PESTICIDE PEER REVIEW UNIT

SCIENTIFIC PANEL ON PLANT PROTECTION PRODUCTS AND THEIR RESIDUES

MINUTES OF THE 101st OPEN PLENARY MEETING

Held on 2-3 October, 2019, Parma (Italy)

(Agreed on 16 October, 2019)

Participants

- Panel Members:

  Paulien Adriaanse, Annette Aldrich, Philippe Berny (via tele-conference), Tamara Coja, Sabine Duquesne, Antonio Hernandez-Jerez (chair), Marina Marinovich, Maurice Millet, Olavi Pelkonen, Silvia Pieper, Aaldrik Tiktak, Christopher Topping, Anneli Widenfalk.

- Hearing Experts:

  Not Applicable

- European Commission and/or Member States representatives:

  Not Applicable

- EFSA:

  Maria Arena, Arianna Chiusolo, Manuela Tiramani, Dimitra Kardassi, Juan Parra Morte, Andrea Terron, Iris Mangas, Federica Crivellente, Daniele Court-Marques (via tele-conference), Mark Egsmose, Frederique Istace, Laszlo Bura, Bruno Dujardin, Benedicte Vagenende.

- Observers:

See Annex I

European Food Safety Authority
Via Carlo Magno 1A – 43126 Parma, Italy
Tel. +39 0521 036 111 | www.efsa.europa.eu

OPEN SESSION

1. Welcome and apologies for absence

The Chair of the Panel, Antonio Hernández-Jerez, welcomed the participants. Apologies were received from Gerrit Wolterink and Ioanna Tzoulaki. The Chair also informed that Anne-Louise Gimsing resigned due to a new job position.

2. Brief Introduction of Panel Members and Observers

Panel members, EFSA and the observers introduced themselves.

3. Adoption of agenda

The agenda was adopted without changes.

4. Declarations of Interest of Scientific Panel Members

Declarations of Interest of Scientific Panel Members 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 Panel members 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.

5. Presentation of the EFSA guidelines for observers

EFSA presented the guidelines for observers for open plenaries.

6. Agreement of the minutes of the 100th Plenary meeting held on 19-20 June 2019, Parma (Italy)

The minutes of the 100th PPR Plenary were agreed via written procedure on 5th July.

7. Report on written procedures since 100th Plenary meeting

None.

8. Update of the General Food Law (Regulation (EC) No. 178/2002)

Following the approval by the European Parliament of the new Regulation on the transparency and sustainability of the EU risk assessment in the food chain, EFSA presented the Regulation priorities (i.e. Transparency, Scientific Value, Engagement and Risk Communication and Governance) and EFSA preparatory work to be ready for implementation in March 2021.

[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

9. Scientific outputs submitted for discussion and/or possible adoption, updates on ongoing activities, new projects

9.1. Development of Adverse Outcome Pathways relevant for the identification of substances having endocrine disruptors properties (EFSA-Q-2019-00492)

EFSA presented the terms of reference and the status of the establishment of the Working Group.

9.2. Scientific Opinion of the PPR Panel for developing Integrated Approaches to Testing and assessment (IATA) case studies on developmental neurotoxicity (DNT) risk assessment (EFSA-Q-2019-00100)

The chair of the Working Group informed the Panel about the progress of the activity and the dates for next meetings. The table of content as well as the case studies were also presented and discussed.

10. Q&A 2nd October

Questions received upon registration as well as questions posed during the meeting were answered by the Panel and EFSA (see Annex II).

9. Scientific outputs submitted for discussion and/or possible adoption, updates on ongoing activities, new projects [Cont.]

9.3 Framework for conducting environmental exposure and risk assessment for transition metals when used as active substances in PPPs (EFSA-Q-2019-00374)

The Panel was informed on the status for the establishment of the PPR Panel Working Group. The appointed chair of the WG, Anne-Louise Gimsing has resigned from the PPR Panel and the Working Group. Silvia Pieper was appointed as the new Working Group chair by the chair of the PPR Panel, according to EFSA's Standard Operating Procedures. Following the above mentioned resignation and in line with EFSA' Standard Operating Procedures, if gaps of expertise are identified, the chair of the Working Group will discuss with the Head of the Pesticide Peer Review Unit the possibility to add additional expertise to the Working Group for addressing the Terms of References in the mandate.

9.4 Cumulative risk assessment of pesticide residues regarding their combined acute effects on the nervous system and the chronic effects on thyroid

The methodology and the draft outcome were presented to Panel and observers. The Panel was informed that a new round of public consultation on the draft reports was launched. The deadline for comments is 15th November. Although the methodologies have been subject to previous public consultations, a proper engagement of stakeholders on their application to the assessment of cumulative risks of pesticide residues is found crucial to ensure a transparent communication of the methodology, results, assumptions and scientific assessment.

11. Update on the ongoing activities of the Pesticide Peer Review (PREV) Unit

The Panel and observers were informed about the on-going developmental activities in the area of mammalian toxicology and environmental risk assessment of the PREV Unit. Additional mandates which are under negotiation with the EU Commission were also presented.

12. Update on the activities of the Scientific Committee

The chair informed the Panel of the statues of the on-going activities of the Scientific Committee.

13. Q&A 3rd October

Questions received upon registration as well as questions posed during the meeting were answered by the Panel and EFSA (see Annex II).

Closed Session

9. Scientific outputs submitted for discussion and/or possible adoption, updates on ongoing activities, new projects [Cont.]

9.5. Request of an opinion on the genotoxic potential of triazine amine (metabolite common to several sulfonylurea active substances) (EFSA-Q-2018-00830)

The progress of the activity was presented. Adoption of the draft opinion is scheduled for the PPR plenary meeting in November. Two Panel members (Marina Marinovich and Olavi Pelkonen) were identified for the peer review of the draft opinion.

AOB

The Panel was informed that the next PPR plenary meeting will be held via Web-conference.

ANNEX I

List of physical observers

Last Name	First Name	Name of Employer	Affiliation
Spirlet	Marie	Certis Europe BV	Private sector
Comito	Veronica	Studio legale Avv. Veronica Comito	Private sector
Khan	Adnan	RIFCON GmbH	Private sector
Schoenmakers	Anne	RIFCON GmbH	Private sector
Weidenauer	Matthias	European Union Copper Task Force, c/o Battelle UK Ltd	Private sector
Ferrario	Antonino	ISAGRO S.p.A	Private sector
Mantovani	Alberto	Istituto Superiore di Sanità - Dept of Food Safety, Nutrition and Veterinary Public Health	University/public research institute
Hernik	Agnieszka	National Institute of Public Health - National Institute of Hygiene	University/public research institute
Baraldi	Elena	University of Bologna	University/public research institute
Collina	Marina	University of Bologna	University/public research institute
Bonerba	Elisabetta	University of Bari Aldo Moro, Department of Veterinary Medicine	University/public research institute
Melching-Kollmuss	Stephanie	BASF SE	Private sector
Terio	Valentina	University of Bari (art. 36)	University/public research-EU

PESTICIDE PEER REVIEW UNIT

List of Remote Observers

Last Name	First Name	Name of employer	Affiliation
Pasquali	Matias	Universtià di Milano	University/public research-EU
Pecoraro Mercier	Claire	Bayer SAS	Private sector
Nadzialek	Stephanie	ECPA	Private sector
Lindberg	Hanna	Finnish Safety and Chemicals Agency	National authority - EU
Jhon Cruz	Eric	National Crop Protection Center - University of the Philippines Los Banos	University/public reseach-nonEU
Le Torrivellec	Audrey	AUDREY LE TORRIVELLEC	Private sector
Rosato	Roberta	Istituto Zooprofilattico dell'Abruzzo e del Molise	University/public research-EU
Mai	Ting-Wei	Chih-Kang Chiang	University/public reseach-nonEU
Semino	Giovanna	Bayer CropScience	Private sector
Campese	Caterina	Università Ca' Foscari di Venezia	University/public research-EU
Haaf	Sonja	Sonja Haaf	Private sector
O Carroll	Nora	Fine Agrochemicals	Private sector
Hamama	Ziva	Ministry of Health	National authority - non-EU
Ozatalay	Jolanta	Fine Americas, Inc.	Private sector
Laporte	Frank	Bayer SAS	Private sector
Malley	Linda	FMC	Private sector
Giner	Marta	DevReg Consulta	Consultancy
Bibars-Reiter	Rene	Rene Bibars-Reiter	Private sector
Ravagli	Stefano	DIACHEM	Private sector
Neumann	Birgit	Bayer AG	Private sector
Solarino	Giorgio	Ministero politiche Agricole	National authority - EU
Mateo Penas	Alfonso	AgroInvestigations	Press/media

Avdikou	Ifigeneia	PERIPHERY OF EPIRUS	National authority - EU
Bothe	Kathrin	Bayer AG	Private sector
Yuan-SIao	Chen	National Taiwan University	University/public reseach-nonEU
Cerioli	Nadia Lucia	Italian Ministry of Environment	National authority - EU
Chiumiento	Francesco	Istituto Zooprofilattico Sperimentale dell'Abruzzo e del Molise "G. Caporale"	National authority - EU
Hallmark	Nina	Bayer AG	Private sector

Annex II

List of questions from observers and answers

Question maker	Question	Answer
Questions related to item 8-Update of the General Food Law (Regulation (EC) No. 178/2002)		
Istituto Superiore di Sanità, Dept of Food Safety, Nutrition and Veterinary Public Health	As EU citizen, I am glad to hear that requirement of transparency will concerns also RMs and request for ensuring this action will be taken on board.	Yes, we are aware and lots of effort are currently being put into finding SMART ways to allow for the required transparency but trying not to delay the scientific process. This is also the reason why the extra support in the preparatory phase is foreseen.
Studio legale Comito, Italy	Has the update of the Regulation 178 any impact on sectorial regulation?	Yes, the law will have impact on al sectorial legislation, namely Regulations No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC. The impact for the sectoral legislation will mainly be on transparency/confidentiality requirements. Specific reference can be found into the new 1381/2019 Regulation here.
Questions related to item 9.1- Development of Adverse Outcome Pathways relevant for the identification of substances having endocrine disruptors properties		
BASF SE	Will the AOP under development be aligned with the other OECD activities on AOPs in the wiki, currently under discussion?	EFSA already developed in the past 3 AOPs; 2 on Parkinson's disease and 1 on childhood leukaemia. Of them, one of the two on PD went through the full OECD process and is published in the OECD web page, the one on CHL is still in the process and the second one on PD is in the waiting list. Indeed, the OECD review process is long and demanding and, in the opinion of this AOP developer, has the potential of being biased.

Question maker	Question	Answer
		As a consequence of this experience, we will go through the OECD process but we intend to challenge the OECD review process by including in the WG the JRC, which is already part of the EAGMST (OECD Expert Advisory Group on Molecular Screening and Toxicogenomics) WG at OECD and part of the review process at OECD level and, even more important for us, by introducing in the development of AOP an evidence based approach using systematic literature reviews, use of an appraisal tool and apply the uncertainties analysis. This could allow us to develop a probabilistic AOP and therefore reducing the uncertainties and limitations of an expert based AOP review.
BASF SE	Is an AOP on Thyroid in plan?	No. However, EFSA is very much interested in the ongoing activities on thyroid AOPs. In the EFSA/ECHA ED GD, there is an appendix specifically dedicated to thyroid, already indicating what should be considered as adverse in terms of thyroid histopathology and thyroid hormones and already gives indication on which data are necessary to support common thyroid mode of action and consideration on human relevance and this is based on the current scientific knowledge and using all available evidence. It is also recognized that a number of activities are already undergoing for supporting thyroid mediated KEs through in vitro studies, that a map of a network of AOPs for thyroid already exist in the wiki and in the US EPA white paper and that some specific AOP (E.G TPO and NIS) already exist in the AOP wiki.
Bayer AG	How are the activities of the working group of the PPR panel connected with similar initiatives within the OECD?	EFSA and the PPR Panel intend to develop all AOPs by following the OECD process as defined in the AOP wiki
Bayer AG	For non-mammalian vertebrates (e.g., fish, amphibians), we often lack information on the MIE due to the fact that in vitro tools are missing for these organisms. Is it possible to	At this stage for information on the MIE (Molecular Initiating Event) information from in vitro studies using mammalian cells are used. This information is considered supportive considering the high conservation of the endocrine system and the homology of endocrine receptors as well as key enzymes involved across

Question maker	Question	Answer
	combine information from mammals and non-mammalian vertebrates in one AOP?	vertebrates. The situation is different when coming to in vivo studies where due the complexity of the biological system, at this stage it is not considered possible to extrapolate effects/lack of effects in vivo across taxa.
Istituto Superiore di Sanità, Dept of Food Safety, Nutrition and Veterinary Public Health	Most potentially ED-related may be produced by different Molecular Initiating Events (MIEs): for instance, impaired male reproductive development may result from events (see AOP wiki) affecting estrogen and androgen receptors, glucocorticoid receptor, PPAR-alpha, 5-alpha reductase and possibly others (ArH, retinoic pathways). For many relevant molecular initiating events and early key events standardized tests are not available. Is this a practical problem in order to link (as required) adverse effects to endocrine mechanisms? How to proceed toward robust AOPs?	EFSA agreed that, on a general rule, MIEs can only be assessed through standardized methods for the EAS modalities. In recognizing this limitation and considering the complexity of the various endocrine systems, the EFSA/ECHA guidance on the identification of endocrine disruptors in the context of regulations (EU) N.528/2012 and (EC) N. 1107/2009 is considering the biological plausibility as the most relevant weight when assessing EATS effects that are considered endocrine mediated (in line with the OECD GD150) to postulate a mode of action. The practical consequence is that, based on the weight of all available evidences, EATS mediated adverse events are biologically plausibly linked to an endocrine activity if the contrary is not proven through an alternative/comparative mode of action analysis (in line with the EFSA/ECHA ED guidance on the identification of endocrine disruptors). EFSA, considering the existing limitations in building the MoA (Mode of Action), is proposing to develop a series of AOPs in order to facilitate the assessment of the biological plausibility, initially for non-endocrine target organs (i.e. uterus) which are however a frequent target in the regulatory toxicological studies. In developing AOPs, the uncertainties due to lack of standardized methodologies will be minimized by the application of modified Bradford-Hill criteria.
Questions related to item 9.2- Scientific Opinion of the PPR Panel for developing Integrated Approaches to Testing and assessment (IATA) case studies on developmental neurotoxicity (DNT) risk assessment		
Istituto Superiore di Sanità, Dept of Food Safety, Nutrition and Veterinary Public Health	IATA approach considers metabolism and internal exposure. Will transplacental transfer be considered?	Indeed, as part of the IATA, ADME data will be included in the framework. There will be also an AOP informed IATA and this will be provided by the testing battery.

Question maker	Question	Answer
BASF SE	Will other MIE be considered in the future than the ones already identified?	This is not the intention. The presented are case studies while the testing battery is intended to cover key events (KEs) representing fundamental processes in brain development and as such be common KE of many MIEs and AOs (Adverse Outcomes).
Bayer CropScience	Which tests are you including in the in vitro battery for DNT?	The battery consists of a combination of 15 assays that provide a good coverage of key neurodevelopmental processes: proliferation, migration, differentiation, apoptosis, synaptogenesis, neurite growth, myelination and neural formation and function (for more information see Aschner M et al., J.ALTEX. 2017;34(1):49-74). The list of assays is as follows: • Proliferation in human neuroprogenitors in neurospheres • Proliferation in human hNP1 neuroprogenitors • Migration (NPC2) • UKN2 MINC assay NCC migration • NPC2/3 - Neuronal migration • Apoptosis (hNP1 – NPC) • Differentiation of hNPC neuronal differentiation (NPC3), hNPC differentiated neurons (NPC4) and hNPC oligodendrocyte differentiation (NPC5) • UKN5 –Neuronal morphol. LUHMES • NPC4 –Neuronal morphology (early) • Neurite outgrowth of iCell Gluta neuron-NPC • Neurite outgrowth of Rat Cortical • Rat Neuronal network formation • Rat Cortical Synaptogenesis.
Bayer AG	What would be the best way for relevant data holders to contribute to the DNT case studies before the public commenting phase?	The applicant for the two active substance might be invited as hearing by the WG to answer specific question that will arise during the development of the case study, if needed. If they provide additional data, new data will be appraised systematically. As hearing experts they might participate in the uncertainty analysis.
FMC	Is there a list of the 12 in vitro assays included in the DNT battery? Is there a list	The list is composed by 121 chemical compounds of those 88 are ToxCast compounds, 13 are compounds to be used in IATA case

Question maker	Question	Answer
	of the 120 chemicals that have been tested in the in vitro DNT battery?	studies, 36 are compounds that have been tested in an test guideline OECD 426 assay, 41 are pesticides active substances and 6 are pesticide metabolites.
Questions related to item 9.3- Framework for conducting environmental exposure and risk assessment for transition metals when used as active substances in PPPs		
European Union Copper Task Force	Q-2019-00374: Timing: application for Cu is 31.12.2022. Framework available in time for studies, validate models, compile a dossier compliant with new framework? Speciation/Bio-availability; will these concepts be included? With specific recommendation how to implement in PEC calculations? With specific models? Data normalisation: Will the framework suggest specific models to be used e.g BLM, regression models lab-to-field adjustments? With realistic worst-case scenarios to be used for data normalization? Assessment factors: appropriate for a homeostatically controlled essential element? will adverse outcomes for deficiency status of organisms be included? PBT: exempt inorganics like REACh/BPD? Scope:. include human health?	EFSA is requested to provide a statement outlining an appropriate scientific methodology for environmental risk assessment for certain transition metals, as active substances in Plant Protection Products. This PPR statement will provide a framework and guidance to applicants, competent authorities of the Member States and EFSA experts when assessing certain transition metal compounds, e.g. copper- and iron compounds. The framework methodology developed should be consistent with the regulatory framework and data requirements for plant protection products under Regulation (EC) No 1107/2009 and address the specific properties of transition metals. Consideration will be given on how to integrate specific approaches in the risk assessment methodology (e.g. speciation, bioavailability, modelling approaches and use of monitoring studies). EFSA will organise a public consultation on the draft statement and the PPR Panel will consider the responses received before finalising the statement. The statement is expected to be adopted by the Panel by February 2021.
European Union Copper Task Force	What is the difference between a statement and a guidance also in terms of taking note procedure? Can the issue of the new statement allow the use of new models?	A Statement is a scientific output in the form of a concise document that does not go into the same level of detail as an Opinion/Guidance. Guidance explains the principles behind EFSA's procedures and approaches to scientific risk assessments to risk assessors (including the Scientific Committee or Scientific Panels), risk managers and/or applicants of dossiers submitted for evaluation. Guidance documents may also specify the information and data

Question maker	Question	Answer
		which industry must provide when submitting applications to EFSA for evaluation prior to their authorisation by risk managers. It is considered unlikely, considering the time available and the activities to be performed that a new model will be developed. The possible need will be highlighted in the statement.
Questions related to item 9.4- Cumulative risk assessment of pesticide residues regarding their combined acute effects on the nervous system and chronic effects on the thyroid		
BASF SE	Did the expert knowledge elicitation consider uncertainties on the assessment groups?	Yes. For each cumulative assessment group, the probability that each pesticide belongs to the group was assessed. The probabilities of the pesticides that contributed the most to the risks, were considered in the final expert knowledge elicitation process.
BASF SE	Do you expect the approach will be accepted by risk managers? Do you expect they will take further risk mitigation measures?	The parameters, assumptions and threshold for regulatory consideration were discussed and agreed with risk managers. Furthermore, risk managers may still provide their views and comments during the public consultation. The outcome of the risk assessment is therefore considered likely to be accepted by risk managers. It should also be noted that the retrospective assessment refers to the reference period 2014-2016. For some of the risk drivers identified in this reference period, European Commission and Member States have already taken risk mitigation measures in the meantime (e.g. chlorpyrifos).
BASF SE	Can the methodology also be applied to prospective assessments (pre-marketing)?	The current methodology relies on a probabilistic approach which relies on monitoring data. In a prospective approach, the number of residue trials data is very limited compared to the high number of monitoring data available. The current methodology can therefore not be applied directly to prospective assessments. However, EFSA intends to initiate a pilot project to investigate how residue trials data can be incorporated in the current methodology.

Question maker	Question	Answer
RIFCON GmbH	Did EFSA consider public literature data for the establishment of cumulative assessment groups?	Please refer to Section 2.1 of the Respective Scientific Reports establishing the CAGs: Establishment of cumulative assessment groups of pesticides for their effects on the nervous system Establishment of cumulative assessment groups of pesticides for their effects on the thyroid Where it also indicated that open literature was searched for additional information on modes of action. In general, the establishment of the CAGs is based on data from the Draft Assessment Report and all supporting documents developed during the course of the peer review. The DAR is based on the dossier submitted by the Applicant. According to Art. 8(5) of Regulation 1107/2009, the applicant's dossier should contain scientific peer-reviewed open literature on the active substance and its relevant metabolites dealing with side-effects on health, the environment and non-target species and published within the last 10 years before the date of submission of the dossier.
Istituto Superiore di Sanità, Dept of Food Safety, Nutrition and Veterinary Public Health	How will EFSA handle the complexity of certain organs such as liver and kidneys?	Considering that a wide range of effects is expected in these organs, the critical point will be the identification of the relevant effects for cumulative risk assessment. This is the reason why EFSA initiated a cross-cutting activity on the grouping of chemicals into assessment groups. These criteria are aimed at facilitating the identification of those relevant effects. Furthermore, EFSA will proceed with a screening on the basis of risks for individual chemicals which will result in a reduction of number of substances to be assessed for cumulative risks. This reduction of substances is also expected to reduce the number of effects to be considered in the assessment.
Istituto Superiore di Sanità, Dept of Food Safety, Nutrition and Veterinary Public Health	Will EFSA develop similar methods/approaches for environmental cumulative risk assessment?	The Scientific Committee's Guidance of the risk assessment of combined exposure to multiple chemicals (published in March 2019) already provides a harmonised framework for human health, animal health and ecological risk assessment. In view of the available resources, EFSA will now focus first on the implementation in human dietary risk assessment. When the

Question maker	Question	Answer
		roadmap for dietary exposure assessment will be established, further implementation in the environmental risk assessment will be considered.
Questions related to item 11-Update on the on-going activities of the PREV Unit		
Istituto Superiore di Sanità, Dept of Food Safety, Nutrition and Veterinary Public Health	Is the Guidance on B&M considering free-range mammals?	The risk assessment for B&M only considers wild mammals likely to be exposed to a.s., PPPs and metabolites.
RIFCON GmbH	Will the OPEX GD/calculator revision incorporate greenhouse model?	Yes, EFSA is currently evaluating greenhouse data (and respective modelling) for the inclusion of the greenhouse scenario for operators in the EFSA calculator (that will be part of the update of the EFSA OPEX guidance).
BASF SE	Will the in vitro comparative metabolism guidance also include the comparative liver enzyme induction?	No, the guidance will not include the comparative liver enzyme induction. It will focus on the identification of unique human metabolite(s).
General Question		
Ministry of Agriculture (Plant Health Regulatory Directorate), Ethiopia	What is the recent/latest/ advised science or technology which is recommend to increase plant production with quality and quantity rather than using pesticide chemicals? because at this time pesticides have a diverse impact in human, environment and in ecology.	Considerations on possible alternatives to the use of pesticides are outside the remit of EFSA and the PPR Panel. The EFSA Pesticide Peer Review Unit is responsible for coordinating the peer review process for the risk assessment of active substances (chemicals or microorganisms) used in Plant Protection Products (PPPs). Based on the risk assessment performed by EFSA and EU Member States, a decision on approval/non approval is taken by risk managers at the European Commission.