Bundesinstitut für Risikobewertung

WHAT DOES THE FUTURE HOLD FOR HARMONISED HUMAN HEALTH RISK ASSESSMENT OF PLANT PROTECTION PRODUCTS?

23rd – 24th November 2017
Auditorium at the German Federal Institute for Risk Assessment (BfR)
Berlin Marienfelde, Germany

SUMMARY REPORT

Introduction

On 23rd and 24th November 2017 the German Federal Ministry of Food and Agriculture (BMEL) organised together with the German Federal Institute for Risk Assessment (BfR) and the support of the European Commission a workshop on the harmonisation and further development of the human health risk assessment of plant protection products. The workshop was held in Berlin, Germany, as a follow up of the dialogue event on the risk assessment of plant protection products organised by the European Commission in 2015. Building on this successful dialogue process, the current workshop aimed to intensify discussions among risk assessors, risk managers and stakeholders in order to understand current needs and to explore possibilities to support the progress towards a harmonised human health risk assessment of plant protection products. At the two-day workshop about 100 participants from the European Commission, the European Food Safety Authority (EFSA), European member states authority's, non-governmental organisations (NGO), industry associations, producer organisations and university's contributed to intensive and lively discussions on a high scientific level. Although sometimes controversial, all discussions aimed towards an improved and harmonised human health risk assessment of plant protection products.

The welcome and introduction were held by Deputy Director-General Ladislav Miko, European Commission, Directorate-General Health and Food Safety; followed by the head of the unit 512 - plant protection - Friedel Cramer, Federal Ministry of Food and Agriculture and completed by the president of the German Federal Institute for Risk Assessment Andreas Hensel, German Federal Institute for Risk Assessment. The different topics were discussed in four successive sessions, chaired by Antje Grobe, Managing Director of DIALOG BASIS. Each session comprised scientific lectures followed by a panel discussion of the lecturers and the opportunity for participants to ask questions and comment on the individual topic. The presentations as well as a summary of each panel discussion are given below.

Session 1: Human health risk assessment – How to realise an independent and reliable evaluation?

In the first session possibilities on how the transparency and quality of studies used in risk assessment and the independence in evaluation can be further improved were discussed. The session was opened by **Karin Nienstedt** giving an overview as regards the generation and reporting of scientific data used as a basis for risk assessment as provided by the EU legislation. The second speaker **Euros Jones** gave a review on information made publicly available by companies and on industries view on financing of studies. This was followed by a presentation of **Peter Clausing** which focused on how peer-reviewed scientific studies could be considered in the regulatory practice. The session was closed by **Antonio F. Hernández** presenting views on the application of human epidemiological studies to pesticide risk assessment.

Presentations

1. Dr. Karin Nienstedt; Independence of scientific data and risk assessments for decision making based on evidence http://www.bfr.bund.de/cm/349/independence-of-scientific-data-and-risk-assessments-for-decision-making-based-on-evidence.pdf

2. Euros Jones; Public availability and financing of studies - An industry perspective http://www.bfr.bund.de/cm/349/public-availability-and-financing-of-studies-an-industry-perspective.pdf

3. Dr. Peter Clausing; Scientific publications in the regulatory practice: An NGO perspective http://www.bfr.bund.de/cm/349/scientific-publications-in-the-regulatory-practice-an-ngo-perspective.pdf

4. Prof Dr. Antonio F. Hernández-Jerez; Application of human epidemiological studies to pesticide risk assessment http://www.bfr.bund.de/cm/349/application-of-human-epidemiological-studies-to-pesticide-risk-assessment.pdf

Panel Discussion

The debate was started with the questions on how the transparency and quality of studies can be further improved. It was stated that the term “transparency” has to be specified and it has to be also clarified at which level more transparency is needed. Regarding public availability of raw data, it was pointed out that the public is often not aware of information which is already freely accessible. Regarding the consideration of epidemiological studies as evidence, it was mentioned that after being checked for reliability and relevance, all studies available to date should be considered.

A second focus of the discussion was the comparability of regulatory studies founded by applicants and studies carried out by academia and published as scientific literature. The

meaning of “independence” in independent studies was questioned. It was mentioned that there are already well-defined protocols of studies agreed at international level and in addition an independent quality system in place (GLP, good laboratory practice), needing to focus on independent verification of the accredited institutions instead of independent study ownership. Thereupon it was stated that data interpretation and histopathologic reviews are steps in experimental studies which always involve expert judgement. The questions raised from the audience were directed at the political implications of setting acceptable threshold values by risk managers or risk assessors and the possibility of falsifying scientific data despite a GLP certification. In the panel it was pointed out that risk assessment is more complex and important than hazard assessment, stating that expert judgment is present in both study interpretation and peer-reviewed scientific studies.

Conclusion

Possible ways for the enhancement of the quality of the risk assessment and the improvement of the transparency were discussed. Peer-reviewed scientific studies performed by academia or authorities and regulatory studies following OECD Test Guidelines (Organisation for Economic Co-operation and Development) and according to GLP performed by applicants both need to be considered adequately in the risk assessment. Peer-reviewed studies should be considered and included in a weight of evidence approach.

It was suggested to reflect on animal studies in combination with epidemiological studies and to take into account no-effect studies which are very often not published (publication bias). No-effect studies might be published in appropriate in-house journals (e.g. BfR journal).

In respect of the regulatory risk assessing process firstly it was suggested to differentiate between the assessment report of the authority opinion and the applicant information and to further improve the description of the evidence selection process (studies and reports). In order to obtain more transparency, the pre-registration of all GLP studies to avoid double testing were proposed. Furthermore, access to raw data from all scientific studies should be feasible, possibly by direct request to the authors. In addition the initiation of an early dialogue with stakeholders is considered necessary.

Session 2: Human health risk assessment – Enhancement of the scientific dialogue between the experts

The second session focused on the question of how to maintain a robust and objective scientific dialogue between government and stakeholder experts. New concepts were presented which are expected to minimise the current difficulties in understanding and interpreting scientific data.

The session was opened by a talk of **Jens Schubert** giving an overview on the EU approval process for active substances followed by examples illustrating current challenges in this field including glyphosate. The second presentation was hold by **Euros Jones** focusing on the stakeholder process for dialogue. After this **Angeliki Lyssimachou** spoke on the importance of transparency in decision making in human health risk assessments and presented the results of a recently conducted survey among their NGO-members. The session was completed by **James Ramsey** presenting the current approach of the EFSA to stakeholder dialogue.

Presentations

1. Dr. Jens Schubert; How to maintain a robust and objective dialogue between government and stakeholder experts? - A national authority perspective
   http://www.bfr.bund.de/cm/349/how-to-maintain-a-robust-and-objective-dialogue-between-government-and-stakeholder-experts-a-national-authority-perspective.pdf

2. Euros Jones; Robust and objective scientific dialogue between government and stakeholder experts - An industry perspective
   http://www.bfr.bund.de/cm/349/robust-and-objective-scientific-dialogue-between-government-and-stakeholder-experts-an-industry-perspective.pdf

3. Dr. Angeliki Lyssimachou; How to maintain a robust and objective scientific dialogue between government and stakeholder experts? - An NGO perspective
   http://www.bfr.bund.de/cm/349/how-to-maintain-a-robust-and-objective-dialogue-between-government-and-stakeholder-experts-an-ngo-perspective.pdf

4. Dr. James Ramsey; Robust and objective scientific dialogue between government and stakeholder experts - An Authority perspective
   http://www.bfr.bund.de/cm/349/robust-and-objective-scientific-dialogue-between-government-and-stakeholder-experts-an-authority-perspective.pdf

Panel Discussion

The first part of the panel discussion centred on the question whether it is possible to initiate a trialogue with member states, industry and NGOs to improve the scientific discourse. There was a general agreement that the dialogue should be as inclusive as possible. It was noted that the already existing dialogue with agencies, industries and NGOs and others could be

broader. It was stated that challenging the risk assessment makes it more robust and that smart engagement of stakeholders is important.

The panel also discussed how it can be ensured that concepts and definitions in the area of health risk assessment are uniformly understood and interpreted by all stakeholders. It was pointed out that communication among stakeholders and the public has to be based on the same understanding of the terminology. It was also stated that all stakeholders have a responsibility to contribute to a clear dialogue but achieving a uniform understanding is challenging due to the high technical complexity, thus the focus should be a good dialogue. A reduction of the human health risk from pesticide use is desirable but should be achieved through technology improvement and scientific support rather than through policy alone. Furthermore it was stated that the public has to understand it is being protected from chemicals by the detailed EU legislation in place.

From the audience it was commented that the uniform understanding needs to start at authority level because the use and interpretation of terminology sometimes differs even between agencies. Another audience member highlighted that an open dialogue would benefit the whole process, however the work of the risk assessors is often dismissed by NGOs while in fact the experts in the public authorities draw their own conclusions and do not just adopt the views of applicants. The need to create more trust among stakeholders was stated.

At the end of this session a representative of one applicant announced several important steps on action in the near future which will increase transparency, addressing the fact that unpublished data raised concern within the public.

Conclusion

In order to broaden the scientific dialogue, stakeholder involvement in the early stages of the process was considered necessary. The use of different dialogue approaches, e.g. small group of representatives, hearings, extensive consultation processes or a combination of all was proposed.

In order to enable various stakeholder representatives to participate in EFSA panels it was suggested to fund the participation of stakeholders, e.g. by EFSA. In order to increase transparency, target-group specific communication, e.g. FAQs (frequently asked questions), release of raw data, was suggested. In this context already existing FAQs (EFSA, BfR) might be further improved. Overall the results of the risk assessment should be inclusive, transparent, well communicated and challenge the quality of the risk assessment. The goal of every stakeholder to obtain quality and not quantity should not be compromised by these efforts.

As a first milestone towards more transparency it was announced that by the end of 2017, one applicant will make summaries of their studies available as well as tutorials to help the general public understand the studies. In addition, in-depth reports will be accessible upon request in 2018.

Session 3: Human health risk assessment – Implementing of new concepts for mixtures

The toxicological assessment of mixtures is a major challenge within EU legal requirements for plant protection products. This session was intended to identify specific concerns and provide incentives for the improvement of cumulative hazard and risk assessment.

The session was started with a presentation by **Christopher Dobe** explaining how data generated under REACH (registration evaluation authorisation of chemicals) can be used for the evaluation of plant protection products. After this **Gilles-Eric Seralini** spoke on the contribution of co-formulants to the overall toxicity of plant protection products using the example of glyphosate. The third speaker **Martin Dermine** than expressed the view that the toxicity of products is underestimated by current evaluation processes. The joint presentation by **Tamara Coja** and **Korinna Wend** addressed issues concerning the use of animal studies and their replacement by the calculation method. The session was closed by a presentation of **Robert Landsiedel** focusing on the testing of mixture effects.

Presentations

1. Dr. Christopher Dobe; Implementation of toxicological data from other legal provisions (e.g. REACH) - An industry perspective
   http://www.bfr.bund.de/cm/349/implementation-of-toxicological-data-from-each-other-legal-provisions-an-industry-perspective.pdf

2. Prof. Dr. Gilles-Eric Seralini; Pesticides, formulants, Declared active principles
   http://www.bfr.bund.de/cm/349/studies-of-pesticide-toxicities-from-data-on-declared-active-substances-and-formulants-an-university-perspective.pdf

3. Dr. Martin Dermine; Tools for a better understanding of cumulative interactions - An NGO perspective http://www.bfr.bund.de/cm/349/tools-for-a-better-understanding-of-cumulative-interactions-an-ngo-perspective.pdf

4. Dr. Tamara Coja, Dr. Korinna Wend; Application of the calculation method in regulatory risk assessment - Part 1 – The issue of animal studies and Part 2 – Calculation method
   http://www.bfr.bund.de/cm/349/application-of-the-calculation-method-in-regulatory-risk-assessment-an-authority-perspective.pdf

5. Dr. Robert Landsiedel; Data from alternative methodologies for cumulative risk assessment - An industry perspective
   http://www.bfr.bund.de/cm/349/data-from-alternative-methodologies-for-cumulative-risk-assessment-an-industry-perspective.pdf

Panel Discussion

The first part focused on the suitability of current data requirements for the evaluation of mixtures. While it was acknowledged that a high quantity of data is available to the regulating agencies, the need for more relevant data was expressed. As an example, the current lack of chronic toxicity studies conducted with plant protection products (PPPs) was addressed. A recent proposal to EFSA was mentioned to include the Ames test into the PPP data requirements. The importance of alternative methods for PPP evaluation was debated, as the regulation of PPPs still allows *in vivo* testing. Hence, the demand for research to phase-out animal testing was raised. In this context it was stressed, that single methods have so-far not proven appropriate to replace animal testing and that the maintenance of an adequate level of protection must be ensured.

The second part aimed at identifying suitable tools and strategies for the future evaluation of mixtures. The adaptation of current methods was considered a necessary means of improving risk assessment immediately. For example, it was suggested to identify when the use of the calculation method can be justified. Regulators replied that an evaluation is currently in progress, addressing this issue. In addition, the scientific need to increase the safety factor was expressed to account for uncertainty until adequate methods for mixture risk assessment are available. However, others did not consider an additional factor sufficiently scientifically justified. In line with the precautionary principle, the establishment of over-conservative models was recommended, which could be refined as soon as relevant data became available. Moreover, concerns were voiced, that not all possible combinations of substances can be assessed, in future. Instead, the identification of critical steps was proposed by focusing on over-additive responses, identifying critical nodes of effects and accounting for kinetic as well as dynamic mixture effects. For this purpose, the suitability of *in silico* methods was emphasised. In addition to the prioritisation of effects, the prioritisation of relevant exposure by analysing the most frequent and highest residues in food was suggested.

Conclusion

More appropriate data on potential mixture effects are required for the risk assessment of plant protection products and their active substances. While a lot of data is already available, it should be used more efficiently in risk assessment. With respect to non-active ingredients, information is in particular available within the legal framework of REACH. The lack of data on chronic endpoints for PPP should be addressed. An integrated test strategy using *in vitro* and *in silico* tests verified for agrochemical mixtures is required to reduce animal testing. Current methods were viewed as insufficient to detect and to quantify cumulative effects of complex pesticides. The prioritization for mixtures with indications for over-additive or long term effects and the identification of relevant exposures might be a first step to deal with the enormous number of possible mixtures. All available information and intelligent testing strategies were therefore proposed to be combined in a scientific based weight of evidence approach to account for PPP complexity and improve risk assessment immediately as well as in the future.

Session 4: Human health risk assessment – Assessment of metabolites from pesticides

The last session questioned the current status of risk assessment of metabolites from pesticides along the lines of the new EFSA Guidance on the establishment of the residue definition for dietary risk assessment. The session started with a talk by **Ivana Fegert** presenting the initial experiences industry has gained with the various modules of this new EFSA Guidance document. **Jose Tarazona** spoke about the importance of pesticide metabolites for human health risk assessments and illustrated by examples the various elements and assessment approaches included in the new EFSA Guidance document. The session was completed by **Xavier Sarda**´s presentation on the MetaPath (metabolism pathways) tool for storing and assessing pesticide metabolism data.

Presentations

1. Dr. Ivana Fegert; Application of the new EFSA Guidance on assessment of metabolites for dietary risk assessment for new submissions - An industry perspective
   http://www.bfr.bund.de/cm/349/application-of-the-new-efsa-guidance-on-assessment-of-metabolites-for-dietary-risk-assessment-for-new-submissions-an-industry-perspective.pdf

2. Dr. José V. Tarazona; Grouping principles, assessment and testing of metabolites for the approval and re-approval of active substances - An authority perspective
   http://www.bfr.bund.de/cm/349/grouping-principles-assessment-and-testing-of-metabolites-for-the-approval-and-re-approval-of-active-substances-an-authority-perspective.pdf

3. Dr. Xavier Sarda; MetaPath, an international database on pesticide metabolism
   http://www.bfr.bund.de/cm/349/metapath-an-international-database-on-pesticide-metabolism.pdf

4. Kristina Wagner; Need for further research on alternative tiered testing strategies
   http://www.bfr.bund.de/cm/349/need-for-further-research-on-alternative-tiered-testing-strategies-an-ngo-perspective.pdf

Panel Discussion

As to the question whether the new EFSA Guidance document would satisfy all the needs and expectations of the panel members, there was a broad agreement that science is permanently progressing, bringing up new solutions but also new questions. To this end, any guidance document can at best reflect the current state-of-the-art. For broad acceptance, EFSA involved various stakeholders and user groups during the development of the guidance document.

According to experience of industry it would be desirable to prioritize in an early stage of the process focusing on a reduced number of metabolites otherwise a huge number of metabolites would undergo further consideration and/or testing increasing the workload for risk assessors. Further the number of animal studies would increase significantly. Moreover ending up in incomplete data packages should be avoided. During the discussion, pros and cons were provided on the question if exposure of the metabolites could be accounted for earlier in the process. While this would probably lead to a more practical and less time-consuming approach, it was on the other hand argued that exposure changes frequently (i.e. with every newly approved use) and residue definitions would require frequent adaptations if exposure was included in an early stage of the process. MetaPath was considered being perhaps a significant step forward in metabolite assessment.

The panel members pointed out, that the new EFSA Guidance document has not been noted in the recent Standing Committee on Plants, Animals, Food and Feed (Residues section) in November 2017. Further the concern was raised over isolating the EU internationally, because the Guidance document was expected to lead to an increasing number of diverging residue definitions between EU and international bodies.

A second focus of the discussion was the panel members´ view and that of the auditorium on the acceptance of the proposed approaches (e.g. *in silico* methods, grouping approaches). There was agreement that a common understanding is urgently needed between competent authorities and applicants regarding the interpretation of test/calculation results at various stages in the new methodology. This should be fostered by common training courses and safeguarding that identical underlying databases are made use of for *in-silico* tools on both sides. EFSA offered support to the member states when dealing with complex grouping approaches. To increase reliability and appropriateness of results, (Q)SAR (quantitative structure–activity relationship) databases need to be trained for pesticides.

Conclusion

EFSA's "Guidance document on the establishment of the residue definition for dietary risk assessment" is aiming on making the best use of all available data and assessment tools. However, neither the tools nor the assessment methodology are considered to be fit for the purpose of metabolite assessment to date. The required endorsement at European level is still outstanding and the international dimension needs to be considered.

Common understanding regarding the interpretation of test/calculation results at various stages in the new methodology is needed and might preferably be promoted by common training courses and safeguarding that identical underlying databases are made use of for *in silico* tools on both sides.

Concerning the grouping of metabolites and the use of (Q)SAR strategies, broad acceptance of these tools needs to be achieved among all stakeholders in the first place. The MetaPath tool for collecting and assessing pesticide metabolism data could be a powerful tool for grouping of metabolites. MetaPath is contained in the current version of the OECD (Q)SAR

ToolBox. For the prediction of pesticide metabolites toxicity the (Q)SAR system might be an appropriate tool. To increase reliability and appropriateness of results, (Q)SAR databases need to be trained for pesticides.

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