Report from the Workshop on Toxicological Risk Assessment of Plant Protection Products
13–14 March 2018

On 13 and 14 March 2018, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) hosted a **Workshop on Toxicological Risk Assessment of Plant Protection Products**. This was a follow-up to the meeting hosted by the Austrian Agency for Health and Food Safety (AGES), in Vienna in June 2015 and by the German Federal Institute for Risk Assessment (BfR), in Berlin in June 2014[1].

The agenda of the meeting was developed by the organising committee. Prior to the meeting a questionnaire on each of the central topics was sent to the partner country participants in order to collect information on their own experiences.

Central topics were:

- the new European Food Safety Authority (EFSA) "Guidance on the Assessment of Exposure for Operators, Workers, Residents and Bystanders in Risk Assessment of Plant Protection Products (PPPs)";
- combined toxicity of active substances in PPPs;
- new developments regarding EFSA guidance on dermal absorption;
- alternatives to animal testing in the context of classification of plant protection products[2].

The meeting was attended by participants from the regulatory authorities of some 20 European countries, plus representatives of the European Chemicals Agency (ECHA), the European Commission (Directorate-General Health and Food Safety), the International Centre for Pesticides and Health Risk Prevention (ICPS), the Joint Research Centre (JRC), the European Crop Care Association (ECCA), the European Crop Protection Association (ECPA), EFSA and the International Biocontrol Manufacturers' Association (IBMA).

The Workshop's aims were to provide an overview of how certain models and guidelines for the assessment of human health risks associated with the uses of plant protection products (PPPs) are implemented in practice, in order to contribute to the harmonisation of practices between partner countries and allow areas for improvement to be identified and promoted.

Welcome address:

1 See Appendix II for links to the programmes and reports of the 2014 and 2015 meetings, plus a list of abbreviations.

2 See Appendix I for key supporting documents and legal texts cited at the present Workshop.

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Françoise Weber (Deputy Director-General for regulated products, ANSES) welcomed attendees and opened the Workshop by emphasising on the need to ensure the protection of human health and to meet societal expectations for the assessment of human health risks associated with the use of PPPs.

Mark Williams (European Commission [COM] DG Health and Food Safety) emphasised the desire and benefits of bringing together stakeholders to discuss important topics and to increase harmonisation of the risk assessment (RA) of PPPs to allow for a smooth and efficient functioning of the authorisation system in the EU. This is to allow assessment and placing on the market as quickly and efficiently as possible, while safeguarding human and animal health and the environment.

Summary and results of the Workshop[3]

The initial topic, on the first day of the Workshop, was the update (2017 - 2021) of the EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in RA for plant protection products

The session was chaired by Hugh Dawick, Chemicals Regulation Division, UK Health & Safety Executive.

Juliette Jobard and Françoise Bouneb (both ANSES) presented a summary of responses to the pre-Workshop questionnaire related to this topic.

For operator exposure, in general, a harmonised approach is noted between Member States (MSs). Field studies are generally accepted outside the EFSA model framework, provided that they fulfil the necessary validity criteria.

A few MSs asked for default values in the EFSA calculator to be further revised. Harmonised guidance is awaited for acute exposure assessment. A majority of MSs do not have additional risk mitigation measures (RMMs) for operators.

For worker exposure, different approaches were identified, with half of MSs responding that they have additional RMMs.

For bystanders and residents, MSs' positions were more heterogeneous; there is relatively little experience with bystander and resident studies.

The principal identified additional scenarios which were not covered by the EFSA guidance were greenhouse uses, seed treatments, plus home and garden uses. A number of other models or parameters are used by MSs for RA or RMMs.

3 There is a synopsis, Conclusions of the Workshop.

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The outcome of the questionnaire was followed by presentations on current experiences on the EFSA guidance, given by Mia Kjæstad (Danish Environmental Protection Agency [EPA]), Jessica Broeders (Ctgb, the Netherlands) and Agathi Charistou (BPI, Greece) for the Northern (N), Central (C) and Southern (S) regulatory zones of the EU, respectively.

Estimates of exposures for the operator, resident, bystander and worker were presented as follows:

OPERATOR:

In general, a harmonised approach is noted between MSs. Field studies are generally accepted outside the EFSA model framework and common criteria are shared by MSs. It has been noted that there were no important differences between the three zones. However, some dissimilarities and needs have been discussed or are known to exist:

- A harmonised approach is missing for exposure estimates related to greenhouse uses, seed uses, amateur uses, or post-harvest treatment. Currently, MSs apply different methodologies.
- Exposure results of operators during knapsack sprayer application should be refined.

When additional exposure data including new material such as closed transfer systems (CTSs) are available, they should be implemented in the EFSA model.

Greenhouses

Sabine Martin (BfR) presented the new Greenhouse Agricultural Operator Exposure Model (AOEM). Exposure factors are selected based on statistical analyses; it is a “log linear” model, suitable for risk assessment of both zonal and national (MS) applications. A tiered approach is possible; limitations were presented (e.g., no data for knapsack sprayers).

Pending the implementation of the greenhouse model into the AOEM, MSs currently use various national models or ECPA models (similarly exposed group [SEG]).

Implementation of the greenhouse model in the EFSA model is planned. Guidance for setting the acute acceptable operator exposure level (AAOEL) is planned, to allow calculation of an acute systemic exposure for the operator, if necessary.

WORKER:

There was agreement that dislodgeable foliar residue (DFR) studies in different countries and on different crops showed great variability, especially after rainfall. The extrapolation of DFR data from one crop to another is not accepted by all MSs and needs a thorough consideration of prevailing conditions.

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Grouping based on morphology structure and size to extrapolate studies from one crop to another is needed.

Some MSs provide refined assessment taking into account the foliar residue dissipation. DFR value is modified by calculation regarding the residue level estimated after a pre-harvest interval (PHI) or a re-entry period. EFSA clarified that Appendices C and D of the EFSA guidance were used to support the default foliar DT_{50} value (30 days), and should not be used for refinement.

In the current EFSA calculator, exposure of workers in orchards, vineyards and other crops is always estimated with the same transfer coefficient (TC) derived from studies where the crop foliage has been treated irrespective of BBCH growth stage and foliar index.

It was considered essential to define “early” and “late” applications. The BBCH scheme may not necessarily be the best indicator; percentage leaf cover or leaf area index (like efficacy) may be more relevant. The worker exposure after a pre-emergence herbicidal application or an application at an early growth stage is much lower than with an application at a later growth stage.

A re-entry project (BROV WG[4]) will present different TCs according to the different tasks in grapes: harvesting, pruning, tying-back and shoot-lifting. New TCs for workers in vineyards wearing re-entry gloves are expected.

To limit worker exposure, two different approaches are currently used by MSs. Some use Personal Protective Equipment (PPE), such as gloves and coverall, while others use a re-entry period based on DFR value, or both.

Greece presented a case study with a combination of both previously mentioned approaches as indicated below:

1st tier: actual exposure taking into consideration 10 % penetration factor for gloves.

2nd tier: refinement by using substance specific DFR and DT_{50} values instead of default values to evaluate safe re-entry time.

It was noted that refinements of re-entry scenarios are necessary: further crop grouping based on morphology, structure and size, to facilitate extrapolation of DFR studies and TC values, new foliar residues data, new activities for workers and further considerations of multiple applications.

BYSTANDER AND RESIDENT:

[4] Bystander Resident Orchard Vineyard (BROV) Working Group

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Bystander

For bystander exposure, limited experience is due to the low number of active substances with an already derived acute acceptable operator exposure level - AAOEL. More experience is required in peer review and further harmonised guidance is awaited for the derivation of the AAOEL.

Resident

For resident exposure, the **four pathways** considered in the EFSA model led to the following discussion or comments:

Spray drift

Currently there is a limited and outdated data set, especially for high (tall) crops. More drift data are needed which could be implemented in the future EFSA model, e.g. with the latest data of the BREAM project[5] (for low crops) and data from new field studies on orchards and vineyards.

For a full foliage scenario, the exposure could be below values obtained with the current EFSA model; for an early scenario it could be higher. In discussion, it was noted that BREAM 2 will not be usable operationally until 2020-2021.

It was mentioned that the drift value is greatest at vertical heights of 1 to 2 metres and furthermore the amount of real drift reduction (50 %/75 %) was not necessarily the amount predicted.

Vapour/volatilisation

In the EFSA guidance, the inhalation exposure to vapour is solely dependent on the vapour pressure and falls into two classes: moderate and low volatility. No direct refinement options are available, which could lead to an overestimation of the resident exposure. More choice in default values or calculation of saturated vapour concentration (i.e., in BROWSE V5.3[6], HEEG opinion 13[7]) are necessary to take into account the actual concentration of active substance applied per hectare or the vapour pressure of the active substance (especially with a low AAOEL and low application rate).

The purpose is to determine a realistic maximum 24-hour mean (for bystander) and a long-term concentration over several days (resident) for each application.

Re-entry into crops - Surface deposit

5 Bystander and Resident Exposure Assessment Model

6 Bystander Resident Operator WorkerS Exposure

7 HEEG opinion 13 Assessment of Inhalation Exposure of Volatilised Biocide Active Substance, 2011, https://echa.europa.eu/documents/10162/19680902/heeg_opinion_13_volatilised_inhalation_exposure_en.pdf

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It was noted by the majority of MSs that for pre-emergence treatment of bare soil, the estimated exposure is always too high when including all pathways.

For example, for a herbicide PPP applied on a sugar beet crop at pre-emergence scale in February, the TC of 7500/2500 cm^2/h over-estimates the re-entry exposure of residents (adult/child), considering the height of the crop (BBCH scale) and the clothes worn by the resident at this period of the year. Some MSs exclude the entry pathway; others use lowered TCs. Furthermore, some MSs consider the re-entry of children in bare soils to be not relevant for RA purposes.

Particular cases of tunnels and greenhouses

Possible questions include bystander/resident exposure from tunnels concerning the Northern and Central zones, depending on the permanent and/or permeable characteristics of the tunnels. However, there is a clear lack of data on representative tunnels due to their diverse nature, and more harmonisation is needed here.

Some MSs cannot use buffer zones (BZs) or low-drift nozzles as RMMs; this is the case particularly in small-scale areas, where large BZs are unrealistic.

PPE

The EFSA calculator allows refinement of the exposure assessment using PPE such as gloves and workwear. Some disagreements persist concerning the use and definition of these RMMs.

The precise nature of “workwear” is unclear: it is considered that at least the arms, body and legs are covered. Protective equipment must be certified.

Gloves are accepted for operators for mixing and loading. This is not applied in the case of workers, most MSs preferring to estimate a re-entry period rather than considering the use of gloves. PPE must to be comfortable whatever the activity and conditions.

CONCLUSION:

The implementation of the EFSA Guidance has helped MSs towards harmonisation but additional refinements are clearly necessary and there is still much to be done. New developments with operator, worker, bystander and resident RA were discussed, specifically, greenhouses, workers and bystanders, plus an update on EFSA guidance. MSs should align their approaches by using the appropriate models according to the dossier’s date of submission.

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After the present Workshop, EFSA will make an open (public) call for data[8]. EFSA invites all participants to submit additional data from activities at MS level and suggestions for additional topics to be further considered in the revised guidance. Revised guidance should then be published in 2021.

The second topic was non-dietary combined risk assessment (CRA), in the context of the new draft Registration Report (dRR) template.

The session was chaired by Tamara Coja, AGES, Austria.

A presentation by Karine Angeli (ANSES) summarised responses to the pre-Workshop questionnaire, which had revealed that a large majority of MSs have already performed non-dietary combined exposure assessment. It was noted that there is an attempt for harmonised approach to address combined exposure by applying first hazard index (HI) or % AOEL as Tier 1. However, there is lack of harmonised methodology for refinement as currently no target-organ-specific reference values are derived at EU level, mainly because the work on cumulative assessment groups (CAGs) is still ongoing.

Intervening via web conference, Federica Crivellente (EFSA) presented the toxicity aspects of CAG methodology for pesticides. Two scientific reports will be produced in 2019, on CAGs for effects on the nervous[9] and thyroid systems. Further CAGs will consider additional organs and systems, among others reproductive and developmental toxicity, adrenals and eyes. Data collection for effects on kidneys, the haematopoietic system and bone is likewise ongoing.

Federica Crivellente (EFSA) explained that it is under consideration whether CRA would be limited in the future to dietary rather than non-dietary aspects.

Bruno Dujardin (EFSA) continued with a web conference presentation on CRA for pesticides (exposure aspects) covering dietary exposure, occurrence, consumption data and modelling. EFSA is working on internal cumulative exposure calculations. He explained that CRA and exposure assessment should be published in 2019 and that if the methods were shown to be successful; it would “go live” with certain CRAs included in annual monitoring. Post-marketing CRA would be initiated in the near future.

The lack of harmonisation was also noted in Christian Küster’s (ECPA) presentation where he described how industry conducted non-dietary CRA, in increasing tiers according to level of knowledge. CAGs are used as Tier III refinements.

8 Post-meeting note: *Call for new scientific information/data related to the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products*, http://www.efsa.europa.eu/en/consultations/call/180618 (published 18 June 2018).

9 Post-meeting note: *Public consultation on the establishment of cumulative assessment groups of pesticides for their effects on the nervous system*, http://www.efsa.europa.eu/en/consultations/call/180508-0 (published 8 May 2018).

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Summarising this discussion, Tamara Coja (AGES) considered it important to clearly differentiate:

a) combined exposure for non-dietary risk assessment, as currently done; and
b) cumulative risk assessment for dietary exposure, as intended to be done in the future.

Cumulative RA, including information on CAGs, includes consumption data and would soon be used in dietary RA. With respect to combined exposure, additivity of effects is assumed and this approach has been used for all dossiers submitted after 1 January 2016.

It was additionally noted that target-organ-specific reference values should be always derived only at European level, once information on CAG is available.

The third topic – on the second day – was the new EFSA Guidance Document (GD) on dermal absorption (DA). The session was chaired by Arianna Chiusolo of EFSA.

Marie-Estelle Gouze (ANSES) summarised responses to the pre-Workshop questionnaire:

All MSs use the EFSA GD (2012)[10] to determine DA values for RA of PPPs: this improves EU-level harmonisation.

Some points (e.g. extrapolations, application of *pro rata* corrections) remain difficult to harmonise as they may still be subject to different interpretation. It is recognised that there will be also sometimes cases where expert judgement has to be applied.

Since the use of animals for the purpose of dermal absorption testing is to be reduced, this could be reflected in European official documents (i.e., EFSA guidance on DA; COM Communication on testing methods; OECD[11] testing guidance).

It was noted that the questionnaire chiefly concerned the current guidance. The new guidance, published in 2017[12], should provide clearer criteria, for example, bridging between formulations.

Jérémy Pinte (COM) explained that it was Regulation (EC) No 1107/2009 which stipulated that animal testing only be undertaken when necessary; this would be clarified in the future Communication on test methods.

[10] Cited in Appendix I

[11] Organisation for Economic Co-operation and Development, cf. http://www.oecd.org/env/ehs/pesticides-biocides/

[12] Cited in Appendix I

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Arianna Chiusolo (EFSA) gave a presentation on the new GD (2017). She highlighted changes to the guidance of 2012, based on new studies on human *in vitro* dermal absorption with PPPs submitted by ECPA and BfR (data sets and study reports). As requested by the COM in the mandate sent to EFSA in 2015, first the scientific quality of newly provided data was assessed as described in the EFSA Scientific Report (2015)[13]. Then the GD was updated based on the analysis of data (default values, how to address variability within results), to provide clearer criteria on parameter calculation ($t_{0.5}$, recovery, pro-rata correction, definition of outliers) and to be more harmonised with regulatory requirements (bridging of similar formulations).

New default values to be used in absence of experimental data have been established, based on concentration status ('concentrate' and 'dilution') and formulation category, since these parameters demonstrated significant impact on DA from statistical analysis.

Among the changes, the active substance concentration threshold (5 % corresponding to 50 g/kg for solids or 50 g/L for liquids) to distinguish concentrated products from in use dilutions has been dismissed since not scientifically justified (due to overlapping concentrations between concentrated products and dilutions in the datasets).

MSs agreed with this outcome from the analysis of data, however the need for a clear recommendation on what would normally be considered a concentrate product and a dilution is necessary. Based on this, the COM was asked to consider the previous threshold of 5 % or another more appropriate, if feasible, as a risk management tool.

Post-meeting note: in May 2018 MSs agreed to implement the GD for applications received after 25 August 2018. The European Commission published an accompanying note (SANTE/2018/10591), to clarify the definition of "concentrate" and "dilution", re-introducing the 5 % threshold[14].

Denise Kurth (BfR) gave a detailed technical presentation on the new evaluation template for *in vitro* dermal absorption studies, created by BfR and published with the new EFSA GD, adding that template is subject to proposals for improvement, if considered necessary. Its chief limitations are the lack of *in vivo* study evaluation, *pro rata* correction and statistical outlier identification. The LoQ will affect the values used in the table and hence decisions will be case-by-case.

Tamara Coja (AGES) gave an MS perspective of the EFSA GD (2017) on dermal absorption, with case studies. With a recovery figure of < 95 %, the DA figure with the new GD can differ significantly from the figure obtained using the earlier version, however this is predominantly the case only where dermal absorption is below 5 %. In cases with dermal absorption below 5 %, missing material should be added rather than normalised. It was also noted that the new GD gives the possibility to exclude replicates

[13] Cited in Appendix I

[14] Note for agreement by Member States' Competent Authorities in the SCoPAFF: Phytopharmaceutical legislation section, https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_tox_dermal-absorp-2018-paff.pdf

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with low recovery from the calculation. However this increases the uncertainty from a lower number of acceptable replicates.

On behalf of ECPA Dermal Absorption Project Team, Christiane Wiemann (BASF) offered industry perspectives. This covered derivation of default values, study evaluation and uncertainty about use of DA in the framework of RA. To resolve current uncertainty, ECPA wishes a consensus to be found by a scientific (statisticians) panel about which statistical methods apply.

Arianna Chiusolo (EFSA) gave the concluding remarks on this session:

- The GD is a useful tool to improve harmonisation with the setting of DA values to be used in the RA of PPPs.
- There are still difficulties with the *current (2012)* guidance, for evaluations case-by-case or expert judgment-based (e.g. extrapolations); the new GD (2017) should improve harmonisation of setting DA values, since clearer criteria are now provided.
- The input tool for data from dermal absorption studies, kindly created by BfR, is very useful to support applicants and risk assessors for *in vitro* data analysis.
- The new default values are better organised, based on new quality-checked data. Different values can result from different data and methods for analysis. EFSA analysis is considered robust, as it integrates different statistical approaches and includes the quantification of uncertainties.
- The *in vitro* experiment using human skin is considered the best approach for predicting DA in humans and it is confirmed as stand-alone methodology.

The fourth and final topic was on alternatives to animal testing in context of classification of plant protection products (PPPs). The session was chaired by Mark Williams, European Commission (DG Health and Food Safety).

A presentation by Jessica Wermuth (ANSES) summarised responses to the pre-Workshop questionnaire. To reduce animal testing, all responding MSs would consider CLP calculation and also validated *in vitro* methods, combined in a weight-of-evidence (WOE) approach. The acceptability of *in vitro* tests requires consultation of several guidance documents (e.g., OECD[15], ECHA[16], IATA[17]). Several sources of data are used for co-formulant toxicology assessment. CLP and REACH data are used by the majority of MSs, followed by MSDSs.

Aude Kienzler of the European Commission's Joint Research Centre (JRC) presented an introduction to alternative methods for assessing toxicological effects of chemicals

15 Cf. https://www.oecd-ilibrary.org/fr/environment/lignes-directrices-de-l-ocde-pour-les-essais-de-produits-chimiques-section-4-effets-sur-la-sante_20745842?page=2

16 Cf. https://echa.europa.eu/fr/information-on-chemicals/cl-inventory-database ; https://echa.europa.eu/fr/guidance-documents/guidance-on-clp

17 integrated approach on testing and assessment

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and their validation, covering the EURL ECVAM[18] mandate and activities; the validation process; validated alternative methods for human health (HH) endpoints; and ongoing projects.

Mark Williams (COM) took the view that MSs manage quite well to classify PPPs. He stressed the importance of using REACH data for co-formulants for this work.

Again, some MSs and industry perspectives followed:

Denise Kurth (BfR) gave a technical presentation about false negatives in acute oral and inhalational toxicity, as well as acute skin and eye irritation for PPPs assessed by the calculation method. A comparison of calculation method and *in vivo* study-derived classification for acute oral and inhalation toxicity resulted in only 47 % of cases with identical classification. With respect to dermal acute toxicity, no comparison could be performed due to the low number of classified products for this endpoint. In general validation of calculation method for pesticide formulations is missing with no information on parameters influencing its *in vivo* predictivity. Therefore, the reliable application of alternative methods should be maximised by using all available information. In addition, it was suggested to systematically validate *in vitro* studies with PPPs – however an insufficient quantity of such *in vitro* tests is currently available to the MSs. An integrated strategy is required: calculations together with some *in vitro* data would be a step forward. Already available *in vivo* information should be included and it should be possible to draw conclusions by expert judgement.

Tamara Coja (AGES) referred to the use of alternative methods for classification of plant protection products. Outlining how bias can occur in animal studies for many different reasons, she described the key aspects and pre-requisites for applicability of the GHS additivity formula. Given the legal and moral obligations to reduce animal testing, vertebrate studies must be seen only as “the last resort”. For most of the complex mixtures there is probably not one single alternative method currently available for reliable classification, but rather a combination of all available data and information should be applied.
After 40 years of “six-pack” testing[19] there was now a paradigm shift. Information should be combined to reduce or avoid animal testing.

Marco Corvaro (DowDupont, for ECPA) presented an industry perspective on the use of alternative methods for classification of PPPs. He outlined a number of alternatives in the EU PPP regulatory framework, citing examples of evidence-/exposure-based testing and waiving, read-across, *in vitro* methods, plus WOE, and use of “six-pack” *in vivo* studies if available (often necessary for other jurisdictions).

Jérémy Pinte (COM) then gave an update on development of the criteria for the identification of unacceptable co-formulants.

[18] European Union Reference Laboratory for alternatives to animal testing (EURL-ECVAM)

[19] Acute inhalational, oral and dermal toxicity; primary skin and eye irritancy; skin sensitisation.

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A discussion on harmonised criteria to notify potential unacceptable co-formulants is ongoing.

Via web conference, Norah O'Farrell (ECHA) gave a detailed technical presentation on the information on co-formulants available in dossiers in the framework of REACH.

Conclusions of the Workshop

Summarising the two days, Mark Williams (COM) recapitulated the following points:

- Efforts to continue harmonisation should be maintained;
- Clear multilateral communication is essential;
- The non-dietary exposure GD is being taken forward to ensure it can be updated to reflect the latest scientific developments;
- The dermal absorption GD is a success: this represents clear progress since the 2015 Workshop;
- More guidance is needed on combined exposure assessments;
- There is consensus on the need to promote and to accept alternatives to animal studies;
- There will be follow-up work and a future Workshop could be envisaged in 2020.

Short- and longer-term actions were identified which need further consideration:

Short-term actions:

1. Integration of the greenhouse AOEM into the EFSA Guidance on exposure;

2. Guidance (common approach) to assess combined exposure of active substances in one PPP.

Longer-term actions:

3. Revised version of the EFSA guidance document, including:
    a. a harmonised approach for additional scenarios (e.g., post-harvest treatment, seed treatment, amateur uses);
    b. refinement of worker re-entry scenarios (e.g., further crop grouping, new foliar residues data, additional activities for workers with relevant TCs, use of PPE);
    c. Consideration of new data and models (e.g., BREAM, BROWSE, BROV) for a refined approach of bystander/resident exposure assessment;
4. Finalisation of all CAGs and further work on establishing the criteria for the related dietary exposure assessment are necessary;
5. For classification of plant protection products, an integrated strategy starting with calculation method and validated *in vitro* testing is strongly encouraged.

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Acknowledgements

Members of the Organising Committee:

Mark Williams, COM
Sabine Martin, BfR, DE
Frédérique Istace, EFSA
Arianna Chiusolo, EFSA
Tamara Coja, AGES, AT
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Appendix I – Presentations and programme of the Workshop on Toxicological Risk Assessment of Plant Protection Products, 13–14 March 2018, near Paris, France[20]

The Workshop programme and presentations given are available on the ANSES website: https://www.anses.fr/fr/thematique/produits-phytopharmaceutiques-biocides-et-fertilisants

Background

First topic: Exposure

Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products
http://www.efsa.europa.eu/en/press/news/141023
http://www.efsa.europa.eu/en/efsajournal/pub/3874
http://www.efsa.europa.eu/sites/default/files/assets/140401ax7.zip (calculator with list of crop types)

Second topic: Combined Risk Assessment

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, Article 4.3 (OJEU 24.11.2009, p. L 309/9)
http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R1107&from=EN

Third topic: EFSA Guidance Documents on Dermal Absorption

EFSA Panel on Plant Protection Products and their Residues (PPR); ***Guidance on Dermal Absorption****. EFSA Journal* ***2012****;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665*
http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2665/epdf

EFSA Scientific Report 'Assessment of new scientific studies on human *in vitro* dermal absorption'. EFSA Journal 2015; 13(11): 4304
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.4304

EFSA (European Food Safety Authority); 2017. **Guidance on dermal absorption.** EFSA Journal **2017**;15(6):4873, 60 pp. https://doi.org/10.2903/j.efsa.2017.4873
http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4873/epdf

[20] *Remark: it may be necessary to use different web browsers for certain of these reference documents to open correctly.*

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Dermal absorption: refined BfR template for *in vitro* calculations (published 07/12/2017)
https://www.efsa.europa.eu/en/press/news/171207-0

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Fourth topic: Co-formulants

Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market
http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32013R0284&from=EN

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006
http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1272&from=EN

Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1907-20140410&from=EN

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Appendix II – References

European Conference on Safe Use of Plant Protection Products, 18-19 June 2014, Berlin, Germany:

Among other subjects discussed at this conference were the then draft EFSA "*Guidance on the Assessment of Exposure for Operators, Workers, Residents and Bystanders in Risk Assessment of Plant Protection Products*", harmonising the derivation of dermal absorption values and allocation of risk mitigation measures.

http://www.bfr.bund.de/en/event/european_conference_on_safe_use_of_plant_protection_products-190862.html

Presentations, programme and report of the Interzonal Workshop on "Harmonisation of risk assessment in section toxicology", 23–24 June 2015, Vienna, Austria:

https://www.ages.at/service/ages-akademie/programm-detail/kalender/detail/event/interzonal-workshop-harmonisation-of-risk-assessment-in-section-toxicology/

Abbreviations used in this report

AAOEL	acute acceptable operator exposure level
AGES	Austrian Agency for Health and Food Safety
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
AOEL	acceptable operator exposure level
AOEM	(Greenhouse) Agricultural Operator Exposure Model
BBCH	Biologische Bundesanstalt, Bundessortenamt und CHemische Industrie
BfR	German Federal Institute for Risk Assessment
BPI	Benaki Phytopathological Institute, Greece
BREAM	Bystander and Resident Exposure Assessment Model
BROV	Bystander Resident Orchard Vineyard
BROWSE	Bystander Resident Operator WorkerS Exposure
BZ	buffer zone
C zone	Central agro-climatic regulatory zone of the European Union
CAG	cumulative assessment group
COM	European Commission

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CRA	combined risk assessment
Ctgb	Board for the Authorisation of Plant Protection Products and Biocides, the Netherlands
CTS	closed transfer system
DA	dermal absorption
DFR	dislodgeable foliar residue
DT_{50}	time taken for 50 % of a substance to dissipate
EC	European Community
ECCA	European Crop Care Association
ECHA	European Chemicals Agency
ECPA	European Crop Protection Association
EEC	European Economic Community
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
EU	European Union
EURL-ECVAM	European Union Reference Laboratory for alternatives to animal testing
g/kg	grams per kilogram
g/L	grams per litre
GD	Guidance Document
HEEG	Human Exposure Expert Group of JRC
HH	human health
HI	hazard index
IATA	integrated approach on testing and assessment
IBMA	International Biocontrol Manufacturers' Association
ICPS	International Centre for Pesticides and Health Risk Prevention
JRC	European Commission Joint Research Centre
LoQ	limit of quantification
MS (MSs)	European Union Member State(s)
N zone	Northern agro-climatic regulatory zone of the European Union
OECD	Organisation for Economic Co-operation and Development
OJEU	Official Journal of the EU
PHI	pre-harvest interval
PPE	personal protective equipment
PPP (PPPs)	plant protection product(s) [pesticides]
RA	risk assessment
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RMMs	risk mitigation measures
S zone	Southern agro-climatic regulatory zone of the European Union
SCoPAFF	(EU) Standing Committee on Plants, Animals, Food and Feed
SEG	similarly exposed group
$t_{0.5}$	half-life
TC	Transfer Coefficient
WG	working group
WOE	weight of evidence

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