TECHNICAL REPORT

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Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology

European Food Safety Authority

Abstract

This technical report reflects the outcome of the mammalian toxicology experts' meeting on general recurring issues noted during the EFSA peer reviews of pesticide active substances under Regulation (EC) No 1107/2009. The main issues identified were related to genotoxicity of products and principles of (Q)SAR and read-across. General presentations on the different EFSA guidance and EFSA developmental activities related to human health risk assessment of pesticides were given.

Key words: (Q)SAR, read-across, genotoxicity, residue definition, dermal absorption, non-dietary exposure

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Summary

During the EFSA peer review of pesticide active substances under Regulation (EC) No 1107/2009, several aspects in the area of mammalian toxicology were identified by EFSA and Member States that needed discussion with experts from national Authorities in order to enhance the harmonisation of the risk assessment of active substances.

The main issues identified for discussion were related to genotoxicity of products and principles of (Q)SARs and read-across. General presentations on the different EFSA guidance and EFSA developmental activities related to human health risk assessment of pesticides were given.

All these issues were addressed in a general session during a mammalian toxicology meeting, the Pesticide Peer Review Meeting 170, that took place from 12 to 14 December 2017.

Recommendations on the assessment of genotoxicity of products and the use of (Q)SARs and read-across were compiled on the basis of the discussions and conclusions achieved at the meeting. These recommendations will be applied during the EFSA peer review of the active substances, and are expected to provide additional clarifications to applicants and rapporteur Member States regarding the scientific interpretation of the relevant guidance documents when preparing the dossiers and the assessment reports.

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1. Introduction

During the EFSA peer review of pesticide active substances under Regulation (EC) No 1107/2009[1] EFSA identified several general recurrent issues in the area of mammalian toxicology which deserved experts' consultation and agreement in order to enhance the harmonisation of the risk assessment of active substances.

To this purpose a general meeting was organised which took place in December 2017 (Pesticide Peer Review Meeting 170, 11-14 December 2017). Member States' representatives with expertise in toxicology attended this meeting. One Member State provided written comments before the meeting.

The main issues identified were related to genotoxicity of products and principles of (Q)SARs and read-across. In addition, EFSA guidance documents on the area of human health risk assessment were presented during the meeting to facilitate their implementation. These include the guidance on the residue definition and on dermal absorption.

In addition, the following document is available as background document of this technical report:

- the comments received from one Member State before the meeting.
- the comments received on the draft technical report following the written procedure launched from 26 July 2018 to 9 August 2018. It is noted that the written procedure was performed with the purpose to enhance readability and correct possible inconsistencies. Since the scope of this technical report was to reflect the meeting discussions and conclusions, the commenting round was not meant to reopen the discussions or to change the outcome of the meeting.

2. Point of discussion

2.1. Genotoxicity of plant protection products

Currently there are no specific data requirements for genotoxicity of plant protection products. The assessment is based on the fact that the components of the products are known and there should not be unacceptable co-formulants in plant protection products according to European Union (EU) legislation.

EFSA invited a hearing expert to give its personal expert opinion on this topic. Experts discussed that if there is a specific request to address the genotoxicity of a plant protection product the testing strategy on the product as defined in the EFSA Scientific Committee (2011) could be followed.

2.2. (Q)SARs principles

During the pesticides peer review (Q)SARs are currently used to assess the toxicological profile of impurities. In some instances they have been used during the peer review to support the assessment of metabolites found as residues in crops and/or livestock. In the recent guidance on the residue definition (EFSA PPR, 2016) the EFSA Panel on Plant Protection Products and their Residues (PPR panel) proposed to use a systematic approach using a combination of (Q)SARs and read across for genotoxicity assessment according to OECD principles. EFSA gave an overview on the best practices using (Q)SARs as part of pesticide risk assessment.

For assessing acceptability of a (Q)SAR prediction, guidance adopted for the REACH regulation (ECHA, 2008, 2016) and OECD guidance on the scientific validation and documentation of (Q)SAR models for regulatory purposes (OECD, 2007) might be used. EFSA highlighted the following main elements to be considered:

[1] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p.1-50.

- The scientific validity of the used model should be demonstrated,
- The model should be applicable to the chemical of interest with the necessary level of reliability,
- The modelled endpoint should be relevant for the purpose (e.g. gene mutation),
- The information should be well documented.

Predictions of a particular endpoint should not be based on the use of a single model alone. In order to optimise the sensitivity/specificity of the prediction, it is recommended, when it is possible, to use two independent models (e.g. based on different training sets and/or algorithms such as knowledge based and statistical-based models) (EFSA PPR, 2016). A 'weight of evidence' approach should be followed, based on an expert judgment on all available information provided by the models, e.g. applicability domain, proposed mechanistic information and prediction for the similar substance.
It has been highlighted that reports generated by the software should be included as part of the dossier whereas, the assessment of the relevance and reliability of the prediction should be part of both the dossier and the assessment report.

2.3. Read-Across principles

During the peer review read-across has been routinely used for the assessment of metabolites found as residues in crops and/or in livestock and in some instances for the assessment of groundwater metabolites. EFSA gave an overview on the best practices using read-across for its regulatory use in pesticide risk assessment.

For assessing the applicability of read-across analysis and in line with the EFSA PPR guidance on the residue definition for risk assessment (EFSA PPR, 2016) EFSA recommends to use the guidance adopted for the REACH regulation (ECHA, 2013), including the updated OECD guidance on grouping of chemicals (OECD, 2014) and ECHA Read-across Assessment Framework (ECHA, 2017).

The key elements for read across which should be considered are:

- Well defined endpoint,
- Identity of the chemicals used in the read across process and assessment of the quality of the available experimental data,
- Assessment of the similarity/dissimilarity between source and target substance(s),
- Assessment of the uncertainties related with the justification of the similarity (structural, toxicokinetic, biological similarity) and with the approach followed for the assessment.

Different approaches for assessment of the similarity exist: chemioinformatics (based on the similarity coefficients); mechanistic (based on the mode of action (MoA)); analogy approach (based on structural, toxicodynamic and toxicokinetic similarity). The most suitable methodology should be selected depending on the read acrossed end point and the available information.

Assessment of the similarity/dissimilarity is related with the working hypothesis for read-across (ECHA, 2008), which should be clearly defined, substantiated and documented.

The acceptable level of the uncertainties depends on the particular regulatory purpose for which the read across is used. The closer the outcome is to a regulatory decision (e.g. hazard identification based approval criteria) the more accurate predictions, or a more detailed justification is needed.

Documentation is essential and should allow external evaluators to judge on the key elements pointed above. A detailed description of each step of the read across including reports provided by software and expert's considerations should be included in the dossier, whereas, the assessment of the reliability and relevance of the prediction should be part of both the dossier and the assessment report.

2.4. Guidance on the Residue Definition

The PPR Panel published the guidance on the residue definition for risk assessment (EFSA PPR, 2016). EFSA and a Member State gave an overview of this guidance to the regulatory Authorities to facilitate its implementation in the peer review and maximum residue level (MRL) processes.

At the time of the meeting the European Commission was discussing the implementation plan for this guidance. It should be pointed out that the guidance has not been noted by the Standing Committee on Plants, Animals, Food and Feed to date and is therefore not binding.

EFSA indicated that there are ongoing follow up activities such as the publication of the EFSA pesticide genotoxicity database in 2017 (Metruccio et al., 2017). The database has been recently integrated in the OECD (Q)SAR toolbox (in January 2018) and will facilitate read-across with other active substances and metabolites. The database is expected to increase the applicability domain of (Q)SARs in the pesticide chemical domain.

Current EFSA activities using this database are the procurement of evaluation of the applicability of existing (Q)SAR models for predicting the genotoxicity of pesticides and similarity analysis related with genotoxicity of pesticides for facilitating the grouping and read-across. The procurement is expected to be due in the first quarter of 2019.

The OECD MetaPath User group is also a project of relevance for the guidance document on the residue definition. EFSA invited Member States to join this group to collaborate and have access to the regulatory database on pesticide containing metabolism data on rats, crops, rotational crops and livestock. MetaPath allows comparison tools between metabolic pathways, searching for common metabolites, electronic submission of data, quality check and quality assurance of the data.

EFSA also mentioned the procurement of the development of an EFSA list of endpoints database. This electronic web database will substitute the list of endpoints available in the EFSA conclusions. The database will allow to search for common metabolites and to identify relevant studies when available. The procurement was first due in April 2018. However, although the structure of the database was completed further development and implementation of the database will be done with other horizontal projects in EFSA.

2.5. Guidance on Dermal Absorption

In order to facilitate its implementation in the peer review process, EFSA gave an overview of the revised EFSA guidance on dermal absorption (EFSA, 2017) and a Member State presented some case studies applying the new rules/clarifications provided in the revised document. An implementation plan has been agreed at the PAFF meeting of 24-25 May: "The use of this revised guidance document is recommended for applicants and Member States for any applications for active substances and/or plant protection products submitted under Regulation (EC) No 1107/2009 after 25 August 2018." EFSA indicated that there are ongoing follow up activities such as the revision of OECD test guidelines (TG) and guidance on dermal absorption and the procurement[2] of the applicability of in silico methods for the prediction of dermal absorption of pesticides.

2.6. Current and planned activities on the area of pesticides

EFSA gave presentations on the current activities regarding methodological developments in the area of human health of pesticides including developmental neurotoxicity and cumulative assessment groups. Feedback from the info session on the use of epidemiology for pesticide regulatory risk assessment was also given. EFSA sought also the view of Member States on the future developmental activities proposed by EFSA regarding workshops on *in vitro* comparative metabolism studies, phototoxicity, historical control data and revision of the guidance on non-dietary exposure. EFSA also invited Member States to share current and future activities regarding methodological developments on the human health area at national level.

2.6.1. Developmental Neurotoxicity

EFSA presented an overview of the current procurement on developmental neurotoxicity with the aim to support the development of alternatives to animal testing for developmental neurotoxicity. The first phase will focus on the development of the test systems, generation of data using relevant chemicals for validation purposes, and the design and employment of data analysis tools (expected to be completed by the end of 2018). The second phase will include the development of data interpretation and use guidance, descriptions of possible application domains, and case studies of data use in an

[2] http://ted.europa.eu/TED/notice/udl?uri=TED:NOTICE:255697-2017:TEXT:EN:HTML&tabId=0

integrated approach of testing and assessment (IATA) context (expected to be completed by the second quarter of 2019).

2.6.2. Cumulative Assessment Groups

EFSA presented an overview of past and current activities regarding the establishment of cumulative assessment groups (CAGs) for effects on the nervous system and the thyroid. In particular, criteria used for establishing and updating such CAGs were described, together with the criteria used for the selection of the Index Compound (IC) and Relative Potency Factor (RPF). The weight of evidence and uncertainty analysis approach used to assess the certainty that the active substances included in a CAG act according to the dose-addition model was briefly described. One example regarding the weight of evidence analysis for the substances included in the CAG affecting the thyroid hormone levels and follicular cells was briefly shown. Finally, the plan and deadlines regarding future activities (including the drafting of the scientific reports by the end of 2018) were presented.

2.6.3. Epidemiology

EFSA presented the program and the purpose of the scientific conference on the use of epidemiological findings in regulatory pesticide risk assessment, held in Parma on 21 November 2017. In particular, the aims of this scientific conference were: a) to discuss the outcomes and recommendations of the two scientific opinions recently published ("Investigation into experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia" and "Follow-up of the findings of the external scientific report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'"); b) to search ways to integrate experimental, epidemiological and regulatory approaches; c) to solicit viewpoints and experiences from academic scientists and d) to survey the opinions of the stakeholders. More than 60 people from academia, regulatory bodies, non-governmental organisations and industry from both EU countries and USA participated. The main outcomes and recommendations for possible further work were mainly dealing with the issue on measuring/estimating exposure, the use of adverse outcome pathway (AOP) in the context of epidemiological findings, the quality issue, the training issue and, finally, the future guidance from scientific committee.

2.6.4. Planned workshop on *in vitro* comparative metabolism, phototoxicity and historical control data

EFSA gave a presentation on planned events that would facilitate further guidance on the area of *in vitro* comparative metabolism, phototoxicity and historical control data already identified as future developmental activities during the general discussion in January 2016 (EFSA, 2016).

A workshop on *in vitro* comparative metabolism will take place on 15-16 November 2018 that will be likely followed by guidance in 2019/2020. This activity will be coordinated with other ongoing activities in the area of toxicokinetics by EFSA and the Joint Research Centre.

Other workshops such as phototoxicity or historical control data will be postponed. Some member states considered that a workshop on the use of historical control data should be given highest priority.

2.6.5. Non-dietary exposure

EFSA has been mandated to update the EFSA guidance on the assessment of exposure of operators, workers, residents and bystanders (i.e. non-dietary exposure) in the risk assessment for plant protection products (EFSA, 2014). An open call was launched from 18 June to 10 December 2018[3] to collect all available data that any stakeholder will be able to submit to EFSA, and these data will be taken into account for an update of the guidance and related calculator. The objectives are to cover scenarios not yet included in the guidance such as greenhouse use and seed treatment; to refine some approaches (such as default factors and risk mitigation options); and to give a first feedback on the experience gained with acute acceptable operator exposure level (AAOEL) derivation. It should be

[3] http://www.efsa.europa.eu/en/consultations/call/180618

pointed out that no final guidance for the derivation of an AAOEL for exposure of operators, workers, residents and bystanders has been implemented.

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Abbreviations

AAOEL	acute acceptable operator exposure level
AOP	adverse outcome pathway
CAG	cumulative assessment groups
ECHA	European Chemicals Agency
EU	European Union
IATA	integrated approach of testing and assessment
IC	Index Compound
MoA	mode of action
MRL	maximum residue level
OECD	Organisation for Economic Co-operation and Development
PAFF meeting	Standing Committee on Plants, Animals, Food and Feed
PPR Panel	EFSA Panel on Plant Protection Products and their Residues
(Q)SAR	(Quantitative) structure–activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RPF	Relative Potency Factor
TG	test guidelines