GENERAL REPORT OF PESTICIDE PEER REVIEW TELECONFERENCE 52

Peer Review Programme under Regulation (EC) No 1107/2009

Subject:

3 May 2021 (h 13:30-18:00 GMT+2, Rome)
- Implementation of isomer guidance Q&A

4 May 2021 (h 9:00-17:00 GMT+2, Rome)
- Residues and MRLs on rotational crops (EFSA draft technical report)

5 May 2021 (h 9:00-13:00 GMT+2, Rome)
- Assessment of residues in honey. Update and Q&A
- Guidance on extraction efficiency

Declarations of interest
In accordance with EFSA's Policy on Declarations of Interests EFSA screened the available Annual Declarations of interest (ADoI) filled in by the nominated experts. In addition, at the beginning of the teleconference the experts were invited to declare orally (Oral Declaration of Interest (ODoI)) any interests which might be considered prejudicial to his/her independence in relation to the items on the agenda. No interests were declared.

In accordance with the ED Decision on Competing Interest Management, Observers are not required to submit DoIs. However, at the beginning of the teleconference the observers were reminded that they have confidentiality obligations.

Date: 3 - 5 May 2021
Venue: Teleconference

Attendance SANTE, EFSA and MS Experts: AT, BE, BG, DE, DK, ES, FI, FR, EL, HR, IE, IT, LT, NL, PL, SE, SI

General comments including comments concerning study requirements and evaluation of studies in the section Residues are listed below. The comments received were discussed in the respective section.

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<tr>
<th>Date</th>
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<tr>
<td>30/4/2021</td>
<td>DE</td>
<td>Comments: Rotational</td>
<td>Comments on the Technical</td>
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General meeting

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<tr>
<td>30/4/2021</td>
<td>HR</td>
<td>Comments: Rotational crops</td>
<td>Comments on the Technical Report_HR.doc</td>
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General documents tabled at the teleconference:

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<tr>
<td>22/04/2021</td>
<td>EFSA</td>
<td>Presentation: Technical guideline on extraction efficiency</td>
<td>Discussions on extraction efficiency_general EM_May21.pptx</td>
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<tr>
<td>23/4/2021</td>
<td>EFSA</td>
<td>Presentation: Assessment of residues in honey</td>
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<td>29/4/2021</td>
<td>EFSA</td>
<td>Presentation: Industry FAQ on isomers</td>
<td>Industry FAQ questions.ppt</td>
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<td>3/5/2021</td>
<td>Italy</td>
<td>Overview table</td>
<td>Isomerism by classes ICPS2021 (003).xlsx</td>
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<td>20/4/2021</td>
<td>EFSA</td>
<td>Presentation: Criteria triggering investigation of residues in rotational crops “tier 0”</td>
<td>Criteria triggering investigation of residues in rotational crops (tier 0).ppt</td>
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<td>26/4/2021</td>
<td>EFSA</td>
<td>Presentation: Implementing the applicable guidance documents on the nature of residues in rotational crops (Tier 1 studies on RCs)</td>
<td>Tier 1 studies on rotational crops.pptx</td>
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<tr>
<td>26/4/2021</td>
<td>EFSA</td>
<td>Presentation: MRL setting to account for residues in rotational crops</td>
<td>MRL setting for RC.pptx</td>
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<tr>
<td>25/4/2021</td>
<td>EFSA</td>
<td>Calculation tool</td>
<td>Rotational crops calculators.xlsx</td>
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Post meeting note: A background document provided by BE for the discussion on honey has accidently not been shared in the meeting documents folder prior to the meeting but is now available.

Appendix

Presentations
General discussion

1. Guidance on risk assessment of pesticide a.s. and transformation products that have stereoisomers – Q&A

The following presentations were given by EFSA to the participants:
- Guidance on the risk assessment of PPP a.s. and their transformation products that have stereoisomers
- Industry FAQ on isomers
- Considerations on the implementation of the EFSA guidance document on stereoisomers in the context of MRL applications (Art. 6 to 10 of Regulation (EC) No 396/2005) and MRL reviews (Art. 12)

EFSA provided a summary presentation on the isomer guidance (https://www.efsa.europa.eu/en/efsajournal/pub/5804; implementation date 1 Aug 2021, see https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app- proc_guide_horiz_stereoisomers.pdf). At a workshop with EFSA last year, former ECPA (now CropLife Europe) has submitted questions that were also shared with attendees together with the answers provided by EFSA.

EFSA presented also the procedural aspects for future Art.12 and Art.10 applications, respectively, with regards to the new isomer’s guidance, specifically the different cases that can occur during the process and what would be the implications. The flow chart should always be considered when dealing with MRL review and applications as by implementation date, and EFSA can be consulted in case of further questions.

Exchange of views among participants and further clarification by EFSA were provided.

2. EFSA draft technical report Residues and MRLs on rotational crops

The following presentations were given by EFSA to the participants:
- Implementation of the OECD Guidance Document on Residues in Rotational Crops
- Criteria triggering investigation of residues in rotational crops (Tier 0)
- Implementing the applicable guidance documents on the nature of residues in rotational crops (Tier 1 studies on RCs)
- MRL setting to account for residues in rotational crops

Prior to the meeting, MS experts provided comments to the draft Technical Report. Some of these comments were discussed during the meeting, others of more editorial nature were not discussed. All comments received will be considered by EFSA in the further update of the Technical Report. An additional week to provide further comments was offered to MS experts after the meeting report was submitted.

EFSA provided a presentation on the legal background and existing guidance documents, the implementation of the guidance documents in regulatory practice and an overview of the assessment of the nature and magnitude of the residues in rotational crops (Tiered approach).

**Tier 0:** The conditions when metabolism studies in rotational crops (RC) are required were presented. The specific case of import tolerance applications was also discussed.

**Tier 1:** The proposal by EFSA to consider the effective application rates (Aeff), representing active substance effectively reaching the soil after plant interception, as the basis of the identification of the critical GAP with respect to rotational crops was presented.

A calculator has been prepared by EFSA (as beta version) to derive the effective application rate (Aeff) for the GAPs under assessment. Some participants stressed that the interception rate is not
appropriate for the last year of application since crop failure is a scenario to be considered according to Reg. VO 283/2013, point 6.6.1.

EFSA invited MS experts to express their views on a number of questions related to Tier 0 and Tier 1, which were further discussed in the meeting.

**Tier 2: Limited RC field trials (OECD TGL 504)**

EFSA presented how the provisions in OECD GD 2018 with respect to the number of limited trials to be performed as Tier 2 need to be interpreted in the EU context and consulted MSs experts in relation to different options to interpret the OECD guidance. Among those:

- number of limited field trials on RCs required,
- independency of the limited residue trials on RCs,
- residue levels from mature and immature crops,
- extrapolation of results of leafy matrices from all crop groups as representative for leafy crops

**Tier 3: Risk mitigation and MRL setting**

The following topics were discussed:

- Risk mitigation measures vs. MRL setting (step 5)

EFSA presented the issues on the option to consider risk mitigation measures versus the alternative of MRL setting for rotational crops. Several MSs stressed that a harmonisation of risk mitigation measures throughout the EU MSs would be beneficial and that risk mitigation cannot be left just to the applicant proposals. Currently risk mitigation measures applied are mainly limited to PBIs and maximum dose rate of application. It was agreed that further discussion is needed involving risk managers.

- Derivation of the input values for exposure calculations

Different options of approaches used in the past were presented and discussed. The need to agree on a harmonized approach was emphasized.

- Derivation of MRLs for rotational crops

With respect to MRL setting, different options of approaches used in the past were presented and discussed. The need to agree on a harmonized approach was emphasized.

The participants presented their views and asked further clarifications to EFSA.

EFSA invited MS experts to express their views on a number of questions related to Tier 2 and Tier 3.

**New fate and behaviour modelling tools (PERSAM)**

EFSA presented new modelling tools from the environmental fate and behaviour section for assessment of the soil compartment. These are ready and expected to be noted at EU level soon. However, effective implementation in the assessment presented in the dossiers will take another 2-3 years. The methodology proposed in the technical report to consider fate information data on the assessment of residues in rotational crops will need to be updated to take on board the new paradigm implemented in the fate models (PERSAM).

The participants presented their views and asked further clarifications to EFSA.
Further discussions with risk managers will take place in the PAFF Residues in June 2021 and the technical report will be amended accordingly, for further consultation by MS prior to its finalisation and publication.

3. **Assessment of residues in honey - Update and Q&A**

The following presentation was given by EFSA to the participants:

- Assessment of residues in honey – case studies, monitoring data and future work

EFSA provided a summary presentation on the Technical Guidelines on pesticide residues in honey (implementation date 1 Jan 2020, see https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_mrl_guidelines_honey.pdf), case studies, monitoring data (EU annual report on pesticide residues) and future work on the area as initiation of the discussion.

### Table: Discussion Pesticides Peer Review Meeting

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<tr>
<th>Question</th>
<th>Response / Feedback</th>
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<tr>
<td>What's the approach of other MSs when data on residues in honey are not provided for PPP? The guidelines are not clear on whether the data must be submitted for PPP applications.</td>
<td>EFSA – if the applications are under the New data requirements, studies on residues in honey need to be provided for PPP.</td>
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| Should residues in honey only be investigated from uses on non-target plants when it concerns a herbicide? Since other categories of active substances are not aimed at non-target plants, and as such the proportion of non-target plants that is being encountered with the active is very small compared to the target crop. This is of course in particular relevant for non-melliferous crops (e.g. cereals). | It was mentioned that applicants want to waive residue studies on honey for applications on non-melliferous crops.  
BE – suggests using AR x Drift Deposition factor to estimate the residues in nectar and pollen from adjacent crops, as indicated in the Bee GD (ecotoxicology). It is noted that this has never been discussed under the current guidelines, but this approach may be used. |

**Post meeting note:** A more detailed explanation of the approach by BE has accidently not been tabled for the meeting. EFSA considers this proposal valid but notes that the Bee GD is currently under review and the approach to consider which type of drift deposition values are applied will need to be reconsidered accordingly. Further to that EFSA proposes discussion of the topic in the OECD working group on Pesticide Residues in Honey.

AT – Non-target plants are not considered for residues in honey in Austria. It is stated that it was internationally agreed (post-Annex I group) not to consider non-target plants for residues in honey.

FR – In the OECD working group on Pesticide Residues in Honey, the question on non-target plants is still under discussion and needs to be clarified. In France the approach used in Austria is not followed. On this topic, reference is made to the example of spirotetramat.

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1 “In order to determine the fraction of the active substance reaching the soil and therefore the flowering weeds after application of spirotetramat on fruit orchards, the applicant applied a formula using interception and wash-off input values as outlined in the EFSA guidance documents for predicting environmental concentrations of active substances of plant protection products and transformation products of these active substances in soil (EFSA, 2014a, 2017b).” (EFSA, 2021)
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<th>Section</th>
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<td>General meeting</td>
<td>The reference to the 'international agreement' (not to consider residues on non-target plants for the time being) should be clarified. Discussion in conferences and WG PAI is not enough. This should be confirmed at SCoPAFF level; now it is mentioned in the EC Guidelines. Residues in honey from non-target plants cannot be ignored.</td>
<td>The issue on the reference to 'international agreement' raised by AT is noted in view of further discussion in future PAFF meeting.</td>
<td>There is an ongoing discussion suggesting that the syrup test could be a solution for assessing residues of herbicides in honey. Unfortunately, there's not yet a wide experience on these studies. Some experiments are ongoing and once the results will be available, they may indicate whether syrup tests are fit for purpose.</td>
<td>It is noted that in the EC guidelines it is indicated that the most critical GAP or scenario should be used to assess residues in honey.</td>
<td>would not be enthusiastic about this approach. DE also mentioned a study on sunflower where they found only very low pollen amounts of the target crop in honey, although the hives were directly located at the treated field. Reference of the study and further information was shared by DE (Moreno S., Galvez O. (2019): Study on the residue behaviour of Pyraclostrobin (BAS 500 F) on flower heads from sunflower, pollen and honey from beehives after treatment with BAS 500 06 F on sunflower crop under field conditions in Italy and Spain, season 2018).</td>
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<td>In case of a herbicide, it will easily be necessary to move the colonies to remote locations (out of the tunnel) due to decay of the plants. Isn’t it expected that this will lead to possible dilution of the residues in the honey?</td>
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<td>Criteria to select the cGAP for residues in honey?</td>
<td>FR – As bees forage on different crops, it would be useful to perform the assessment on residues in honey from a worst-case scenario using the highest AR from the a.s. cGAP and Phacelia as a surrogate. The results will then cover the application of the a.s. in all other crops. This approach may lead to a high MRL, but it will still be representative of a cGAP. For the specificity, it is recommended to have tunnel trials, so it is sure bees forage on the treated crop.</td>
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<td>How to establish if an a.s. is systemic? It is noted that a footnote is included in the EC guidelines.</td>
<td>EFSA – It is noted that a footnote is included in the EC guidelines stating that “If metabolism studies in crops (studies conducted according to OECD guideline 501) clearly establish that neither the parent nor toxicologically-relevant metabolites are present in a non-treated part of the plant when the active substance is applied according to critical GAPs, then it can be considered that the active substance is not systemic. Indications can also be found in the rotational crop studies.”</td>
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<td>Question</td>
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<td>It must be noted that data from metabolism studies on different parts of the plants are not always present. FR - It must be noted that the uptake of rotational crops from roots may differ from the uptake from the leaf when an a.s. is applied via foliar applications.</td>
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| What is the approach used for cereals, considering that buckwheat is included in the list of crops with melliferous capacity, while other cereals are not? This question is referring to an MRL application. | EFSA – if the GAP is for all cereals (thus covering buckwheat which is listed in Appendix II as a melliferous crop), then residues in honey should be considered according to the criteria set in the EC Guidelines. It was noted that without the specifics of the application it was not possible to advise further on this issue. LT – one of the criteria included in the Guidelines: “Residues in honey can occur when a substance with systemic properties is applied prior to the flowering stage (before BBCH 60), including treatment of seeds, of a crop which is foraged by bees”.

FR - FR would apply proportionality. |
| Can proportionality be applied for residues in honey?                     | The majority of experts commented they do not have experience on that. HR added the use of SPE 8 sentences for protection of bees. LT – “If applicant do not provide residue data on honey and the application is during flowering, we put mitigation measures in the label.”

LT provided an oral clarification/amendment: applications on PPPs are rejected if data on residues in honey are not provided for the following cases: - If the PPP is applied during flowering - if the PPP is applied before flowering in the case the a.s. is systemic. It was added that, for emergency authorisation they do not ask for data on residues in honey.

FR – FR would apply proportionality. |
| Have any of the MSs experiences on setting risk mitigation measures to restrict residues in honey? |                                                                                                                                                                                                          |
| Do residues in honey need to be addressed in Mutual recognition applications? (based on assessment from other MS prior to implementation of Honey guidance) | BE – “date of submission in reference MS is decisive to establish which GD should be applied”.

FR – “We would not require data if the initial assessment was made before the date of application of the guideline”.

FI – “We have same experiences with the mutual recognition applications, where the Review Report is often from before 2020 and often miss data for residues in honey. It is our understanding that with mutual applications, mainly only data concerning local conditions could be requested, such as environmental data.”

This topic was not further discussed. |
4. Guideline on extraction efficiency

The following presentation was given by EFSA to the participants:

- Application of technical guideline on extraction efficiency: sharing of Authorities’ views

EFSA introduced the topic indicating that the scope of this discussion was to share its view on how to apply the SANTE extraction efficiency guideline (see https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_mrl_guidelines_wrkdoc_2017-10632.pdf) and to exchange views on how to demonstrate that the extraction efficiency requirements are met.

EFSA noted that the assessment of extraction efficiency is not new as it was already a requirement under the old and new data requirements. What is new in the extraction efficiency technical guideline is when and how to assess extraction efficiency. It was noted that extraction efficiency cannot be established during method validation with fortified samples and should be assessed with samples bearing incurred residues. This guideline applies to both pre- and post-registration methods. The extraction efficiency should be evaluated for all matrix groups for which residue analytical methods are required and for all analytes included in the residue definition for monitoring for post-registration methods and all analytes included in the residue definition for risk assessment for pre-registration methods. Ideally the evaluation is done from samples with radiolabelled pesticides used for metabolism studies. However, as the sample material with radiolabelled incurred residue is typically available for approval of active substances only, the evaluation of the extraction efficiency for additional matrices or for different solvents could be performed in cross-validation experiments with samples containing incurred residues (residue trials samples or monitoring samples).

Concerning the applicability of this guideline, EFSA indicated that the guideline is applicable for:

- new active substance approval and renewal of active substances (EU level) submitted after 22 November 2019
- new product authorisations and renewal of product authorisations (relevant at MS level)
- applications for new MRLs under Art. 6 of Reg. (EC) No 396/2005 (EU level) made after 22 November 2019
- MRL reviews and specific MRL assessments under respectively Art. 12 and Art. 43 of Reg. (EC) No 396/2005 (EU level) where the data requirements for the latest approval or renewal should be considered, so proof of extraction efficiency in line with this document will only be required if it was required for the latest approval or renewal.

According to the guideline it is required that the applicant addresses the extraction efficiency of the methods used to generate residue trials and for the enforcement method. The information provided by the applicant should be evaluated by the RMS/EMS and reported in the DAR/RAR/ER submitted to EFSA. It was highlighted that if the information on extraction efficiency is not reported in DAR/RAR/ER for applications submitted after 22 November 2019, EFSA will request clarifications considering the requirements of the extraction efficiency Guideline.

Discussion Pesticides Peer Review Meeting

It was questioned by a MS if this trigger date refers to the date of application or date of submission of the dossier. EFSA will double check and provide this information after clarifying it with the Commission.

Post-meeting note: Regarding the applicability from 22 November 2019, Commission clarified the following as the reference dates in the different processes:
- for MRLs applications pre-Transparency Regulation (submissions before 27.03.2021), the reference date is the submission date of the application form while for post-Transparency Regulation (submissions after 27.03.2021) is the date of submission of the IUCLID dossier;
- for MRLs review the reference date is the date of the launch of the data collection;
- for approval or renewal of active substances the reference date is the date of submission of the dossier.
A MS questioned what will happen in the process of renewal when the applicant has not submitted any data on the extraction efficiency. They understand this will not be a reason to invalidate the residue trials. So, if no data on extraction efficiency are reported, could the residue data be considered validated or should new residue trials be asked?

EFSA indicated that while the Guideline is now applicable there is not much experience in applying it yet and it could be a case by case decision on how to deal with the validity of residue trials when the extraction efficiency is not provided. In any case, it would be up to the applicant to make a case why the residues trials should be regarded as valid and to the RMS/EMS to have a view if the argumentations are acceptable. EFSA further indicated that if the information on extraction efficiency is not reported in the DAR/RAR/ER submitted after the triggering date for the applicability of the Guideline, EFSA will require further clarifications. Then if the lack of information on extraction efficiency is affecting the validity of the residue trials and it should be considered as a data gap it will depend on the validity of the arguments the applicant could put forward. Moreover, in case of a data gap, EFSA’s view would be to set this data gap for the analytical method and not for the residue trials. So, in first instance, the request could be to clarify the extraction efficiency of the analytical method and only if this is not proved and the analytical method considered not suitable, then the residue trials should not be considered valid. It should be also noted that the Guideline does not say that new data have to be generated but that the extraction efficiency could be demonstrated by existing data (e.g. by means of cross-validation studies).

Another MS indicated it would be strange that if the extraction efficiency is not addressed it will not have an impact on the validity of the residue trials. This is part of the validation of a method to confirm the reliability of the residue trials values. This means we have a data gap to address the extraction efficiency of the method used for trials to support the existing or new MRLs. A different MS indicated if the extraction efficiency could be seen as a confirmatory data requirement, meaning that the residue trials could be valid pending the extraction efficiency is proved. This approach could be used particularly in renewal where there is very large data package. The applicability of this data requirement and possible confirmatory data/data gaps in the different processes should be better reflected and clarified in the different processes (Art.10, Art.12, peer-review).

EFSA indicated that in Art.10 it is difficult to reject trials based on the extraction efficiency not proved. Reasoned opinions with pending conclusions are not looked on favourably by the risk managers. So, the approach could be to ask for clarifications or stop the clock if the issue is not addressed or fully justified. Further clarifications with the Commission could also be sought.

Post-meeting note: Commission recommended further discussion on the impact of the lack of proven extraction efficiency on the validity of residue trials at the PAFF Residues meeting in June 2021, and also further discussion with the experts in the EURLs is envisaged.

The experts then discussed the cases when the metabolism group is not matching the analytical method category. A MS expressed the wish to harmonise the two tables with the different categories as in the metabolism study the categories are quite large while in the analytical method the categories are more specific. Another MS suggested that the applicant should make the case why they think extraction efficiency would be applicable. This could depend on the properties of the compound and the nature of the matrix. In case where this is not possible, it may be considered acceptable if extraction efficiency is shown for the other matrix types for which identical/similar extraction procedure is used. Additionally, references could be made to known internationally recognized analytical methods in which identical/similar extraction procedure are used for the same compound as these methodologies are often used in monitoring labs, which are subjected to proficiency/ring testing with incurred residues. However, this should be evaluated with care and on a case by case basis. Another MS questioned the use of PTs (proficiency testing) for cross-validation purposes as although in some PTs the distributed sample material bears incurred residues, the material is not radiolabelled. Another MS suggested consulting EURLs for data on PTs.

The next point addressed was related on ownership of data and access to full study report on metabolism, EFSA questioned how the extraction efficiency could be proved without the access to
the full study report. One MS indicated the possibility to build a database with the available data to facilitate the work and give information without the need of the complete study report. EFSA and some MSs questioned whether the database could be effectively built in view of intellectual property protection. Another MS indicated that if data is available to the MS (but not for the new applicant), in their opinion this information can still be used to assess the extraction procedure followed. The fact that access to the full metabolism study is not available for the new applicant does not mean that the extraction efficiency is not shown if the same extraction procedure is used for the same compound in the same matrix group. This interpretation was supported by other MSs.

Finally, it was discussed how to deal with matrices difficult to analyse, e.g. hops. A MS raised this question as it concerns quite often minor crops such as caraway, which is an important crop for this MS. They indicated that for these difficult-to-analyse matrices such as spices very often no extraction efficiency data or samples with radiolabelled incurred residues are available. Then they proposed to consider on a case by case basis data from another similar group like e.g. oilseeds in the case of caraway. In general, EFSA would be supportive of this approach on difficult-to-analyse matrices. It was noted that the extraction efficiency Guideline for difficult-to-analyse matrices states that in principle an evaluation of the extraction efficiency would be desired as well, depending on availability of radiolabelled sample material or samples with incurred residues. There was agreement that such situations should be analysed case by case and a justification needs to be provided and included in the evaluation report.

A MS presented a possibility for proceeding when extraction efficiency of residue analytical methods for further uses not belonging to the matrix groups covered by the metabolism studies is not addressed. Provided that available metabolism studies cover at least three crop categories and that the metabolic pathway is identical in these groups, an indirect evaluation was proposed based on the extraction of samples containing incurred residues > LOQ: 1) with the solvent systems of the metabolism studies and 2) with the solvent systems commonly used in residue analytical methods for the matrix group in question not covered by the metabolism study. For the cross-validation, at least 3 extractions per solvent system should be performed and the extraction efficiency could be considered as sufficient if the residue analytical method extracts at least 70% of the amount extracted by the most efficient solvent system used in the metabolism studies. No other MSs commented on this approach. It was clarified that this should not be seen as an alternative always applied by default.

It was concluded that more practical examples would be desirable to see how to apply the extraction efficiency guideline in future. Further discussions and reflections would be needed also to address the initial question when the applicant has not submitted any data on extraction efficiency and how clarifications and/or data gaps could be set in order to finalize the assessment performed in the different processes.

Appendix
Guidance on the risk assessment of PPP a.s. and their transformation products that have stereoisomers

J. Oriol Magrans

Pesticide Residues Unit
Regulated Products Dept.
EFSA
In October 2016, the European Commission sent a request to EFSA to produce an EFSA guidance to address the risk assessments for active substances of PPP that have isomers and for its transformation products that may have isomers.

The Terms of Reference had been previously agreed at the EFSA Pesticide Steering Network (PSN) meeting with the EU Member State risk managers.

The Guidance document was adopted by EFSA on 22 July 2019 and was noted in the PAFF legislation on 3/4 December 2020 with an implementation date of 1 August 2021.
What are stereoisomers?

**Definitions**

- **Isomers** are substances that share the same molecular formula.

  E.g. ethanol CH₃CH₂OH and ether CH₃OCH₃ both have the molecular formula C₂H₆O

- **Stereoisomers** are substances that share the same molecular formula, connectivity and bond multiplicity, and differ in the spatial arrangement of two or more atoms.

- **Enantiomers** are pairs of stereoisomers constituted by molecules consisting on the two non-superimposable mirror images of otherwise identically connected molecular structures.

- **Diasteromers** are stereoisomers that are not enantiomers (have identically connected molecular structures but those do not correspond as mirror images of each other).
Examples

stereoisomers

enantiomers

diastereoisomers
An active substance is an *active substance containing stereoisomers* when its three-dimensional chemical structure can give rise to stereoisomers (by the exchange of two or more atoms).

The term *applies to*: 

- active substances containing *several components consisting of stereoisomers*, or,
- active substances *consisting of a single component that has the potential of having stereoisomers* (which may eventually be present impurities or formed by the active substance transformation).

The *same criteria applies for* a transformation product considered as a *metabolite containing stereoisomers*.

**IMPORTANT !!!** Metabolites containing *stereoisomers* may be generated from substances that do not contain stereoisomers.
Active substances containing several components consisting of stereoisomers

cypermethrin (8 isomers), fenvalerate (4 isomers), dichlorprop (2 isomers), metalaxyl (2 isomers), diniconazole (2 isomers), metolachlor (4 isomers, generated by a chiral carbon and the impeded rotation: atropisomers), (2 isomers), acetochlor (2 isomers, rotamers atropisomers), alachlor (2 isomers, rotamers atropisomers), fenamiphos (2 isomers), fonofos (2 isomers), malathion (2 isomers), imazapyr (2 isomers), imazaquin (2 isomers).

Active substances consisting of a single component that has the potential of having stereoisomers.

dichlorprop-P (R isomer of dichlorprop), metalaxyl-M (R isomer of metalaxyl), diniconazole-M (R isomer of diniconazole), mecoprop-P (R isomer of mecoprop).
Examples II

Striking complex situations... e.g. Cypermethrin related active substances.

Isomer 2 (\(1S,\text{cis}, \alpha R\)) is the most biologically active. Isomers 3, 5 and 8 are between 30 and 100 times less active and isomers 1, 4, 6 and 7 between 100 and 10 000 times less active than 2.\(^1\)

**Alpha–Cypermethrin** is the racemic mixture of 2 and 4 and it is the most biological active cypermethrin in the market.

**Cypermethrin**: mixture of the 8 isomers

**Beta–Cypermethrin**: isomers 2, 4, 6 and 8

**Zeta-cypermethrin**: isomers 1, 2, 7 and 8

**Theta-cypermethrin**: isomers 6 and 8

---

Since they may show different chemical (diasteromers) and biological (all) properties, **stereoisomers** must be treated as **different chemical components** with respect to the risk assessment.
Issues the guidance intends to address

- On **how to address the data requirements** in the case of substances containing or generating stereoisomers.

- On **how to make the best use of available information** in situations when information on individual stereoisomers is not available or difficult to obtain.

- On **how to optimize the studies performed** and decide the best design for them to obtain the maximum information on stereoisomers properties.
Regulation (EU) 283/213 requires

-to establish and provide a **detailed description** (specifications) of the active substance, which will include **isomeric composition** and perform tests required with material representative of such specifications

-to report the **relative biological activity of isomers**, both in terms of **toxicity and efficacy**

-to assess toxicological ecotoxicological **relevance of isomers present as impurities**
Regulation (EU) 283/2013 requires that when the substance is a mixture of isomers, it should be clarified how this influences on the effects, based on the mode of action of the individual isomers.
Candidates for substitution

One of the conditions for considering a substance as a candidate for substitution is that it contains a significant proportion of non-active isomers (Regulation (EU) 1107/2009 ANNEX II, point 4)
- **Chemical analysis** to separately quantify the *stereoisomers* during the course of the studies.

  To identify if conversion or preferential transformation of stereoisomers occurs.

  To adequately relate the effects observed to the different stereoisomer composition.

- **Additional effect experiments** with materials containing *purified stereoisomers* or different proportions of stereoisomers from those in the a.s.

  To individualize the effect of each isomer.

  To assess the effect of the actual mixture of isomers to which organisms will be exposed to.
**Bridging studies** may allow to infer the general relative behavior and biological effects of different stereo isomers on basis of a limited amount of tests.

**Use of data** generated for **different active substances** consisting on different proportions of the same stereoisomers.
Consideration of stereoisomerism

Stereoisomers may differ in their toxicological potency or profile, changes in the stereoisomeric composition need to be considered in the risk assessment. Eventual differences in the stereoisomeric composition of the toxicologically tested substance and the stereoisomeric composition of the actual residue to which humans and animals may be exposed to need to be addressed.
Metabolism, distribution and expression of the residues

- Metabolism studies must elucidate preferential metabolism, distribution of stereoisomers and stereoisomer interconversion.
- If the a.s has enantiomers a “chiral” analytical method must be used.
- Metabolism legacy studies (not addressing stereoisomerism) can be used if enough information on stereoisomers behavior has been obtained in field trials and animal feeding studies.
Magnitude of residues, plant and animal trials.

- Stereoselective analytical methods may or not be needed depending on the results of the metabolism studies.

- Nevertheless, the use of stereoselective methods in field trials and animal feeding studies is **strongly recommended** to increase the robustness of the metabolism data and to allow the use of legacy metabolism studies.
Residue definition

- Guidance does not add study requirements to those already established in the regulation but helps to clarify the information that needs to be collected in these studies.

- Application of the guidance helps to minimize the need to separately monitor stereoisomers, providing strategies to perform worst case risk assessment in situations where information on levels of separated stereoisomers is not available.
Residues in food and feed

Residue monitoring

- Decision on the need of stereoselective monitoring is out of the scope of the guidance. Such decision may be considered by risk managers based on the relative toxicological properties of stereoisomers and the need to monitor them separately for adequate risk assessment and GAP enforcement.
Degradation in soil

- Stereoisomeric composition of the residue in soil needs to be investigated and changes with respect to a.s. stereoisomeric composition are considered a transformation.

- Degradation and/or formation of individual stereoisomers of the active substance or its metabolites should be characterized.

- Changes of stereoisomeric composition $\geq 10\%$ s.e are considered significant with respect to the environmental risk assessment.
On the ≥ 10 % s.e trigger

- Changes ≥ 10 % s.e in the residue with respect to the substance as manufactured are considered potentially significant.
- The trigger should not be considered a “hard trigger” but on a case by case basis and weight of evidence.
- Stereoisomeric excess is only defined for pairs of stereoisomers.
- Stereoisomeric excess changes may be matrices' dependent.
- The relative change between stereoisomers may depend of the initial proportion.
- Effect of analytical method errors need to be considered.
- Further information in Appendix A of the guidance.
Uncertainty factor

-If information is incomplete to determine the changes in stereoisomeric composition of the residue or their relative toxicological potency, an uncertainty factor can be introduced in the risk assessment.

- The uncertainty factor is calculated with the worst-case assumption that the toxicity of the original mixture can be attributed to a single stereoisomer and that this isomer constitutes the totality of the residue.

- Less worst-case can be assumed if information on the relative toxicity or residue stereoisomeric composition is available.

- Further information on the calculation of the uncertainty factor can be found in Appendix B of the guidance.
Thanks for your attention
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Analytical methods and uncertainty factors

- **Is there a need to use UF when residues are < LoQ and or LoD?**
  The UF should be applied on residues < LoQ in a first instance. This may be further refined when residues are consistently non detected (< LoD).

- **Is there a requirement for chiral monitoring methods?**
  Depending on the residue definition, non-chiral and chiral monitoring methods may be needed by risk managers for the monitoring and enforcement needs (e.g. to distinguish two different active substances in the market).

- **Should a chiral method be developed for each enantiomer of conjugates which are natural products (e.g. sugar conjugates) when the aglycon itself has no chiral center?**
  In special situations, such as active substances that are constituted by only natural products, the analytical methods should allow to separate only those components known or expected to occur naturally. This is also the case for metabolites consisting of conjugates of a synthetic active substance to natural products (e.g. sugar conjugates), where the synthetic component does not contain a stereogenic element.
Do we need to consider for further isomer assessment food and feed items or are food items sufficient?

Feed items are considered for livestock.

Could the analysis of the liver (central organ for metabolism) in animal metabolism studies with regard to the isomer ratio be sufficient or are the other matrices (e.g. muscle, kidney) still of interest?

If no different metabolites are found in other matrices (e.g. milk and muscle) the isomer ratio in liver may be used as a surrogate for other matrices. If metabolites are specific to a given matrix the isomer ratio will need to be investigated in that matrix.

The test material should in principle reflect the ratios of isomers in the terminal residue. A “representative” ratio should be considered for the material to be used in the test studies. How can this “representative” ratio be defined?

On the basis of the available data from metabolism studies and / or residue trials.
10% TRR is discussed but for example in Consumer Safety mg/kg is also a ‘trigger value’. Concentration must be taken into account for technical feasibility?

10 % in the guidance refers to e.e or, more in general, s.e (stereoisomeric excess) and no change with respect to other percentile or absolute level trigger is proposed. See Appendix A of the guidance for further explanations.

It is difficult to understand how the 10% se change trigger should be employed for molecules with >2 chiral centers.

For more complex mixtures of stereoisomers, it is recommended to use residue decline studies to investigate the fate of each individual stereoisomer in order to decide if the stereoisomers behave differently during metabolism and ageing of the residues (see Appendix A for further discussion and examples).
Considerations on the implementation of the EFSA guidance document on stereoisomers\(^1\) in the context of MRL applications (Art. 6 to 10 of Regulation (EC) No 396/2005) and MRL reviews (Art. 12)

The guidance document on isomers provides specific options how to perform the dietary risk assessment for stereo isomers in food/feed resulting from the treatment with active substances:

- isomeric mixtures unchanged compared to a.s. applied or
- isomeric mixture different to a.s. applied.

Stereoisomers occurring in different amounts compared to a.s. applied should be considered as a specific type of metabolites that need to be assessed in view of consumer health risks. In contrast to other metabolites, the guidance document offers tools for their assessment, and options to avoid the generation of new studies.

The guidance document does not introduce new data requirements.

Purpose of the following flowcharts

- The introduction of new guidance documents for pesticides has implications on the assessments performed by EFSA in the different workflows (i.e. approval or renewal of the approval of active substances under Regulation (EC) No 1107/2009, MRL reviews under Article 12 of Regulation (EC) No 396/2005 and MRL applications under Art. 6 to 10 of Regulation (EC) No 396/2005).

- For assessments of the approval/renewal of active substances and for import tolerance applications for new active substances not assessed previously in the EU, a comprehensive data set as specified in the legal data requirements is provided by the applicants and assessed by EFSA/EMS/RMS. In these cases, the assessment will follow the GD without the need for further considerations.

- The assessment of MRL applications (active substances assessed previously in the EU) typically focuses on the specific data required to support the intended uses only, taking over conclusions of the approval and the MRL review process.

- Existing uses which were assessed previously and for which MRLs have been implemented in Regulation (EC) No 396/2005 undergo a comprehensive review in the framework of Article 12 of Regulation (EC) No 396/2005 taking over conclusions of the approval.

- The following flowcharts describe the approach for assessment of stereoisomers in the context of MRL applications Art. 6 to 10 (except import tolerances for substances not assessed previously at EU level) and Art. 12:
  - Slides 3 to 5 provide explanations on the procedural aspects for Art. 12
  - Slides 6 to 8 outline the procedural aspects for Art. 6 to 10
  - Slides 9 to 11 visualise the scientific assessment as suggested in the EFSA Guidance document.

- The general principle of the approach to be taken for MRL applications and MRL reviews is that the assessment of isomers (either by providing data to address the hazard of the individual isomers or the exposure to the individual isomers) should follow what has been done in previous assessments of the active substance in the peer review.

- If the approval/renewal or the MRL review was performed without mentioning the isomer aspects, the assessment of isomers would not become an issue in a subsequent MRL assessment under Art. 6 to 10 of Regulation (EC) No 396/2005 and MRL reviews.
No data gaps related to isomers:
Hazard characterisation for individual isomers is available;
information on isomeric composition of residues for the existing uses are available

Assessment according to the principles of EFSA GD

No consumer risk identified
- Derive MRL recommendations

Acute risk identified for one or several existing uses
- Propose a refinement identifying a fall-back MRL or proposing to lower the MRL to the LOQ

No acute risk for existing use, but chronic risk identified
- Propose a possible refinement considering fall-back GAPs or proposing to lower the MRL to the LOQ
Data gaps related to stereo isomers were identified in peer review (hazard data and/or information on isomer ratio in treated crops)?

Yes, confirmed in approval decision:
- Confirmatory data were requested in approval decisions to be addressed within 2 years from the adoption of a GD on isomers.

Yes, but data gaps were not formally taken over in approval decision:
- Confirmatory data were not formally requested in approval decision.

No:
- Possible preferential degradation/conversion to other isomers or the specific toxicity of isomers was not assessed in the peer review.

Data gaps of peer review were fully addressed; no data gap for the existing uses:
- Data gaps were addressed by new data submitted under MRL review; no data gap for the existing uses.
  - Assessment of isomer data according to EFSA GD; derive tentative MRL asking for confirmatory data.

Data gaps were not addressed:
- Data submitted under MRL review; additional data gap for the existing uses.
  - Assessment of isomer data according to EFSA GD; derive tentative MRL asking for confirmatory data.

Data gaps still open; data gaps are also relevant for the existing uses:
- Data gaps still open; data gaps are also relevant for the existing uses.
  - Derive Tentative MRL asking for confirmatory data.

Data gaps of peer review were not fully addressed; data gap for the existing uses:
- Data gaps of peer review were fully addressed; no data gap for the existing uses.
  - See Part 1.

Confirmatory data were requested in approval decisions to be addressed within 2 years from the adoption of a GD on isomers.

Confirmatory data were not formally requested in approval decision.

See Part 3.

Derive MRL recommendations.

Derive Tentative MRL asking for confirmatory data.
Data gaps related to stereo isomers were identified in peer review (toxicological data and/or information on isomer ratio in treated crops)?

- Yes, but data gaps were not formally taken over in approval decision
  - Confirmatory data were not requested in approval decision
  - Derive tentative MRL asking for confirmatory data

- No
  - Possible preferential degradation/conversion to other isomers or the specific toxicity of isomers was not assessed in the peer review
  - Information submitted, but not fully addressing all existing uses or no data on toxicological properties of isomers/information on isomer ratio in existing uses were submitted; data gaps for the existing uses

Relevant information is submitted with the MRL review; no data gaps for the existing uses

- Assessment in accordance with EFSA GD, See Part 1

During the completeness check EFSA asks whether data to address data gap on isomers can be made available (request for clarification);

If information is not available, RA is performed without consideration of the possible isomerization.

Derive MRL recommendations highlighting uncertainties in RA due to lack of information on isomers; in the recommendation table concerned MRLs will not be flagged for further considerations by risk managers.
No data gaps related to isomers:
Hazard characterisation for individual isomers is available (peer review, MRL review or previous Art. 10 applications); information on isomeric composition of residues for intended uses are available.

Assessment according to the principles of EFSA GD

No consumer risk identified
- Derive MRL recommendations

Acute risk identified for intended use
- No modification of existing MRL recommended

No acute risk for intended and existing use, but chronic risk identified for existing + intended use
- Present the data for intended use for further risk management consideration

No chronic risk for existing + intended uses, no acute risk for intended use, but acute risk for existing MRL(s)
- MRL recommendation for intended use; Inform RM on concerns for existing MRL

Procedural aspects for MRL applications (Art 10) for isomers – Part 1
Data gaps related to stereo isomers were identified in peer review/MRL review (hazard data and/or information on isomer ratio in treated crops)?

Yes, confirmed in approval decision/MRL regulation implementing the Art. 12.

- Confirmatory data were requested in approval decisions/MRL regulation implementing Art. 12 to be addressed within 2 years from the adoption of a GD on isomers.

Yes, but data gaps were not formally taken over in approval decision/MRL regulation implementing Art. 12.

- Confirmatory data were not requested in approval decisions/MRL regulation implementing Art. 12.

Not yet assessed.

- Possible preferential degradation/conversion to other isomers or the specific toxicity of isomers was not assessed in the peer review/MRL review.

Data gaps of peer review/MRL review were fully addressed; no data gap for intended use.

- See previous page

Confirmatory data submitted under MRL application; no data gap for intended use.

- Assessment of isomer data according to EFSA GD; see previous page

Confirmatory data submitted under MRL application; additional data gap for intended use.

- Clock-stop for missing data

Confirmatory data were not requested in approval decisions/MRL regulation implementing Art. 12.

Data gaps still open; but not relevant for intended use.

- Assessment of intended uses according to EFSA GD; highlight uncertainties of RA for uses not assessed under Art. 10 appl.

Data gaps still open; data gaps are also relevant for intended uses.

- Request missing information (clock-stop)

Procedural aspects for MRL applications (Art 10) for isomers – Part 2
Data gaps related to stereo isomers were identified in peer review/MRL review (toxicological data and/or information on isomer ratio in treated crops)?

Yes, but data gaps were not formally taken over in approval decision/MRL regulation implementing Art. 12

Confirmatory data were not requested in approval decision/MRL regulation implementing Art. 12

Relevant information submitted with MRL application, no data gap for intended use, but lack of information on isomer ratio for existing uses

Assessment in accordance with EFSA GD, See slide 6

No clock-stop, but contact EMS to ask whether data to address data gap on isomers can be made available (request for clarification); If information for existing uses is not available, perform RA with current RD RA and TRV, highlighting uncertainties; additional RA scenario for intended uses in accordance with GD

No data on toxicological properties of isomers/information on isomer ratio in existing uses were submitted; data gap for intended and existing uses

No clock-stop, but contact EMS to ask whether data to address data gap on isomers can be made available (request for clarification); RD RA If information for intended and existing uses is not available, perform RA is performed with current and TRV Highlight uncertainties in RA due to lack of information on isomers

Not yet assessed

Possible preferential degradation/conversion to other isomers or the specific toxicity of isomers was not assessed in the peer review/MRL review

Relevant information is submitted with the MRL application; no data gaps for existing and intended use
Case 1: a.s. is a mixture of stereoisomers

1) Toxicological properties of individual constituent isomers are available?
   - Yes
   - No

2) Constituent isomers are of same toxicity
   - Yes
   - No

3) Change of isomer ratio?
   - No change of isomer ratio (ee<10%)
     - Exposure for individual isomers according to ratio of isomers in a.s., TRV for individual isomer, considering RPF
   - Change of isomer ratio (ee>10%)
     - Exposure to individual isomers according to the actual isomer ratio, TRV for individual isomers, considering RPF
   - Not known
     - Exposure with Σ of isomers, TRV for mixture/RPF

\[ se(\%) = \left(\left| F_{A1} - F_{A2} \right| \times 100\right) \%
\]

\[ F_{A1}, F_{A2} : \text{mole fraction of stereoisomer A1 and stereoisomers A2} \]
Case 1: a.s. is a mixture of stereoisomers

1) Toxicological properties of individual constituent isomers are available?
   - No

2) Change of isomer ratio?
   - Metabolism studies, residue trials, processing studies, feeding studies
     - No change of isomer ratio (ee<10%)
       - Exposure for $\Sigma$ of isomers, TRV for mixture
     - Change of isomer ratio (ee>10%)
       - Exposure to $\Sigma$ of isomers, TRV for mixture/UF
     - Not known
       - No RA possible

UF: uncertainty factor, calculated based on isomer ratio in a.s. used in toxicological studies
$UF = \frac{100}{\text{isomer}_{\text{min}}}$
$\text{isomer}_{\text{min}}$: minor isomer (% in a.s. mixture of isomers)
Case 2: a.s. is a single isomer

1) Conversion to other isomers is possible (ee>10%)? (Equivalent to the formation of a metabolite for which isomer specific assessment is required)

- **Yes**
  - 2) Formed isomers is of same toxicity as a.s.? (Yes)
    - Exposure assessment with Σ of isomers, Compare with TRV of a.s.
  - 2) Formed isomers is of same toxicity as a.s.? (No)
    - 1) Exposure to a.s., compare with TRV for a.s., 2) Exposure to isomer, TRV for isomer (RPF)
      - Combine exposure 1 and 2

- **No**
  - No specific requirements for RA
  - Not known
    - No RA possible
Implementation of the OECD Guidance Document on Residues in Rotational Crops

Hermine Reich
Senior Scientific Officer
Treatment of primary crops with pesticides...

...can lead to residues in soil.

Depending on the properties of the active substance, the soil and other factors....

...these residues may still be present in the soil at harvest of the primary crop.

In succeeding/rotational crops not treated with the pesticide residues may occur via uptake from soil.

The assessment of the nature and magnitude of residues in succeeding crops is important
• to ensure that consumers are sufficiently protected.
• Legal limits (MRLs) or restrictions for rotational crops are defined to guarantee that rotational crops are safe and compliant with MRLs.
Introduction

Parameters relevant for assessment of rotational crops

- Soil type
- Temperature
- Humidity
- Metabolic activity

- Persistence/stability of a.s.
- Degradation kinetics
- Formation of soil metabolites
- Degradation rate of metabolites

- Type of crop
- Timing of planting

- Type of crop
- Application rate
- Number of treatments
- Crop development

Complex system, requiring interdisciplinary assessment approach with close collaboration of residue and soil experts
General provisions on data requirements
para 1.1 of the Annex to Regulation (EC) No 283/2013
Information to be submitted, its generation and its presentation:

The *information* shall be sufficient to *evaluate foreseeable risks*, whether immediate or delayed, which the *active substance may entail for humans*, including vulnerable groups, animals and the environment. The dossier shall *contain* at least the information and results of the *studies* referred to *in this Annex*. 
Studies concerning residues in rotational crops shall be performed to allow the determination of

- the **nature** and extent of potential residue accumulation in rotational crops from soil uptake and
- the **magnitude of residues** in rotational crops under **realistic field conditions**.

Legal basis: Regulation (EC) No 283/2013
How to perform the assessment?

Provisions of the different guidelines and guidance documents are not fully compatible, leave room for interpretations, do not define clear criteria for assessment (trigger values, thresholds).

EFSA started to prepare technical report to define how to implement the OECD TG and OECD guidance document in EU regulatory practice. Consultation of Member State experts and risk managers essential to provide clear guidance and practical solutions compatible with the legal framework (a.s. approval, MRL applications, MRL reviews).
Tiered approach

‘Tier 0’
Pre-conditions for rotational crop assessment

Tier 1
OECD TG 502
• Confined studies with radiolabelled a.s. in three different crop groups

Tier 2
OECD 504
• Limited field studies if triggered by Tier 1

Tier 3
OECD
• Field studies for deriving MRLs if triggered by Tier 2

OECD guidance document on residues in rotational crops (2018)
Additional clarifications mainly on OECD TG 504;
Examples on current practices in different OECD countries;
Guidance on MRL setting for rotational crops and possibility to define label restrictions;
Recommendations not binding.
pesticide is used only in permanent or semi-permanent crops

uses do not lead to residues in soil
- e.g. post-harvest uses, cultivation in hydroponic systems or in artificial substrates, structural treatment

no uptake of a.s. and soil metabolites
- e.g. from metabolism studies in primary crops (root crops)

a.s. and metabolites are not stable/persistent in soil, significant concentrations of metabolites in soil do not occur
**EU guidance document:**
Trigger value which was interpreted as DT$_{90}$ in soil for a.s. >100 d

**OECD documents:**
No trigger values defined

**EFSA technical report:**
- Definition of trigger values for a.s and relevant soil metabolites
- Guidance how to identify relevant endpoints to decide whether Tier 1 studies are triggered
- Guidance for import tolerance applications
  - Under which conditions are data on rotational crops required?
Purpose of Tier 1 studies

Tier 1 studies should

▪ provide an estimate of the total terminal residues in the relevant portion of crops at harvest of rotational crops following treatment of the preceding crop as proposed;

▪ identify the major components of the total terminal residue;

▪ indicate the distribution of residues between relevant crop parts;

▪ quantify the major components of the residue;

▪ allow to decide on the necessity of field residue trials in rotational crops (limited field studies);

▪ provide information on the components to be analysed for in higher tier studies;
OECD TG 502 Metabolism in rotational crops

- Representative crops for the three crop groups
- Study design
  - Application rate for Tier 1 studies (max. seasonal application rate of a.s.)
  - Plant Back Intervals (PBIs) simulating
    - crop failure (7-30 d),
    - typical rotation after harvest of primary crop (60-270 d) and
    - crop rotated in the following year (270-360 d)
- Parts of the crops to be analysed
- Interpretation of results
  - Trigger values for residue concentration (mg eq/kg and % of TRR) that require characterisation/identification.
EFSA technical report

- Further guidance on study design and practical examples on
  - application rate for a.s. and metabolites that accumulate in soil;
- Practical examples on how to consider crop interception
- Interpretation of results of Tier 1 studies
  - Scaling if studies were performed with higher dose rates than expected under realistic conditions
- Considerations on residue definitions for RC
Tier 2 studies should

- determine the amount of pesticide residues which may accumulate in rotational crops via soil uptake (semi-quantitative aspect);
- allow to decide whether Tier 3 studies are required;
OECD TG 504 Residues in rotational crops (Limited Field Studies)

- Study design and crops to be tested: very general, high level advice
- Analytical aspects: only general provisions


- Application rate for Tier 2 studies, considering the soil plateau concentration
- Considerations of metabolites mentioned, but no detailed provisions
- Examples for crops in which Tier 2 studies should be performed
EFSA technical report

- Further guidance on study design to be representative for predicted PEC soil
  - Option 1: separate testing of parent and metabolites,
  - Option 2: study with parent only (soil aging and analysis of residues in soil),
  - Practical examples to calculate the application rates for a.s. and metabolites that accumulate in soil

- Interpretation of results of tier 2 studies
  - Scaling if studies were performed with higher dose rates than expected under realistic conditions
  - Scaling for parent and metabolites for option 2
Tier 3 studies should
▪ provide data for MRL setting,
▪ provide information to estimate the impact of restrictions on residue levels in rotational crops.
No precise requirements defined in OECD TG 504


- Selection of crops for Tier 3 studies for the ‘Super crop groups’
  - Number of trials required
  - Examples of possible extrapolations of results to other crops
- Proposes an approach to derive MRL proposals based on rotational crop studies and where relevant primary crop uses
- Considerations how to perform risk assessment
  - How to derive input values for risk assessment
- General considerations of MRL setting versus restrictions
Practical implementation Tier 3

EFSA technical report

• Under which circumstances the setting of MRLs should be considered?
  • What are realistic worst case conditions (worst case PECsoil, plateau level reached after x years)?
  • Which are realistic plant back intervals (PBIs)?
• Number of trials required for European situation
• Practical advice how to perform risk assessment
  • Input values for risk assessment
  • How to combine risk assessment for primary crops and rotational crops
• Practical advice how to derive MRL proposals
• Further guidance on extrapolations of results to derive MRLs for crops in which no tier 3 studies are available.
• Which restrictions for rotational crops should be considered?
Implementation of provisions of OECD TG and guidance is complex and requires collaboration of residue and fate experts. Further guidance/practical advice is required.

EFSA started to work on a technical report to address the open issues for assessment of residues in rotational crops.

For future, relevant endpoints for assessment of residues in rotational crops should be reported explicitly in the List of Endpoints (LOEP).

Calculation tools for soil endpoints relevant for residue assessment.
Thanks for your attention!

Thanks to EFSA colleagues working on the technical guidance document and Member State experts who share their experience!

Thanks to Maja and Ilvie for illustrations.
Criteria triggering investigation of residues in rotational crops “tier 0”

Rotational crops FOCAL point

PRES

4th May 2021
When residues in rotational crops need to be investigated?

Regulation (EC) No 283/2013

Studies concerning residues in rotational crops shall be performed to allow the determination of the nature and extent of potential residue accumulation in rotational crops from soil uptake and of the magnitude of residues in rotational crops under realistic field conditions. Rotational crop studies shall not be required for uses of plant protection products in permanent crops (such as citrus and pome fruits crop group), semi-permanent crops (such as asparagus, pineapples) or fungi, where rotations on the same substrate are not part of the normal agricultural practices.

The information shall be sufficient to evaluate foreseeable risks, whether immediate or delayed, which the active substance may entail for humans, including vulnerable groups, animals and the environment and contain at least the information and results of the studies referred to in this Annex.
Metabolites that are reported in the LoEP (section “Environmental fate and behaviour; Residues requiring further assessment; Soil”) need to be considered with respect to potential residues rotational crops and in the context of the Technical Report are classified as significant soil metabolites.

Example

**Residues requiring further assessment**

Environmental occurring residues requiring further assessment by other disciplines (toxicology and ecotoxicology) and or requiring consideration for groundwater exposure.

- **Soil:** Fluxapyroxad (BAS 700 F) and the metabolites M700F001 and M700F002
- **Surface water:** Fluxapyroxad (BAS 700 F) and the metabolites M700F001, M700F002 and M700F007
- **Sediment:** Fluxapyroxad (BAS 700 F)
- **Ground water:** Fluxapyroxad (BAS 700 F) and the metabolites M700F001 and M700F002
- **Air:** Fluxapyroxad (BAS 700 F)
When are rotational crop metabolism studies are necessary?

Metabolism (tier 1) studies are required if the following conditions are met:

- The PPP is **used in crops which are grown in rotation** with other crops (Section 2.2 and Appendix A) and

- The use of a **pesticide leads to residues in soil** (Section 2.3) and

- The **active substance and/or its soil metabolites are sufficiently stable/persistent in soil** to be present in relevant amounts at the time of planting the rotational/succeeding crops (Section 2.4) and

- The **active substance and/or its soil metabolites are taken up via roots by the rotational/succeeding crops** (Section 2.5).
Regulation (EC) No 283/2013

**Metabolism studies** in rotational crops shall be provided if the parent compound or soil metabolites are persistent in soil or significant concentrations of metabolites in soil occur.

“Old” data requirements (Regulation (EC) No 544/2011)

Where data generated in accordance with point 7.1 of this Annex or point 9.1 of the Annex to Regulation (EU) No 545/2011 shows that significant residues (>10% of the applied active substance as a total of unchanged active substance and its relevant metabolites or degradation products) remain in soil or in plant materials, such as straw or organic material up to sowing or planting time of possible succeeding crops, and which could lead to residues above the limit of determination in succeeding crops, consideration shall be given to the residue situation.
Persistence triggers

Two basic triggers are proposed

▪ The active substance or any of the significant soil metabolites show a DT$_{90}$ ≥ 100 d in soil, tier 1 studies need to be provided.

▪ In case the soil DT$_{90}$ of the parent compound and the significant soil metabolites are individually below 100 days, but the sum of the soil DT$_{90}$s for the parent and the significant metabolites in any lineal degradation pathway exceeds 100 days, tier 1 studies are required.

The DT$_{90}$s to be considered in these triggers are those consistent with the end points selected as result of the fate and behaviour assessment to be used for the calculation of the PEC soil.
- DT90 for a.s. and/or significant soil metabolites


<table>
<thead>
<tr>
<th>Method of calculation</th>
<th>DT90 (d): 670 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field: longest non-normalised field DT50</td>
<td></td>
</tr>
</tbody>
</table>

Application data:
- Crop: Leafy veg
- Depth of soil layer: 5cm
- Soil bulk density: 1.5g/cm³
- % plant interception: 70
- Interval (d): 70
- Application rate(s):
  - Leafy Veg: 1 or 2 x 120 g a.s./ha (1 application per successive crop)

**SFO Kinetics: DT90 = DT50 × 3.32**
(first order kinetics)
DT90 for a.s. and/or significant soil metabolites

PEC soil (Regulation (EU) No 284/2013, Annex Part A, points 9.1.3 / 9.3.1)

Parent
Method of calculation

Focus standard PEC soil

DT90 (d) = 348 days (k1=0.07037, k2=0.002, q=0.575)

Kinetics: DFOP
Field or Lab: representative worst-case from lab studies

Rate of degradation in soil (aerobic) laboratory studies active substance (Regulation (EU) No 283/2013, Annex Part A, point 7.1.2.1.1 and Regulation (EU) No 284/2013, Annex Part A, point 9.1.1.1)

<table>
<thead>
<tr>
<th>Parent</th>
<th>Dark aerobic conditions</th>
<th>pH&lt;sub&gt;0&lt;/sub&gt;</th>
<th>t. °C / % MWHC</th>
<th>DT&lt;sub&gt;0&lt;/sub&gt; / DT&lt;sub&gt;10&lt;/sub&gt; (d)</th>
<th>DT&lt;sub&gt;90&lt;/sub&gt; (d) 20 °C pF2/10kPa&lt;sup&gt;a&lt;/sup&gt;</th>
<th>St. (v&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Method of calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yolo</td>
<td>Loam</td>
<td>7.2</td>
<td>20 / 50% MHC</td>
<td>34 / 791</td>
<td>348</td>
<td>1.27</td>
<td>DFOP (slow phase)</td>
</tr>
<tr>
<td>RefSol 03-G</td>
<td>Loam</td>
<td>6.2</td>
<td>20 / 50% MHC</td>
<td>12 / 249</td>
<td>129</td>
<td>1.83</td>
<td>DFOP (slow phase)</td>
</tr>
<tr>
<td>Site E1</td>
<td>Silt Loam</td>
<td>5.9</td>
<td>20 / 50% MHC</td>
<td>11 / 148</td>
<td>116</td>
<td>1.43</td>
<td>DFOP (slow phase)</td>
</tr>
<tr>
<td>Site I2</td>
<td>Loamy sand</td>
<td>7.4</td>
<td>20 / 50% MHC</td>
<td>2.5 / 30</td>
<td>8.9</td>
<td>7.08</td>
<td>FOMC (DT90/3.32)</td>
</tr>
</tbody>
</table>

pH dependence: No

<sup>a</sup> Measured in 1:1 soil/water ratio

<sup>b</sup> Normalisation not necessary since soils were incubated at 20 °C and Walker equation coefficient of 1 (soils were at moisture level > pF2)

Non-SFO Kinetics: take highest DT90 from aerobic rate of degradation in soil

Soil degradation

Soil concentration

Time

DFOP
If it can be **clearly demonstrated** that soil residues are **not taken up** by certain rotational crop groups, no further investigations are required for the relevant crop groups.

The use of simplified screening tests, such as **hydroponic assays**, may be **only acceptable on a case-by-case basis**. The studies must be representative of the relevant rotational crop groups and must allow extrapolation of the results from the assay to the soil situation. Currently, OECD is developing a Test Guideline to determine the uptake of chemicals by plant roots (OECD Project 3.15, OECD, 2019). The application of this test as a screening tool on the investigation of residues in rotational crops may deserve further consideration once it is adopted and published.
Waiving option

If all significant soil metabolites are identical with metabolites identified in primary crop as part of the residue definitions, Tier 1 studies can be omitted, and the assessment for rotational crops could directly start with the assessment of the magnitude of residues in rotational crops (Tier 2 studies, limited filed trials).
Studies on rotational crops in the framework of import tolerance applications are required when:

- **EU MRLs are established for metabolites occurring in rotational crops** (e.g., for trifluoroacetic acid, TFA): Since imported products need to comply with the EU MRLs, data on the occurrence of soil metabolites in annual crops resulting from critical uses in the country of origin that are likely to lead to residues in rotational crops are required.

- **Metabolites in rotational crops included in the EU residue definition for RA:** need of tier 2 and, if triggered, tier 3 studies for crops under consideration.

- **Active substance not (yet) fully assessed in the EU for presence of residues in rotational crops:** tier 1 studies and, if triggered, toxicological studies to characterize the toxicological profile of soil metabolites taken up by rotational crops and eventually higher tier studies might be required (**to further discuss with risk managers**).
Flow chart for rotational crop metabolism studies

When tier 1 required?

Grown in rotation?
  yes
  e.g. permanent crop
  no
  not required

Soil residues?
  yes
  e.g. hydroponic
  no
  not required

Persistent?
  yes
  < 10% soil residues at time of planting rot crop
  no
  not required

yes
Flow chart for metabolism studies

Plant uptake?

<table>
<thead>
<tr>
<th>Yes</th>
<th>Soil metabolites == primary crop metabolites?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Tier 1 studies are required</td>
</tr>
<tr>
<td>No</td>
<td>Under certain conditions, tier 1 studies can be omitted and jump directly to tier 2 studies</td>
</tr>
</tbody>
</table>

Under certain conditions, tier 1 studies can be omitted and jump directly to tier 2 studies.
End of “tier 0”
Implementing the applicable guidance documents on the nature of residues in rotational crops (Tier 1 studies on RCs)

Focal Point Group on Rotational crops
EFSA Pesticide Residues unit, 4 May 2021
Support the implementation of OECD TG 502

- Provisions of the different guidelines and guidance documents are not fully compatible, leave room for interpretations, do not define clear criteria for assessment (trigger values, thresholds).

- **OECD TG 502 on metabolism studies on rotational crops**: absence of values triggering the need for such studies (tier 0), no info available on how to identify the critical GAP and maximum seasonal rate, PEC(s) for a.s. and metabolites not discussed, accumulation in soil not considered, protocol specific to the a.s. only (provision for application of relevant metabolites in soil not available).
Tier 1 studies are required if soil residues constituted by parent and significant metabolites after 100 d are higher than 10 % of applied amount on molar basis.

A trigger based on the soil DT$_{90}$ is proposed to assess this criterium:

Total (a.s. plus metabolites) DT$_{90}$ > 100 d
Tier 1 studies: general considerations

- **Purpose of metabolism studies on rotational crops:** Identify the major residues taken up by rotational crops, establish residue definitions for rotational crops and decide whether limited rotational crop field trials (tier 2 studies) should be performed. Tier 1 studies can also serve as a basis to decide on restrictions in crop rotation.

- **Tier 1 studies, need to be conservative:** In order to ensure that tier 1 studies are representative for the critical situations encountered in practice as regards the active substance and its metabolites in soil, they should be performed with soil concentrations representative for the most critical case, taking into account the application rate in primary crops, plant interception, soil metabolism and possible accumulation of a.s. and/or metabolites in soil.

  If the studies are overdosed, results can be proportionally scaled-down.
Tier 1 studies decision tree

Are the Tier 1 studies appropriate?

Are studies for three crop groups available (i.e., root and tuber veg, small grain, leafy veg) (see 3.9)?

Request Tier 1 study on additional crops

Was the radiolabelling of test substance appropriate?

Request Tier 1 study with appropriate labelling

Was the application rate appropriate (see 3.9)?

Request Tier 1 study with appropriate application rate

Were different rotational intervals investigated?

Request Tier 1 study with additional rotational intervals

Request Tier 1 study analysing all relevant plant parts.

Were the relevant plant parts sampled and analysed (i.e., App A, Table A.1)?

Proceed with the assessment
Three crop groups to be considered, covered by OECD TG 502
- Root and tuber vegetables,
- Small grain (cereals) and
- Leafy vegetables

However,
- Oilseeds are not discussed in OECD TG 502

Tier 1 studies with oilseeds (oilseed rape or soybeans) may be requested if the three mandatory crop studies do not allow to derive a definitive conclusion on residue definitions for rotational crops (e.g. if the results in the three mandatory crop groups differ substantially or lipophilic substances are among the expected residues).
For tier 1 studies the tested substances shall be appropriately radiolabeled (OECD TG 502)

- Is the application rate appropriate?
How significant soil metabolites are investigated?

**Following OECD 2018 Guidance document:**

- Soil metabolites can be investigated with separate studies where the metabolite is appropriately applied or dosed to the soil.

- Alternatively, rotational crop studies may be performed by dosing the soil with a mixture of active substance and the significant soil metabolites.

- Finally, studies where only the parent active substance is applied can also be used to investigate residues of soil metabolites in rotational crops if it is demonstrated by chemical analysis that those are formed in soil at sufficient amount in at least one of the plant back interval investigated.
How the critical GAP is identified?

**General principle:**

- The critical GAP is the one resulting in the highest soil residues at the time of planting the rotational crop. This GAP does not necessarily coincide with the most critical GAP in primary crops which is selected to derive MRLs.

**Main driving factors**

- Application rate and the number of applications.
- Timing of the application (crop development) and the crop interception

Since it is difficult to determine the exact time of planting rotational crops and the residues at that time, it is assumed that a direct proportionality will be maintained between the applied substance and the amount remaining at the time of planting. Therefore, it is proposed that the effective application rates ($A_{\text{eff}}$) for each GAP under assessment can be calculated to identify the critical GAP which would be the one with the highest $A_{\text{eff}}$. 
Calculation of the $A_{\text{eff}}$

- A **calculator** is available to derive the effective application rate ($A_{\text{eff}}$) for the GAPs under assessment. The calculation of $A_{\text{eff}}$ is based on agreed crop interception values per crop and growth stage used in the environmental assessments (Focus, 2001) and uses as input value the annual application rate of the GAP under assessment.

- The GAP resulting in the highest estimated $A_{\text{eff}}$ (i.e. highest residues reaching the soil) would be the critical GAP and the estimated $A_{\text{eff}}$ for this GAP will be used to derive the appropriate application rate to use in tier 1 studies.
How to calculate the application rate (or soil dose) for rotational crop studies?

- **In metabolism studies on rotational crops the substance applies directly in soil.** OECD recommends to rely on bare soil application rather than on application to crops in all tiers of rotational crop testing, because the envisaged soil concentrations can be more easily achieved (OECD guidance, 2018).

- **The target concentration in soil to be attained in the study is the maximum concentration of the substance in soil (max \( \text{PEC}_{(s)} \)).** The conc. of the active substance in soil (\( \text{PEC}_{(s)} \) in mg a.s./kg soil) over a 20 cm horizon can be calculated from the effective application rate (\( A_{\text{eff}} \)) of the active substance estimated for the critical GAP.
How to calculate the application rate (or soil dose) for rotational crop studies?

Active substances not accumulating in soil (DT90 < 365 days)

- **If the substance is applied directly to soil.**
  OECD recommends to rely on bare soil application rather than on application to crops in all tiers of rotational crop testing (OECD guidance, 2018). $A_{\text{eff}} \, (\text{g a.s/ha})$ determines the application rates in these studies.

- **If the study is done in container, with soil dosed, the target concentration in soil is the initial concentration of the a.s. in soil (initial PEC$(_{s})$).**
  The initial PEC$_{s}$ over a 20 cm horizon can be calculated from the effective application rate ($A_{\text{eff}}$) of the active substance estimated for the critical GAP.

\[
\text{PEC}_{s20\text{cm}} \, (\text{mg a.s/Kg soil}) = \frac{(A_{\text{eff}} \, (\text{g a.s./ha}) \times 1000 \, (\text{mg a.s / g a.s}) \times \frac{0.2 \, (\text{m}) \times 1.5 \, (\text{Kg/ dm}^3) \times 1000 \, (\text{dm}^3/\text{m}^3))}{100000 \, (\text{m}^2/\text{ha})}}
\]
Active substances accumulating in soil (DT90 > 365 days)

- **If the substance is applied directly to soil.**
  The “accumulated” application rate $A_{acc}$ (g a.s / ha) determines the application rates in these studies. $A_{acc}$ takes into account accumulation after multiple years of application of the a.s. on the crop. OECD provides a method to calculate $A_{acc}$ (OECD guidance, 2018). Since the OECD method only works with substances degrading following first order kinetics, the Technical Report describes a procedure to derive the $A_{acc}$ using the Peak accumulated PEC$_{(s)}$ calculated by fate and behavior which is not kinetic dependent.

- **If the study is done in a container, with soil dosed, the target concentration in soil is the one derived from the accumulated peak PEC$_{(s)}$ 20 cm**
  Peak accumulated PEC$_{(s)}$ over a 20 cm horizon must be used as target dosing concentration.
Application rate for metabolites tested in tier 1 studies

As a general principle, target concentration in soil in the study should correspond to the maximum $\text{PEC}_{(s)}$ (if metabolite $\text{DT}_{90} < 365 \text{ d}$) or accumulated $\text{PEC}_{(s)}$ (if metabolite $\text{DT}_{90} > 365 \text{ d}$) over the 20 cm soil horizon.

- **Case 1. GAP under assessment identical to one peer reviewed GAP**
  
  Available $\text{PEC}_{(s)}$ (converted to 20 cm horizon) can be directly used to dose the study or calculate the application rate of the metabolite.

- **Case 2. Critical GAP under assessment is not addressed in the peer review**
  
  Technical Report provides a method to linearly convert the available $\text{PEC}_{(s)}$ in the GAP of reference (form the peer review) to the GAP under assessment.
In order to study significant metabolites in soil under tier 1:

- If maximum PEC$_{(s)}$ 20 cm (or accumulated PEC$_{(s)}$ 20 cm) of significant metabolite for 5cm soil horizon available in the peer review conclusions, conc. of metabolite to apply in bare soil (PEC$_{(s)}$ 20cm) estimated by converting the available PEC$_{(s)}$ 5cm in the excel calculator.

- If PEC(s) (or accumulated PEC$_{(s)}$) of significant metabolite for 5cm soil horizon not available in the peer review (extension of use not previously considered), conc. of metabolite to apply in bare soil (PEC$_{(s)}$ 20cm) estimated
  (i) by converting the PEC$_{(s)}$ 5cm to PEC$_{(s)}$ 20cm in the excel calculator and
  (ii) multiplying the result by an adjustment factor (AF):

  \[
  \text{PEC}_{(s)} \text{ 20cm [GAP under assessment]} = \text{PEC}_{(s)} \text{ 20cm [peer reviewed GAP]} \times \text{AF}
  \]

  \[
  \text{AF} = \frac{A_{\text{eff}} \text{ GAP under assessment}}{A_{\text{eff}} \text{ for representative GAP}}
  \]
It is **recommended that tier 1 studies are performed with exaggerated rates** compared with the application rate required to obtain the maximum concentration in soil based on the most critical identified GAP.

- Results of tier 1 studies can be scaled down, using the proportionality approach.

- Underdosed tier 1 studies are not recommended but upscaling from underdosed tier 1 studies may be accepted if adequately demonstrated that metabolites occurring below LOQ have not been overlooked (e.g., based on information in fate in the environment data).
In order to check if an available study has been adequately dosed or to derive the scaling factor, N rate can be calculated as follows:

\[
N \text{ (active substance)} = \frac{\text{application rate in the study (g/ha)}}{A_{\text{eff}} \text{ (or the } A_{\text{acc}} \text{) for critical GAP (g/ha)}}
\]

= 

\[
\frac{\text{dose in the study (mg a.s / kg soil)}}{\text{PEC}_{(s) \, 20 \, \text{cm}} \text{ (initial or accumulated peak) for critical GAP (mg a.s / kg soil)}}.
\]
For metabolites N rate can be calculated as follows:

- For metabolites the same formulas are applicable if the study design implies the direct application or dosing of the metabolite to soil.

- If soil metabolites are generated in the study dosed with the parent, then chemical analysis of the soil at the beginning of the test must be performed to demonstrate that the soil concentrations of the soil metabolites are within the desired range by calculating the N rate for the corresponding metabolites.

\[
N \text{ (metabolite)} = \frac{\text{measured concentration of the metabolite in soil at planting}}{\max \text{ PEC}_{(s) 20 \text{ cm}}}
\]

(or Peak accumulated \( \text{PEC}_{(s) 20 \text{ cm}} \), in case of metabolites with \( DT_{90} > 365 \text{ d} \))
Important considerations

- Different N rates can be obtained for a study depending on if the nominal rates or soil analysis are considered.
- Scaling of the residues observed is justified when N significantly deviates from 1. Small deviations that can be justified on basis to the experimental variability do not trigger the need to scale observed plant residues. This is especially true for the case of metabolites.

Calculation of the scaling factor

The scaling factors are the inverse of the N rate and are calculated as follows:

\[\text{Scaling factor} = \frac{1}{N}\]
- Were different rotational intervals investigated? (Covered by OECD TG 502)

- Are relevant parts of the plant sampled and analysed?
Are relevant parts of the plant sampled and analysed?

<table>
<thead>
<tr>
<th>Crop group</th>
<th>Matrix</th>
<th>Barley or Oats or Rye or Wheat or Any other cereal crop (Table B2)</th>
<th>Grain</th>
<th>Forage</th>
<th>Hay</th>
<th>Straw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1 representative crop</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Leafy crops</strong></td>
<td>Immature leaves(^{(a)})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lettuce or Spinach or Soyabean(^{(b)}) or Any other leafy crop (Table B2)</td>
<td>Mature leaves</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Root and tuber vegetables</strong></td>
<td>Roots</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beetroots or Carrots or Radishes or Sugar beets or Any other root and tuber vegetable crop (Table B2)</td>
<td>Leaves</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oilseeds</strong></td>
<td></td>
<td>Oilseed rape or Soyabean or Any other oilseed crop (Table B2)</td>
<td></td>
<td>Forage</td>
<td></td>
<td>seeds</td>
</tr>
</tbody>
</table>

\(^{(a)}\) Harvested at crop stage representing approx 50% of the normal time period for the plant to reach full maturity
For each substance (a.s./met), results to report per crop, PBI and part of plant analysed.

**Results to be scaled to the nominal rate if tier 1 studies over- or underdosed.**

Proceed with identification/characterization based on table by OECD TG 502

Derive **residue definitions** for rotational crops (open, results from higher tier studies performed with more realistic conditions should also be considered).

<table>
<thead>
<tr>
<th>Relative amount (%)</th>
<th>Concentration (mg/kg)</th>
<th>Required Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>&lt; 0.01</td>
<td>No action if no toxicological concern</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>0.01 – 0.05</td>
<td>Characterize. Only attempt to confirm identity if straightforward, e.g., a reference compound is available or the identification is known from a previous study.</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>&gt; 0.05</td>
<td>Characterisation/identification needs to be decided on a case-by-case basis taking into account how much has been identified.</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>&lt; 0.01</td>
<td>Characterize. Only attempt to confirm identity if straightforward, e.g., a reference compound is available or the identification is known from a previous study.</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>0.01 – 0.05</td>
<td>Significant attempts to identify should be made especially if needed to establish a pathway, ultimately characterisation might be accepted.</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>&gt; 0.05</td>
<td>Identify using all possible means.</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>&gt; 0.05 unextracted radiolabel</td>
<td>Unextractable radiolabel – See paragraphs 42-46 and Figure 1.</td>
</tr>
</tbody>
</table>

**OECD TG 502**
When results from tier 1 studies trigger the need for tier 2 studies?

- **If TRR < 0.01 mg/kg plant** for a.s./metabolite (expressed as parent) at all plant parts and PBIs, no further assessment required.

- **If TRR ≥ 0.01 mg/kg plant** for a.s./metabolite (expressed as parent) at any plant matrix and PBI ≥ 30 days (for discussion), studies on tier 2 are required.
MRL setting to account for residues in rotational crops

4 May 2021
Current practice for MRL setting in rotational crops
Presentation of the main steps and related questions for the MRL setting for rotational crops
Presentation and discussion on possible approaches
Current practice for MRL setting in rotational crops

- Peer review:
  - Based on critical representative use
  - In the past, usually specific group MRLs set for a crop group based on field studies

- MRL review:
  - Based on critical authorised GAP on primary crops, selected from all authorized uses in EU
  - MRL proposals based on residues from primary uses and rotational crop soil uptake considering the most critical GAP, but in most of the cases recommendation to implement risk mitigation measures

- Art 10:
  - Based on critical new use on primary crop
  - Upon request by the application, especially for rotational crops
  - For import tolerances - if requested by the applicant
  - Eventually proposals for risk mitigation measures (i.e., plant back intervals)
Main steps for MRL setting in rotational crops

Step 1. Selection of cGAP on primary crop
Step 2. Calculation of PECsoil for the cGAP
Step 3. Calculation of the N-rate
Step 4. Selection of rotational crop residue data (PBI, mature/immature crop, extrapolation)
Step 5. Verify whether risk mitigations are possible and decide for which crops MRLs should be derived
Step 6. Derive the input values for exposure calculations (consumers and livestock)
Step 7. Derive MRLs

Steps 1 to 3 covered by Tier 0/1 ppt
For each step of the MRL setting covered by this ppt (4 to 7), a list of questions/points for reflection has been identified (reported in red).

**MSs experts are invited to look at the questions and bring their experiences and views for discussion at the meeting.**
When are the limited RC field trials required?

- From the metabolism studies, residues of the parent compound or relevant metabolites either from plant or soil metabolism are ≥0.01 mg/kg in food commodities and ≥0.05 mg/kg in feed commodities.

Purposes of these trials?

- To determine the magnitude of the pesticide residues which may accumulate in rotational crops via soil uptake considering the critical GAPs.
- To decide on the need for MRLs in rotational crops - extended field trials (see also steps 6 and 7).
- To establish crop rotations restrictions (if residues according to the DoR are <0.01 mg/kg for at least one PBI tested).

Experimental design of the trials

- The trials conducted in two different geographical regions (major areas of cultivation) and over two different test sites within a region.
Application of the pesticide according to the critical GAP (maximum seasonal application rate/appropriate application rates), either to the primary crop or to bare soil

Representative rotational crops: root crops, small grain (cereals), leafy vegetables

An additional representative crop group may also need to be included if a crop important to the rotation is not covered by these crop groups, e.g., soybean in the US

These trials should focus on the crops/crop groups with significant residues (≥0.01 mg/kg) identified in the RC metabolism studies or to replace a crop group from the RC metabolism studies where no significant residues occur by another crop group (e.g., oilseeds, brassica vegetables)

Standard plant back intervals: 7-30 d; 60-270d and 270-365 d (?)

**Sampling**

RACs as food and feed items

Crops harvested immature for consumption (young leaves of spinach/salad)
Questions/points for reflections:

- **Which is the number of independent RC limited field trials on crops representative of the relevant crop groups that should be required for NEU/SEU/Indoor?**

  Example: flutolanil (PPR Meeting 09)(2NEU/2SEU)

  - If sufficient number of limited field trials have been submitted for certain rotational crop groups, provided that an appropriate application rate has been used in these trials, in principle these crops should not be tested again for the extended field trials.

- **Soyabean – P/O crop group can be considered relevant for EU?**

  - Limited field trials on oilseeds are in principle not required according to the OECD TGL 504. Is it acceptable to consider this crop group in place of a representative crop group?

- **How to select the residue levels based on the RC limited field trials?**

  - Consider always the highest residues throughout the different parts of the crops and PBIs investigated?
  - Consider results from mature or immature crops? (If the highest residue levels occur in immature crop parts, this may lead to an overestimation of the residue levels, e.g., immature to mature spinaches)
- **Which “extrapolation rules” can be applied?**
  - In absence of crops representative of leafy vegetables, can the upper leafy parts of the root crops be representative for leafy vegetables?
  - Vegetation period length of crops (from which crops mature leaves and from which immature (sugar beet leaves vs. lettuce))
  - Is there a need to develop a list with possible extrapolations for crops that are food and feed items? See proposals made under the assessment of Dimethomorph (PPR Meeting 191)
If in Tier 1 or 2 studies residues in rotational crops were <0.01 mg/kg at PBIs ≥ 30 days and at appropriate application rates (i.e. after scaling, if necessary), **no label restrictions and no MRLs are needed and Tier 3 studies are unnecessary.** If in Tier 2 studies residues in rotational crops reach significant levels (≥0.01 mg/kg), a **Tier 3 assessment** is necessary based on an “extended RC field study data package” to decide on appropriate **risk mitigation measures and/or to set MRLs**’ (para 40 from OECD, 2018).

Possible risk mitigation measures (label restrictions) (para 74 from OECD, 2018):

- Types of crops excluded from being planted directly in rotation.
- Plant-back intervals.
- Controls on the number of applications of the active ingredient per year.
- Controls on the maximum amount of the active ingredient applied per season or year.
- Controls on use of the active ingredient in consecutive years.

Label restrictions may be used to allow registration of products while additional higher tier studies are undertaken (para 75 from OECD, 2018).
Example: MRL review methoxyfenozide (EFSA, 2014).

The magnitude of the residues of methoxyfenozide was investigated in leafy vegetables (mustard), fruiting vegetables (tomatoes, cucumbers), root and tuber vegetables (potatoes, carrots, turnips, radish, sugar beet, green and bulb onions), pulses and oilseeds (beans, peas, soya beans) and cereals (wheat, sorghum, rice).

The results of the rotational crop field studies showed that it is not excluded that residues of methoxyfenozide occur at levels above the LOQ of the method (0.01 mg/kg), particularly in the edible matrices of leafy vegetables, root and tuber crops and in feed commodities (straw, forage, hay) when grown in rotation with treated crops according to the authorized European uses.

Furthermore, in view of the high persistence of the parent compound (DT90field> 1000 days), EFSA is of the opinion that additional field trials covering the maximum soil plateau concentration of methoxyfenozide are required in order to address the actual residue levels of methoxyfenozide in the rotated crops.

EFSA therefore concludes that Member States granting authorisations for methoxyfenozide should take the appropriate risk mitigation measures in order to avoid the presence of residues of methoxyfenozide in leafy vegetables, root and tuber vegetables and the feed commodities (cereals straw, forage and hay) used in rotation.
Questions/points for reflections:

- Should risk mitigation measures considered as the first option to avoid ‘unnecessary residues’ to occur in not-treated crops also considering that they can be limited to the most critical uses only?

- Other risk mitigation/label restrictions possible?

- Risk mitigation not harmonised among MS, further guidance from risk management to be provided/expected (as done in ecotox)
When MRL proposals should derived based on the available rotational field trials?

If the additional contribution by rotational crop residues is >25% of the residues arising after primary treatment, this contribution is considered significant and has to be considered in MRL setting (OECD, 2018)
Questions:

- Do you agree with the approach proposed by the OECD GD?
- How to apply the 25% principle (comparing HR_{RC} to HR or MRL of primary crop?)
- At which PBI (30 days?; irrespective if residues at longer PBIs<LOQ)?

Other possible options to set combined MRLs in rotational crops:

- if calculated MRL for RC is lower than the EU MRL for primary crop = no need to consider rotational crop residues for MRL setting
- if significant uptake (residues>0.01/0.05 mg/kg according to the RD for enforcement) can be excluded at certain PBIs = no need to consider rotational crop residues for MRL setting

- Is it possible to take into account monitoring data to conclude on whether there is the need to raise the MRL (at least in the MRL review where all the existing uses are considered but relevant also for the renewal)?
OECD, 2018:

The MRL should then be established based on an adjusted residue data set: the highest residue value obtained in GAP-compliant or scaled field rotational crop studies are added to each residue value obtained in GAP-compliant (primary) crop field trials.

The (MRL), STMR and HR is calculated from these adjusted residue values.
Step 6 Derive input values for exposure calculations – initial considerations

The goal is to **estimate** the residue levels (**residue distribution**) in a rotational crop, when residues may come from two **independent sources**.

1. **Uptake from soil** (**RC uses**)
   
   a. level of residues reaching the soil
   b. accumulation of the residues in soil (properties of the a.s./metabolites; climatic conditions, soil type)
   c. Uptake by the succeeding crops

2. **Primary treatment of the succeeding crop, if relevant** (**PC uses**)
Option 1a: derive the RA from the PC and RC field trials, separate risk assessment, the acute and the chronic exposures are combined

Option 1b: HR rotational crops + HR primary crops; STMR rotational crops + STMR primary crops;

Option 2a: adjusted residue (each individual PC residue value + HR<sub>RC</sub> ).

Option 2b: adjusted residue (each individual PC residue value + STMR<sub>RC</sub> ).

Option 3: HR/STMR derived for primary crop and rotational crops; select higher RA value.

### Examples for risk assessment value derivation (1)

<table>
<thead>
<tr>
<th>Crop</th>
<th>Residues in trials</th>
<th>PC only</th>
<th>RC only</th>
<th>Option 1b</th>
<th>Option 2a</th>
<th>Option 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary crop residues</td>
<td>Rotational crop residues</td>
<td>STMR</td>
<td>HR</td>
<td>STMR</td>
<td>HR</td>
</tr>
<tr>
<td>Broccoli</td>
<td>&lt; 0.01; 0.02; 0.05; 0.14</td>
<td>0.02; 0.03; 0.09</td>
<td>0.4</td>
<td>0.14</td>
<td>0.03</td>
<td>0.09</td>
</tr>
<tr>
<td>Brussel sprouts</td>
<td>0.01; 4x 0.04; 2x 0.07; 0.14</td>
<td>0.02; 0.03; 0.09</td>
<td>0.4</td>
<td>0.14</td>
<td>0.03</td>
<td>0.09</td>
</tr>
<tr>
<td>Head cabbage</td>
<td>3x &lt; 0.01; 3x 0.01; 0.02; 0.04; 0.08</td>
<td>0.02; 0.03; 0.09</td>
<td>0.01</td>
<td>0.8</td>
<td>0.03</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Step 6 Derive input values for exposure calculations

Example: head cabbage

<table>
<thead>
<tr>
<th>Residue concentration PC</th>
<th>Residue concentration RC (soil uptake)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>*</td>
</tr>
<tr>
<td>0.08</td>
<td>*</td>
</tr>
<tr>
<td>0.12</td>
<td>*</td>
</tr>
<tr>
<td>0.15</td>
<td>*</td>
</tr>
<tr>
<td>0.03</td>
<td>0</td>
</tr>
<tr>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>0.1</td>
<td>0.09</td>
</tr>
<tr>
<td>0.15</td>
<td>0.17</td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Sum of residues - derivation of RA values**

Option 1a: \( \sum \) separate risk assessment for PC + RC

Option 1b: \( \sum \) STMR PC + STMR RC; \( \sum \) HR RC+HR PC

Option 2a: \( \sum \) each PC residue value + HR RC.
Option 2b: \( \sum \) each PC residue value + STMR RC.

Option 3: higher RA value selected from PC or RC.
### Step 6 Derive input values for exposure calculations – existing approaches

<table>
<thead>
<tr>
<th>Approach</th>
<th>Pros/cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Option I</strong></td>
<td></td>
</tr>
<tr>
<td>A) HR/STMR primary</td>
<td><strong>Pros:</strong>&lt;br&gt;- less resource intensive/easy to update for GAP changes - less subject to mistakes&lt;br&gt;- more transparent: if concern identified, source is clearer - easier &amp; more targeted actions can be proposed (RMMs/or need for fall-back MRL)&lt;br&gt;- Suitable for complex RD RA for rotational crops (only relevant for option IA)&lt;br&gt;&lt;br&gt;<strong>Cons:</strong>&lt;br&gt;- deviates from OECD, 2018&lt;br&gt;- statistical analysis?&lt;br&gt;- require summing up results 2 different exposure calculations (only relevant for option IA)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>B) STMR primary + STMR rotational</td>
<td></td>
</tr>
<tr>
<td>HR primary + HR rotational</td>
<td></td>
</tr>
<tr>
<td>(boscalid/flupyradifurone (for DBC only)/fluopyram)</td>
<td></td>
</tr>
<tr>
<td><strong>Option II</strong></td>
<td></td>
</tr>
<tr>
<td>Individual residue values primary crop + HR rotational</td>
<td><strong>Pros:</strong>&lt;br&gt;- OECD, 2018 compliant&lt;br&gt;&lt;br&gt;<strong>Cons:</strong>&lt;br&gt;- statistically not sound, combines incompatible data sets (HR RC vs potentially large PC data set etc.)&lt;br&gt;- resource intensive - difficult to adapt for GAP changes&lt;br&gt;- use of STMR adjusted with HR value for calculations based on median residue levels (&quot;bulk&quot; commodities, feed by-products) - overestimates (acute/chronic) exposure</td>
</tr>
<tr>
<td>Use of OECD MRL calculator to derive the STMR and HR</td>
<td></td>
</tr>
<tr>
<td>(dimethomorph, fluxapyroxad)</td>
<td></td>
</tr>
<tr>
<td><strong>Option III</strong></td>
<td></td>
</tr>
<tr>
<td>highest RA values between PC and RC datasets (chloridazon)</td>
<td><strong>Pros:</strong>&lt;br&gt;- easy to perform&lt;br&gt;- easy to update&lt;br&gt;&lt;br&gt;<strong>Cons:</strong>&lt;br&gt;- May it underestimate exposure?&lt;br&gt;- deviates from OECD, 2018 core text - case 5: example how MRL setting done in the EU</td>
</tr>
</tbody>
</table>
Questions:

- Practices/observation of the MSs?
- Experiences, if any, with deriving RA values? (acute/chronic concern identified, etc..)
- Preferences?
OECD, 2018:

- **MRLs** should be set at a level that covers the residues from application to the commodity as a **primary crop** and residues arising from **rotational sources** (residue soil uptake) (OECD, 2018)

- If the **additional contribution by rotational crop residues is >25% of the residues arising after primary treatment**, this contribution is **considered significant** and has to be considered in MRL setting (OECD, 2018)

- **Combined MRL**: The **highest residue** (HR) value obtained in GAP-compliant or scaled field rotational crop studies are added to **each residue** value obtained in GAP-compliant primary crop field trials (OECD, 2018)

  - the approach not legally binding
  - not harmonized
  - and what about **specific rotational crop MRL** = reflecting only the residue soil uptake in cases where **untreated crop** is grown in soils containing residues at soil plateau concentrations
The MRL shall be:
✓ Realistic to avoid overestimation
✓ Simple and practical to implement
✓ Harmonised
✓ Transparent source of an MRL to easily identify

Current combined MRLs:
not harmonised
not transparent
not practical
not flexible (for revisions)

improvements required
### Combined MRL
*residues in crop from primary use and the soil uptake*

### Pros/cons

<table>
<thead>
<tr>
<th>Option</th>
<th>MRL primary + HR rotational → sum rounded to nearest highest MRL class (boscalid/flupyradifurone)</th>
<th>Pros:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>more transparent, less subject to mistakes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>less resource intensive/easy to update for GAP changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>source of concern is more apparent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>results lower MRL than Option II*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cons:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-methodology new</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-extrapolations between PC and RC not always one to one</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-statistical analysis?</td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>May residues be accounted for twice?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*see case study by NL on fluopyram/flupyradifurone</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Option II</th>
<th>Individual values primary + HR rotational</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Use of MRL calculator (dimethomorph, fluxapyroxad)</td>
</tr>
<tr>
<td>Pros:</td>
<td>-OECD, 2018 compliant</td>
</tr>
<tr>
<td>Cons:</td>
<td>-not statistically sound method (addition of HR)</td>
</tr>
<tr>
<td></td>
<td>-combines incompatible data sets (large/small, etc)</td>
</tr>
<tr>
<td></td>
<td>-resource intensive</td>
</tr>
<tr>
<td></td>
<td>-results in higher MRL than in Option I*</td>
</tr>
<tr>
<td></td>
<td>-artificially high mean residue*</td>
</tr>
<tr>
<td></td>
<td>-difficult to adapt for GAP changes</td>
</tr>
<tr>
<td></td>
<td>-source of MRL may not be transparent</td>
</tr>
<tr>
<td></td>
<td>-individual residue data for primary crops may not always be available (e.g. MRL based on CXL/IT)</td>
</tr>
<tr>
<td>Comments</td>
<td>*see case study by NL on fluopyram/flupyradifurone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Option III</th>
<th>MRL rotational v.s. MRL primary → max MRL (chloridazon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OECD MRL calculator</td>
<td>Pros:</td>
</tr>
<tr>
<td></td>
<td>-easy to perform</td>
</tr>
<tr>
<td></td>
<td>-less resource intensive/easy to update</td>
</tr>
<tr>
<td></td>
<td>Cons.</td>
</tr>
<tr>
<td></td>
<td>-might not account for combined residues</td>
</tr>
<tr>
<td>Comments</td>
<td>Could this be followed in case applicant does not request a higher MRL for certain RC?</td>
</tr>
</tbody>
</table>
### Rotational crop specific MRL

*in cases when crop is not treated as primary crop but grown in soils with background residue concentrations*

<table>
<thead>
<tr>
<th>Option</th>
<th>Details</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Option I</td>
<td>Rounding of HR rotational crop to nearest MRL class (pydiflumetofen)</td>
<td>Widely used approach</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Easy to calculate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transparent/Easy to update</td>
</tr>
<tr>
<td>Option II</td>
<td>MRL calculation using OECD MRL calculator</td>
<td>Statistical methods for estimating residues in RC not applicable (JMPR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normally small datasets available</td>
</tr>
</tbody>
</table>
Specific rotational crop MRL:

➢ normally based on a small residue data set

Use of OECD MRL calculation – not really applicable (*JMPR: “use of statistical methods for the estimation of MRL is not possible when considering potential carryover of residues in succeeding crops since the basis arising from the additional root uptake cannot be adequately calculated, using OECD MRL calculator”*)

➢ higher uncertainty due to low number of trials
➢ calculator not developed for that purpose

**Q:** Merging of SEU/NEU/indoor data to expand data set?

**Proposed approach**

**HR in rotational crop selected from the critical PBI and rounded to nearest highest MRL class**

**Q:** Critical PBI applicable to all crops (also those with long vegetation periods)?

Other arguments?
Combined MRL! provided that the steps 1-6 leading to MRL setting are harmonised

**Option I** (MRL_{PC} + HR_{RC}): new methodology, other concerns?

**Option II** (each PC residue + HR_{RC}): use of OECD MRL calculator

- Mean +4SD – more realistic?
- 3*Mean*CF – inflated?

Q: entry of values at the LOQ?
- addition of HR increases mean value

**Option III** (MRL_{PC} vs. MRL_{RC}): use of OECD MRL calculator for RC MRL not supported

Q: Practices/observation of the MSs?

Q: Experiences, if any, with existing combined MRLs? (compliances, exceedances..)

Q: Perhaps a different option available/proposed? (e.g., HR primary crops + HR rotational crop, rounded to next highest MRL class; without using OECD MRL calculator/Individual values primary crops plus STMR rotational crop, using OECD MRL calculator)
**Proposed approach:** MRL primary crop + HR rotational crop, rounded to next higher MRL class

25% (contribution) to be applied

Rounded/unrounded (?) MRL primary crop compared with HR rotational crop

HR derived for the enforcement residue definition

Separate consumer exposure calculations for primary crops/animal commodities

Separate exposure calculation for untreated crops that can take up soil residues

exposure combined (summed)
**Examples for MRL calculation (1)**

<table>
<thead>
<tr>
<th>Residue</th>
<th>MRL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crop</strong></td>
<td><strong>Primary crop residues</strong></td>
</tr>
<tr>
<td>Potato NEU</td>
<td>13x&lt;0.01; 18x&lt;0.02; 2x0.02; 0.04</td>
</tr>
<tr>
<td>Potato SEU</td>
<td>7 x &lt;0.05</td>
</tr>
<tr>
<td>Potato SEU+NEU</td>
<td>13x&lt;0.01; 18x&lt;0.02; 2x0.02; 0.04; 7x&lt;0.05</td>
</tr>
<tr>
<td>Broccoli</td>
<td>&lt; 0.01; 0.02; 0.05; 0.14</td>
</tr>
<tr>
<td>Brussel sprouts</td>
<td>0.01; 4x 0.04; 2x 0.07; 0.14</td>
</tr>
<tr>
<td>Head cabbage</td>
<td>3x &lt; 0.01; 3x 0.01; 0.02; 0.04; 0.08</td>
</tr>
</tbody>
</table>

---

**Option 1:** MRL primary + RC HR -> rounded to next MRL class

**Option 2:** Each individual PC residue value + HRRC using the OECD MRL calculator; calculations performed with, or without * if residues values from primary treatment are <LOQ.

**Option 3:** MRL PC vs. MRL RC

- a) Derived with OECD calculator
- b) In brackets combined residue input value is considered with “*” in OECD calculator, if residues from primary treatment are <LOQ.
Option 1: MRL primary + RC HR -> rounded to next MRL class
Option 2: Each individual PC residue value + HR<sub>RC</sub> using the OECD MRL calculator; calculations performed with, or without * if residues values from primary treatment are < LOQ.

a) Derived with OECD calculator

b) In brackets combined residue input value is considered with “*” in OECD calculator, if residues from primary treatment are < LOQ

<table>
<thead>
<tr>
<th>Residue</th>
<th>MRL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crop</strong></td>
<td><strong>Primary crop residues</strong></td>
</tr>
<tr>
<td><strong>Potato</strong></td>
<td><strong>Broadcast application</strong>&lt;br&gt;6x &lt;0.01; 0.016, 0.019</td>
</tr>
<tr>
<td></td>
<td><strong>Adjusted residue data set:</strong>&lt;br&gt;6x 0.03; 0.036, 0.039</td>
</tr>
<tr>
<td></td>
<td><strong>In furrow at sowing</strong>&lt;br&gt;&lt;0.01, 2x 0.018, 2x 0.020, 0.024, 0.029, 0.032</td>
</tr>
<tr>
<td></td>
<td><strong>Adjusted residue data set</strong>&lt;br&gt;0.03, 2x 0.038, 2x 0.040, 0.044, 0.049, 0.052</td>
</tr>
</tbody>
</table>
Thanks for your attention and contribution!
Application of technical guideline on extraction efficiency: sharing of Authorities’ views

Luis Carrasco Cabrera, PhD
Scientific Officer, PRES unit

General experts’ meeting
05 May 2021
Background and Scope of this session

- In preparation for PAI (post Annex I inclusion) meeting (March 2021), EFSA provided comments for discussion on the applicability of the technical guideline on extraction efficiency. PAI meeting suggested to discuss the at the General expert meeting EFSA-MSs.

- How to apply the "Technical guideline on evaluation of extraction efficiency (SANTE 2017/10632 Rev.3)" to exchange views on how to demonstrate that the extraction efficiency requirements are met.

- This session is intended as an exchange platform for experiences gained by MSs and relevant for assessments at EU level (not for product authorization). It is not intended to present the content of the technical guideline.
OUTLINE

- Studies and samples used for evaluation of extraction efficiency according to SANTE 2017/10632 Rev.3
- Application of SANTE 2017/10632 Rev.3
- EFSA considerations
- Questions on how to apply SANTE 2017/10632 Rev.3: Feedback from MSs (NL, IT, FI, SE, AT). Open to further discussions
GD on extraction efficiency: SANTE 2017/10632

- To assess suitability of extraction procedures applied in pesticide residue analytical methods was already required in e.g., SANCO/825/00.

- The new GD give advice on when and how to assess extraction efficiency (new!).

- Extraction efficiency cannot be established during method validation with fortified samples.

- Extraction efficiency should be assessed with samples bearing incurred residue.

- Extraction efficiency might (strongly) depend on extraction solvent used.

- It applies to both, pre- and post-registration methods, i.e., data generation and monitoring methods, for plants and animals.
Extraction efficiency should be evaluated for all matrix groups (including matrices difficult to analyse, depending on availability of radiolabeled sample material or samples with incurred residues) or animal commodities for which residue analytical methods are required.

All analytes included in the residue definition for monitoring (relevant for post-registration methods).

All analytes included in the residue definition for risk assessment (relevant for pre-registration methods).

When analytes included in the residue definition differ for a certain matrix, the extraction efficiency should be evaluated for the corresponding analyte/matrix combination.
Studies and samples used for evaluation / 2

- Samples from **metabolism studies** with primary crops or rotational crops (depending on the predominance of the considered analyte(s)) and with animals (and **feeding studies**, where applicable) with radiolabeled pesticides.

- The sample material with radiolabeled incurred residue is typically available for approval of active substances, only. For the **evaluation of the extraction efficiency** for **additional matrices** or for **different solvents**, food samples containing incurred residues should be used (**cross-validation**).

- **Crop field trials** or from food monitoring can be used for **cross-validation studies** from non-radiolabeled samples.

- For internationally standardized **multi-residue methods**, a huge amount of validation data was already published. Nevertheless, these data are normally not generated by using sample materials with known concentrations of incurred residues. Consequently, an **evaluation of the extraction efficiency** is also necessary for the **solvents and conditions used in multi-residue methods**.
Application of SANTE 2017/10632

Concerns the data requirements (old – Reg. (EC) No 544/2011 and new – Reg. (EC) No 283/2013) for:

- New active substance approval and renewal of active substances (EU level) submitted after 22 November 2019

- New product authorisations and renewal of product authorisations (MS level)

- Applications for new MRLs under Art. 6 of Reg. (EC) No 396/2005 (EU level) made after 22 November 2019

- MRL reviews and specific MRL assessments under respectively Art. 12 and Art. 43 of Reg. (EC) No 396/2005 (EU level): the data requirements for the latest approval or renewal should be considered, so proof of extraction efficiency in line with this document will only be required if it was required for the latest approval or renewal.
EFSA considerations

- According to the technical guideline, it is **required** that **applicant addresses extraction efficiency** of the methods used to generate residue trials and for enforcement methods. The **EMS/RMS** should **evaluate** information provided by the applicant on **extraction efficiency** in the ER/DAR/RAR submitted to EFSA.

- If the information on **extraction efficiency** is not reported in the ER (for MRL applications), DAR/RAR **submitted after November 2019**, **EFSA will require clarifications**. Data requirements will be set during the peer-review process.
Questions on how to apply the GD / 1

- When metabolism group does not match with the analytical method categories: e.g., the metabolism study was performed on citrus fruits and the new MRL application/representative uses under renewal are e.g., on avocado. Citrus and avocado fall in the same metabolism group (fruits), but not on the same analytical method categories (high acid vs high oil content), how then to prove extraction efficiency?

- Feedback from NL, IT
Questions on how to apply the GD / 2

- How the technical guideline can be implemented for new MRLs applications where the new MRL will be set based on extrapolation from another commodity belonging to a different analytical group? E.g., extrapolation from tree nuts to chestnuts.

- Feedback from NL, IT
Questions on how to apply the GD / 3

- How to deal with matrices difficult to analyze, e.g. hops? According to the technical guideline, it is desirable that extraction efficiency is proven for the matrix difficult to analyze (depending on availability of radiolabeled sample material or samples with incurred residues), but how to do it if the radiolabeled material is not available for this crop? Would it be acceptable in that case that extraction efficiency will not be proved?

- Feedback from FI, IT
It can be foreseen that often the situation will be that the applicant of the metabolism studies was different to the one submitting a new MRL application. How to prove the extraction efficiency without the access to the full study report?

Feedback from NL, IT
Assessment of residues in honey – case studies, monitoring data and future work

TC 52 General peer review meeting

Giulia BELLISAI, Miguel SANTOS
PRES Unit
- The EC guideline
- Case study 1: MRL for thiacloprid (Art 10)
- Case study 2: MRL for boscalid (Art 10)
- Case study 3: MRL for spirotetramat (Art 10)
- Case study 4: bixafen (Art 12)
- Case study 5: alpha-cypermethrin (Peer Review)
- Available monitoring data in EU
- EU annual report in pesticides residues
- Work under OECD guidance residues in honey
- Questions to the experts’ group
The EC guideline

- To fill the gap on type and conditions of the studies to be performed to address the new data requirements (Regulation (EC) 283/2013) as regards residues in pollen and bee products for human consumption.

- Guideline includes test studies: syrup test, semi-field (tunnel tests) and field residue trials.
Case study 1: MRL in honey for thiacloprid (2016)

- Supervised residue trials from Germany compliant with the GAP for rapeseed (table 4; next slide)
- Monitoring data from 2013 (table 7, next slide)
Case study 1: MRL in honey for thiacloprid (2016)

Monitoring data confirm the MRL from field studies!

Based on these data and using the OECD MRL calculator (OECD, 2011), an MRL of 0.2 mg/kg is proposed for thiacloprid in honey (MRL_{OECD}: 0.18/0.2) with a median (STMR) and highest (HR) residue values of 0.06 and 0.08 mg/kg respectively. However, this MRL proposal is driven by various uncertainties:

- Relevant information on the experimental designs was missing and has not been provided (e.g., general overview of the experimental sites, information on the surrounding crops...),
- Pollen analyses have not been performed, to confirm whether the sampled honey results effectively from the foraging on rapeseed,
- The 2006 experiments were conducted with a single application and not according to the critical GAP defined for rapeseed with a total of 2 treatments,
- The metabolism and detoxification pathways of thiacloprid in bees has not been investigated.

<table>
<thead>
<tr>
<th>Location</th>
<th>g/ha</th>
<th>Treatment (2)</th>
<th>Dates</th>
<th>Hives installation</th>
<th>Honey harvest date</th>
<th>DAT (days)</th>
<th>Plot size (ha)</th>
<th>mean level (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burscheid</td>
<td>72</td>
<td>T1/2, T1, T/1</td>
<td>11/05/06</td>
<td>05/05/06</td>
<td>27/05/06</td>
<td>18</td>
<td>1.5</td>
<td>0.056</td>
</tr>
<tr>
<td>Norterhöved</td>
<td>72</td>
<td>T1/2</td>
<td>05/06/06</td>
<td>05/06/06</td>
<td>18/06/06</td>
<td>22</td>
<td>7</td>
<td>0.057</td>
</tr>
<tr>
<td>Lemneth</td>
<td>72</td>
<td>T1/2</td>
<td>25/06/06</td>
<td>20/06/06</td>
<td>13/07/06</td>
<td>25</td>
<td>4</td>
<td>0.016</td>
</tr>
<tr>
<td>Schildern</td>
<td>72</td>
<td>T1</td>
<td>05/07/06</td>
<td>05/07/06</td>
<td>22/07/06</td>
<td>10</td>
<td>2</td>
<td>0.087</td>
</tr>
<tr>
<td>Lehneth</td>
<td>72</td>
<td>T1/2</td>
<td>05/08/06</td>
<td>25/08/06</td>
<td>13/08/06</td>
<td>25</td>
<td>2</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Table 4: Summary of the experimental designs and residue levels in honey (mg/kg)

Table 7: MRL estimations for thiacloprid in honey

FAO approach for the setting of the MRL in spices

<table>
<thead>
<tr>
<th>Number of samples ≥ LOQs</th>
<th>94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest residue level</td>
<td>0.233 mg/kg</td>
</tr>
<tr>
<td>Lowest residue level</td>
<td>0.002 mg/kg</td>
</tr>
<tr>
<td>95th percentile</td>
<td>0.113 mg/kg (Rank: 89.3)</td>
</tr>
<tr>
<td>Upper confidence interval</td>
<td>0.101 mg/kg (Rank: 93.4)</td>
</tr>
<tr>
<td>MRL proposal (rounded)</td>
<td>0.2 mg/kg</td>
</tr>
</tbody>
</table>

FAO approach for the setting of EMRLs

<table>
<thead>
<tr>
<th>Number of samples</th>
<th>562</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest residue level</td>
<td>0.233 mg/kg</td>
</tr>
<tr>
<td>Lowest residue level</td>
<td>&lt;0.001 mg/kg</td>
</tr>
<tr>
<td>Median residue level (STMR)</td>
<td>0.010 mg/kg (Rank: 559.2)</td>
</tr>
<tr>
<td>EMRL at 90th percentile</td>
<td>0.111 mg/kg (Rank: 556.4)</td>
</tr>
<tr>
<td>MRL proposal (rounded)</td>
<td>0.15 mg/kg</td>
</tr>
<tr>
<td>EMRL at 95th percentile</td>
<td>0.071 mg/kg (Rank: 548.0)</td>
</tr>
<tr>
<td>EMRL at 99th percentile</td>
<td>0.045 mg/kg (Rank: 533.9)</td>
</tr>
</tbody>
</table>
Case study 2: MRL in honey for boscalid (2019)

- Honey technical guidelines published but not in force yet!

https://doi.org/10.2903/j.efsa.2019.5897
Case study 2: MRL in honey for boscalid (2019)

Few **RECOMMENDATIONS** based on how to apply the EC, 2018 and current knowledge:

- More guidelines/clarity on requirements for MRL in honey
- Recommendations on how to conduct the residue trials for determining magnitude of residues in honey
- Clarification on the decision tree and the “systemic properties” of a.s.
- Recommendations on which data should be clearly reported for giving robustness of the MRL
- Consideration of stability and processes inside the hive and/or in field that might alter the nature of residues in honey
Honey technical guidelines in force

- **Phacelia** considered a valid surrogate crop to estimate residues in honey;

- Tunnel test performed according to the most critical scenario.

- Tunnel test conducted in two geographical zones (NEU and SEU)

- Amount of honey sampled was 10-120 g, but this was considered a minor deficiency not affecting validity of trials

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https://doi.org/10.2903/j.efsa.2021.6517
Few **RECOMMENDATIONS** based on how to apply the EC, 2018 and current knowledge:

- **Risks to bees was outside the scope of the MRL application:** bee health is in the remit of national competent authorities.
Case study 4: bixafen MRL review (2020)

- Honey technical guidelines not yet in force

1.2.4. Residues in honey

For information only, a study investigating the magnitude of residues in honey is reported. Two tunnel trials were performed to investigate residue transfer of bixafen residues to the nectar/honey via direct foraging of bees on a treated crop (Czech Republic, 2019). Following two applications of 75 g a.s./ha on oilseed rape during full flowering residues of bixafen and M21 were below the LOQ of 0.01 mg/kg in honey/nectar samples taken from the beehives within 7 days following the last application. The study was carried out before guidance became available. Due to deficiencies compared to the Guideline on MRL setting in honey (European Commission, 2018), the study was considered as supportive information by the RMS (Czech Republic, 2019). The available information suggests that residues in honey are not expected, provided that bixafen is applied in compliance with the GAPs reported in Appendix A.

- Tunnel tests performed before guidance was available
- Deficiencies identified in the conduction of the tests compared with EC guideline
- Study considered as supportive only
- Residues not expected to occur in honey

https://doi.org/10.2903/j.efsa.2020.5998
Case study 5: alpha-cypermethrin peer review (2018)

- Honey technical guidelines not yet in force
- Field residue trials with *Phacelia* and OSR
- Residues not detected in the field trials
- Residues not expected to occur in honey based on low translocation from met studies and lipophilic properties of substance

Field residue trials on *Phacelia* and on oilseed rape were submitted to analyse the residues of alpha-cypermethrin in flowers, pollen and nectar. In the residue trials on *Phacelia* (application at flowering), residues of alpha-cypermethrin were analysed in honey and were not detected (< 0.003 mg/kg) whilst in the residue trials on oilseed rape, residues of alpha-cypermethrin analysed in nectar and pollen showed a considerable decline after application, with residue levels ≤ 0.05 mg/kg in pollen and were not detected (< 0.003 mg/kg) in nectar. Considering that a low translocation of alpha-cypermethrin residues in the different plant parts was observed in the plant metabolism and taking into account the lipophilic properties of the active substance, further residue trials for the determination of residues of alpha-cypermethrin and its relevant metabolites in honey in regards to the other representative uses are not required to address the data requirement for the determination of residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom.

https://doi.org/10.2903/j.efsa.2018.5403
In 2018, 762 samples of honey and other apicultural products were analysed. In 601 samples (78.9%), no quantifiable residues were found.

In 152 samples (19.9%), residues at or above the LOQ but below or at the MRL were identified.

MRL exceedances were reported in 9 samples (1.2%), at least for one of the residues analysed.

The pesticides uniquely reported in honey and other apicultural products above the LOQ were thiacloprid (106 samples), amitraz (25 samples), acetamiprid (24 samples) and dimoxystrobin (14 samples).

MRLs were exceeded for the following substances: glyphosate (5 samples), acetamiprid (RD) (2 samples), boscalid (2 samples) and dimoxystrobin (RD) (2 samples).

**RECOMMENDATIONS**

Honey is a minor contributor to dietary exposure to pesticide residues. Therefore, EFSA recommends honey samples to be analysed by Member States under their national programmes, keeping the analytical scope as wide as possible. As a minimum, the following pesticides should be included: acetamiprid, amitraz, boscalid, dimoxystrobin, glyphosate and thiacloprid.
OECD WG residues in honey

- OECD drafting group on pesticides residue in honey;
- Includes representatives from regulatory national agencies, EFSA, DG SANTE, IND, and Academia;
- Starting point was the EC guideline;
- Work on the residue definition, list of melliferous crops, flowchart (decision tree) and MRL setting;
- Study design and test conditions still to be addressed in the WG.
Questions to the experts’ group

- Should residues in honey only be investigated from uses on non-target plants when it concerns a herbicide? Since other categories of active substances are not aimed at non-target plants, and as such the proportion of non-target plants that is being encountered with the active is very small compared to the target crop. This is of course in particular relevant for non-melliferous crops (e.g. cereals).

- In case of a herbicide, it will easily be necessary to move the colonies to remote locations (out of the tunnel) due to decay of the plants. Isn’t it expected that this will lead to possible dilution of the residues in the honey?

- How to establish if an a.s. is systemic?

- Criteria to select the cGAP for residues in honey?