Network on Pesticide Steering
Consultation on Draft Guidance of the PPR Panel on Residue definition for dietary risk assessment
Minutes

WEB/TELE-conference, 25 May 2016

(Agreed on 03 June 2016)[1]

Participants

- **Network Representatives of Member States (including EFTA Countries):**

Country	Name[2]
Austria	Tamara COJA
Germany	Kristina SCHUIERER
Ireland	Alan BREEN
Netherlands	Caroline VAN DER SCHOOR
United Kingdom	Ian DEWHURST
United Kingdom	Rebecca SCRIVENS

- **Hearing Experts**

n/a

- **European Commission:**

n/a

- **EFSA:**
  - Pesticides Unit (José V. Tarazona, Head of Unit, Chair)
  - Pesticides Unit (Anja Friel, Residues team, Co-Chair)
  - Pesticides Unit (Luc Mohimont, Deputy Head of Unit)
  - Pesticides Unit (Andrea Terron, PPR team)
  - Pesticides Unit (Rositsa Serafimova, PPR team)
  - Pesticides Unit (Juan Parra, Toxicology team)
  - Others (Thomas Kuhl; PPR Panel Member, Observer)

1 The publication of the minutes shall be made without delay in compliance with the Founding Regulation and no later than 15 working days following the day of their agreement.

2 Indicate first full name and them surname (John Smith) all throughout the document

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Abdelkarim Abdellaue, representative from Norway, who did not participate due to technical obstacles encountered.

2. Adoption of agenda

The agenda was adopted without changes.

3. Discussion on PPR Panel Draft guidance on residue definition for risk assessment

3.1. Presentation of content of the Draft guidance

An overview presentation of the content and new features of the PPR Panel Draft guidance on Residue Definition for Risk assessment was held by Anja Friel, Andrea Terron and Juan Parra.

3.2. Overview of comments from public consultation

As for the comments received during the public consultation, Rositsa Serafimova presented an analysis regarding the involvement of different country organisations and the most commented issues.

3.3. Discussion on the Draft guidance

No.	Discussed comment by PSN Member / nominated expert	Conclusion and recommendations by the PSN
3.3.1 Sequence of hazard characterisation and exposure estimates incl. TTC / Complexity of approach		
1)	AT: In general AGES very well understands the principles of genotoxicity and "single exposure event provoking a genotoxic effect" hypothesis, unless a threshold can be proven. However, we seriously doubt if the extensive procedure, as currently proposed in the document, will bring more certainty into the assessment. Although we understand the rationale behind genotoxicity assessment for all metabolites we would rather propose to first seriously consider the relevant potential exposure.	**The possibility for consideration of the relevant potential exposure (TTC) preceding the extensive procedure of genotoxicity assessment for all metabolites should be given.** **If the TTC thresholds are not breached, this could be an early exit option.** **Is it appropriate to use cumulative TTC as approach with regard to the genotoxicity threshold?**
2)	UK: It seems for all metabolites, if the TTC thresholds are not breached, then there are no concerns (whether genotoxicity, neurotoxicity or other proposed toxicological profile); could this be an early exit option?	
3)	UK: We are concerned that the overall process to assess all the metabolites is complex and very time consuming, and would welcome any opportunities for simplification, especially since consideration of the risk assessment residue definition is an important and intrinsic part of every evaluation. The guidance is wordy and cumbersome in places and might benefit from some simplification in some parts of the document.	**The overall process to assess all the metabolites is too complex and time consuming and should be simplified.** **For substances with many metabolites, there should be an extra step to simplify the assessment and exclude a greater number of metabolites a priori.**
4)	UK: The case studies are helpful, but they also illustrate the complexity of the assessment; when there are so many metabolites identified in nature-of-residues studies, the scheme requires so many calculations, so many assumptions, so many expert considerations that we doubt whether it is achievable routinely or, indeed, at all. For substances with so many metabolites, there should be an extra step to simplify the assessment and exclude a greater number of metabolites a priori.	

No.	Discussed comment by PSN Member / nominated expert	Conclusion and recommendations by the PSN
3.3.2 Potency / toxicity considerations for metabolites on basis of parent reference values		
5)	AT: We are rather of the opinion that the consideration of potency for metabolites, based on the reference values of the parent substance, might be an obstacle and would propose to reconsider it. This is while reference values of parent substances frequently change during the e.g. renewal of the substance and the whole testing strategy might be questioned at the very late stage of the procedure, not allowing any additional evaluation.	**Consideration of potency for metabolites, based on the reference values of the parent substance may challenge the testing strategy if parent reference values are lowered at a very late stage of the review procedure.** **Simplification towards dropping the potency approach may be considered. Alternatively the percentile of the distribution to define potent compounds could be reconsidered (i.e. lowered) by the PPR Panel.**
6)	UK: It is our understanding that if genotoxicity is excluded, then the toxicological assessment continues only for major metabolites. We suggest this needs to be made much clearer in the document. This toxicological assessment requires a high level of expert judgement as it needs to be determined whether the metabolite is structurally similar to the parent and hence covered by the ADI and ARfD of the parent or whether it is significantly different to require additional animal testing to derive specific ADI and ARfD values or relative potency factors. We consider that further guidance should be given on how to determine structural similarity between the parent and the metabolites, on which additional testing should be performed and how to derive these specific ADI, ARfD or relative potency factors.	**Further guidance should be given on how to determine structural similarity between the parent and the metabolites, on which additional testing should be performed and how to derive these specific ADI, ARfD (adding extra factors and which?) or relative potency factors.** **Amending the text towards more clarity of the proposal and steps to be taken by the assessor is proposed.** **It should be reconsidered whether it is appropriate to include the MTD in the testing strategy since only Risk assessment should be considered.**

No.	Discussed comment by PSN Member / nominated expert	Conclusion and recommendations by the PSN
3.3.3 Number of vertebrate studies necessary		
7)	UK: We support the need for a proportionate approach to ensuring consistent assessment and to cover the main contribution of the risk in the residue definition for risk assessment. Wherever possible this should be done without an increased need for animal testing (the guidance tends towards a significant number of vertebrate studies). As currently written there is the potential for a significant number of vertebrate studies to be initiated. This is contrary to recital (40) of Regulation (EC) No 1107/2009, which makes clear that non-animal test methods and other risk assessment strategies should be use wherever possible and vertebrate testing should be undertaken as a last resort.	**The need for animal testing should be decreased wherever possible. The guidance tends towards a significant number of vertebrate studies.** **Further clarification on acceptance of alternative testing is needed, and in the GD text the concept of alternative testing should be highlighted.**
8)	FR: The implementation of the guidance will trigger significant difficulties, for instance the possibility to apply the TTC approach will be generally hampered by the absence of adequate exposure data, therefore a large number of additional toxicity studies would probably be requested, without these studies a large number of data gaps could be identified.	**The TTC approach will be generally hampered by the absence of adequate exposure data; therefore a large number of additional toxicity studies would probably be requested.** **The Panel may consider whether it is possible to set criteria to guide consistency in deciding on acceptability of exposure estimates.**
3.3.4 Toxicological burden coverage by the risk assessment residue definition		
9)	IE: It is stated that metabolites or groups of metabolites comprising > 75% of the toxicological burden are relevant for the residue definition. It is not clear what this means or how hitting this threshold is to be determined? If we consider the characteristics of toxicity for example; multiple target organs; lead and secondary toxicity; multiple metabolites with limited data; differing animal models and differing toxicological	**It is suggested to clarify the definition of toxicological burden in the GD.** **The decisions to be taken regarding inclusion of metabolites into the relevant 75% of the toxicological burden and how that can be**

No.	Discussed comment by PSN Member / nominated expert	Conclusion and recommendations by the PSN
	profiles between parent and metabolites. It appears difficult to be able to state with any degree of certainty that > 75% of the toxicological burden has been covered.	**attempted with consistency should be better described.**
10)	UK: We support the final proposal that, if these major metabolites contribute ≥ 75% of the overall toxicological burden in the consumer risk assessment, then they should be considered relevant for inclusion in the residue definition. However, again, this could be explained much more clearly in the guidance.	
11)	UK: As currently written the guidance would lead to an inclusion of many more low level metabolites in the risk assessment residue definitions than we would have thought necessary.	**Too many low level metabolites appear to be included in the risk assessment residue definitions.** **The case study of Isoproturon should be reviewed and the need for inclusion of M03 in the RD reconsidered. Based on this example, further judgement should be permitted based on absolute residue levels of metabolites, and the decision should not be strictly linked to the 75% toxicological burden only.** **In general, there should be scope for some suitable balanced judgements to be made taking account of exposure/toxicology.**
12)	UK: Following the former points on [conversion factors between the enforcement residue definition and the risk assessment] and [Complexity of residue definition] it would be better to conclude more simply on risk assessment residue definitions, and leaving some low level metabolites out that have been found in the rat mammalian metabolism, and to have more workable proposals that are not 'provisional'. HSE is concerned that inclusion of very low level metabolites which are covered in the mammalian metabolism is not the best prioritisation approach, which should be the key aim of the risk assessment residue definition. It will remain the case that the risk assessment residue definition dictates which metabolites should be studied in quantitative field trials and feeding studies, and the approaches need to be reasonable and prioritised in order to cover the main aspects of expected risk. The current balance of the guidance seems to be aiming to include many more metabolites than HSE/UK would anticipate (as shown by the example in point [Isoproturon]).	
13)	UK: The introduction recommends the use of relative exposures (page	

No.	Discussed comment by PSN Member / nominated expert	Conclusion and recommendations by the PSN
	6) and this is how metabolites can be excluded via TTC, whereas the scheme (in deciding on components for the residue definition) considers a different decision criteria % total toxicological burden. HSE strongly considers that there should be scope for some suitable balanced judgements to be made taking account of exposure/toxicology. For example, in the isoproturon example, it seems that metabolite M03 is finally proposed as the residue definition for rotational crops. However relevant studies show that the maximum amount for M03 observed was a maximum of 0.01 mg/kg in the rotational crop metabolism (only found in the rotational crop metabolism), and also this metabolite was found at >10% in mammalian metabolites. Had this component remained unidentified due to analytical constraints in the rotational crop metabolism studies, it likely would not have been considered a key data gap if the study was to bare soil (and for example if the applicant could make a case regarding the presence of a similar chromatographic component in the rat/mammalian metabolism).	
3.3.5 Other issues		
14)	UK: We consider it will be highly problematic to explain the uncertainties clearly for specific residue definition proposals for each metabolite in a consistent way for risk managers to consider. We would prefer the guidance to address the possible uncertainties. Whilst field trials are the best approaches for quantitatively assessing metabolite levels, it should be recognised that mostly it will be metabolism studies used for doing risk assessment for metabolites in the context of this work, where there might not be much consideration of the spatial and temporal changes that can occur with the metabolite (and parent) residues. (This form of uncertainty was not included in the list of uncertainties for the example for isoproturon, perhaps indicating	**Uncertainties regarding exposure estimates for TTC should be better described. When is the uncertainty considered too great to use the TTC approach, for instance?**

No.	Discussed comment by PSN Member / nominated expert	Conclusion and recommendations by the PSN
	that trying to state the uncertainties is subject to variations.)	
15)	UK: HSE considers that the guidance should address the principle of conversion factors between the enforcement residue definition and the risk assessment residue definition. The concept of having a complex risk assessment residue definition works when it is possible to propose a reasonable conversion factor between 'monitoring' and 'risk'. The outcomes say for spiroxamine on page 104 look very complex and the need to aim to maintain this dual residue definition principle have not been considered here. These conversion factors are not currently used in a specific way when doing risk assessment for the EU monitoring programme (EFSA Annual Reports), however they feature in the proposed new IESTI model. In the monitoring work, the programme of analysis work needs to be achievable wherever possible using multi-residue testing methods. The proposals might lead to difficulty in multi-residue testing if the principle of dual residue definitions (monitoring) and (risk assessment) cannot be supported with suitable conversion factors.	**Difficulties in enforcement are expected if suitable conversion factors cannot be set to convert between the simple monitoring and complex RA definition.** **Further activities giving guidance in this direction are required to complete the Residue definition assessment (recommendation in the GD for future activities?).**
16)	UK: We consider that exposure to metabolites in livestock products (e.g. milk, meat etc), rotational and primary crop metabolites in raw and processed items to be consumed by humans, need to be fully considered in such a scheme. However, the approach to metabolites that are purely found in crop feed items that are fed to livestock, in commodity items that are not consumed by humans such as straw or grassland, would warrant a different consideration. The nature of residues in items such of straw can help consideration of the animal dietary burden and whether the livestock metabolism studies have involved appropriate feeding of the animals in the studies. However, it is considered that these feed item residues should not need to be treated the same in the scheme. It is appreciated that sometimes residues are found in straw as	**Additional guidance should be added on how to handle metabolites that are exclusively consumed by animals (e.g. straw compared to grain).** **A tailored approach for these cases should be considered. More clarification of the issue is requested.**

No.	Discussed comment by PSN Member / nominated expert	Conclusion and recommendations by the PSN
	residues are commonly at higher levels in straw than the levels found in grain. In some of these cases, the residues in grain would not be well characterised as the residues are present at a low level and not identified. However, when residues are not identified (in accordance with guidelines and due to low levels and analytical constraints), these are then effectively excluded as metabolites from the risk assessment.	

In addition, comments and suggestions for improving both text comprehension and schemes have been received and will be considered by the PPR Panel Secretariat as appropriate.

4. Any Other Business

None

5. Conclusions (s)

The conclusions of the PSN are listed in the third column of the table displayed under agenda item 3.3 above. Upon approval of the minutes, the conclusions and recommendations will be sent to the PPR Panel WG on the Residue definition for risk assessment for consideration.

6. Closure of the meeting