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Mode of Action and Human Relevance Framework in the context of Classification and Labelling (CLH) and regulatory assessment of biocides and pesticides

Workshop Proceedings
Helsinki, 4 November 2014

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Reference: ECHA-14-R-23-EN
Date: December 2014
Language: English

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1. Introduction

A workshop entitled "Mode of Action and Human Relevance Framework in the context of Classification and Labelling (CLH) and regulatory assessment of biocides and pesticides" took place on the 4th of November 2014 at ECHA. The workshop was organised by ECHA in collaboration with EFSA.

The aims of the workshop were to:

- Present the current scientific activities on modes or mechanisms of action (MoA), human relevance framework (HRF) and adverse outcome pathways (AOPs)
- Present the regulatory status of human relevance analysis in Europe under CLP, PPP, and BP Regulations
- Review existing tools, analyses and frameworks, in the context of CLH, which could help to translate scientific knowledge in support of regulatory decisions
- Address scientific challenges by promoting and developing the scientific and regulatory capacity of scientific committees and other actors.

The workshop was attended by 55 participants from the Member States competent authorities, industry representatives from the pesticides sector, academia, EFSA and ECHA. The workshop was also attended by 84 participants via Webex.

2. Background

The term 'mode of action' generally describes the key events and processes resulting in a biological effect whereas 'mechanism of action' implies a more detailed understanding and description of the steps at the molecular level (ILSI, 2009). The mode or mechanism of action (MoA) and human relevance framework (HRF) was developed in initiatives of the International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO) and the International Life Sciences Institute Risk Sciences Institute (ILSI-RSI). MoA/HRF concepts continue to evolve as experience increases in their application (e.g. Meek et al. 2013, WHO/IPCS-ECETOC, 2013).

The analysis of MoA/HRF in hazard and risk assessment for human health can significantly affect the outcome of a regulatory decision. The ongoing work at OECD and WHO/IPCS to develop AOPs for well-established effects, to maintain an accessible electronic repository, to set up an information template/workflow and to issue technical guidance is important. Some regulatory authorities assess common MoA for the purpose of PPPs cumulative risk assessment (e.g. EFSA, EPA). For CLH, the experience with MoA/HRF is limited to a few cases that have recently been assessed by the ECHA Risk Assessment Committee (RAC).

It is the view of regulators and industry that the generation of mechanistic information is of scientific and regulatory value. It is also understood that the scientific knowledge leading to a comprehensive MoA and a HRF analysis may influence approval of an active substance for plant protection and biocidal products under Regulations 1107/2009 and 528/2012. Under CLH, the toxicological endpoints of concern (e.g. target organ toxicity after repeated exposure and CMR properties) are compared with the classification criteria laid down in Regulation 1272/2008 (CLP). Some toxic effects may be dismissed as they occur in tissues with no human equivalent or because some MoA are generally considered within the scientific community as irrelevant to humans (see CLP Guidance, section 3.6.2.3.2).

However, data on MoA may be incomplete for most toxicological effects produced even when these effects are relevant for humans and critical for approval of an active substance or authorisation of a biocidal product. A minimum set of mechanistic data should ideally be reported to identify those events that are most crucial in causing the toxicity. Conducting and reporting studies is not harmonised within the scientific community and not compulsory, especially because they are dependent on the events itself and possible divergent regulatory requirements. On the other hand, when such mechanistic studies are available, they may be of limited or no relevance for CLH due to their lack of tools/guidance for a systematic evaluation by RAC. General principles and minimum standard requirements for each experiment which aims to identify and explain the most crucial events should be documented and performed according to best practices, e.g. the systematic use of relevant controls. For CLH, the formats used to present such complex scientific data should be clear and consistent from one dossier to another.

In view of the complexity and amount of information that may be generated, an agreed and harmonised MOA/HRF/AOP terminology and format/template is needed. For interested parties involved in CLH and EFSA review, there is a need for guidelines that would streamline science-based regulatory decisions.

3. Summary of workshop discussions

During the workshop the following aspects were covered through a series of presentations:

- An overview of the guidance and templates on mode of action (MoA) and human relevance framework (HRF) as developed by the International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO) has been presented;
- An overview of OECD activities in the field of adverse outcome pathways (AOPs) regarding the AOP accessible electronic repository, guidance and templates for the assessment of AOPs;
- An overview of the CLH process and CLP Guidance in relation to mode of action;
- Mode of action within the Plant Protection Products Regulation and combined exposure/cumulative assessment projects (EFSA);
- Case studies of pesticides where the mode of action human relevance framework has been applied (e.g. WHO JMPR, Pesticides Industry).
- For CLH, the experience with MoA/HRF is limited to a few cases that have recently been assessed by ECHA's Risk Assessment Committee (RAC).

It is the view of regulators and industry that the generation of information that enables the mode analysis and human relevance framework to be applied is of scientific and regulatory value since it builds confidence and reduces uncertainty in decision-making processes. Mode of action information, even at the hypothesis level, enables better decisions to be made on testing strategies. It has been recognised that the revisions of chemical regulations regarding information requirements may trigger the need for further research on MoA.

It was identified that current test guidelines may not always provide the information needed for MoA analysis and better integration of parameters, that are necessary for establishing mode of actions, into new test guidelines is needed.

The case studies presented during the workshop highlighted that the scientific knowledge leading to a comprehensive MoA and an HRF analysis may influence approval of an active substance for plant protection and biocidal products under the Plant Protection Products Regulation (EC No. 1107/2009) and Biocidal Products Regulation (EC No. 528/2012) respectively and would also be supportive for cumulative risk assessment under the Pesticides Residues Regulation (EC No. 396/2005).

Under CLH, hazard classes (e.g. target organ toxicity after repeated exposure and CMR properties, taking into account kinetic and dynamic data) are compared with the classification criteria laid down in the Classification, Labelling and Packaging Regulation (EC No. 1272/2008). In addition, case studies demonstrated that using a structured way of presenting the information on key events within mode of action analysis allows consistent assessment by regulators.

Certain hurdles were presented in the case studies regarding the impact of dosing levels into the establishment of human relevance for effects seen in animal studies. The existing MoA/HRF using WHO/IPCS framework allows the incorporation of exposure considerations into the establishment of human relevance for such effects.

It was highlighted that regulators need to be able to assess data quality elements for MoA establishment. It was also highlighted that presenting the MoA concisely is crucial for an efficient and transparent decision-making process under e.g. CLH.

Regulators need to enhance communication and dialogue with different actors to enable the right elements to be addressed (including new methods such as omics) in MoA analysis early in the process (e.g. PPP approval or REACH registration).

It is often not clear how much information is needed to decide that a specific MoA is established. It is also not clear whether alternative MoAs have been excluded. However, the existing international guidance on MoA analysis and the available templates allow these elements to be considered at the problem formulation stage (e.g. what is the decision context, can the MoA help inform the decision), facilitating the dialogue between regulators for decision making.

The extent to which MoA analysis needs to be performed depends on the regulatory endpoint under question. MoA analysis can be resource intensive and therefore at the problem formulation stage it needs to be clarified how detailed the mode of analysis should be and what the expected benefits would be including the impact on testing strategies. These elements would also need to take into account the stage at which the regulatory process is and specific deadlines imposed by EU regulations. When new data become available that may change the conclusions regarding the MoA analysis, these can be taken into account.

There was strong support that the guidance and templates as developed by WHO/IPCS (available at http://www.who.int/ipcs/methods/harmonization/areas/cancer/en/) provide good tools for weight of evidence analysis and transparent documentation of MoA/HRF. They also allow user flexibility depending on the regulatory context and clarify the terminology.

The existence of a database with established MoA/AOPs as being developed by the OECD (https://aopkb.org/) is considered of importance for future work in this area as it will be making the agreed MoA/AOPs available to the regulatory community so that they can also be considered in the context of CLH. All participants were encouraged to join the OECD efforts in populating the AOPwiki database with MoA/AOPs. However, it should be taken into account that at present the AOPs included in the AOPwiki have not undergone any approval process and should not be considered as globally accepted.

It was also emphasised that MOA/AOPs are conceptually identical as terms though the focus for the AOP is often on the molecular initiating event, whereas for the MOA, the focus is frequently on quantitative dose-response for later key events and doesn't imply adversity by default. The regulatory implications on how to contextualise the molecular initiating event (MIE) when dealing with single chemical evaluation or when dealing with QSAR/read across should be clarified as a different data set will be necessary i.e. toxicokinetic data.

The ongoing work at OECD level on guidance to elaborate how confidence levels (high, moderate, low) are defined within MoA/HRF was further supported.

It was recommended that, in the near future, ECHA and EFSA should facilitate further uptake of the existing WHO/IPCS MoA/HRF templates for use in biocides and PPP active substances hazard assessment and under the CLH process (including for industrial chemicals) in collaboration with the respective Committees and working groups. Additional workshops were recommended to follow up practical use of the existing guidance for mode of action. When more experience is gained from the practical use of the templates further needs on guidance can also be identified.

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