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Klaus Berend
European Commission
DG Sante - Unit E.4 - Pesticides and Biocides
1049 Brussels
klaus.berend@ec.europa.eu

Laurent Oger
Director of Regulatory Affairs
+32 (0)2 663 1561
laurent.oger@ecpa.eu

ECPA input for SCOPAFF meeting 23-24 March 2020

- **EFSA Isomer Guidance Document**
- **Amendment to General Food Law, new transparency rules**
- **Annex III of Regulation 1107/2009 (unacceptable co-formulants)**

Dear SCOPAFF members,

Ahead of the SCOPAFF phytopharmaceuticals-legislation meeting on 23-24 March 2020, ECPA would like to provide our input on several key issues on the agenda:

Due to the current situation with the Covid-19 and the fact that most national authorities and company staff are working remotely, ECPA member companies will duly inform competent authorities in advance should there be an impact on submissions (e.g. actual reception of dossiers and official deadlines). Any other delays will be also properly explained, this can be the case for planned field work like efficacy or residue trials which might not have the time this season to receive samples and to treat the crop. This can also be the case for laboratory studies in case test animals are not available. We believe timely communication and some flexibility will allow to minimise the impact of this situation.

EFSA Guidance on the risk assessment of PPP A.S. and their transformation products that have stereoisomers (A.07)

Since the publication of the document by EFSA, despite responses provided after the public consultation by EFSA, numerous additional clarification questions were received from ECPA member companies. A first list is available in Annex at the end of this letter. **We would invite EFSA and the European Commission to set up a dedicated webinar to try to solve as many technical and regulatory questions as possible so companies can adapt their testing strategies and dossier preparation**. This would also limit the risk of incomplete dossiers in the future and the creation of unnecessary delays.
ECPA would like to highlight the need for a suitable transition period. We believe the timeframe to perform the new studies, the need to develop additional analytical methods, followed by additional toxicity data for isomeric metabolites and impurities, can take much longer than 2 years. **We would request a pragmatic and workable transition period with an implementation date by end 2022.**

New Transparency rules: General Food Law amendment and implementation (A.14)

In the context of the implementation of the General Food Law amendment, ECPA is an active member of the newly created EFSA technical groups working on the pilot project to use IUCLID

for pesticide dossier and the notification of studies database. While we fully support the need for increased transparency and standardisation of formats we would like to raise our concerns on the envisaged timing for implementation and the lack of engagement on other crucial aspects.

Regarding the use of IUCLID format, the pilot work shows that more than 500 hours were needed to complete the transfer of an “easy” dossier, Clodinafop, into this new format. A majority of dossiers are much more complex and would require to input more information for which some OECD harmonised templates are still lacking today (e.g. on higher tier ecotox studies). While EFSA envisage a minimal viable product by the application date of the regulation on the 27 March 2021, numerous submissions are being prepared after that date due to the renewal programmes in place (AIR4 and AIR5). We seriously doubt that once technical specifications are clearly set and communicated to all applicants, companies will have sufficient time to physically comply with the requirement. Proper information to companies and member states on what should be in the new format, and what should be in the old format should be given at the latest by September 2020 to allow adequate resource planning in the companies, this is especially important for smaller companies.
A proposal would be to first use IUCLID for certain areas of the dossier like in the areas of physico-chemical properties and potentially toxicology regarding data submitted also under REACH and CLH processes.

There is a lack of information regarding the development of modalities for the disclosure of documents. The process will take place on company owned documents and we believe applicants should be part of the discussion regarding disclosure modalities. Confidentiality claims is also a topic for which applicants view should be considered. We understand guidance documents are being prepared and would welcome any opportunity to provide comments on draft versions.

The new regulation is already changing internal practices for companies. We would highlight the urgent need for early clarity on many pending elements. While we understand the need for EFSA to address all sectors at once, one has also to take into account that the level of data coming from the pesticide sector is clearly higher than for other regulated sectors (we estimate that 300-400 studies are part of a PPP AS dossier, compared to 30-40 for a GMO application). **Given the significant changes that the new regulation will entail, We believe a specific discussion is needed on several implementation elements for the pesticide sector as a whole, and ECPA together with other associations representing applicants, is ready to engage and provide direct information.**

Annex III of Regulation 1107/2009 (unacceptable co-formulants) (Agenda item B.01)

We understand that the draft Commission regulation modifying Annex III of Regulation 1107/2009 (unacceptable co-formulants) is on the SCPAFF agenda for an exchange of views and possible opinion.

In advance of the exchange of views during the meeting, we would reiterate the following key issues:

- An adequate transition time for reformulation of any impacted formulations must be provided, acknowledging that using hazard based cut-off criteria does not equate to a risk with using these co-formulants.
- ECPA has consistently requested a transparent and consistent process for the identification of unacceptable co-formulants for addition to Annex III. If hazard based cut-off criteria are used for identification purposes, it is essential that only harmonised classifications are used which have been agreed by the relevant competent authority and have been adopted at the European level, i.e. via ECHA and the CLH process.
- For the consistent interpretation of Annex III, ECPA is supportive of setting a *de minimis* level for impurities in finished formulations. However, we would strongly recommend that full consistency with the declaration cut-offs specified in the REACH and CLP

legislation is maintained. In general this is 0.1%, rather than the proposed 0.01%. We are aware of no legislative basis for a lower threshold than 0.1%.
- Due to the lack of harmonised classification for crystalline silica, parallel legislative activities aimed at controlling exposure to this substance, and complexities involving the route of exposure, we believe crystalline silica should not be listed in Annex III at this time (neither itself i.e. quartz, cristobalite, tridymite) nor as an impurity in another co-formulant (i.e. Kieselguhr, Kaolin).

ECPA would also like to share the attached two position papers covering the above-mentioned issues in more detail:
- *Doc 32274 – Position paper on co-formulants unacceptable for use in PPPs*
- *Doc 32331 – Position paper focussing on draft Annex III impurity limits*

We would welcome a more detailed discussion on these issues. If you have any questions regarding the ECPA views, please do not hesitate to contact me.

Yours sincerely

Laurent Oger
Director of Regulatory Affairs

cc. Karin Nienstedt
Manuela Tiramani

Attachments:
Attachment 1 - 32274 – Position paper on co-formulants unacceptable for use in PPPs
Attachment 2 - 32331 – Position paper focussing on draft Annex III impurity limits

This letter will published on the ECPA website and will be available at: http://www.ecpa.eu/transparency-policy.

Annex 1 – Clarification questions from ECPA member companies on the EFSA Guidance on the risk assessment of PPP A.S. and their transformation products that have stereoisomers

General questions for clarification

1. Regarding the interpretation of biological activity as a Candidate for substitution, should this be done according to SANCO/221/2000?

2. How to deal with active substances that have confirmatory data on stereoisomers (expected 2 years after guidance entry into force) and an on-going renewal evaluation which will not be voted before the 2 years:
    - Would the confirmatory data be postponed until the active substance is renewed?
    - If confirmatory data need to proceed as expected (after the 2 years) could they refer to the renewal representative uses for which evaluation is on-going or should it refer to the representative uses included in the previous approval?

3. Concentration is a parameter which has not been taken into account in the guidance. 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.

4. If 10% is still preferred how can it be guaranteed that it is really a significant isomeric shift when a 10% change in stereoisomer excess (se) could happen by changing the placement of tick marks for integration even within the same chromatogram (high inaccuracy in the measurement because of potential high background noise)?

5. It is difficult to understand how the 10% stereoisomer excess (se) change trigger should be employed for molecules with >2 chiral centers. Any further clarification would be welcomed.

6. In general, it is not clear whether a chiral method should be developed for each enantiomer of metabolites consisting of conjugates which are natural products (e.g. sugar conjugates) but the aglycon itself has no chiral center.

7. For a mixture of isomers, the biological activity of each isomer will be determined which will reflect their efficacy and contribution to the mode of action. Is there any additional analysis needed to clarify each isomers impact on the mode of action? If so, what would be requirements?

8. Natural products often consists of multiple chiral centers which will make analysis and monitoring changes at each chiral center technically challenging, if not impossible. For natural products, is it possible to assume, unless known otherwise, the AI stereochemistry exists in a single form and will not naturally experience changes at any chiral center. Based on this assumption, our interpretation is to apply the guidance to the analysis of stereoisomers of natural products only when resulting metabolites create a new stereocenter, except for natural conjugates. Can this interpretation be confirmed ?

9. The requirement that all stereoisomers should be accounted together (e.g. 10% TRR in food) when confronted with the triggers used to decide whether further assessment is needed is practically not feasible for metabolites. Do the triggers only apply to the active substance as defined by ISO where the stereoisomers are known and therefore can be counted together or also to metabolites?

10. *"When the amounts measured are close to the LOQ, quantification errors may be higher than 5% of the actual % AR value measured. Consequently, it would be impossible to determine if the trigger of 10% se is actually breached […] Due to the limitations of analytical quantification, a change in the stereoisomeric excess of 10% is in general of low relevance when the total amount is already below 10% of AR."* This is quite problematic, as laboratories are actually warning that for degradation studies, it will become very difficult to maintain resolution of analysis on chiral columns. Undoubtedly, there will be many instances when no meaningful information can be drawn towards the end of the study. In this context, would the results at the end of the study not be considered if they appear too uncertain?

11. Can metabolite conclusions on differentiated transformation of stereoisomers and stereoisomer interconversion be drawn from parent applied studies, if the available data is appropriate?

12. *"Because some chemical reactions can induce racemisation of pure enantiomers"* In some cases, it will be possible to predict that racemisation is not chemically possible for specific structures; therefore is it possible to submit a paper argumentation of non-racemisation in the context on achiral environments, that is to say for sterile hydrolysis and sterile aqueous photochemical degradation studies?

13. In Appendix B, what does "*At least one of the individual isomers has higher toxicity than the others in the mixture"* mean? Can it be clarified what "higher" means ?

14. In Appendix B, an important criterion to make decisions for the risk assessment is the value of the stereoisomer excess (higher or lower than 10%). How is this applied for four-way mixtures [or more] when the stereoisomer excess cannot be calculated?

15. Do we need to consider for further isomer assessment all kind of stereoisomers (e.g. tautomers, atropisomers)?

Non-dietary risk assessment:

16. Which and how many experimental data will be required to satisfy the analysis of the stereoisomeric ratio for conducting the worker risk assessment, also in terms of bridging between different regulatory zones and crops?

17. In case of a herbicide application, when the crop itself is not treated (e.g. band application), which information has to be provided for analysis of the stereoisomeric ratio to conduct the worker risk assessment without additional uncertainty factors? Are data for soil needed?

18. In case crop residue data do not show any significant change in stereoisomeric ratio, do applicants have to provide any additional experimental data to avoid uncertainty factors for worker risk assessment?

Mammalian toxicology:

19. Based on this guidance our understanding is that stereoisomers are considered to be covered by genotoxicity studies (adequately tested) if the sum of the individual isomers contributed to more than 10% of the tested material or the administered dose in terms of total radioactive material recovered in urine as detected in ADME studies for in vivo genotoxicity studies. For an active substance consisting of two stereoisomers that means that both stereoisomers are covered by genotoxicity studies independent of the ratio experimentally tested (e.g. 99:1, 50:50, 1:99) as long as the sum of both contributed to 10% or more of the tested material. Can this interpretation be confirmed?

Consumer Safety:

20. Do we need to consider for further isomer assessment food and feed items or are food items sufficient?

21. We would welcome an additional more complex case study (e.g. in the area of consumer safety) in the Appendix of the guidance document in order to have a practical guidance which data is needed in more complex cases.

22. 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?

23. The test material should in principle reflect the ratios of isomers in the terminal residue. Certainly, this ratio cannot be expected to be exactly the same in all the studies. Based on EFSA comments a "representative" ratio should be proposed for the residue definition for risk assessment and this is the one to be considered for the material to be used in the test studies. How can this "representative" ratio be defined?

Ecotoxicology / Fate

24. *"For active substances containing stereoisomers, separate risk quotients may need to be established for each of the isomers when either their fate into the environment is different (e.g. preferential degradation, stereoisomers interconversion) or when the toxicological and/or ecotoxicological properties of each isomer is different."* - If there is no indication from environmental fate studies that stereoisomeric interconversion might take place (breaching the trigger), and if no concern from toxicological perspective is raised, one would assume that consequently no further

evaluation is deemed necessary for ecotox, i.e. no analytical measurements of different (potential) stereoisomers, and no further ecotoxicological tests. Can this interpretation be confirmed?

25. In case of higher tier data for ecotoxicological risk assessment that needs to be generated and test concentrations are very low: due to technical reasons it might not be possible to set up analytical methods to quantify the interconversion and/or degradation of separate stereoisomers. How to proceed in such cases?

26. Table B.2: "*The available long-term toxicity tests on daphnids indicate that A1 isomer is more toxic than A2 and the a.s. as manufactured."* – What does "more" mean in this case, by which factor ?

27. Which media need to be considered and therefore which areas of the ecotoxicological risk assessment? Soil/water are obvious and are covered but what about foliage/pollen/nectar? Can extrapolation from one medium to another be considered ?