EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Safety of the Food Chain
Pesticides and Biocides

WORKING GROUP OF THE ADVISORY GROUP ON THE FOOD CHAIN, ANIMAL AND PLANT HEALTH

Ad hoc Dialogue event on risk assessment of active substances in plant protection products

24 April 2015, 09.30h – 17.30h

Centre Albert Borschette, rue Froissart 36, room 4 B

SUMMARY REPORT

Participants:

European Commission:
DG Health and Food Safety (DG SANTE)

Members of the Advisory Group:
COCERAL, COPA-COGECA, ECCA, ECPA, ESA, EUROGROUP FOR ANIMALS, FOODDRINKEUROPE, FRESHFEL EUROPE, PAN EUROPE

Non-members of the Advisory Group:
Representatives of the following Member States and EFTA countries:
Belgium (BE), Croatia (HR), Denmark (DK), France (FR), Germany (DE), Ireland (IE), Latvia (LV), the Netherlands (NL), Poland (PL), Portugal (PT), the United Kingdom (UK); Norway

Decentralised agencies:
European Chemicals Agency (ECHA), European Food Safety Authority (EFSA)

The objective of the meeting was to address a number of issues about the general approach to risk assessment of active substances (a.s.) in plant protection products (PPPs) that are regularly the topic of debate and therefore merit further discussion in a broad context.

Delegates representing 9 different stakeholder organisations, 2 decentralised agencies, 11 Member States and 1 EFTA country participated in the meeting. Following the

welcome and introduction by Acting Director-General Ladislav Miko, European Commission, DG Health and Food Safety, the different topics were discussed in eight successive sessions, chaired by Michael Flüh, Head of Unit SANTE E.3, and Wolfgang Reinert, Head of Sector, SANTE E.3.002, respectively. Each session comprised an introduction from two to three expert panellists and the opportunity for all participants to ask questions and comment on the individual topic.

Session 1: Possible conflicts of interest raised by studies conducted by industry

Jose Tarazona (EFSA) identified two important sources of information for the risk assessment of a.s. in PPPs: mandatory guideline studies according to the data requirements, and reviews of the scientific peer-reviewed open literature, which are both relevant but complementary. He referred to the EFSA guidance on submission of scientific peer-reviewed open literature for the approval of pesticide a.s. under Regulation (EC) No 1107/2009 and the need to have sufficient information to verify the data. EFSA places a high value on interaction with the scientific community, stakeholders and the wider public and organises public consultations on draft assessment reports for a.s., for which it encourages the participation of the above mentioned groups.

Michael Walsh (DG SANTE) pointed out that the burden of proof is on the applicant to demonstrate the existence of safe uses of an a.s. This concept is not unique for pesticides but also applies to food additives, genetically modified organisms, airplanes, cars, etc. He underlined the importance of scientific peer-reviewed open literature for the risk assessment.

Eurogroup for Animals considered that more studies do not necessarily mean better studies. They noted that ECHA has an effective system to engage stakeholders and encouraged EFSA to exchange best practices in this regard.

PAN referred to its analysis that only a fraction of the scientific peer-reviewed open literature is identified by applicants, and wondered whether this will change when the EFSA guidance becomes fully applicable. EFSA clarified that the identification of open literature by applicants was not yet mandatory for a.s. evaluated under Commission Regulation (EU) No 1141/2010 (AIR-2 programme) but is now mandatory for a.s. evaluated under Commission Implementing Regulation (EU) No 844/2012 (AIR-3 programme).

DE observed that guidelines have been more and more developed and a change is visible in the quality of the studies over time. It is important to improve the quality (and reporting) also of university studies. Inversely, not all industry studies are accepted, as some of them lack the necessary quality or are outdated.

ECPA raised the question whether a potential bias existed not only for industry but also at the academic side, since it is necessary to have a good story to tell in order to for a manuscript to be accepted for publication in a highly-ranked journal.

Session 2: Independence of experts of the authorities in the approval of active substances

Marina Marini (DG SANTE) noted that independence and transparency are very important in the approval process of a.s. These two elements are covered both by Regulation (EC) No 178/2002 (the General Food Law) and Regulation (EC) No 1107/2009 (the PPP Regulation). She described the layers of the current evaluation system, where the Rapporteur Member State and co- Rapporteur Member State perform a first evaluation, followed by a peer review by the other MS and EFSA, and a public consultation. All information is made publicly available, allowing for public scrutiny of the process. Moreover, all the decisions are collegial, not individual. These elements contribute to the constant safeguard incorporated into the system.

Jose Tarazona (EFSA) concurred that all information, including comments and peer review reports, is published on EFSA's website. Furthermore, divergent views are explained in the EFSA Conclusions on the peer review of the pesticide risk assessment of a.s. He acknowledged that due to the far-reaching transparency and the resulting volume of information, specific items of interest are sometimes difficult to find. EFSA is working to improve accessibility and user-friendliness, and welcomes feedback from stakeholders on those efforts. EFSA requires a declaration of interest from experts, which is then scrutinised according to EFSA standards.

ECPA agreed that EFSA maintains a high level of transparency in its procedures, but considered that the level of conservatism applied in risk assessment is sometime less clear to applicants. EFSA replied that the level of conservatism is a risk management decision, and that not all areas are clearly defined in legislation.

The Chairman invited the Member States present to share information on their system to ensure independence of experts at national level. Several Member States explained their system of independence and transparency.

Session 3: Klimisch score as a method for the assessment of reliability of toxicological studies

Norbert Bornatowicz (ECHA) stated that the Klimisch score is the current standard to check the reliability of a study. Academic studies can achieve a good Klimisch score, even if they are not carried out to GLP/OECD standards. However, frequently the reports of such studies suffer from insufficient description, including on the identity of the test material. He pointed to alternatives to the Klimisch score that have been proposed since its introduction.

Manuela Tiramani (EFSA) remarked that the huge amount of data necessitates standardised comparison, and the identification of suitable parameters. In 2011, EFSA published its guidance on submission of scientific peer-reviewed open literature for the approval of pesticide a.s. under Regulation (EC) No 1107/2009 that sets out how to identify and evaluate scientific peer-reviewed open literature. The EFSA guidance does not favour the Klimisch score over other tools as there are several alternatives. She referred to ongoing work to further improve the existing good system, and noted that most suggested improvements use the Klimisch score as the starting point to add other elements.

PAN criticised that by using the Klimisch score, due to oversimplification, certain studies identifying adverse effects might be missed, but emphasised that this is a criticism of the application of the tool, rather than the tool itself.

Looking at the recent evaluation of the a.s. glyphosate as an example, DE reported that a large number of old studies had to be rejected or downgraded, although they were still acceptable during the previous assessment in 1999. On the other hand, even some newly submitted studies were rejected based on the Klimisch criteria. DE considers the Klimisch criteria as not ideal, but the most appropriate so far. It identified as an issue with open literature studies that these often use formulated PPPs (in contrast to regulatory studies, most of which are carried out with the a.s.). Since this may help to provide additional information, it is worth to invest in improving such open studies to make them more useful for regulatory purposes.

The UK uses the Klimisch score as a tool but acknowledge that as all tools it is oversimplifying. The assessment goes beyond, as also expert judgement needs to be applied. It cautioned against too strong a focus on GLP compliance only, as study design according to OECD guidance is also very important (methodology, number of animals used, etc.).

ECHA observed that editors (of scientific journals) try to avoid inclusion of (in their view) unnecessary data in the printed article, and suggested that such data could be published on a website. GLP is a system to ensure traceability and reproducibility of data.

EFSA remarked that academic studies are not per se worse than regulatory studies, but their reporting is often limited and they were carried out for a different purpose. It differentiated between the reliability and the relevance of studies.

DE, EFSA and ECHA would participate in the development of a more complex system to evaluate the reliability of a study. However, EFSA stressed that for the time being, the current guidance is applicable and first some experience should be gained to inform a review of the system. It does not favour recommending one single tool but considers a clear documentation of the approach necessary.

Session 4: Use of oral toxicity studies for risk assessment of operators, workers, bystanders and residents

Susy Brescia (UK) discussed the pros and cons of oral toxicity studies versus inhalation and dermal studies. A balance needs to be struck between detection of an effect and the minimisation of the use of test animals. The chance to detect an effect increases with high doses. She considered the benchmark dose model as a more scientific approach than the NOAEL that may also help with the detection of low-dose effects. However, there is currently insufficient evidence to shift the risk assessment paradigm.

Rudolf Pfeil (DE) raised two questions: whether it is appropriate to base the risk assessment for operators and workers on the use of oral toxicity studies, and whether studies on the a.s. rather than studies with formulated PPPs should be used. The main route of exposure of consumers is orally to the a.s. (via residues in food). Other routes of exposure or exposure to formulated PPPs are less common. Therefore, it is appropriate to lay the focus on the a.s. and its metabolites. In contrast, operators and workers are mostly

exposed to the formulated PPP, and via the inhalation and dermal routes. He considered it not necessary, and due to animal welfare reasons not appropriate, to repeat all oral studies also via the dermal and inhalation routes. A route to route extrapolation based on oral toxicity studies is possible, as most of the effects do not differ in function of the route of administration. Few route-specific studies with formulated PPPs are required for the risk assessment for operators and workers.

Manuela Tiramani (EFSA) added on the issue of sensitivity that the OECD standards are the result of panel discussions and testing activities, with a view to balance the detection of an effect vs. the use of animals.

Eurogroup for Animals agreed that the oral route is usually most critical, and recommended the use of in vitro methods to assess dermal exposure.

Session 5: Use of historical control data for the risk assessment of active substances

Susy Brescia (UK) introduced the definition and guidelines for use of historical control data. Commission Regulation (EU) No 283/2013 provides clear guidance for the use of such data, which should be on a case-by-case basis. It is important to address the normal variability. Only relevant and good quality studies should be included in the historical control dataset. Historical control data is never used to dismiss adverse effects, but is one aspect among others that are taken into account for the weight of evidence.

Marloes Busschers (NL) explained that historical control data is a combination of control groups from several studies to obtain a larger data set. The larger statistical base allows differentiating whether an observed effect is due to an increase of the measured parameter in the test group or due to exceptionally low measurements in the control group. While in principle the control group in the study takes precedence over historical control data, the latter should be used to put the study control data into perspective. She recommended that consideration should be given to the implementation of recent OECD guidance in historical control data by EFSA resp. in the EU.

PAN stated that when study control results are suspected to be abnormal, the study should be repeated. It acknowledged the use of historical control data to check if the study control group is within expectations, and considers it safest to use both a study control and historical control data.

DE uses historical control data for validity/quality control purposes, when certain criteria are met, and finds it useful for rare tumours or malformations. It sees a need for a free, publicly accessible database. This request was supported by several other experts. Currently, a database on historical control data exists, but it is not freely available, since it was sponsored by industry.

ECHA added that without the use of historical control data, many more animals would be needed to achieve comparable statistics.

BE pointed out that if dose dependency is observed, this cannot be disregarded on the basis of historical control data, and that practically only data within a five-year timeframe (as per time of the index study) can be used.

Session 6: Need for further research and data requirements on repeated dose toxicity, including carcinogenicity and reproductive toxicity, and low dose effects

Lars Niemann (DE) reported that the conventional toxicological paradigm "the dose makes the poison" is now challenged by new concepts, such as the low-dose-effect paradigm. While the latter is currently a minority view, it must be seriously considered. He pointed out that on the other hand pesticide a.s. are well studied compared to other chemicals. Detection of subtle effects would require very large amounts of test animals to be used, and efforts to improve testing may be more effective in areas such as formulations, synergistic and cumulative effects, as well as health and environmental monitoring after approval.

Andrea Terron (EFSA) acknowledged that standard toxicological studies, whose principal aim is hazard characterisation, have limitations with respect to the detection of possible low-dose effects, since they are designed to characterise apical effects. There is a lack of agreement within the scientific community on the concept of low-dose effects, in particular regarding endocrine disruptors. He outlined EFSA activities in relevant areas, including a grant on a review on non-monotonic dose responses, as well as working groups on weight of evidence, benchmark dose, and endocrine disruptors.

PAN stated that the issue of endocrine disruptors triggered the discussion on non-monotonic dose responses. It does not ask to completely change the toxicological data package but to take into account important aspects such as prenatal and transgenerational effects.

DE replied that prenatal exposure is a question of study design rather than low doses. A.s. in PPPs are among the best investigated chemicals, with data requirements including studies with prenatal exposure that are followed through to the F1 generation. While DE took note of requests for more research, such efforts are ongoing. However, the regulatory system must be based on solid and reliable knowledge and not on minority opinions. They may be right but historically have more frequently turned out to be wrong. At the moment, there is insufficient evidence to change the regulatory system.

The UK pointed to reproducibility as an important aspect of science that is however often not the case for effects observed once at low doses. It proposed moving from the NOAEL concept to the benchmark dose approach because it is more scientific and not based on one sample resp. one experiment. This was supported by other Member States and ECPA but would require implementation in the regulatory system. The UK referred to activities at OECD level with a view to amending the guidelines.

DE agreed that endocrine disruption exists and mentioned classical examples observed in wildlife and in humans. Endocrine disruption follows a dose-response, even if it is not linear, and can still be detected in toxicological studies. It sees an important role for mechanistic investigations, as it is not sufficient to count tumours in animals but relevance for humans needs to be established.

ECCA acknowledges the existence of low-dose effects but highlighted that not all effects are adverse. The precautionary principle is an important element of risk management but not applicable if the results of one study disagree with the entire rest of the toxicological data package.

PAN doubts the practicality of testing many dose groups and following them through several generations, and therefore requests application of the precautionary principle if an effect is observed but its adverse nature not yet established.

EFSA referred to an opinion of its Scientific Committee published in 2012. Toxicological studies may not show a causal link but will detect the effect, then mechanistic studies are needed.

Session 7: Assessment of toxicological properties and kinetic data and the residue behaviour for co-formulants

Marloes Busschers (NL) held the view that it is impractical and undesirable to do many toxicity tests and conduct the risk assessment repeatedly for all co-formulants, as the same co-formulant can be present in different PPPs. It is preferable to access other sources of information to identify real concerns. She referred to Article 27 of Regulation (EC) No 1107/2009, which provides for the establishment of a list of unacceptable co-formulants, and enquired on its implementation.

Christian Sieke (DE) proposed the development and implementation of data requirements for co-formulants, and a harmonised tiered approach to identify co-formulant substances of concern, comprising assessment of physico-chemical information, consideration of exposure to humans, and generation of actual data. Currently, this depends on the initiative of individual regulatory authorities. The responsibility should be on the applicant to demonstrate the safe use of a co-formulant. Efforts should initially focus on known substances of concern and high-tonnage co-formulants.

ECPA would agree to regulate co-formulants via REACH for all their uses, including in PPPs, and signalled interest to inform regulatory authorities on which information is already available.

DE suggested using the chapters in the relevant guidance document for the biocides sector that are applicable to PPPs, rather than developing new guidance, and cited the example of the guidance document on dermal absorption. Generation of new data on co-formulants is not practical. Instead, EFSA and ECHA should identify practical tools to improve the access to REACH data. It asked ECPA to work on ways to enable PPP applicants to submit the available data on co-formulants.

ECHA makes the dossier available on its website, and access to EUCLID files is available to Member States.

ECHA supports the use of information available at one agency by other agencies, which could also be useful for industry and Rapporteur Member States.

The UK sees the need to first define the term “unacceptable co-formulant” under Regulation (EC) No 1107/2009, before criteria for their identification and regulatory consequences can be elaborated.

The Commission reported that work on Article 27 of Regulation (EC) No 1107/2009 is ongoing, and information on further plans for its implementation will be provided soon.

Session 8: More extensive toxicological investigation of co-formulants for a better assessment of cumulative and mixture effects between the active substance and the co-formulants

Roland Solecki (DE) used the case of glyphosate as an example to show that the toxicity of some co-formulants is higher than that of the a.s., necessitating further investigation. Discussions are needed to reach agreement on how to assess cumulative and mixture effects. He proposed to introduce a screening step to ensure that efforts are focused on relevant substances, and referred to ongoing research, some of which is financed through the EU Research and Innovation programme, Horizon 2020. Coordination with the biocides sector is desirable.

Susanne Hougaard Bennekou (DK) stated that current animal testing is not geared towards cumulative effects. While work on cumulative risk assessment is ongoing in EFSA and elsewhere, more research on the mechanism is required, both for a.s. and for co-formulants. She noted an imbalance in the assessment of these two groups of substances. Alternative methods, including in vitro testing, should be pursued even though currently there is a lack of agreement on the extent of their usefulness. In the framework of Horizon 2020, the Commission made resources available to improve the safety testing of chemicals.

In response to concerns raised by PAN on mixture effects, DK considered that if suitable data on individual substances (both a.s. and co-formulants) are available, the risk assessment can conclude on such effects.

DE acknowledged that in the current system, the assessment of formulated PPPs is focused on acute rather than chronic effects. In the case of glyphosate-containing PPPs, many effects were triggered by certain co-formulants, leading to the replacement of tallowamines as surfactant in PPPs in Germany.

DE further mentioned that the comments received during the public consultation on the draft renewal assessment report for glyphosate contributed to improving the revised report, e.g. as regards the assessment of public literature on oxidative stress.

The Chairman thanked the panellists and participants for their valuable input to the discussion, making an interesting exchange on horizontal issues possible. He summarised the key points that should inform further discussions among risk assessors, risk managers and stakeholders:

- Agencies should exchange best practices, e.g. on efficient engagement of stakeholders.
- While the current regulatory system is very transparent, in particular with public availability of documents, improvements should be made to enable the efficient search for specific information.
- It is worth to invest in improvements to open literature/academic studies and the way in which they are published, with a view to making them more useful for regulatory purposes.
- Member States and agencies should explore improvements to existing tools to make them more comprehensive, e.g. than the Klimisch score.
- The implementation of the benchmark dose as an alternative to the NOAEL should be considered.

- The implementation in the EU of OECD guidance on historical control data should be considered.
- Historical control data should be freely and publicly available in a database.
- While there is currently no agreement on low-dose adverse effects, including in the scientific community, other areas of risk assessment merit further discussion, such as testing of formulated PPPs, synergistic/cumulative effects and post-approval monitoring of health and environmental effects.
- For co-formulants, existing approaches and data, e.g. from the biocides sector and REACH, should be used, rather than to generate new data.
- The Commission should continue to support research on improved safety testing of chemicals, including through Horizon 2020.