), body weight (gain) (BW(G)) and increased testes weight in F0 males. • **Reproductive toxicity NOAEL** is established at 55 mg/kg bw per day based on increased incidence of stillborn pups, decreased viability, and decreased number of implantation sites per dam; • **Offspring NOAEL** is established at 12 mg/kg bw per day based on impaired BW(G), delays in developmental landmarks, decreased thymus and spleen weights, liver discolouration, cardiomegaly (PND 21 only) and milky fluid in the abdomen. **Enhanced one generation study in rat:** • **Parental NOAEL** is established at 4 mg/kg bw per day (high dose) • **Reproductive NOAEL** is established at 4 mg/kg bw per day (high dose) • **Offspring NOAEL** is established at 1.5 mg/kg bw per day based on increased incidence of dilated renal pelvis

Subject	Conclusions Pesticide Peer Review Meeting
	Rat developmental toxicity: • **Maternal NOAEL** is established at 60 mg/kg bw per day based on reduced FC and reduced BWG • **Developmental NOAEL** is established at 60 mg/kg bw per day, based on increased incidence of dilated renal pelvis **Rabbit developmental toxicity (study 1):** • **Maternal LOAEL** is established at 25 mg/kg bw per day based on mortality, clinical signs, reduced FC and BWG • **Developmental NOAEL** is established at 50 mg/kg bw per day based on reduced gravid uterus weight, increased resorption rate and increased post-implantation loss and increased incidence of foetuses/litters with fused sternebrae **Rabbit developmental toxicity (study 2):** • **Maternal NOAEL** is established at 5 mg/kg bw per day based on mortality, clinical signs, reduced FC and BWG • **Developmental NOAEL** is established at 20 mg/kg bw per day based on reduced gravid uterus weight, increased resorption rate, increased post-implantation loss and increased number of foetuses with fused sternebrae **Overall rabbit maternal NOAEL** is established at 5 mg/kg bw per day and **developmental NOAEL** is established at 20 mg/kg bw per day (RMS disagreed on the overall developmental NOAEL in rabbits). Dimoxystrobin has harmonized classification for developmental toxicity Repr. Cat. 2, H361d. **Open point:** RMS is kindly requested to report in the final revised RAR the revised historical control data (HCD) on fused placenta in the rat developmental toxicity study.
Expert's consultation 2.6 Experts to discuss the neurotoxic potential for dimoxystrobin.	**Acute neurotoxicity study in rat:** • **NOAEL for neurotoxicity** is established at 2000 mg/kg bw • **LOAEL for systemic toxicity** is established at 500 mg/kg bw based on clinical signs. Subchronic neurotoxicity study in rat: • **NOAEL for neurotoxicity** is established at 305 mg/kg bw per day • **NOAEL for systemic toxicity** is established at 21 mg/kg bw per day based on decreased body weight gain.
Expert's consultation 2.7	**Screening study, BAS 505F- Administration in the diet and determination of serum iron after 2 and 6 days:**

Subject	Conclusions Pesticide Peer Review Meeting
Experts to discuss the information on dimoxystrobin mode of action (MoA), including the NOAEL for the screening study '*BAS 505F- Administration of serum iron after 2 and 6 days*' (KIIA 5.8.2/7, BASFDoc ID: 2002/1014245).	• NOAEL is established at 4 mg/kg bw per day based on effects on iron serum levels. Hypothetised mode of action (MoA) responsible for duodenal tumours in mice and for thickening of the duodenal mucosa in mice and rats involves the interaction of dimoxystrobin with iron uptake at the duodenal receptor level. Human relevance cannot be excluded.
Expert's consultation 2.8 Experts to discuss the endocrine disruption (ED) potential for dimoxystrobin.	**T-modality** The data set for the T-modality was considered complete. Overall, no T-mediated adverse effects were observed in a sufficient dataset. The scenario 1a is applicable. It is concluded that dimoxystrobin does not meet the ED criteria for the T-modality in humans according to point 3.6.5 of Annex II of Regulation 1107/2009. **EAS-modality** The data set for the EAS-modality was considered complete. No evidence of a pattern of EAS-mediated adversity was observed in the dataset. The scenario 1a is applicable. It is concluded that dimoxystrobin does not meet the ED criteria for the EAS-modality in humans according to point 3.6.5 of Annex II of Regulation 1107/2009.
Expert's consultation 2.9 Experts to discuss the rationale for grouping metabolites as well as the toxicity profile of metabolites 505M01, 505M02, 505M04, 505M84, 505M08, 505M09, 505M88, 505M89, 505M94, 505M33, 505M76, 505M105, 505M78 (glucoside conjugate of 505M02), 505M81 (glucoside conjugate of 505M09), 505M06, 505M79,505M80, 505M95.	**Group 1-Cleavage products** • **505M01** (groundwater metabolite): not mutagenic in bacterial and mammalian cells and not clastogenic based on *in vitro* studies, however aneugenicity is not investigated, therefore the genotoxic potential cannot be concluded. No general toxicity data are available to exclude the potential for reproductive toxicity and carcinogenicity of the parent. • **505M80** (crop metabolite): conjugate of 505M01, therefore toxicity profile is considered to be covered by 505M01. **Group 2- Hydroxylation products** • **505M04:** is not mutagenic in bacterial cells and not clastogenic/aneugenic in *in vitro* tests, therefore it can be concluded unlikely to be genotoxic. Applicability of the reference values (RVs) of the parent could be considered based on read-across. • **505M51** (livestock metabolite), **505M91** (crop metabolite): conjugates of 505M04, therefore genotoxicity potential and general toxicity profile are considered to be covered by 505M04. • **505M02** (livestock and plant metabolite): negative predictions for mutations in bacterial cells and positive predictions for chromosome

Subject	Conclusions Pesticide Peer Review Meeting
	aberration (CA). Aneugenicity is also not addressed, therefore the genotoxicity potential cannot be concluded. No data on general toxicity are available and no read-across can be applied. • **505M06, 505M50 (livestock metabolite), 505M84, 505M78 (livestock metabolite), 505M95 (crop metabolite):** conjugates of 505M02, therefore the genotoxicity potential and general toxicity profile are considered to be covered by 505M02. • **505M03:** negative predictions for mutations in bacterial cells and positive predictions for CA. Aneugenicity is also not addressed. Therefore, the genotoxicity potential cannot be concluded. Applicability of the RVs of the parent could be considered based on read-across. • **505M79** (livestock metabolite): conjugate of 505M03, therefore the genotoxicity potential and general toxicity profile are considered to be covered by 505M03. **Group 3-carboxylation products** • **505M08** (groundwater metabolite): not mutagenic in bacterial and mammalian cells. It shows equivocal results in *in vitro* CA test, however negative results were obtained in *in vivo* micronucleus (MN) test with proof of systemic exposure. Therefore, it is unlikely to be genotoxic. It is not expected to induce effects on iron serum levels and in duodenum on the basis of a 7-day study in rat, however the reproductive toxicity properties of the parent cannot be excluded, and parent's RVs cannot be applied. • **505M09** (groundwater metabolite, livestock, plant metabolite): not mutagenic in bacterial and mammalian cells. It was negative in *in vitro and in vivo* MN test with proof of systemic exposure. Therefore, it is unlikely to be genotoxic. It is not expected to induce effects on iron serum levels and in duodenum on the basis of a 7-day study in rat, however the reproductive toxicity properties of the parent cannot be excluded, and parent's RVs cannot be applied. • **505M81** (livestock metabolite): found at 10% in the rat bile data, and the toxicity profile can be considered covered by the parent. **Group 4-products with modifications at the side chain** • **505M88:** negative predictions for mutations in bacterial cells and positive predictions for CA are reported. Aneugenicity is also not investigated, therefore the genotoxic potential cannot be concluded. No data/information on general toxicity profile and no read-across can be applied. • **505M89, 505M94 (crop metabolites):** conjugates of 505M88, therefore the genotoxicity potential and general toxicity profile are considered to be covered by 505M88. **Group 5-hydroxylated and carboxylated products**

Subject	Conclusions Pesticide Peer Review Meeting
	• **505M33, 505M76** (livestock metabolite), **505M105**: negative predictions for mutations in bacterial cells and positive predictions for CA are reported. Also aneugenicity is not addressed, therefore the genotoxic potential cannot be concluded. No data/information on general toxicity profile and no read-across can be applied.
Expert's consultation 2.10 Experts to discuss the toxicological reference values (TRVs) of dimoxystrobin.	**The acceptable daily intake (ADI) is established at 0.015 mg / kg bw per day** based on the offspring NOAEL from the enhanced one-generation study, supported by the NOAEL for systemic toxicity from the long-term rat study, applying a standard uncertainty factor (UF) of 100. **The acute reference dose (ARfD) is established at 0.04 mg / kg bw** based on the overall NOAEL of 4 mg/kg bw per day (from the 7-day mechanistic study in rats and the new 7-day mechanistic study in 3 weeks old rats) and applying a standard UF of 100. **The acceptable operator exposure level (AOEL) is established at 0.007 mg / kg bw per day**, considering the same basis as the ADI, applying a standard UF of 100 and a correction for oral absorption value of 46%. **The acute AOEL (AAOEL) is established at 0.018 mg / kg bw**, on the same basis as for the ARfD, applying an UF of 100 and a correction for oral absorption value of 46%.
Expert's consultation 2.11 Experts to discuss the dermal absorption values for formulated dimoxystrobin.	Based on the *in vitro* studies using human skin, **dermal absorption values for formulated dimoxystrobin are 0.1 % and 13 %** for the concentrate and in use-dilution, respectively. Based on the *in vitro* studies using human skin, **dermal absorption values for boscalid in the representative formulation are 7 % and 5.6 %** for the concentrate and in use-dilution, respectively. **Open point:** RMS to provide revised non-dietary exposure estimates with the agreed toxicological endpoints for dimoxystrobin (and agreed dermal absorption values for boscalid). RMS to consider implications of the agreed TRVs also for the consumer risk assessment.

REPORT OF PESTICIDE PEER REVIEW TC 70

ALUMINIUM SILICATE – AIR IV **Rapporteur Member State: EL**

2. Mammalian toxicity

Date: 19 January 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
National Institute of Public Health	CZ
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Danish Environmental Protection Agency	DK
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Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
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National Food Chain Safety Office	HU
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
EKO-FUTURA Sp. z oo	PL
National Institute of Public Health	SI
University of Veterinary Medicine and Pharmacy	SK
Hearing Expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MS experts to discuss the results of the 2-week toxicity study by inhalation (mainly the bronchoalveolar lavage analysis of the supernatant and the incidence of alveolar macrophage aggregates) and the use of an additional safety factor in AOEC setting to account for the uncertainty due to deviations from OECD TG 412.**	**The NOAECs were set at 47.6 and 55.0 µg/L for Kaolin and Kaolinitic Clay, respectively, based on: mucus cell hyperplasia/metaplasia at 103 µg/L Kaolin and Kaolinitic Clay; increased adjusted lungs and bronchi weight in females treated with 103 µg/L Kaolinitic Clay; changes in BAL values, though of unclear toxicological relevance.**
Experts' consultation 2.2 **MSs experts to discuss reference values in an experts' meeting.**	**Based on the toxicity profile of the test material ADI, ARfD or AAOEL were not needed.** **The AOEC was set at 1.4 mg / m³. This was based on the NOAEC of 47.6 mg/m³ in the 2-week inhalation toxicity study, to which the following safety factors were applied:** **-UF of 25 (10 for intraspecies variability, and 2.5 for interspecies toxicodynamic variability; the factor accounting for toxicokinetic differences was considered not relevant for the local effects on the nose and lungs), and** **-a corrective factor to normalise the 6-hour inhalation exposure in the rat subacute study to 8 hours exposure for an occupational setting.**

REPORT OF PESTICIDE PEER REVIEW TC 70

LIMESTONE – NAS 1107 **Rapporteur Member State: CZ**

2. Mammalian toxicity

Date: 19 January 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
National Institute of Public Health	CZ
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Danish Environmental Protection Agency	DK
Finnish Safety and Chemicals Agency (Tukes)	FI
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
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National Food Chain Safety Office	HU
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EKO-FUTURA Sp. z oo	PL
National Institute of Public Health	SI
University of Veterinary Medicine and Pharmacy	SK
Hearing Expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 In light of the additional data requested and weight of evidence analysis, experts to discuss the need for setting toxicological reference values for limestone.	Considering the representative uses (as a paste), and the toxicological profile, no toxicological reference values for limestone are concluded to be needed. For other potential uses triggering inhalation exposure, e.g. spray, and considered for national authorisations, an AOEC (acceptable operator exposure concentration) could be based on the NOAEC of 0.212 mg/L (=212 mg/m³) identified for treatment-related changes in the lower airways (increased lung weight accompanied by slight increases in bronchoalveolar lavage-derived inflammation and cytotoxicity biomarkers) in a 90-day inhalation toxicity study with a nanoform of $CaCO_3$. Open point for the RMS: to check alignment with the list of endpoints (LoEP) of the EFSA conclusion on calcium carbonate issued in February 2021[3].

[3] https://www.efsa.europa.eu/en/efsajournal/pub/6500

REPORT OF PESTICIDE PEER REVIEW TC 68

METIRAM – AIR III **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 12 January 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
National Institute for Agricultural and food research and technology (INIA)	ES
TRAGSATEC	ES
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
University of Milan, Department of Pharmacological and Biomolecular Sciences	IT
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
National Institute of Public Health	RO
Hearing Expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.11 **Identified following consideration of comments received during the MS/APPL/public consultation on the assessments following the ED clock stop:** **There is disagreement between EFSA, the RMS and the Applicant; an expert consultation is required to conclude on the T modality according to the ED scientific criteria in Regulation (EC) 2018/605 further implemented in the EFSA/ ECHA ED Guidance.**	**There is evidence of a pattern of T mediated adversity (i.e., thyroid follicular cell hypertrophy and hyperplasia) and endocrine activity (i.e., changes in THs and TSH) observed in multiple studies and species. Mechanistic studies conducted with the endogenous metabolite ETU indicate that an endocrine mediated MOA is plausible through thyroid peroxidase (TPO) inhibition. The LOAEL for the effect thyroid follicular cell hypertrophy/hyperplasia is 9 mg/kg per day in 2-generation study (OECD TG 416) observed in parental animals (rats). No NOAEL can be derived but a BMDL was calculated corresponding to 5 mg/kg per day. It should be noted that at the lower dose of 6/8 mg/kg per day in the 3-month rat study, there is no effect in the thyroid at the histopathological assessment.** **Criteria for the T modality are met for Metiram.** **Open point: RMS to update the ED assessment in the RAR in line with the conclusion of the expert consultation.**

REPORT OF PESTICIDE PEER REVIEW TC 68

THIABENDAZOLE – confirmatory data **Rapporteur Member State: ES**

Mammalian toxicity and Ecotoxicology joint ED session

Date: 12 January 2022

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
National Institute for Agricultural and food research and technology (INIA)	ES
TRAGSATEC	ES
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
University of Milan, Department of Pharmacological and Biomolecular Sciences	IT
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
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Hearing Expert	CH

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Discussion points/Outcome

Mammalian toxicity and Ecotoxicology joint ED session

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation Mammalian toxicity **Peer Review as a follow up to the EFSA confirmatory data Technical Report (EFSA Supporting publication 2020:EN-1854):** **Experts to discuss the assessment of the endocrine disrupting (ED) properties of thiabendazole including which additional tests are needed to conclude on the ED properties for humans, if appropriate.**	**T-modality:** **There is evidence of a pattern of T-mediated adversity (i.e. follicular cell hypertrophy and hyperplasia observed in several studies in rats and in dog, follicular cell adenomas observed in the carcinogenicity study in rat) and endocrine activity (i.e. increased TSH, decreased T3, increased T4 clearance and distribution).** **There is also limited evidence of a pattern of endocrine activity, with drop in T4 and increase in TSH. The uncertainty analysis indicated that a mode of action (MoA) based on increase in T4 clearance is a possibility, but several uncertainties exist.** **The ED criteria established by Commission Regulation (EU) 2018/605 for the T-modality are met based on evidence of adverse thyroid effects in multiple studies conducted in rat and dog.** **Open point: RMS to update the assessment of the Comparative Thyroid Assay study and the ED assessment in the confirmatory data addendum in line with the conclusions of the expert consultation.** **EAS-modality:** **E-modality is sufficiently investigated, whereas A- and S-modalities were not.** **Overall, no EAS-mediated pattern of adversity was observed.** **ToxCast data showed that the compound was inactive in both E and A models. ToxCast data showed that thiabendazole was not bioactive**

Subject	Conclusions Pesticide Peer Review Meeting
	for the steroidogenesis pathway. In line with the EFSA-ECHA (2018) ED Guidance further studies are required: 1. A modality: A study in line with OECD Test Guideline (TG) 458 (Androgen Receptor-Mediated Stably Transfected Transcriptional Activation (AR STTA) assay); 2. S modality: A study in line with OECD TG 456 (H295R Steroidogenesis Assay) and a study in line with OPPTS 890.1200 (Aromatase assay) In case of OECD TG 458, 456 and OPPTS 890.1200 are negative, a study in line with OECD TG 441 (Hershberger Assay) is required. If the above studies are negative, the scenario 2a(ii) applies and the ED criteria are not met for EAS modalities. However, if these studies are positive for at least one modality, the scenario 2a(i) applies and further data will be needed to support the MoA analysis: a study in line with OECD TG 443 (with cohort 1a/1b including the mating of cohort 1b to produce the F2 generation, OECD 2018) or with OECD TG 416 (according to the latest version of 2001). Regarding the E-modality, additional information is not required because there are ToxCast ER model data with negative results.
Experts' consultation Ecotoxicology Peer Review as a follow up to the EFSA confirmatory data Technical Report (EFSA Supporting publication 2020:EN-1854): Experts to discuss the assessment of the endocrine disrupting (ED) properties of thiabendazole including which additional tests are needed to conclude on the ED properties for non-target organisms, if appropriate.	Thiabendazole is considered to meet the ED criteria for humans for the T-modality. Adversity was based on changes in thyroid histopathology. No other apical effects were observed in the mammalian data package. For non-mammalian species, no information on ED related parameters was available; therefore, adversity and endocrine activity for the EATS modalities were not sufficiently investigated. The testing strategy for thiabendazole was therefore discussed and agreed. During the commenting phase on the addendum on the confirmatory data, a proposal from the applicant to conduct a test according to OECD TG 230 including gonad histopathology instead of OECD TG 229 was proposed. Considering the similarity of the protocols and that an impact on fecundity/fertility as a parameter observed in a level 3 study would need further testing to confirm the adversity, the experts at the meeting considered that the applicant's proposal is reasonable. Further testing for thiabendazole would be needed as follows:

Subject	Conclusions Pesticide Peer Review Meeting
	- An Amphibian Metamorphosis Assay (AMA) according to OECD TG 231 (T-modality); and - A 21-d fish screening assay according to OECD TG 230 including the gonad histopathology (for EAS-modalities). If positive evidence of endocrine activity is observed in those tests, further testing would be required to investigate adversity by conducting level 4/5 studies for the pertinent modality. Open point: RMS to reflect the outcome of the discussion in a revised confirmatory data addendum.

REPORT OF PESTICIDE PEER REVIEW TC 64

CYMOXANIL – AIR IV **Rapporteur Member State: LT**

2. Mammalian toxicity

Date: 19 November 2021

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Institute for Risk Assessment (BfR)	DE
Federal Environmental Agency (UBA)	DE
National Institute for Agricultural and food research and technology (INIA)	ES
Finnish Safety and Chemicals Agency	FI
Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environment et du Travail (ANSES)	FR
International Centre for Pesticides and Health Risk Prevention (ICPS)	IT
State Plant Service under the Ministry of Agriculture	LT
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Hearing Expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the reliability of the ADME studies and the oral absorption of cymoxanil.**	**The oral absorption value for cymoxanil was calculated from a biliary excretion study in cannulated rats.** **The derived absorption value was based on sum of % urine, bile, cage wash, liver and kidney leading to 72.73% for males and 73.25% for females. Taking the mean of the results, the resulting value was 73% oral absorption (rounded). Although some uncertainties were observed on the dimorphism in excretion (observed in 1 out of 4 studies), the overall weight of the evidence indicates that dimorphism in absorption is unlikely.**
Experts' consultation 2.2 **Experts to discuss about the relevance of the phototoxicity studies for Cymoxanil.**	**Taking into account the profile of UV absorption of cymoxanil and the availability of a method to assess the phototoxicity potential of the UVB absorbers a data gap was agreed.** **Data gap** **Phototoxicity test should be conducted. Because phototoxicity cannot be excluded, photomutagenicity potential of the substance could not be ruled out.**
Experts' consultation 2.3 **Experts to discuss the adversity of the effects observed and to discuss the setting of the NOAEL and**	**<u>90-day rat study n. 1:</u>** **the overall NOAEL is 100 ppm (equivalent to 6.54 mg/kg bw per day in males) based on increased relative testes weight and correlate histopathological findings in testes observed at the next higher dose level of 750 ppm (102 mg/kg bw per day).**

Subject	Conclusions Pesticide Peer Review Meeting
LOAEL in the 90-day rat studies and in the 90-day mouse study.	<u>90-day rat study n.2:</u> the overall NOAEL is 1000 ppm (equivalent to 85.1/97.8 mg/kg bw males/females) based on reduced body weight, body weight gain and food consumption, increased total bilirubin, increased creatinine (in males), increased in relative kidney weight and relative liver weight (in males) observed at the next higher dose level of 2000 ppm (174.3/187.7 mg/kg bw males/females). <u>90-day study in mice:</u> the overall NOAEL is 450 ppm (equivalent to 84.4/97.3 mg/kg bw per day males/females) based on decreased body weight gain, increased total bilirubin (males) and total protein (females), and increased in relative liver weight (females) observed at 1350 ppm (256.6 mg/kg bw per day in males and 302.5 mg/kg bw per day in females). Open point The RMS to revise the RAR including in the definition of adversity for the 90-day rat study n.2, the statistically significant increase in total bilirubin observed in females at 2000 ppm.
Experts' consultation 2.4 In the 90-day dog study 2, experts to discuss the adversity of the effects (particularly on thymus, lymph nodes, brain and testis) observed and to discuss the setting of the NOAEL and LOAEL. For the 1-year dog study 2, experts to discuss the adversity of the effects, particularly on thymus, cataract, testis (histopathological changes in testes) and epididymis observed and to discuss the setting of the NOAEL and LOAEL. For the 1-year dog study 1, experts to discuss the adversity of the effects,	The database of dog studies includes two 90-day dog studies and two 1-year dog studies. A pattern of changes was observed when using all the studies conducted in dog, indicative of testicular toxicity. However, when mapping the histological picture of the dog at puberty, the spontaneous histological changes in the testes in adult dog and the observed histological changes in one of the two 1-year dog study, the overall weight of evidence was indicative that the testes are target organ for cymoxanil. <u>90-day dog study n. 2:</u> the overall NOAEL is 200 ppm (equivalent to 4.9 mg/kg bw per day in males) based on reduced body weight and body weight gain, reduced food consumption, clinical signs, reduced absolute and relative thymus weight and histological alterations in thymus (lymphoid atrophy) with a dose-related increase in severity observed at the next higher dose of 400 ppm (equivalent to 9.7 mg/kg bw per day in males). <u>1-year dog studies:</u> Several uncertainties exist for one of the two 1-year dog study, where testicular histopathological changes were recorded. The overall weight of evidence, when considering all the studies conducted in dog, indicates that the testes are target organ in the dog and that

Subject	Conclusions Pesticide Peer Review Meeting
particularly the testicular and the cataract findings, and to discuss the setting of the NOAEL and LOAEL. Experts to discuss the target organ classification and the STOT RE 2 proposal for classification (blood, thymus, eyes).	adverse effects are observed at the dose of 200 ppm and above. Although histological changes were also observed at lower doses (as well as in control animals), the setting of the overall dog NOAEL is 100 ppm (equivalent to 2.8 mg / kg bw per day) was considered sufficiently conservative based on the assessment of the uncertainty and the overall weight of evidence. Open point RMS to update in a revised RAR the NOAEL of the 1-year dog study n. 2 as suggested in the Pesticide Peer Review Meeting.
Experts' consultation 2.5 Experts to discuss the acceptability of the study 1 considering the deviations compared to the OECD 473 (1997, 2014 and 2016) and the interpretation of the results of the mammalian chromosome aberration study 1.	Item 2.5 was discussed together with 2.6. the reader should refer to the conclusion reported there. Please, see the following point.
Experts' consultation 2.6 Experts to discuss the bone marrow exposure and acceptability of the *in vivo* micronucleus assays and to conclude on the genotoxicity profile of cymoxanil.	All of the experts agreed that bone marrow exposure has been proved in the data package of *in vivo* micronucleus studies. As an overall conclusion on genotoxicity, based on the available data package, all experts agreed that cymoxanil is unlikely to be genotoxic *in vivo*.
Experts' consultation 2.7 For the two 2-year rat study, experts to discuss the adversity of the effects, particularly on increase in retinal atrophy in males and to discuss the setting of the NOAEL and LOAEL.	2-year rat study n. 1: NOAEL is 100 ppm (equivalent to 4.08/5.36 mg/kg bw per day males/ females) based on clinical findings decrease body weight and body weight gain, histopathological findings (i.e. elongate spermatid degeneration, increase incidence of retinal atrophy, sciatic nerve degeneration) at the next higher dose of 700 ppm (30.3/38.4 mg/kg bw per day males/ females). 2-year rat study n. 1: The NOAEL is 100 ppm (equivalent to 4.7 mg/kg bw per day in males) based on histopathological findings (i.e. lymphoid hyperplasia in gut associated lymphoid tissue in the rectum

Subject	Conclusions Pesticide Peer Review Meeting
	and lymphoid hyperplasia in the gut associated lymphoid tissue in the colon) at the next dose level of 500 ppm (23.5 mg/kg bw per day). Cymoxanil did not reveal any oncogenic potential and the NOAEL for carcinogenicity was the highest dose tested in both studies.
Experts' consultation 2.8 Experts to discuss the generational toxicity studies and the setting of parental, reproductive and offspring NOAELs. Experts should also discuss and agree on an overall NOAEL for reproductive toxicity effects.	The overall parental NOAEL is 450 ppm (equivalent to 31.6/42.8 mg/kg bw per day males/females), based on decreased body weight gain and food consumption observed at 1350 ppm (94.0/ 116.3 mg/kg bw per day males/females). The overall reproductive NOAEL is 450 ppm (equivalent to 31.6/42.8 mg/kg bw per day males/females), based on reduced mean number of corpora number of implantations lutea, reduced mean, reduced post-implantation loss, reduced mean litter size, reduced live pups born at the next higher dose of 1350 ppm (94.0/ 116.3 mg/kg bw per day males/females). The overall offspring NOAEL is 150 ppm (equivalent to 10.5 / 14.9 mg/kg bw per day males/females), based on reduced body weight of F1 pups (both sexes combined) on days 14 and 21, and reduced body weight of F2 pups (both sexes combined) on days 7, 14 and 21 observed at 450 ppm.
Experts' consultation 2.9 Expert to discuss the setting of maternal and developmental NOAELs for the developmental toxicity studies in rats and rabbits. and to discuss the overall developmental and maternal NOAELs. Specifically, it should be discussed: - For study n.2 in rats, the relevance of reduced bwg and food consumption at 60 mg/kg bw in dams and the delayed skeletal ossification observed at 30 mg/kg per day in offspring. For study n. 4 in	<u>Developmental toxicity Study n. 2 (rats).</u> The majority of the experts agreed to lower the maternal NOAEL to 30 mg/kg bw per day considering that a drop in body weight gain of 25% is of a sufficient magnitude to be considered as adverse. The developmental LOAEL is 30 mg/kg bw per day based on increased incidence of skeletal minor anomalies (dumb-bell shaped thoracic vertebra 6/13). <u>Developmental toxicity Study n. 4 (rabbits)</u>. The maternal NOAEL is 8 mg/kg bw per day based on clinical observations (anorexia, reduced faecal output) and decrease body weight gain observed at 16 mg/kg bw. The majority of experts agreed that the developmental LOAEL should be set at 8 mg/kg bw per day based on increased incidences of skeletal malformations. A NOAEL cannot be established. <u>Developmental toxicity study n. 5 (rabbits)</u> The developmental NOAEL is 8 mg/kg bw per day, based on increased incidence of external/visceral malformations observed at the next high dose of 32 mg/kg bw per day.

Subject	Conclusions Pesticide Peer Review Meeting
rabbit, the relevance of reduced bwg (> 10%) at GD 6-10 and 6-19 in dams at 16 mg/kg bw per day and the relevance of the increase incidence of skeletal malformation - For study n. 5 in rabbit the relevance of skeletal malformation (vertebra and/or rib alterations) observed in offspring at 4 mg/kg bw per day should be discussed also in relation with the new HCD provided - For study n. 6 in rabbit the relevance and adversity of foetal abnormalities observed at 15 mg/kg bw per day. The experts to discuss also if the criteria for classification according to Regulation (EC) No 1272/2008 (ECHA, 2017) may be met for reproductive toxicity and on which bases.	<u>Developmental toxicity study n. 6 (rabbits)</u> The majority of experts agreed that the NOAEL proposed by RMS should be dropped at 5 mg/kg bw per day based on renal pelvis dilatation findings observed at 15 mg/kg bw per day. The majority of the experts agreed that the overall developmental LOAEL should be based on the study n. 4 (rabbits) and set at 8 mg/kg bw per day.
Experts' consultation 2.10 Expert to discuss the ED properties of cymoxanil.	The dataset for the T modality was considered sufficiently investigated and no adversity was observed. The dataset for the AS modality was considered not sufficiently investigated. AS mediated target organ toxicity was observed in the male reproductive toxicity for which several uncertainties and inconsistencies were noted. An endocrine mediated mode of action could not be postulated on the available evidence and additional data are necessary to conclude on the AS modality. The E modality is considered sufficiently investigated. For the T modality criteria are considered not met. For the AS modality, the following studies, in agreement with the EFSA/ECHA ED guidance should be conducted: - A study in line with the OPPTS 890.1200 (Aromatase assay)

Subject	Conclusions Pesticide Peer Review Meeting
	- A study in line OECD TG 458 - A study in line OECD TG 456 - If the above studies are negative a Level 3 study in line with OECD TG 441 (Hershberger Assay) should be conducted. - If the above studies are negative, the scenario 2a(ii) applies and ED criteria are not met. If endocrine activity is observed, the scenario 2a(i) applies and further data will be needed to support the MoA analysis i.e. extended one-generation study with inclusion of the cohort 1a and 1b including the mating of cohort 1b to produce the F2 generation (OECD TG 443, Level 5) or an OECD TG 416.
Experts' consultation 2.11 Experts to discuss the toxicological data of the metabolites included in the residue definition. In particular the following metabolites and toxicological data should be discussed: for IN-JX915, IN-KQ960 (also a GW metabolite), IN-R3273 only genotoxicity and for IN-KP533, IN-U3204, IN-W3595 and AS999 both general toxicity and genotoxicity data.	IN-JX915 A data gap has been set for genotoxicity (i.e. gene mutation, chromosome aberration and aneugenicity). A comparative assessment could be done for gene mutation and chromosome aberration with IN-KQ960. IN-KP533 Based on comparative assessment with cymoxanil and experimental data (i.e. in vitro data: 2 AMES and 2 in vitro Chromosome aberration negative), the metabolite is considered unlikely to be genotoxic. The reference values of the parent compound (cymoxanil) can be applied for metabolite IN-KP533. ADI is 0.027 mg/kg bw per day; ARfD is 0.027 mg/kg bw. IN-KQ960 A data gap has been set for genotoxicity (i.e. gene mutation, chromosome aberration and aneugenicity). IN-R3273 A data gap has been set for genotoxicity (i.e. gene mutation, chromosome aberration and aneugenicity). A comparative assessment could be done for gene mutation and chromosome aberration with IN-KQ960. IN-U3204 A data gap has been set for genotoxicity (i.e. gene mutation, chromosome aberration and aneugenicity). A comparative assessment could be done for gene mutation and chromosome aberration with IN-KQ960. General toxicity cannot be concluded for the metabolite IN-U3204 due to the absence of data.

Subject	Conclusions Pesticide Peer Review Meeting
	Open point for EFSA: Pending final assessment by Residues, EFSA to consider if a data gap (i.e. repeated dose toxicity study) is needed in the conclusion to assess the general toxicity for IN-U3204. **IN-W3595** The reference values of the parent compound (cymoxanil) can be applied to metabolite IN-W3595. ADI is 0.027 mg/kg bw per day; ARfD is 0.027 mg/kg bw. **AS999/M-5** Based on comparative assessment with cymoxanil, QSAR and experimental data (i.e. Ames test negative), the metabolite is considered unlikely to be genotoxic. The reference values of the parent compound (cymoxanil) can be applied to metabolite M5 (AS999). ADI is 0.027 mg/kg bw per day; ARfD is 0.027 mg/kg bw.
Experts' consultation 2.12 Experts to discuss the setting of toxicological reference values (ADI, ARfD, AOEL and AAOEL) for cymoxanil. The outcome of neurodevelopmental toxicity NOAEL should also be discussed and could be taken into consideration for the setting of ARfD and AAOEL.	The agreed reference values are: ADI: 0.027 mg/kg bw per day based on the LOAEL of 8 mg/kg bw/day in the developmental rabbit study (with an UF of 300). AOEL: 0.02 mg/kg bw per day. Including correction for oral absorption of 73%. ARfD: 0.027 mg/kg bw per day based on the LOAEL of 8 mg/kg bw/day in the developmental rabbit study (with an UF of 300). AAOEL: 0.02 mg/kg bw. Including correction for oral absorption of 73%. **Open point** RMS is kindly requested to provide a final revised RAR including all agreed endpoints during the expert meeting.
Experts' consultation 2.13 For the representative product Cymoxanil 45WG, experts to discuss the refinement of the DFR value, the handheld application scenario and the acceptability of the studies for deriving the DT50 value	For the representative product Cymoxanil 45 WG, the refined DFR value for grapes is 3.19 µg/cm²/kg a.s./ha based on the study with the most representative formulation (WG). For tomatoes, the refined DFR is 1 µg/cm²/kg a.s./ha, while for potatoes the refined DFR is 2 µg/cm²/kg a.s./ha. All experts agreed with an overall DT_{50} of 1 day for all crops.

Subject	Conclusions Pesticide Peer Review Meeting
in grapes for residents and bystanders. For the representative product Rival duo, experts to discuss the refinement of the DFR value. For the representative product Dauphin 45, experts to discuss the refinement of the DFR value, especially the acceptability to use the DFR value derived from the grapes or the default values for the use in potatoes and tomatoes.	For the representative product Rival duo, used in potatoes, a refined DFR value of 2.82 µg/cm²/kg a.s./ha and a refined DT_{50} value of 1 day were agreed based on a DFR study with potatoes. For the representative product Dauphin 45 / FDJ03, used on grapes, a refined DFR value of 3.33 µg/cm² /kg a.s./ha and a refined DT_{50} of 1 day were agreed based on a DFR study with grapes. Open point (Cymoxanil 45WG): RMS to provide revised exposure estimates with the agreed endpoints: - oral absorption: 73% - AOEL: 0.02 mg/kg bw per day; AAOEL: 0.02 mg/kg bw - dermal absorption: 0.056% for the concentrate, 16% for the dilution in grapes, 19% for the dilution in greenhouse tomatoes, 13% for the dilution in outdoor tomatoes and potatoes. Please note that, for the use on grapes, exposure estimates for both dilutions (i.e. for both dermal absorption values 19% for 1200L water/ha, and 16% for 1000L water/ha) should be provided. - refined DFR values of 3.19 for grapes, 1 for tomatoes, 2 for potatoes (µg a.s./cm²/kg a.s./ha); and refined DT_{50} value of 1 day for all crops. - for workers re-entering grapes, as the use of gloves is not implemented in the EFSA guidance, only an extension of the re-entry interval can be considered for the revised exposure estimates (up to 28 days since this is the minimum pre-harvest interval indicated in the table of representative uses for grapes). - including the scenario of handheld application on grapes since it could be applicable at EU level. Open point (Rival Duo): RMS to provide revised exposure estimates for the use on potatoes with the agreed endpoints: - oral absorption: 73% - AOEL: 0.02 mg/kg bw per day; AAOEL: 0.02 mg/kg bw - dermal absorption: 50% for cymoxanil in the concentrate and the dilution; 10 and 50% for propamocarb in the concentrate and in the dilutions respectively. - refined DFR value of 2.82 µg/cm²/kg as/ha for potatoes, and refined DT_{50} value of 1 day. - available risk mitigation measures should be considered separately (stepwise approach) for the single exposure to cymoxanil and the combined exposure to cymoxanil and propamocarb, in order to

Subject	Conclusions Pesticide Peer Review Meeting
	demonstrate what is required to reach exposure levels below 100% of the (A)AOELs. **Open point (Dauphin 45):** RMS to provide revised exposure estimates with the agreed endpoints: - oral absorption: 73% - AOEL: 0.02 mg/kg bw per day; AAOEL: 0.02 mg/kg bw - dermal absorption: 10 and 50% for the concentrate and the dilution respectively. - refined DFR value of 3.33 µg a.s./cm²/kg a.s./ha for grapes, and refined DT_{50} value of 1 day for all crops (grapes, tomatoes, potatoes). - for workers re-entering grapes, as the use of gloves is not implemented in the EFSA guidance, only an extension of the re-entry interval can be considered for the revised exposure estimates (up to 28 days since this is the minimum pre-harvest interval indicated in the table of representative uses for grapes).
Experts' consultation 2.14 For the representative product Dauphin 45/FDJ03, experts to discuss the use of default values for the dermal absorption for the concentrate and dilution and to recalculate the exposure estimates for operators, workers, bystanders, and residents.	For the representative product Dauphin 45/FDJ03, the default dermal absorption values are applicable: 10% for the concentrate and 50% for the in-use dilution, since the tested formulation and the representative product do not meet similarity criteria according the EFSA Guidance on Dermal Absorption (EFSA, 2017). Please, refer to the Open point set under **Experts' consultation 2.13.**

REPORT OF PESTICIDE PEER REVIEW TC 64

RAPE SEED OIL – AIR IV **Rapporteur Member State: NL**

2. Mammalian toxicity

Date: 19 November 2021

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Institute for Risk Assessment (BfR)	DE
Federal Environmental Agency (UBA)	DE
National Institute for Agricultural and food research and technology (INIA)	ES
Finnish Safety and Chemicals Agency	FI
Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environment et du Travail (ANSES)	FR
International Centre for Pesticides and Health Risk Prevention (ICPS)	IT
State Plant Service under the Ministry of Agriculture	LT
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
Hearing Expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Based on the weight of evidence analysis for genotoxicity and the additional information provided, the experts to discuss the genotoxicity potential of rape seed oil including aneugenicity, clastogenicity and mutagenicity.**	**All available information on rape seed oil including its nature (food grade quality) and EFSA's assessment on similar substances was taken into account by the experts for the weight of evidence approach on genotoxicity.** **All the experts agreed with the RMS that rape seed oil is unlikely to be genotoxic.** **The experts also agreed that if the EFSA Panel on Food Additives and Flavourings (FAF) assessment on some components of grill flavour concentrate (vegetable), common to some components of rape seed oil, is finalised and raised concerns for genotoxicity, the relevance of these findings for rape seed oil as a PPP should be further considered.**
Experts' consultation 2.2 **Experts to discuss whether it is scientifically justified to waive the ED assessment.**	**Based on the accepted low toxicity of rape seed oil to mammals, the natural occurrence of the substance, the widespread traditional use as feed- and food-stuff and lack of known adverse effects all the experts agreed to waive the ED assessment.** **All experts agreed that it is highly unlikely that rape seed oil will meet the endocrine disruption criteria based on its intrinsic properties and available evidence.** **Open point: The RMS to indicate in the assessment that although rape seed oil is acting on the lipid metabolism, the overall weight of evidence indicates that this has no consequences on the thyroid hormone system.**

REPORT OF PESTICIDE PEER REVIEW TC 64

ISOFLUCYPRAM – NAS 1107/2009 **Rapporteur Member State: FR**

2. Mammalian toxicity

Date: 19 November 2021

List of participants:

Institute	Member States Country code
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Federal Institute for Risk Assessment (BfR)	DE
Federal Environmental Agency (UBA)	DE
National Institute for Agricultural and food research and technology (INIA)	ES
Finnish Safety and Chemicals Agency	FI
Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environment et du Travail (ANSES)	FR
International Centre for Pesticides and Health Risk Prevention (ICPS)	IT
State Plant Service under the Ministry of Agriculture	LT
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
Hearing Expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the value to be derived for systemic availability in expert meetings.**	**Based on ADME studies all the experts agreed with the proposed post-hepatic systemic availability of 50 % and oral absorption of >80 %.** **The experts agreed that as the liver is a target organ of isoflucypram in all repeated-dose toxicity studies the oral absorption and not the post-hepatic systemic is more suitable input parameter for the risk assessment. The experts agreed that being oral absorption higher than 80% no correction for oral absorption is needed for setting the systemic AOEL/AAOEL.**
Experts' consultation 2.2 **MSs experts to discuss the residue definition in body fluids.**	**Based on ADME and TK data the experts proposed the residue definition in body fluids as isoflucypram and the metabolites M11 and M58. It is noted that this residue definition is applicable only to plasma. Furthermore, the experts agreed not to propose a residue definition for urine due to extensive metabolism of the compound where neither parent compound nor major metabolites could be detected in significant amount.** **Open point (to be transfer to the Phys/Chem section) for EFSA: To consider whether a data gap should be set for a validated method for monitoring purposes considering the agreed residue definition for body fluids.**
Experts' consultation 2.3	**The study confirmed the extensive metabolism of the isoflucypram but was considered as supportive due to uncertainties/limitations detected.**

Subject	Conclusions Pesticide Peer Review Meeting
experts to discuss the outcome of *in vitro* comparative metabolism study	Based on the metabolization rate (% of unchanged parent) in the different species, all the experts agreed that human microsomes metabolized the compound less rapidly than other species and the metabolic profile is qualitatively similar in all species and suggest that no human-specific metabolite would appear. Data Gap: Considering the current data and the uncertainties detected from the study, it was concluded that not enough data concerning the comparative *in vitro* metabolism are available for isoflucypram.
Experts' consultation 2.4 Experts to discuss the 90-days mouse study in relation to the liver histopathological findings, i.e. multinucleated hepatocytes observed in males from the mid dose.	The experts discussed the results of the 90-day mouse study in relation to the increased incidence of multinucleated hepatocytes observed in males from the mid-dose 51 mg/kg bw per day. The effect was clearly considered treatment-related. Based on the information available a firm conclusion could not be drawn on the potential adversity of this effect. However, based on the uncertainties the effect was considered for setting the NOAEL. The experts agreed with the proposed NOAELs of 100 ppm (17 mg/kg bw per day) in males based on multinucleated hepatocytes and 300 ppm (60 mg/kg bw per day) in females based on increased liver weight and hepatocellular vacuolation.
Experts' consultation 2.5 MSs experts to discuss the 90-days and 1-year dog studies.	<u>90-days dog study:</u> The experts discussed the results of the study and agreed that adverse effects on body-weight gain at the mid or low-doses were incidental and therefore not adverse. The experts agreed with the proposed NOAEL at the mid dose of 500 ppm, equivalent to 15.9 / 16.2 mg / kg bw per day in both sexes based on decreased body weight and liver findings. <u>1-year dog study:</u> The experts discussed the results of the study and agreed that the decreased body weight gain observed at the low dose in males was incidental and therefore not adverse. The experts agreed with the proposed NOAEL at the low dose of 4.2 mg / kg bw per day in males and females based on decreased body weight and body weight gains, liver weight increases, and the liver findings observed from the mid dose.

Subject	Conclusions Pesticide Peer Review Meeting
	The experts agreed to set an overall NOAEL of 4.2 mg / kg bw per day in dogs by considering that both studies have been performed in the same laboratory and during the same time-period.
Experts' consultation 2.6 Endocrine disrupting assessment related to EATS-modalities should be discussed and agreed also in view of the new data that will be submitted by the applicant.	The dataset for the T modality was considered as sufficiently investigated with evidence of thyroid mediated adversity observed in one species. A liver mediated mode of action was postulated for which several uncertainties exist. Additional molecular initiating events leading to alternative mode of actions cannot be however excluded based on the available evidence. There is an unacceptable level of uncertainty, based on the available evidence, on the impact of the observed changes in the thyroid on the most sensitive population of concern for thyroid toxicity (dams, foetuses and new borne). The dataset for the EAS modalities was considered as sufficiently investigated with no evidence of adversity. Because of lack of data in the most sensitive population of concern, the ED assessment for the T- modality cannot be concluded. A study in line with the US EPA Comparative Thyroid Assessment Guidance for Thyroid Assays in Pregnant Animals, Foetuses and Postnatal Animals. (US EPA, Office of Pesticide Programs, Health Effects Division, Washington (DC). 12 pp. Available online: https://www.epa.gov/sites/production/files/2015-06/documents/thyroid_guidance_assay.pdf) should be conducted. Such study should be conducted following these recommendations: - the doses should be high enough to allow a proper exploration of thyroid toxicity. - a positive control should be included. - iodine content in the diet should be controlled. - the methodology for sampling and the analytical method to evaluate THs and TSH should be provided. - laboratory documentation of the method validation for the assessment of THs and THS with inclusion of the limit of determination for foetuses and pups should be provided. Alternatively, a DNT study in line with the OECD TG 426 including measurements of thyroid hormones and thyroid pathology can be conducted. For the EAS modalities, ED criteria were considered not met.
Experts' consultation 2.7 Experts to discuss the results of	All the experts agreed to consider the V79 / HPRT mammalian mutagenicity test valid despite the limitations. The study results were considered negative.

Subject	Conclusions Pesticide Peer Review Meeting
V79 / HPRT mammalian mutagenicity study to assess genotoxicity potential.	
Experts' consultation 2.8 Experts to discuss the bone marrow exposure.	Overall, most of the experts agreed with the proposal that evidence of bone marrow exposure can be considered from the clinical signs reported in most of the animals of the *in vivo* mouse micronucleus assay and from the supportive ADME data of other toxicological studies performed in mice and rats where systemic availability of isoflucypram and/or its metabolites was demonstrated. Therefore, most of the experts (only one-member state disagreed) considered that isoflucypram and its metabolites have likely reached the bone marrow in the mouse micronucleus assay and the negative results of the micronucleus assay are reliable.
Experts' consultation 2.9 Experts to discuss the dose selection of the 2-years rat study and its relevance for detecting potential carcinogenicity.	The experts agreed that the benchmark dose calculations and the physiologically-based pharmacokinetic modelling, as provided by the applicant, failed to support that the MTD was reached. The experts considered that the MTD was not reached and that higher doses should have been tested in the long-term/carcinogenicity study. The experts' conclusion was consistent with the RAC Opinion Oct 2020.
Experts' consultation 2.10 Experts to discuss the effects observed on vaginal opening in the 2-generation study and particularly, considering also the results from Uterotrophic assays, if this effect can be related to one impurity. In addition, experts to discuss the NOAEL of the study and classification for reprotoxicity (fertility).	All the experts agreed that the delay in the vaginal opening at the high dose should be considered adverse. The experts agreed with the proposed NOAELs for the 2-generation study in rats: Offspring: The NOAEL of 34.1 mg/kg bw per day was established based on the delay in vaginal opening, increased incidence of dilated renal pelvis and increased liver weight. Reproductive: The NOAEL of 34.1 mg/kg bw per day was established based on statistically significant effects delay in vaginal opening and the slight decreased gestation length in F1 females. Parental: The MTD was not reached in the study. The NOAEL of 34.1 mg/kg bw per day was established based on decreased thymus weight in males and females, liver effects in females and clinical chemistry changes consisting of increased calcium and total proteins in males.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.11 Experts to discuss and agree on the NOAEL for maternal toxicity in the rabbit developmental study.	All experts agreed that the significant decrease in the body weight gain at the beginning of the study (75%) at the mid dose and taking into account a clear dose-relationship the experts agreed with the proposed maternal NOAEL of 10 mg/kg bw per day in the rabbit developmental toxicity study.
Experts' consultation 2.12 Experts to discuss the NOAEL for the rat developmental toxicity study also considering the HCD to be provided by the applicant.	After the discussion of the data including the historical control data (HCD) all the experts agreed with the proposed NOAELs for the rat developmental toxicity study: Developmental: The NOAEL of 25 mg/kg bw per day was established based on the increased fetal and litter incidences of skeletal variations observed at 125 mg/kg bw per day. Maternal: The NOAEL of 125 mg/kg bw per day was established based on reduced body weight gain and food consumption as well as liver toxicity observed at 625 mg/kg bw per day.
Experts' consultation 2.13 Experts to discuss toxicity of metabolites.	The experts' conclusions are: M12: Based on the experimental data available M12 is not genotoxic but, as a groundwater metabolite, need to be considered that the parent active substance is classified as Repr 2 H361f (ECHA-RAC, Oct 2020) and that no data is available to demonstrate that M12 did not share the same reproductive toxicity potential. M12 is a relevant groundwater metabolite. M01 and its conjugates M18, M19 and M21: Considering the ADME/TK data and the structural similarity with the parent, the genotoxicity of M01 is covered by the data of isoflucypram. Its glycoside or glucuronide conjugates are likely to be cleaved into M01 in the gastrointestinal tract and are then covered by M01, and thus by the parent (i.e. unlikely to be genotoxic and references values of the parent can be applied, if needed). M02 and its conjugates M20 and M22: Considering the ADME/TK data and the structural similarity with the parent, the genotoxicity of M02 is covered by the data of isoflucypram. Its glycoside or glucuronide conjugates are likely to be cleaved into M02 in the gastrointestinal tract and are then covered by M02, and thus by the parent (i.e. unlikely to be genotoxic and references values of the parent can be applied, if needed).

Subject	Conclusions Pesticide Peer Review Meeting
	M06 and its conjugates M37 and M41: Considering the ADME/TK data and the structural similarity with the parent, the genotoxicity of M06 is covered by the data of isoflucypram. Its glycoside or glucuronide conjugates are likely to be cleaved into M06 in the gastrointestinal tract and are covered by M06, and thus by the parent (i.e. unlikely to be genotoxic and references values of the parent can be applied, if needed). **M07 and its conjugate M36: Overall, considering the negative QSAR prediction for M07 and the structural similarity with M06 (and also with M01 and M02), the same conclusions as M06 applies (genotoxicity covered by the genotoxicity data of isoflucypram). M07 is not expected to be of higher toxicity than M06, therefore the same conclusions as M06 applies (i.e. covered by parent)** **Its glucuronide conjugate is likely to be cleaved into M07 in the gastrointestinal tract and are covered by M07, and thus by the parent.** **M10, M11 and M12:** **M12 and M11: Based on ADME and structural similarity to the parent were considered as cover by parent (i.e. unlikely to be genotoxic and references values of the parent can be applied, if needed).** **M10: Overall, negative QSAR prediction for genotoxicity and considering its chemical structural it not expected to be of higher toxicity than M12 and therefore the same conclusion as M12 applies (i.e. unlikely to be genotoxic and references values of the parent can be applied, if needed).** **M49 and M58: Considering the ADME/TK data the genotoxicity of M58 is covered by the data of isoflucypram.** **For M49 considering the structural similarity with M58, M49 would not be of higher toxicity than M58 and then genotoxicity and general toxicity of M49 is covered by the data of isoflucypram (i.e. unlikely to be genotoxic and references values of the parent can be applied, if needed).** **M50: Based on *in silico* assessment and weight of evidence, no conclusion can be drawn on the genotoxic potential.** **M66 and M67: Based on *in silico* assessment and weight of evidence, no conclusion can be drawn on the genotoxic potential.**

Subject	Conclusions Pesticide Peer Review Meeting
	M52 and M54: Structures not resolved (i.e. position of OH, Cys and GSH, and position of the deletion of Fluor unclear). Not possible to perform an *in silico* assessment and therefore the toxicological evaluation was not feasible. M77: Based on *in silico* assessment and weight of evidence, no conclusion can be drawn on the genotoxic potential.
Experts' consultation 2.14 The ADI, ARfD, AOEL and AAOEL should be discussed and agreed.	The acceptable Daily Intake (ADI) is 0.04 mg / kg bw per day, based on the overall NOAEL of 4.2 mg/kg bw per day in dogs and applying an uncertainty factor of 100. The experts considered that the margin of safety to the highest tested dose in the rat carcinogenicity would be 465 in males and 1165 in females, reassuring that the ADI would be protective enough regardless the limitation of the dose selected in the rat carcinogenicity study. The Acute Reference Dose (ARfD) is 0.1 mg / kg bw based on the maternal NOAEL of 10 mg/kg bw per day from the developmental study in rabbit and applying an uncertainty factor of 100.The experts agreed that setting an ARfD is appropriate because of the early and significant onset of decrease body weight gain reported in the rabbit developmental toxicity study. The Acceptable Operator Exposure Level (AOEL) is 0.04 mg / kg bw per day, based on the overall NOAEL of 4.2 mg/kg bw per day in dogs and applying an uncertainty factor of 100 and due to the oral absorption of >80%, there was no need to correct the AOEL. The Acute Acceptable Operator Exposure Level (AAOEL) is 0.1 mg / kg bw considering the same point of departure as for the ARfD and based on the maternal NOAEL of 10 mg/kg bw per day from the developmental study in rabbit and applying an uncertainty factor of 100 and without correction for limited oral absorption.
Experts' consultation 1.1 Experts to discuss the toxicological relevance of impurities.	Based on the toxicological data package of the impurities (genotoxicity and/or general toxicity), the experts discussed and agreed on the relevance of the impurities. A proposed toxicological level of each impurity in the technical material was set. Some impurities were considered toxicologically relevant.

Pesticide Peer Review TC 64 (15-19 November 2021)
Isoflucypram

Subject	Conclusions Pesticide Peer Review Meeting
	Open point for EFSA (to be transfer to section 1): To consider if data gap according regulation 283/2013 should be set for the impurities considered toxicologically relevant.
New Experts' consultation proposed by the RMS and EFSA: Experts to discuss the toxicological relevance of SDHI for isoflucypram	The experts discussed the updated data presented by the RMS and the toxicological relevance of succinate dehydrogenase inhibition (SDHI) by isoflucypram concerning the risk assessment associated. The experts agreed that in order to address the concern related with the uncertainty of adverse effects occurring because of SDH inhibition, additional data would be helpful and as a first step, the comparative study on *in vitro* metabolism of isoflucypram should be repeated in human and animal hepatocytes, using two different radiolabels, with the objective to identify and quantify main metabolites. Thereafter, major human metabolites could be tested *in vitro* for their potential to inhibit SDH (complex II) and other complexes which are involved in the electron transport chain (ETC). The experts agreed that the topic of SDH / ETC inhibition require further consideration. However, the experts acknowledged that the set of required pivotal toxicological studies with isoflucypram did not provide evidence of effects that could be attributed to SDH inhibition as the mechanism of action. Therefore, currently there is no reason to preclude the toxicological evaluation of this substance in the context of the current regulatory requirements.

REPORT OF PESTICIDE PEER REVIEW TC 64

HEPTAMALOXYGLUCAN – AIR IV **Rapporteur Member State: FR**

2. Mammalian toxicity

Date: 19 November 2021

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Institute for Risk Assessment (BfR)	DE
Federal Environmental Agency (UBA)	DE
National Institute for Agricultural and food research and technology (INIA)	ES
Finnish Safety and Chemicals Agency	FI
Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environment et du Travail (ANSES)	FR
International Centre for Pesticides and Health Risk Prevention (ICPS)	IT
State Plant Service under the Ministry of Agriculture	LT
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
Hearing Expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Experts to discuss the justification provided by the applicant for waiving the endocrine disruption (ED) assessment as recommended in the ECHA/EFSA ED Guidance.**	**The ED assessment was waived for heptamaloxyloglucan based on the following considerations and therefore the ED criteria are not considered to be met for EATS-modalities:** • **Heptamaloxyloglucan is not absorbed as an unchanged molecule and has no bioaccumulation potential;** • **Heptamaloxyloglucan has a non-toxic mode of action;** • **There is no indication of EATS-mediated adversity in the 28-day oral study;** • **Carbohydrate compounds similar to heptamaloxyloglucan are largely distributed in soil and fruits. Furthermore, the level of exposure via PPP use is extremely low in comparison to the natural background via food consumption.**
Experts' consultation 2.2 **In view of the identified data requirements (e.g. inhalation toxicity, clastogenicity, etc) the need (or absence) for toxicological reference values (TRVs) and consequent risk assessment considerations should be confirmed in an experts' meeting.**	**Genotoxicity** **Genotoxicity assessment for mutagenicity, aneugenicity and clastogenicity is required for all active substances.** **Heptamaloxyloglucan is negative for gene mutations *in vitro*. No data or information have been submitted addressing the other two genotoxic endpoints.** **Even though the concern for heptamaloxyloglucan genotoxicity is low given the nature of this active substance, a "formal" data gap for clastogenicity and aneugenicity has been set in the absence of a robust rationale for waiving this data requirement and of additional literature, *in silico* data or data available from the assessment of the substance in other regulatory contexts.**

Subject	Conclusions Pesticide Peer Review Meeting
	<u>Acute inhalation toxicity</u> Heptamaloxyloglucan is applied as a plant protection product by spraying, that is a condition requiring acute inhalation toxicity assessment according to Regulation (EU) No 283/2013. A data gap for inhalation toxicity has been agreed in the absence of an appropriate study, other data or a robust justification for waiving an inhalation toxicity study, although the physico-chemical properties of the substance do not support inhalation systemic toxicity as a likely outcome. <u>Long term toxicity / carcinogenicity, reproductive toxicity and neurotoxicity</u> No adverse effects are expected to be elicited by heptamaloxyloglucan in long term-, reproductive- and neurotoxicity studies based on the absence of mutagenicity, acute, short term or target organ toxicity. In the absence of *in silico* predictions or any robust justification for waiving such studies, a formal data gap could be set. Nonetheless, no additional animal studies would be needed. Open point for RMS: to review the RAR by providing further consideration on the read across with tamarind seed gum (18-month study in mice and 24-month study in rat). <u>Reference values</u> Reference values are not considered needed, because of the nature of this active substance (low concern), its high dietary exposure levels in comparison with the possible exposure from the use as plant protection product, and based on the limited toxicological evidence available. <u>Non dietary exposure assessment</u> Exposure to heptamaloxyloglucan via the dermal route was agreed as not relevant. If compared with the estimated background levels of dietary exposure, the relative contribution of non-dietary exposure (mainly by inhalation) to heptamaloxyloglucan resulting from its use as a plant protection product would be very limited. This approach was considered pragmatic in the absence of information on acute inhalation toxicity.

REPORT OF PESTICIDE PEER REVIEW TC 64

ASPERGILLUS FLAVUS **STRAIN MUCL54911 – NAS 1107/2009** **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 19 November 2021

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Institute for Risk Assessment (BfR)	DE
Federal Environmental Agency (UBA)	DE
National Institute for Agricultural and food research and technology (INIA)	ES
Finnish Safety and Chemicals Agency	FI
Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environment et du Travail (ANSES)	FR
International Centre for Pesticides and Health Risk Prevention (ICPS)	IT
State Plant Service under the Ministry of Agriculture	LT
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
Hearing Expert	CH

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Discussion points/Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 6.1 Experts to discuss the infectivity/pathogenicity potential of *A. Flavus* strain MUCL54911.	All experts agreed that, due to the observed findings and the deviations reported for the inhalation toxicity study on *Aspergillus flavus* MUCL54911, no conclusion could be drawn on the infectivity and pathogenicity potential of this strain. **Data gap** Further assessment of pathogenicity and infectivity should be provided by the applicant, including at least weight of the evidence considerations and/or experimental data for the inhalation route of exposure.
Experts' consultation 6.2 Experts to discuss the non-dietary exposure assessment for workers, operators, bystanders, and residents. In particular, the approaches used to estimate the exposure (e.g. data from acute toxicity studies, supplementary data from OECD 65 and from EPA	All the experts agreed that no risk assessment is needed if the infectivity/pathogenicity of the strain is ruled out. It was acknowledged that for microbials, PPE/RPE is always recommended to reduce the exposure by inhalation, at least for mixing and loading procedures, in view of the sensitisation potential of microbials. **Data gap** Pending on the whole genome sequencing (WGS) results, risk assessment to secondary metabolites shown to be produced by the strain *A. Flavus* MUCL 54911 may need to be further considered.

Subject	Conclusions Pesticide Peer Review Meeting
Handbook), the lack of appropriate consideration with regards to children inhalation exposure and the exposure to secondary metabolites (pending on the evaluation of their production) should be discussed by the experts.	

REPORT OF PESTICIDE PEER REVIEW TC 60

FENPYROXIMATE – AIR IV **Rapporteur Member State: AT**

2. Mammalian toxicity

Date: 15 September 2021

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Ministry of Environment and Food of Denmark, Environmental Protection Agency	DK
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
Istituto Superiore di Sanità	IT
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
National Institute of Public Health	SI
European Chemicals Agency (ECHA)	
Hearing Expert	CH

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Discussion points / Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **Oral absorption value for fenpyroximate to be discussed by the experts.**	**The oral absorption value for fenpyroximate was calculated from two biliary excretion studies in cannulated rats. Although some uncertainties were observed, i.e. lack of data on bile excretion during the first 4-hours, the experts agreed to calculate the mean of the mean from the data of the studies.** **The derived oral absorption value was based on sum of % bile and % urine leading to 57-60% for males and 55-57% for females. Taking the mean of the means the resulting value was 60% oral absorption (rounded).**
Experts' consultation 2.2 **Genotoxic potential of fenpyroximate to be discussed by the experts.**	**The experts considered the test battery of *in vitro* and *in vivo* assays acceptable.** **For the *in vivo* micronucleus assay in mouse, it was agreed that bone marrow cells were exposed to the compound.** **Overall, the experts concluded that fenpyroximate is unlikely to be genotoxic.** **Open point for RMS: To include further details in the revised RAR, as commented during the meeting, regarding reliability of the publication concerning the *in vitro* genotoxicity study and induction of H2Ax in cultures of human cells line.**
Experts' consultation 2.3 **Carcinogenicity and long term toxicity of fenpyroximate in rats and**	**<u>For 2-year rat study:</u> The NOAEL is 25 ppm (0.97 mg/kg/day in males and females).** **The rationale for setting the NOAEL was that the decrease in body weight/body weight-gain at toxicity phase at 25 ppm is not considered treatment-related, it was only observed in males and**

Subject	Conclusions Pesticide Peer Review Meeting
mice to be discussed by the experts.	there was not a clear dose-response. Furthermore, the decrease was not observed in the oncogenicity phase of the study at 25 ppm. For 18-month mouse study: The NOAEL is 25 ppm (2.4 mg/kg/bw/day in males and 2.5 mg/kg/bw/day in females). Concerning the ovarian atrophy reported in the study: The experts agreed that it might be a common age-related finding and it was not observed in short-term studies. However, the increase of ovarian atrophy starting from (400 ppm) is outside the historical control data and was considered treatment related. The historical control data provided were considered relevant and acceptable.
Experts' consultation 2.4 Multigeneration rat study to be discussed by the experts, considering effects on or via lactation and additional tabulated results.	The experts discussed the data and results from the (two-generation reproduction toxicity study in rat). They considered not appropriate proposing classification for lactation effects (Lact. (H362) for fenpyroximate. All the experts confirmed the NOAELs as proposed by the RMS. General toxicity (parental and offspring): NOAEL is 30 ppm corresponding to 2 mg/kg bw per day, based on reduction in body weight/body weight gain (>10%) at the high dose. For reproductive toxicity the NOAEL is 100 ppm corresponding to 6.6 mg/kg-bw per day, the high dose tested.
Experts' consultation 2.5 MS experts to discuss the rat and rabbit (main and range-finding) developmental toxicity studies.	The experts confirmed the NOAELs in developmental toxicity studies as proposed by the RMS: • Rat developmental toxicity study: Maternal NOAEL 4.3 mg/kg bw per day based on decreased body weight and food intake. Developmental NOAEL 4.3 mg/kg bw per day based on increased incidence in supernumerary ribs at the high dose.

Subject	Conclusions Pesticide Peer Review Meeting
	• Rabbit dosage range-finding study: Maternal NOAEL 2.5 mg/kg bw per day based on decreased bodyweight gain, slightly reduced food and water consumption and reduced faecal output in the high dose group. Developmental NOAEL 2.5 mg/kg bw per day based on increased post implantation loss. • Rabbit main study: Maternal NOAEL 2.5 mg/kg bw per day based on decreased bodyweight gain, slightly reduced food and water consumption and reduced faecal output in the high dose group. Developmental NOAEL 2.5 mg/kg bw per day based on increased incidence of slightly folded retinas (grey zone anomalies). The experts considered the rabbit developmental toxicity as acceptable with limitations based on the low number females with implantation sites. Open point for the RMS: To add further details in the revised RAR regarding the incidence of slightly folded retinas (grey zone anomalies).
Experts' consultation 2.6 MS to discuss the neurotoxicity potential of fenpyroximate, including acute and repeated rat neurotoxicity studies and possible mode of action of mitochondrial complex I inhibition	The results of the two neurotoxicity studies in rats and data from literature references relevant for this issue were analysed to conclude on the possible mode of action of mitochondrial complex I inhibition by fenpyroximate. In conclusion, the experts agreed on the following points: • There are uncertainties on the reliability of the *in vivo* studies, these uncertainties are mainly due to the intrinsic difficulties in measuring and counting dopaminergic neurons in the *substantia nigra pars compacta* projecting into striatum as a consequence of a chemical treatment. In addition, the study design to capture these changes is not standardised and no gold standard study design can be identified. • Experts agreed that a mechanistic understanding in the context of the existing AOP for Parkinsonian adverse outcome would represent the most reliable approach. • Experts agreed that in AOP informed IATA for fenpyroximate with the inclusion of ADME data suitable for IVIVE suitable for PBPK modelling should be set up as a data gap. All available data including the evidences for chemicals that used a similar approach should be included. Open point for RMS: To include the additional assessment as presented during the meeting in the revised RAR.

Pesticides Peer Review TC 60 (13-17 September 2021)
Fenpyroximate

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.7 **Experts to discuss the acceptability and the results of the 2 additional dog studies (tolerated dose and 5 day repeat dose, and single dose study).**	**After the discussion of the data and the results of the two additional studies in dogs, all the experts agreed to change the acceptability of them to "acceptable with limitation".** **The experts discussed the results of the studies and data from others toxicological studies in dogs and considered diarrhoea as a treatment-related effect.** **The tolerated dose and 5-day repeated dose study in dog: The NOAEL is 2 mg / kg bw per day based on the incidence of diarrhoea in the treated animals.** **Single dose study in dogs: The LOAEL is 2 mg / kg bw per day based on the incidence of diarrhoea in the treated animals.**
Experts' consultation 2.8 **MS experts to discuss the ED potential of fenpyroximate and to conclude on the data to be generated.**	**Regarding T-modality: All experts agreed that the dataset is complete, and T-Modality criteria were not met.** **Open point for RMS: Update the RAR vol 1, p.47, concerning the speculative argumentation on use of histology as a surrogate endpoint for lacking development and thyroids hormone measurements.** **Regarding E-modality: All experts agreed that the dataset is complete, and E-Modality criteria were not met.** **The AS-Modalities have not been sufficiently investigated:** **Further data are required to conclude on the A and S modalities:** • **A-modality: the level 2 OECD TG 458 assay to be conducted. In case this proves negative, the OECD TG 441 to be conducted.** • **S-modality: the H295R Steroidogenesis Assay (OECD TG 456 or OPPTS 890.1550) and the aromatase assay (OPPTS 890.1200) to be conducted.** **If the above studies on activity negative: the scenario 2a(ii) applies and ED criteria are not met.** **If endocrine activity is observed: the scenario 2a(i) applies and further data needed to support mechanism of action analysis since EAS-mediated adversity was not sufficiently investigated, i.e. extended one-generation study with the inclusion of the cohort 1B (OECD TG 443, Level 5).**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.9 MS experts to discuss the relevance of all metabolites detected above 0.1 µg/L in groundwater.	Not discussed since there were not metabolites exceeding the trigger value of 0.1 ug/L.
Experts' consultation 2.10 MS experts to discuss the genotoxicity profile of the metabolites M-1, M-3, Z isomer of M3, N-desmethyl M-3, N-desmethyl M-3 acid, M-9, M-11, M-12, M-15, M-20, M-21, M-22 , M24 and Fen-OH including considerations of the reliability and acceptability of available QSAR data/analysis regarding the chromosome aberration endpoint. MS experts to discuss the general toxicity of metabolites M1 (Z isomer of the parent), M3, Z isomer of M3, M12 and Fen-OH should be discussed. Residue definition for plant and animal commodities as well as for processed commodities will need to be discussed in experts' meeting.	**M-1** Genotoxicity: Negative (based on experimental data) General toxicity: Cover by parent compound (based on structural similarity and mechanistic data). **M3** Genotoxicity: Available experimental data do not raise concern for genotoxicity however adequate experimental data are missing to address aneugenicity potential. General toxicity: Similarities with parent based on structural similarities however differences based on *in vitro* mechanistic data. Possible higher chemical reactivity. No conclusion reach. **Z isomer of M3** Genotoxicity: Same conclusion as M3. General toxicity: Same conclusion as M3. **N-desmethyl M-3** Genotoxicity: Same conclusion as M3. General toxicity: Same conclusion as M3.

Subject	Conclusions Pesticide Peer Review Meeting
	N-desmethyl M-3 acid **Genotoxicity:** **Same conclusion as M3.** **General toxicity:** **No discussion.** **M-9** **Genotoxicity:** **Available information is not sufficient to conclude on the genotoxicity potential. Alerts triggered** **General toxicity:** **No discussion.** **M-11** **Genotoxicity:** **Available information is not sufficient to conclude on the genotoxicity potential. Alerts triggered** **General toxicity:** **No discussion.** **M-12** **Genotoxicity:** **Available experimental data (Ames test) do not raise concern for genotoxicity however experimental data are missing to address aneugenicity/clastogenicity potential.** **General toxicity:** **Based on the structural similarities and the *in vitro* mechanistic data the metabolite might be considered cover by the parent compound. However, the experts were not on the position to reach a conclusion on general toxicity until genotoxicity potential will be properly addressed.** **M-12 isomer** **Genotoxicity:** **Same conclusion as for M-12** **General toxicity:** **Same conclusion as for M-12**

Subject	Conclusions Pesticide Peer Review Meeting
	M-15 **Genotoxicity:** **No alerts from QSARs, however QSARs analysis was not considered sufficient, read-across to a major rat metabolite was not possible.** **Overall, Available information not sufficient to conclude.** **Testing it as a standalone compound is proposed to address it.** **General toxicity:** **Not discussed.** **M-20** **Genotoxicity:** **Same structural alert than parent and structurally similarities, however specific reactivity not excluded. Overall, Available information not sufficient to conclude.** **General toxicity:** **Not discussed.** **M-21** **Genotoxicity:** **Same structural alert than parent, however specific reactivity not excluded. Available information not sufficient to conclude** **General toxicity:** **Not discussed.** **M-22** **Genotoxicity:** **Same structural alert than parent, however specific reactivity not excluded. Available information not sufficient to conclude** **General toxicity:** **Not discussed.**

Subject	Conclusions Pesticide Peer Review Meeting
	M-24 **Genotoxicity:** **Same structural alert than parent, however specific reactivity not excluded. Available information not sufficient to conclude** **General toxicity:** **Not discussed.** **Fen-OH** **Genotoxicity:** **After hydroxylation of parent it is not expected to change the outcome of genotoxicity with regards to the gene mutation potential. Data are missing to address aneugenicity/clastogenicity potential.** **General toxicity:** **Based on the structural similarities to parent, and being possible an intermediate metabolite, the metabolite might be considered cover by the parent compound. However, the experts were not on the position to reach a conclusion until genotoxicity potential will be properly addressed.** **Grouping** **Group 1:** **Grouping and testing is proposed to addresss genotoxicity potential of M-21, M9, M11, M24. M-21 as lead compound considering functional groups.** **Group 2:** **Grouping and testing is proposed to address genotoxicity potential of M-22 and Fen-OH.** **Group 3:** **Grouping and testing is proposed to address genotoxicity potential of M-3, Z isomer of M3, N-desmethyl-M3 and acid, M-12, M-12 isomer, M-20.** **Considering all functional groups, lead compound could be desmethyl-M3, although an Ames test already exists for M3 and M12.**

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.11 MS experts to discuss toxicological reference values for fenpyroximate (ADI, ARfD, AOEL and AAOEL).	The Acceptable Daily Intake (ADI) is 0.005 mg/kg per day, based on 2-year rat study NOAEL of 0.97 mg/kg/day. An additional uncertainty factor of 2 was applied to the standard UF of 100. The Acute Reference Dose (ArfD): is 0.01 mg/kg based on single dose dog toxicity study LOAEL of 2 mg/kg. An addtional UF of 2 was applied to the standard UF of 100. AOEL is 0.004 mg/kg per day based on 90-d rat oral toxicity study NOAEL of 1.3 mg/kg. An additonal UF of 2 was applied to sandard Uf of 100. Correction for 60% oral abpsortion was applied. The Acute Acceptable Operator Exposure Level (AAOEL) is based on the same basis as the ARfD but correction for 60% oral absorption was applied. The resulting AAOEL is 0.006 mg/kg/day. Open point to RMS: Consumer and non-dietary risk assessment to be recalculated based on the new reference values. RMS to present further details regarding benchmark dose approach in the revised RAR.
Experts' consultation 2.12 MS experts to discuss the dermal absorption values in light of the re-evaluation of the studies according to the new EFSA Guidance (2017) in an experts' meeting.	The agreed dermal absorption value is 9.9% for concentrate and in-use dilution (0.04 g/L). Open point for RMS: To include in the revised RAR the new calculations for dermal absorption as agreed in the meeting and update the non-dietary exposure.

REPORT OF PESTICIDE PEER REVIEW TC 60

NOVALURON – MRL Art. 12 review **Rapporteur Member State: DE**

2. Mammalian toxicity

Date: 15 September 2021

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Ministry of Environment and Food of Denmark, Environmental Protection Agency	DK
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
Istituto Superiore di Sanità	IT
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
National Institute of Public Health	SI
European Chemicals Agency (ECHA)	
Hearing Expert	CH

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[1] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf
[2] http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Discussion points/Outcome

2. Mammalian toxicity

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Minutes might be revised due to pending data gaps at the time of the meeting and /or eventual need for further follow up consultation after the meeting. If needed, the final agreement will be made available in the meeting report published at the end of the peer review process.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 **MSs experts to discuss the NOAEL/LOAEL of the 90-day toxicity study in mice.**	**The LOAEL of the 90-day oral toxicity study in mouse is 4.2 mg/kg bw per day based on the presence of inclusion bodies in reticulocyte smear.** **Open point for the RMS to include the new tables/clarification of the effect in a revised ER.**
Experts' consultation 2.2 **MSs Experts to discuss the NOAEL/LOAEL of the 90-day toxicity study in dogs and the overall relevant short-term NOAEL in dogs.**	**The overall short-term LOAEL in dogs is 10 mg/kg bw per day based on haematological changes being indicative of haemolytic anaemia, high sulfhaemoglobin formation and increased reticulocyte count.** **Open point for the RMS to include the new tables/clarifications in a revised ER.**
Experts' consultation 2.3 **MSs experts to discuss the overall NOAEL/LOAEL of the 90-day toxicity studies in rats.**	**The overall critical short-term NOAEL in rat is 0.7 mg/kg bw per day based on findings being indicative of slight anaemia and increased spleen weight at the next higher dose level of 22.2 mg/kg bw per day in a 90-day oral toxicity study.** **The overall short-term LOAEL in rats is 3.5 mg/kg bw per day for increased body weight gain in another 90-day oral toxicity study.** **Open point for the RMS to include the new tables in a revised ER.**

Pesticide Peer Review TC 60 (13-17 September 2021)
Novaluron

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.4 **MSs experts to discuss the overall short-term NOAEL for dermal toxicity in rats.**	**Due to time constraints, this point was not discussed. Since this endpoint is not critical to import tolerances or derive toxicological reference values, EFSA concludes based on the RMS conclusion and comments received.** **The RMS agreed with a commenter proposal to lower the NOAEL of the 28-day dermal toxicity study in rat from 400 to 75 mg/kg bw per day based on a statistically significant increase in methaemoglobin formation at 400 mg/kg bw per day.** **In the 14-day dermal toxicity study in rat, the systemic LOAEL is 10 mg/kg bw per day, based on increased body weight gain in females. A dermal (local) NOAEL can be established at 10 mg/kg bw per day based on scab formation observed at 30 mg/kg bw per day and higher.** **In the 28-day dermal toxicity study in rat, the systemic NOAEL is 75 mg/kg bw per day based on increased methaemoglobin formation at 400 mg/kg bw per day. A dermal (local) NOAEL can be established at 400 mg/kg bw per day based on very slight erythema, exfoliation and eschar formation at 1000 mg/kg bw per day.** **The overall short-term dermal $LOAEL_{systemic}$ in rat is 10 mg/kg bw per day for increased body weight gain from the 14-day dermal toxicity study. The overall dermal $NOAEL_{local}$ is 30 mg/kg bw per day for scab formation in the same 14-day dermal toxicity study.**
Experts' consultation 2.5 **MSs experts to discuss the genotoxic potential of novaluron in view of the lack of an appropriate *in vivo* micronucleus test.**	**The acceptability of the *in vivo* MN test is pending on further clarification regarding lines of evidence for bone marrow exposure. However, there is no concern over genotoxicity based on negative *in vitro* test battery.** **Open point is set for the RMS to revise the lines of evidence regarding bone marrow exposure in a revised ER to conclude on the acceptability of the *in vivo* MN study. This open point is not critical to conclude on genotoxicity.**
Experts' consultation 2.6 **MSs experts to discuss the carcinogenic and general toxicity NOAEL of the 2-year toxicity and carcinogenicity study in rat.**	**In the 2-year study in rat, the NOAEL is 1.1 mg/kg bw per day based on haematological findings indicative of haemolytic anaemia and liver toxicity (periacinar hepatocytic hypertrophy) at 30.6 mg/kg bw per day.** **There is no concern over the carcinogenic potential of novaluron in rats.**

Subject	Conclusions Pesticide Peer Review Meeting
	Open point for the RMS to include more details on the BMD approach (regarding the level of uncertainty) and include the new tables in a revised ER.
Experts' consultation 2.7 MSs experts to discuss the carcinogenic and general toxicity NOAEL of the 18-month study in mouse and the carcinogenic potential of novaluron.	In the 18-month carcinogenicity study in mice, the LOAEL is 3.6 mg/kg bw per day based on increases in reticulocytes and Heinz bodies. There is no concern over the carcinogenic potential of novaluron in mice.
Experts' consultation 2.8 MSs experts to discuss the neurotoxic potential of novaluron.	The NOAEL for neurotoxicity in the acute neurotoxicity study is 2000 mg/kg bw, the highest dose level tested. In the same study, a LOAEL for general toxicity is set at 200 mg/kg bw for fast respiration, piloerection and irritable behaviour. Short-term neurotoxicity has not been addressed and is missing.
Experts' consultation 2.9 MSs experts to discuss the ED potential of novaluron.	The criteria are not met for the T-modality in a sufficiently investigated dataset. The dataset is not complete for the AS modalities, some EAS mediated endpoints were affected (spermiogenesis and oestrus cycle), but these were not considered sufficient to indicate that an AS-mediated pattern of adversity exists. No additional studies are necessary to investigate the E modality, in line with the EFSA/ECHA ED GD, since the ToxCast E-model is negative. Uncertainties exist on potential for novaluron to affect non-EATS mediated endocrine pathways, in particular a concern exists for an endocrine mediated mode of action affecting metabolism (e.g. metabolic syndrome), this is mainly based on the recurrent observations in the dataset, of increase in bw gain in the absence of an increase in food consumption, increase in serum cholesterol, triglycerides and glucose levels. Data are missing according to scenario 2a(iii) of the EFSA/ECHA guidance on endocrine disruptors: - OECD TG 458 (AR STTA assay) - OECD TG 456 (H295R steroidogenesis assay) - OPPTS 890.1200 (Aromatase assay) In case of negative results in the three studies, Hershberger assay (OECD TG 441) would be needed. In case of positive results in one of the studies: OECD TG 443 or OECD TG 416 (2001) with the inclusion of additional endocrine

Subject	Conclusions Pesticide Peer Review Meeting
	sensitive parameters would be needed (EFSA, 2020, https://doi.org/10.2903/sp.efsa.2019.EN-1837). Regarding non-EATS mediated modalities, in line with the EFSA/ ECHA guidance and lacking clear testing and MoA for non- EATS mediated pathways, the ED assessment for non-EATS pathway will remain inconclusive. It was also noted that all available data in ToxCast investigating potential non-EATS mediated molecular initiating events should be reported and weighted as part of the ED assessment.
Experts' consultation 2.10 MSs experts to discuss the completeness of the dossier and agree on eventual data gaps regarding missing acute dermal toxicity, skin and eye irritation, skin sensitisation, phototoxicity, immunotoxicity, medical data and data on technical specification versus tested material and toxicological relevance of impurities that were not addressed in view of the purpose of import tolerances.	A number of endpoints were not addressed by the applicant as considered not relevant for import tolerance applications. Some endpoints were not considered relevant to import tolerance (e.g. skin and eye irritation). Some endpoints are difficult to assess for import tolerances (e.g. toxicological relevance of impurities since there is no technical specification agreed at the EU level). Other endpoints (phototoxicity or immunotoxicity) might be mainly linked to the intrinsic hazard of the substance and would not require an additional UF in deriving the ADI or ARfD. Missing endpoint will be listed as uncertainties mainly linked to the intrinsic hazard of the substance, but do not currently require additional uncertainty factors when deriving the ADI and ARfD. However, it does not preclude that once these data are available the setting of reference values would need to be reconsidered. Open point for the RMS to include the information of impurities in a revised ER.
Experts' consultation 2.11 MSs experts to discuss the ADI and ARfD of novaluron.	The ADI is 0.01 mg/kg bw per day, based on the NOAEL of 1.1 mg/ kg bw per day for haematological changes indicative of haemolytic anaemia and liver toxicity in the 2-year toxicity study in rats and applying an UF of 100. The JMPR established the same ADI in 2005, based on the same dataset. Observed effects potentially relevant to establish an ARfD are limited to methaemoglobin formation that was only shown as relevant in rats after 90-day treatment, but not after 28-day and would therefore not be relevant to a single administration. The JMPR did not establish an ARfD based on the same dataset. The ADI is 0.01 mg/kg bw per day. The setting of an ARfD is not required, as unnecessary.

Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.12 **MSs experts to discuss the *in vitro* metabolism study**	**This point was not discussed due to time constraints, it was added to the discussion based on a comment received from the applicant previously to the meeting. It is not critical to conclude on the TRVs or import tolerances.** **The RMS concluded that the formation of human metabolites cannot be completely excluded as the test item was converted to a higher percentage compared to the negative control in series 1 and 2 of the experiment. This may add a slight uncertainty in the risk assessment.** **No human-specific metabolite was identified, however could not be completely excluded as the test item was converted to a higher % than the negative control. Higher conversion was found in rabbits (one peak above 5% of total radioactivity) > rats > dogs > mice > humans (no peak identified for either mice or humans. The 2 peaks obtained were not identified.**

REPORT OF PESTICIDE PEER REVIEW TC 60

OXAMYL – AIR III **Rapporteur Member State: IT**

2. Mammalian toxicity

Date: 13-14 September 2021

List of participants:

Institute	Member States Country code
Austrian Agency for Health and Food Safety (AGES)	AT
Federal Environmental Agency (UBA)	DE
Federal Institute for Risk Assessment (BfR)	DE
Ministry of Environment and Food of Denmark, Environmental Protection Agency	DK
Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	FR
ASST FBF SACCO	IT
Istituto Superiore di Sanità	IT
Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)	NL
National Institute of Public Health	SI
European Chemicals Agency (ECHA)	
Hearing Expert	CH

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Discussion points / Outcome

2. Mammalian toxicity

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Subject	Conclusions Pesticide Peer Review Meeting
Experts' consultation 2.1 MS experts to discuss the data available on *in vitro* comparative metabolism.	Based on a new GLP-compliant comparative in vitro metabolism study using mouse, rat, rabbit, dog and human hepatocytes, no unique metabolites of [14C]oxamyl were identified in humans and no major species differences were observed.
Experts' Consultation 2.2 MS experts to discuss the results of the sensitisation test and the possible need for additional studies to address the skin sensitising potential of oxamyl in an experts' meeting.	The lack of a skin sensitising effect of oxamyl was agreed based on the weight of the evidence (WoE). Open point: The inclusion of the QSAR analysis and a more detailed explanation supporting the WoE in a revised RAR are still pending actions for the RMS
Experts' Consultation 2.3	An overall NOAEL of 0.930 mg / kg bw per day was agreed from the two 1-year oral toxicity studies in dog, based on the inhibition of erythrocyte acetylcholinesterase (AChE)

MS experts to discuss the two 12-month studies in the dog and the rationale behind the setting of the NOAEL in an experts' meeting.	activity, taken as the most sensitive toxicological endpoint for oxamyl. Open point: the RMS should rephrase the text in a revised RAR to better describe the findings of Study 2.
Experts' Consultation 2.4 MS experts to discuss the evidence of bone marrow exposure and the results of the *in vivo* micronucleus test in mice.	Proof on bone marrow exposure was provided by the onset of overt systemic effects in mice in the same in vivo micronucleus (MN) test. No indication of genotoxicity was found for oxamyl.
Experts' Consultation 2.5 MS experts to discuss the acceptability and the NOAEL of the long term feeding study in mice and in rat in an experts' meeting.	In rats, the systemic toxicity NOAEL was agreed at 25 ppm in females (1.32 mg/kg bw per day) based on ovary atrophy and at 50 ppm in males (1.97 mg/kg bw per day) based on decreased body weight and body weight gain, clinical signs, plasma cholinesterase inhibition at 100 ppm and higher. In rats, the NOAEL for carcinogenicity was > 6.99/ 11.1 mg/kg bw per day (M/F) based on the absence of carcinogenicity at the top dose tested. In mice, the systemic toxicity NOAEL was agreed at 25 ppm (4.2 mg/kg bw per day in males) based on decreased body weight. In mice, the NOAEL for carcinogenicity was >13.5/16.8 mg/kg bw per day (M/F) based on the absence of carcinogenicity at the top dose tested. Open points: RMS to include the derivation of the NOAEL for carcinogenicity for both rat and mice studies, and modify the rat systemic toxicity NOAEL, to request and include historical control (HCD) data and revise the RAR as suggested in the Expert Meeting report.

Experts' consultation 2.6 **MS experts to discuss the outcome and NOAELs from all generational reproductive studies.**	**Based on the rat two-generation reproduction study:** **the relevant parental NOAEL was agreed at 1.43 mg/kg bw per day, based on decreased body weight and body weight gain, reduced food consumption and efficiency during treatment in both males and females of both generations;** **the relevant reproductive NOAEL was agreed at 4.22 mg/kg bw per day, based on decreased pup survival and decreased litter size in both generations;** **the relevant Offspring NOAEL was agreed at 1.43 mg/kg bw per day, based on a significant treatment-related reduction in pup mean body weights.**
Experts' consultation 2.7 **MS experts to discuss the outcome and NOAELs from all developmental toxicity studies in an experts' meeting.**	**Based on a rabbit developmental toxicity study:** **the maternal NOAEL was agreed at 1 mg/kg bw per day, based on decreased maternal body weight gain;** **the developmental NOAEL was agreed at 1 mg/kg bw per day, based on increased resorptions.** **Based on a rat developmental toxicity study:** **the maternal NOAEL was agreed at 0.5 mg/kg bw per day, based on decreased maternal body weight gain, reduced food consumption and clinical signs;** **the developmental NOAEL was agreed at 0.5 mg/kg bw per day, based on decreased foetal weight.**
Experts' consultation 2.8 **NOAELs / points of departure for the neurotoxic endpoints, uncertainty factors underlying health-based guidance values and potential data gaps need to be discussed in an experts' meeting.**	**Acute neurotoxicity is the critical adverse effect of oxamyl.** **In rats, the acute oral neurotoxicity NOAEL was agreed at 0.1 mg/kg bw per day for males/females based on clinical signs on day 1, decreases in body weight, perturbations in a Functional Observation Battery (FOB) and in motor activity parameters, and decreased plasma and erythrocyte cholinesterase activities.** **Open point: RMS to check the BMDL20 calculations for day 1 AChE inhibition in cerebellum made by the applicant.** **In rats, the subchronic oral neurotoxicity NOAEL was agreed at 10 ppm in females (0.67 mg/kg bw per day) based on not statistically significant, but treatment-related increase in exophthalmos, and at 30 ppm in males (1.69 mg/kg bw per day) based on significant reductions in body weight, food consumption and food efficiency, perturbations in FOB and**

	motor activity parameters and significant reductions in plasma, erythrocyte and brain cholinesterase activity. Open point: RMS to include the new NOAEL for females and a critical reasoning for the erythrocyte AChE in a revised RAR. A data gap for a DNT study was set, to address possible age-related differences in susceptibility of brain acetylcholinesterase to oxamyl, in compliance with the Regulation EC 283/2013 data requirements.
Experts' Consultation 2.9 MS experts to discuss the immunotoxicity potential of oxamyl in an experts' meeting.	In the absence of specific data, but considering the available toxicological data package, and the critical effect being acute neurotoxicity, an immunotoxic potential for oxamyl was not supported by the Expert Meeting.
Experts' consultation 2.10 Experts need to discuss the ED potential of oxamyl in an experts' meeting	The ED criteria for T-modality were not met for oxamyl. The applicable scenario is Scenario 1A. Open point. RMS to include the rationale for dose selection indicating the adequacy of the pubertal and thyroid function studies in male and female rats. The ED criteria for EAS modalities were not met for oxamyl because no endocrine activity and no adversity have been observed. The applicable scenario is Scenario 2a (ii).
Experts' consultation 2.11 MS experts to discuss the toxicity profile and the reference values for the following metabolites: IN-QKT34, IN-L2953, IN-N0079 and thiocyanate (metabolites in residues) and GW IN-A2213, IN-D2708 (metabolites in residues and GW).	Based on ADME data, IN-A2213, IN-L2953 (free and glucoside conjugates), IN-D2708 (DMOA), IN-KP532, IN-QKT34 (IN-A2213 glucoside), IN-N0079 (DMCF), and IN-T2921 are major rat metabolites of oxamyl. Therefore, the reference values of parent compound are considered to cover for their toxicity. For thyocianate, a data gap for general toxicity was set (pending confirmation by the Residues Team)

Experts' consultation 2.12 **The values proposed (reference points and safety factors) for ADI, ArfD and AOEL need to be discussed by the experts (representative from EU MS) in order to come to an agreed EU view.**	**The ADI, ARfD, AOEL and AAOEL were set at 0.0001 mg/kg bw per day based on the NOAEL of the rat acute neurotoxicity study divided by an overall UF of 1000 (composed of the standard uncertainty factor of 100 to cover for inter- and intra-species differences, and an extra factor of 10 to account for the DNT data gap).** **Open point: RMS to amend the RAR accordingly.**
Experts' Consultation 2.13 **MS experts to discuss dermal absporption data for Oxamyl 10GR and Oxamyl 10SL in an experts' meeting.**	**For the granular formulation, in the absence of an acceptable experimental study in line with the EFSA guidance, the default dermal absorption value of 10% was agreed.** **Open point: RMS to amend the RAR accordingly.** **For the liquid formulation, a dermal absorption value of 5.4% was agreed based on the *in vitro* human skin study (6h time point).** **Open point: RMS to amend the RAR accordingly.**
Experts' Consultation 2.14 **MS experts to discuss exposure data for Oxamyl 10GR and Oxamyl 10SL in an experts' meeting.**	**Open point: RMS to redo the non-dietary exposure calculations for both the granular and liquid formulations taking into account the newly set AOEL and AAOEL at 0.0001 mg/kg bw per day, the default dermal absorption value of 10% for the granular formulation and the dermal absorption value of 5.4% for the liquid formulation. Furthermore, specific suggestions from the experts are reported in the Expert Meeting report.**