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Quantitative risk assessment of skin sensitising pesticides: Clinical and toxicological considerations

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ABSTRACT

Like many other consumer and occupational products, pesticide formulations may contain active ingredients or co-formulants which have the potential to cause skin sensitisation. Currently, there is little evidence they do, but that could just reflect lack of clinical investigation. Consequently, it is necessary to carry out a safety evaluation process, quantifying risks so that they can be properly managed. A workshop on this topic in 2022 discussed how best to undertake quantitative risk assessment (QRA) for pesticide products, including learning from the experience of industries, notably cosmetics, that already undertake such a process routinely. It also addressed ways to remedy the matter of clinical investigation, even if only to demonstrate the absence of a problem. Workshop participants concluded that QRA for skin sensitisers in pesticide formulations was possible, but required careful justification of any safety factors applied, as well as improvements to the estimation of skin exposure. The need for regulations to stay abreast of the science was also noted. Ultimately, the success of any risk assessment/management for skin sensitisers must be judged by the clinical picture. Accordingly, the workshop participants encouraged the development of more active skin health monitoring amongst groups most exposed to the products.

1. Introduction

Chemical skin sensitizers have the potential to produce allergic contact dermatitis (ACD), one of the most frequent occupational diseases associated with skin exposure to chemicals (Diepgen, 2003; McDonald et al., 2006; Mahler et al., 2017). Three main factors drive allergic responses to skin sensitizers: (1) the amount of substance applied per area of exposed skin (expressed in μg/cm^2, referred to as external dose), (2) the potency of the skin sensitizer, and (3) the frequency of exposure (Friedmann, 2007; Kimber et al., 2008; Paramasivan et al., 2010). A risk assessment for skin sensitising chemicals would ideally combine a quantitative model comparing predicted exposures to a specific skin sensitizer with an endpoint that has been derived considering these three influencing factors. A number of authors have proposed such quantitative risk assessment (QRA) approaches for skin sensitising chemicals, primarily focusing on cosmetic and household products and

Abbreviations: ACD, Allergic Contact Dermatitis; CLP, EU Classification, Labelling and Packaging Regulation; OECD, Organisation for Economic Co-operation and Development; PPP, Plant Protection Product; QRA, Quantitative Risk Assessment; REACH, EU Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation.

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the risk for consumers (Api et al., 2008, 2020; Basketter et al., 2008; Kimber et al., 2017; Marcelis et al., 2022; Fukushima et al., 2022). In addition to the main driving factors mentioned above, such approaches also consider several other variables, e.g., exposure matrix and skin condition, which may impact the acquisition of skin sensitisation. Although application of QRA to the safety evaluation of skin sensitisers has been subject to critical review (e.g., SCCS, 2017), it has been able to evolve (Basketter and Safford, 2016; Api et al., 2020). A further challenge will be its adaptation to avoid the use of *in vivo* tests, which remains a work in progress in a rapidly evolving field (Basketter et al., 2020; Gilmour et al., 2022; Lee et al., 2022). It is important to keep in mind that the whole focus of the workshop concerned avoiding the primary induction of contact allergy. Obviously, where ingredients in products (e.g., preservatives) have already caused significant allergy in an exposed population, consideration must be given to the risk of the elicitation of skin disease.

For plant protection products (PPPs), Sanvido et al. (2018) proposed a QRA approach by combining the methodology to derive a substance-specific threshold for skin sensitizers, a Derived No-Effect Level (DNEL) (ECHA, 2012) with an agricultural exposure model. PPP applications on agricultural crops typically occur either with tractor-mounted boom sprayers or manually with knapsack sprayers or backpack mist blowers. The main route of exposure is the dermal route, while exposure through inhalation contributes only slightly to the total exposure (Baldi et al., 2006). The ensuing debate about some of the principles applied in the proposed QRA methodology, in particular the allocation of the proposed sensitisation assessment factor (SAF) values (Jowsey et al., 2019; Sanvido et al., 2019) demonstrated the need for further evolution of this approach to the risk assessment for skin sensitizers across different industry sectors, ensuring harmonization and sharing of best practice.

Given the lack of a harmonized QRA approach for pesticides and the substantial knowledge built in other sectors such as the cosmetics and fragrance industry, it was decided to hold a workshop bringing together experts from various fields. The term 'pesticide' was used to cover both PPPs and biocides, acknowledging that a QRA methodology should be able to encompass both substances and substances in mixtures. PPPs, for example, are often complex mixtures composed of one or more active substances plus adjuvants and co-formulants, all possibly being skin sensitizers. Consequently, the ingredient causing the skin sensitising reaction in such products often is not the active substance but a preservative such as isothiazolinone (Berthet et al., 2017).

The workshop on QRA of skin sensitising pesticides was hosted by the Swiss Centre for Applied Human Toxicology (SCAHT) and the Swiss State Secretariat for Economic Affairs (SECO) on 23rd and 24th August 2022 at the University of Basel in Switzerland. Although the main focus of the workshop was QRA and exposure assessment of skin sensitising pesticides, hazard assessment and related test methods were also addressed. A key aim of the workshop was to consider lessons from other sectors such as industrial chemicals covered by REACH (i.e., Registration, Evaluation, Authorisation and Restriction of Chemicals), cosmetics and ongoing efforts by organisations such as the Organisation for Economic Co-operation and Development (OECD). The target audience were risk assessors from regulatory agencies, industry and academic experts.

The workshop addressed the following themes.

- Ways to collect data on the incidence of ACD to pesticides
- Update on current strategies to quantify the hazard of skin sensitising chemicals (e.g., next generation risk assessment [NGRA], new approach methodologies [NAMs])
- Ways to investigate and quantify exposure to skin sensitising pesticide products
- Learning from other sectors and organisations (e.g., cosmetics, biocides, OECD Integrated Approaches to Testing and Assessment (IATA), REACH)
- Strategies for QRA of skin sensitising pesticides

The workshop built on a preceding webinar series (Webinar Series (nih.gov)) "Current Concepts in Quantitative Risk Assessment for Skin Sensitisation", jointly produced by the National Toxicology Program's Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), SCAHT and SECO. Workshop plenary sessions provided an overview of the current state of the science in this rapidly developing field. Participants divided into breakout groups to discuss topics in detail. Each breakout group responses to pre-defined questions were presented and discussed by all participants at the end of the workshop. This workshop report summarizes the state of scientific knowledge, data gaps, agreements/disagreements, opportunities and challenges, concluding with recommendations for future work.

2. Plenary sessions

2.1. Session 1: Clinical dermatology and field data

The presentation *Field data from toxicovigilance schemes Europe: Phyt'attitude France by Gérard Bernadac, Mutualité Sociale Agricole (MSA) France,* provided an example of an existing surveillance scheme for occupational incidents relating to pesticide exposure organised by the French agricultural social security organisation MSA. Details are investigated by occupational physicians and other experts, who make a judgment on the likelihood of a causal relationship. Skin effects are the largest category,[1] accounting for about a 25% of symptoms, with >80% described as irritation or itching. Differentiation between skin irritation and sensitisation is rarely possible as follow-up diagnostic procedures are lacking in occupational settings. Patients (and particularly farmers) suffering from skin problems do not necessarily consult their physician, which leads to underreporting of cases. If a physician is consulted, general practitioners, even dermatologists, may have insufficient time or expertise regarding ACD to pesticides in PPP or even to biocides. Secondly, the reporting procedure of skin diseases (commonly irritant or allergic contact dermatitis) has diverse reporting pathways in many countries. There may be few incentives for dermatologists to report sensitisation data beyond (mandatory) reporting trajectories for occupational skin diseases. Communication between regulating authorities, companies, occupational health insurances, and physicians to standardize reporting and follow-up on identified problems appears insufficient. The access to data is consequently laborious. Furthermore, a lack of homogeneous schemes complicates comparisons across countries.

In preparation for the first breakout group, the content of the first webinar in the pre-workshop series was briefly summarised based on a presentation prepared by *Wolfgang Uter, University of Erlangen/Nürnberg Germany*. The webinar provided an overview of the changing nature of hazard assessment methods used to identify and classify skin sensitising chemicals. It also stressed the importance of diagnostic patch testing by dermatologists to establish an accurate diagnosis as well as population-based epidemiology to help monitor the success of regulatory measures in the case of potent allergens such as glyceryl monothioglycolate and methylisothiazolinone (Uter et al., 2006; Urwin et al., 2017).

2.2. Session 2: QRA methods and exposure assessment of skin sensitising pesticides

Two presentations in the introductory session illustrated established and currently proposed approaches on how quantitatively to assess exposure and risk from skin sensitising chemicals.

The presentation *A quantitative risk assessment for skin sensitising plant protection products: Linking derived No-Effect levels (DNELs) with*

[1] Other categories include neurological and digestive symptoms, neurosensory symptoms of the nose and the eyes, as well as respiratory symptoms.

agricultural exposure models by Olivier Sanvido, State Secretariat for Economic Affairs Switzerland, was based on a published case study (Sanvido et al., 2018), which initiated recent discussion on QRA for skin sensitising PPPs. An overview was given on the current European implemented regulatory approaches to assess PPPs and biocides containing skin sensitisation components from hazard and risk assessment perspective. Recommendations for QRA of chemicals and biocides exist, for example by the European Chemicals Agency (ECHA, 2012, 2017) by comparing exposure to the DNEL. The DNEL for the initiating event of sensitisation is the critical parameter to protect people from sensitisation, but a widely accepted method for the DNEL derivation is not yet available. As the current PPP exposure models estimate systemic exposure, they may not provide appropriate estimations of exposure to skin sensitizers. Potency of skin sensitizers and frequency of exposure of as well as other uncertainties, may be addressed by sensitisation assessment factors (SAFs) as applied for example for cosmetic ingredients (e.g., Api et al., 2020).

The *Exposure assessment for the QRA for cosmetics by Petra Kern Procter & Gamble,* illustrated the current approach for cosmetics according to the following equation:

$$Exposure = \frac{Frequency \times Amount \times Retention \times Concentration}{Surface\ Area}$$

While not all skin sensitising ingredients in cosmetic products have been routinely subjected to QRA for skin sensitisation, a number of known preservatives and fragrance allergens have been evaluated in the past (Basketter et al., 2008; Api et al., 2020). As a first tier, the Scientific Committee on Consumer Safety (SCCS, 2017) proposes to conservatively estimate exposure by dividing frequency of application, amount applied, retention factors, and concentration of a substance by a specific skin surface area (Basketter et al., 2018). Probabilistic data may be used for refinement in a second tier (Bil et al., 2017) requiring population based data on each of the input factors to estimate exposure across an entire exposed population. While more resource intensive, this approach is also more realistic and typically less conservative (Api et al., 2020).

The scene for the breakout group was set by Denise Bloch, Federal Institute for Risk Assessment (BfR) Germany, in a wrap-up presentation on the preparatory pre-workshop Webinar 2, of December 2021: *Methods for hazard and exposure assessment* summarizing the presentations given by Nicole Kleinstreuer, National Institute of Environmental Health Sciences (NIEHS) United States, on *International progress in skin sensitisation hazard and risk assessment* and by herself on *Introduction to exposure and quantitative risk assessment of skin sensitising chemical* (Webinar Series (nih.gov)).

2.3. Session 3: Towards next generation risk assessment of skin sensitisers

This session introduced recent developments towards QRA of skin sensitisers based on new approach methods. The presentation *Isothiazolinone Biocides: quantitative risk assessment of dermal sensitisation risk using in vitro and in silico methods by Timothy F. McMahon, United States Environmental Protection Agency (US EPA),* provided a case study where, for the first time, endpoints derived from *in vitro* and *in chemico* assays were used by US EPA in a regulatory decision-making capacity to support the QRA of skin sensitisation risk to Isothiazolinones (ITs). US EPA concluded that a NAM approach integrating methods with associated OECD guidelines, covering multiple key events in the skin sensitisation AOP, was more reliable and relevant than the Local Lymph Node Assay (LLNA) for assessing skin sensitisation of the ITs and, thus, appropriate for extrapolating to dermal human health risk (Strickland et al., 2022).

The presentation *International progress in skin sensitisation hazard and risk assessment by Nicole Kleinstreuer, NIEHS/National Toxicology Program Interagency Center for Evaluation of Alternative Toxicological Methods (NICEATM),* offered an overview of the regulatory requirements around the world for the skin sensitisation endpoint. The role of the OECD in this effort was highlighted (e.g., OECD, 2021). The presentation also considered an alternative skin allergy risk assessment (SARA) procedure, based on a Bayesian statistical model being developed as a collaboration between Unilever and NICEATM (Reynolds et al., 2022). The model endeavours to provide Globally Harmonized System (GHS) classification of skin sensitisers, including potency sub-categories, and to deliver a human-relevant point of departure for QRA.

The brief *Wrap-up of webinar 3 and setting the scene for the breakout group was presented by Leona Merolla, Syngenta.* The Webinar had shown how experience gained over the last three decades on how to conduct risk assessments based upon NAMs had allowed development of a non-animal NGRA framework for skin sensitising cosmetic ingredients (Gilmour et al., 2020). It had also illustrated how the skin sensitisation potential and potency of PPPs could be assessed with advanced NAMs. A case study comparing the performance of different NAMs to predict the potency of a selected number of PPP formulations with *in vivo* reference data concluded that NAM based assessment of agrochemical formulation hazard classes was possible, however, NAM based identification of mixture potency was not yet achievable (Kolle et al., 2023).

3. Breakout groups

3.1. Breakout-group 1: how to improve current (clinical) monitoring and toxicovigilance schemes to detect cases of allergic contact dermatitis

(Chair: Martin Wilks SCAHT, Rapporteurs: Aurélie Berthet Unisanté, Nancy Hopf Unisanté).

The first breakout group focused on different aspects of toxicovigilance and surveillance schemes for PPPs and biocides.

The discussion focused on the areas which are important for monitoring and surveillance of skin sensitisation with a particular focus on PPP.

3.1.1. Existing monitoring schemes

The legal basis or obligations to report skin sensitisation cases are country dependent, reported symptoms are not associated with exposure, and biomarkers specific for skin sensitisation do not exist. These shortcomings lead to underreporting, underdiagnosis, and poor exposure assessment.

Underreporting: Data reporting quality appeared to be quite diverse in the countries represented at the workshop. In France, patients choose to report or not while in Denmark, it is mandatory to report. Denmark and Germany have quite complete occupational skin sensitisation data, although not on PPPs. The potential for underreporting of Occupational Skin Diseases (OSD) related to PPP exposures should be further investigated.

Underdiagnosis**:** Exposure information is necessary to relate symptoms to the sensitising substance causing skin disease but they are generally not available in surveillance schemes for occupational skin diseases, partly because no information is collected from farmers, who are often self-employed and do not have the same health surveillance than employees (Graczyk et al., 2018). Poison control centres have useful records on PPP acute toxicity, but these are not available in all countries. Complicating the matter further is that one farmer usually uses a variety of different PPPs during a growing season.

Poor exposure assessment: The workgroup also discussed the use of biomonitoring to survey worker exposures, but biomarkers specific for skin sensitisation do not exist beyond advanced research level. Questionnaires are helpful in epidemiological studies, but cannot define whether the participant is really exposed or not. There are no standardised schemes to collect exposure data across countries.

3.1.2. Post-marketing surveillance

The workgroup discussed a future mandate for PPP similar to the existing legislation on pharmacovigilance (European Commission, 2010). This would need to comprise information on amount and

frequency of PPP purchases as well as flag problem areas and at-risk groups by linking exposure databases with health registers. Data would need to be collected in a standardised way to ensure coherence and continuity. Risk reduction strategies such as closed-transfer systems should be highlighted in a risk assessment feedback loop and provided during re-registration of the PPP product. Medical and incidence data should be reviewed by the producers/importers on a regular basis to keep their registration. There should be a reward system for reporting and company data should be included in toxicovigilance schemes.

3.1.3. Shortcomings of current schemes

There is a need for identifying specific substances and populations at risk. This task requires additional work that could not be addressed during the workshop. Several recommendations were made after mapping current and future changes (Fig. 1).

3.2. Workgroup recommendations

1. Obtain the full PPP formulation ingredient list and make it easily accessible by industry for medical practitioners and users.

Co-formulants need to be listed, as they are often more likely to be sensitisers compared to the active ingredients. This will help design individual patch testing and treat patients with ACD.

2. Transfer pharmacovigilance knowledge to PPP toxicovigilance.

PPP toxicovigilance should be based on current pharmacovigilance (detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem) (World Health Organization, 2023). PPP toxicovigilance should include training of operators (i.e., agricultural workers, PPP applicators, and harvesters), and surveillance of PPP exposure and disease. The aim of the surveillance program is to obtain more data with the objective of elucidating possible relationships between PPP exposures and ACD. The training program should be on a reoccurring basis and the trainee should be encouraged to recognize and report skin problems.

3. Give more tools to the physicians.

A tool to help physicians obtain health hazard information associated with the PPP and characterise exposures. This would increase PPP awareness among physicians and information obtained by the treating medical doctor should be fed into a common database for further use.

4. Give access to a future common database describing observed associations between PPP formulations, patch tests, and diseases.

This future database would not only serve as a tool for medical doctors but also for researchers, policy makers, and professional associations as well as industry providing actual sets of numbers of cases and formulations.

5. Provide additional data to construct QRAs.

Incorporating PPP toxicological potencies, PPP exposures from animal toxicological studies as well as human exposure (not just “yes” or “no” answers) and clinical data would improve the QRA predictions.

6. Continuously improve risk assessments.

Once the PPPs are approved by the regulators, the necessary information for a QRA should be required from industry, PPP users, medical practitioners, and inspectors to create a feedback loop striving to continuously improve the RAs.

7. Encourage industry to provide more data/parameters to drive the process towards QRAs.

The group felt strongly about obtaining field data including measured exposures from industry because this could provide help in understanding chronic exposures as well as diseases. Re-registration of PPPs should also include medical and incidence data relevant to skin sensitisation to detect early warnings of possible associations between exposure and disease. All data should be reviewed by the producers/importers on a regular basis to keep their registration.

8. Develop PPP use and disease maps (heatmaps).

The group suggested creating a system to associate health registers

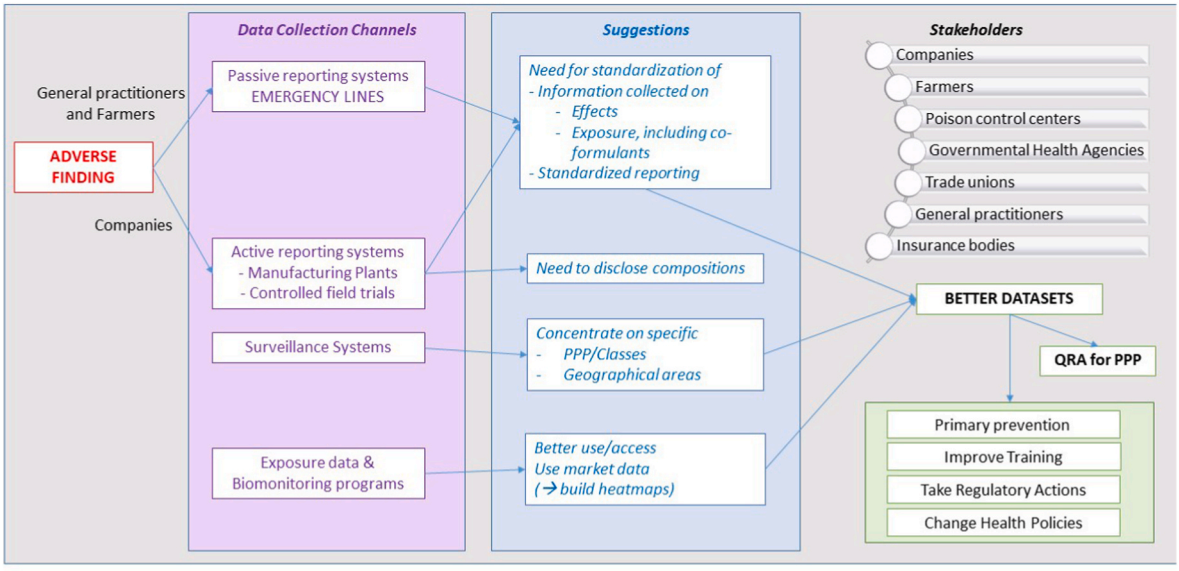

Fig. 1. The different steps in place and needed approaches between stakeholders to achieve QRAs for PPPs. The main stakeholders are in black, the channels identified to collect data on PPP exposures and ACD are in violet, suggestions specific to each channel for collecting data are in blue, and the resulting outcomes are in green.

reporting ACD to PPP exposure systems. This would need participation from selected physicians that would spend additional time (paid incentives) on skin problems of farmers related to PPP exposures.

Fig. 1 below captures the different steps in place as well as needed approaches between stakeholders (black) to achieve QRAs for PPPs. There are three levels identifying adverse finding (i.e., ACD) which can help to improve the QRAs for PPPs. The data collection channels (purple) should be more structured or adapted (harmonised, systematic, shared, and available), and some suggestions (blue) are recommended for each of these channels to include and generate human clinical data. This would result in better datasets and improve outcomes (green), including QRAs.

3.3. Breakout-group 2: best strategies to perform a QRA for skin sensitising pesticides

(Chair: Denise Bloch BfR, Rapporteurs: Olivier Sanvido SECO, Christiane Wiemann BASF).

The second breakout group's aim was the discussion of best practice strategies for performing a QRA for skin sensitising pesticides and their products. The discussion focused on (1) the sufficiency of the current level of protection to avoid skin sensitisation upon PPP contact, (2) effective QRA strategies for PPPs, and (3) the need for additional regulatory action.

Without QRA, the sufficiency of operator, worker, resident and bystander protection is difficult to assess. At the same time, positive evidence that QRA functions adequately is limited by the absence of clinical data with the potential of underreporting adverse health effects from exposure to skin sensitisers. Moreover, relevant exposure information in the general population and, specifically, in residents and bystanders is missing. Hence, first protection goals need to be defined (e.g., what population protection level should be adopted for different groups - operators, workers, bystanders, residents?).

The group concluded that QRA should be conducted wherever exposure to sensitising substances occurs. It would be useful to define differing threshold values for specific groups of exposed people (operators, bystander etc.) to be used in a QRA. However, it may also be possible to define upper thresholds for potency or exposure, above which QRA would generally indicate an unacceptable level of risk. These could arise for example from the current limitations and uncertainties in exposure prediction and available mitigation measures.

An effective QRA strategy requires exposure assessment and the derivation of sensitising threshold values, applying relevant uncertainty factors. For example, Sanvido et al. (2018) demonstrated how the Agricultural Operator Exposure Model (AOEM) model (EFSA et al., 2022) could be used for exposure assessment. However, this approach may not be feasible where QRA is based on co-formulants instead of PPP active ingredient studies. Co-formulant concentrations may fall below the applicability domain of these models and may therefore be subject to high uncertainty. Current models, such as the deterministic AOEM, are prone to overestimation of exposure. Their tendency towards worst case predictions results in the addition of uncertainty from different sources, which could render QRA useless. The implementation of probabilistic exposure models and exposure data with higher resolution of the exact exposure site (e.g., lower arm) as well as exposure duration and frequency would improve their applicability for skin sensitising substances and mixtures.

The derivation of relevant threshold values requires a harmonised decision on the appropriate benchmark ratio for point of departure (PoD) estimation. Furthermore, it requires adequate uncertainty assessment and sensitisation assessment factor (SAF) derivation (Api et al., 2020; Basketter and Safford, 2016; Ezendam et al., 2018; Nijkamp et al., 2015; Sanvido et al., 2018). Other considerations could include.

- NAM-based threshold values may require additional kinetic considerations
- The relevance of substances accumulating in the skin
- Differences in PoD studies and real life exposure scenarios (e.g. operator exposure to the concentrated product versus bystander/ resident exposure to the diluted product)
- Frequency of exposure and co-exposure
- So far, cross-reactivity is disregarded, however, combinatory effects of dissimilar chemicals are not to be expected.
- Regulatory action should begin with discussion on the adequacy of concentration limits for the classification and labelling of substances in mixtures.
- Before a substance is banned from use, QRA should be conducted to inform risk managers about possible management strategies.

A list of recommendations was formulated.

1. Review of plant protection and biocidal product exposure models

Currently available exposure models should be critically evaluated with regard to their applicability to QRA for skin sensitising plant protection and biocidal products. Experts should focus on the applicability domains of such models and the translation of systemic to maximum local exposure concentrations. In particular, exposure models need to be adopted to assess co-formulant in addition to active ingredient exposure.

2. Review expertise from other sectors

This should include a review of exposure models and their applicability for plant protection and biocidal products, the application and justification of SAFs to account for uncertainty, and the methods and protocols used for the derivation of toxicological threshold values. In addition, occupational monitoring data should be shared across regulatory silos to identify and minimise risk.

3. Provide guidance for SAFs

The group did not have sufficient time to discuss SAFs in detail. Therefore, they proposed additional discussions with a group of experts intimately involved in this field. This group should view and summarise available evidence on uncertainty for different exposure scenarios and toxicological methods, provide guidance on their applicability, and deduce means of reducing uncertainty.

4. Conduct case studies and publish a guidance document

The group recommend the conduct of further case studies similar to the one on plant protection products by Sanvido and co-authors (2018). Those case studies provide a basis for further scientific discussion and, ultimately, a skin sensitisation QRA guidance document for plant protection and biocidal products.

5. Adapt regulations to include requirements for QRA for sensitising pesticides

Once a guidance document has been established, experts need to review current regulations and data requirements to conclude on potential needs for amendments of these regulations. It is important to note that QRA for sensitising pesticides only protects from new sensitisation in non-sensitised persons. In addition to the provision of regulatory requirements to avoid skin sensitisation, regulatory action (such as proper labelling of sensitising substances on pesticides) for the prevention of elicitation in already sensitised persons should be considered (and which would align with the first recommendation made by breakout group 1).

3.4. Breakout group 3: how do we adapt current NGRA approaches to pesticides?

(Chair: Nicole Kleinstreuer, NICEATM, Rapporteurs: Leona Merolla, Syngenta; Janine Ezendam, National Institute for Public Health and the Environment (RIVM), The Netherlands).

Break out group 3 considered opportunities and challenges associated with the application of the latest risk assessment approaches, including NAMs and NGRA that are based on input(s) from non-animal models.

3.4.1. Is the current portfolio of non-animal tests generally applicable to pesticides?

It is important to differentiate between active ingredients and formulations. Regarding the NAMs currently included in the OECD Test Guideline programme, pesticidal active ingredients fitting the applicability domain can be tested in NAMs. Industry experience has shown application of some NAMs for hazard assessment of active ingredients, however NAMs are largely untested and unvalidated for formulations. The historical assessment of sensitising potential of cosmetics has demonstrated that approaches based on evaluation of individual ingredients are suitably robust to support meaningful risk assessment of formulations. However, for pesticide products, some regulatory agencies stipulate generation of data for the active both as a separate test item and in a formulation. Therefore, driven by a regulatory requirement, tests are currently conducted on formulated pesticide products despite the tests themselves not being validated for that purpose. The development of NAMs are expected to be as predictive as current test systems, therefore testing of individual components should continue to provide meaningful risk assessments. The National Toxicology Program is currently assessing the application of the Direct Peptide Reactivity Assay (DPRA), Keratinosens™ and the human Cell Line Activation Test (h-CLAT), and associated defined approaches, for substances as well as for pesticide formulations. Further considerations of the most appropriate benchmarks for test validation is needed, as recent work has demonstrated that the relevant *in vivo* guideline assays may be less predictive of human outcomes.

There is potential for reconstituted human epidermis (RHE) based tests currently in development (e.g., SENS-IS, EpiSensA) to offer advantages over the existing NAM portfolio, for example overcoming certain technical limitations related to some *in vitro* models (e.g., solubility of the test compound). Cell based NAMs should use gravimetric approaches and paired cytotoxicity readouts, to overcome the lack of information on molecular weight of formulations. There is less certainty about the usefulness of such approaches for adapting *in chemico* assays like DPRA to be applicable to formulations.

To explore further the applicability of NAMs, the unique aspects of pesticides that need to be considered when using NAMs were discussed.

- Pesticides are not fundamentally different from other chemicals in terms of their physico-chemical properties and therefore should not be an exception to the use of existing NAMs. However, the applicability domain of the assays should be considered, for example highly fluorinated actives may bind to plastics and precipitation issues can occur in submerged cell cultures. The unique properties of biopesticides (e.g., antibiotics, pyrogenic contaminants from fermentation processes) may give rise to different challenges on application of NAMs.
- The predictivity of the LLNA for human hazard has been well characterised for cosmetic chemicals, however a comparative reference database for pesticides is essential to benchmark results from new test methods. For pesticides, human data is also extremely limited.
- The current regulatory accepted NAMs do not represent realistic skin exposure scenarios, nor dermal penetration or metabolism. Therefore, while suited to hazard identification, they will be a poor predictor of risk from typical, in-use pesticide exposures. Industry partners hold significant proprietary data which could enable a more comprehensive assessment of exposure and risk.
- Formulations contain a variety of chemistries, including co-formulants, e.g., substances of unknown/variable composition (UVCBs), such as natural products, and polymers. This limits the application of computational approaches and no existing NAMs (nor existing *in vivo* approaches) are validated for formulations.
- Many test methods require information on molecular weight, which cannot be calculated for formulations. Gravimetric approaches are being included in the OECD test guidelines of cell based NAMs.

3.4.2. Do any of the non-animal tests offer the prospect of standalone use and if not, how can combined approaches be deployed?

There is no clear consensus on the stand-alone utility of available NAMs. Industry partners have conflicting evidence on the hazard predictivity of different assays (including h-CLAT and Genomic Allergen Rapid Detection (GARD) assays, for example). Hence, based on these variable results, it is essential to integrate data from different NAMs for both hazard and potency. Full thickness epidermis models that are currently being developed may be useful standalone models, but research on the applicability of these models for pesticides is still ongoing. Some partners also support the use of *in silico* strategies combining predictions for each co-formulant, whereas others deemed hazard assessment of formulations will always be reliant on IATA/WoE (Weight of Evidence) approaches. Full definition of the Adverse Outcome Pathway (AOP) for sensitisation, including any potential role of innate immune responses (pathogen/danger associated receptors such as TLR4)), should also be considered.

- Further research is required to define relative applicability domains, particularly for formulation assessment and further data are required to support development of Defined Approaches (DA)/IATA hazard identification strategies (considered likely to yield to most relevant outcomes).
- For potency assessment, hCLAT quantitative data is informative, as are using regression models to derive a quantitative metric. An exercise to compare active ingredient data to formulation data would also help understand formulation potency assessments.
- The standardisation of approaches to QRA based on animal data or NGRA based on NAMs (or both) is highly complex.

3.4.3. Is it feasible to apply outputs on potency assessment to pesticide risk assessment?

For the hazard assessment of active ingredients, the NGRA developed for cosmetics may be a useful starting point (Gilmour et al., 2022), however the exposure assessment needs to be aligned to scenarios relevant for pesticides. Also, defined approaches that provide a potency estimate can be used for active ingredients within the applicability domains (OECD, 2021). However, the lack of a reference database for pesticides may impair the acceptance of hazard and risk assessments.

Application of NAMs for sensitisation assessment is heavily influenced by regulatory data requirements, which differ significantly between regions. Primarily, there is a clear divergence between global approaches to risk assessment which are the subject of a global review (Daniel et al., 2018). The openness of the US government to NAMs is not yet reflected by the acceptance of data from NAMs in several other regulatory regions. The European Union (EU) have typically been heavily hazard-focused, although recent examples from the United Kingdom (UK) and Germany of risk assessment for sensitisation have been identified. This is in sharp contrast to the US regulations, which have for some time been open to risk assessment using alternatives. For hazard identification the global acceptable processes are similarly mis-matched. For example, Brazil requires *in vitro* data (2 assays) before proceeding to *in vivo* testing of formulations. The EU now accepts OECD GL497 for formulations after a step-wise approach to assess sensitisation potential of ingredients. If the *in vivo* test is more sensitive, the more

conservative outcome must be used. However, in China, reliance is on the *in vivo* tests, and a LLNA result must be confirmed with a Buehler test.

When considering the formulation testing, many countries rely on active substance data, however the EU Northern zone guidance also requires co-formulant data (Northern Zone, 2021). Different thresholds referring to potentially sensitising materials, in all products are applied in calculation methods by varying stakeholders (e.g., EU CLP classification assessment requires inclusion of materials present at >1% threshold, but Denmark applies a threshold of 0.0001%). Clearly, global harmonisation of data requirements as well as approaches to characterisation of uncertainty (including use of SAFs or probabilistic risk assessment) is lacking and there is a clear need to generate a unified data set and promote global acceptance.

In order to achieve regulatory acceptance and alignment it is important to interrogate the application of the existing *in vivo* approaches as the relevant gold standard, and thereby create and propose an appropriately robust novel paradigm.

A series of recommendations and proposed actions were compiled, grouped into 4 categories.

1) Method Development/Evaluation
   - Develop Liquid Chromatography/Mass Spectrometry (LC/MS) based assay for adduct formation specifically for formulations
   - Development of full-thickness skin models for testing formulated products
   - Comparison of matched active ingredient and formulation data from current approaches
   - Develop reference standard repository of active ingredients and formulations for sensitisation
2) Data Collection and Computational Analyses:
   - Develop a comprehensive database of *in vitro* and *in vivo* data on active ingredients, co-formulants, and formulations, including human exposure and incidence data, pharmaceutical data on similar substances, and pharmacovigilance programmes (e.g., topical fungicides)
   - Define the chemical space of active ingredients as well as co-formulants/inerts by collecting existing sensitisation data, running Quantitative Structure-Activity Relationship (QSAR) predictions, and comparing to the OECD Defined Approaches on Skin Sensitisation (DASS) reference chemical space (based on physico-chemical properties, molecular feature coverage, etc.) (OECD, 2021).
   - Federated data sharing model for proprietary data from industry (encryption options to enable Artificial Intelligence/Machine Learning model building)
3) Risk Assessment
   - Apply existing DASS to derive quantitative potency estimates for formulations with existing *in vitro* data, and compare to *in vivo* data
   - Compare outputs of traditional and probabilistic risk assessments
   - Investigate incorporating dermal absorption data into hazard risk assessments
4) Communication
   - Community of practice user forum to share knowledge and experiences
   - Communication, training and education on probabilistic risk assessments approaches

4. Overall conclusions and recommendations

The workshop was a unique opportunity to combine the expertise of risk assessors from regulatory agencies and industry with academic specialists plus the experiences from various industry sectors (pesticides, cosmetics, fragrances) to discuss possible QRA approaches for skin sensitising pesticides. The discussions benefited from the substantial knowledge built in other sectors such as cosmetics and fragrances. The participants agreed that there is a need for a QRA for skin sensitising pesticides and that such an approach would improve the overall risk assessment for pesticides. The workshop clearly helped to set the scene, gain a common understanding of the relevant issues and define the way forward. Key questions to be answered in view of a harmonized QRA for skin sensitising pesticides include the definition of appropriate SAFs, an agreement on the relevant PoD for the derivation of endpoints, and a review of appropriate exposure models with regard to their ability to assess co-formulant, in addition to active ingredient, exposure. Further discussions are also needed on how NAMs and NGRA can assist QRA for skin sensitising pesticides. The question of how NAMs can be used to determine the potency of complex mixtures such as pesticides is still open.

Finally, an important point that was addressed in each of the three breakout groups concerned the question of whether there is a real clinical problem given the lack of data on reported cases of ACD due to exposure to pesticides. Future activities should therefore explore whether there is indeed any clinical problem or whether the lack of reported cases is primarily due to insufficient monitoring schemes and/or underreporting of occurring cases.

Given the number of open questions to be resolved, workshop participants welcomed the idea to continue the initial discussions that have helped pave the road for a QRA for skin sensitising pesticides. It was proposed to continue the activities under the auspices of an international organisation such as e.g., OECD. As a first step, it would be helpful to work on one or more specific case studies to answer the most pressing questions directly on a concrete example. An ultimate goal should be the development of a guidance document for QRA of skin sensitising pesticides.

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CRediT authorship contribution statement

Olivier Sanvido: Project administration, Writing – original draft, Writing – review & editing, Funding acquisition. **David A. Basketter:** Writing – original draft, Writing – review & editing. **Aurélie Berthet:** Writing – original draft. **Denise Bloch:** Writing – original draft. **Janine Ezendam:** Writing – original draft. **Nancy B. Hopf:** Writing – original draft. **Nicole Kleinstreuer:** Writing – original draft. **Leona L. Merolla:** Writing – original draft. **Wolfgang Uter:** Writing – review & editing. **Christiane Wiemann:** Writing – original draft, and. **Martin F. Wilks:** Project administration, Writing – original draft, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Leona Merolla reports a relationship with Syngenta that includes: employment. Christiane Wiemann reports a relationship with BASF Corp that includes: employment. The authors listed immediately below are members of CropLife Europe expert groups and are employed as toxicologists and risk assessors who put plant protection products on the market that may become subject to quantitative risk assessment for skin sensitisation: Leona Merolla, Christiane Wiemann.

Data availability

No data was used for the research described in the article.

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