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Assessing the risk of induction of skin sensitization to plant protection products: A quantitative approach

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ABSTRACT

Exposure to skin sensitizers is common and regulated in many industry sectors. For cosmetics, a risk-based approach has been implemented, focused on preventing the induction of sensitization. First, a No Expected Sensitization Induction Level (NESIL) is derived, then modified by Sensitization Assessment Factors (SAFs) to derive an Acceptable Exposure Level (AEL). The AEL is used in risk assessment, being compared with an estimated exposure dose, specific to the exposure scenario. Since in Europe there is increased concern regarding exposure towards potentially sensitizing pesticides via spray drift, we explore how existing practice can be modified to allow Quantitative Risk Assessment (QRA) of pesticides for bystanders and residents. NESIL derivation by the Local Lymph Node Assay (LLNA), the globally required *in vivo* assay for this endpoint, is reviewed alongside consideration of appropriate SAFs. Using a case study, the principle that the NESIL in $\mu g/cm^2$ can be derived by multiplying LLNA EC3% figure by a factor of 250 is adopted. The NESIL is then reduced by an overall SAF of 25 to establish an exposure level below which there is minimal bystander and resident risk. Whilst this paper focuses on European risk assessment and management, the approach is generic and universally applicable.

1. Introduction

Chemicals with skin sensitizing potential (recognized clinically as contact allergens), are present in most household and personal care products as well as many topical medicaments and can thereby lead to allergic contact dermatitis (ACD). Dermal exposure to allergenic constituents within these products, particularly preservatives, fragrances and acrylates, has been a cause for concern for quite some time (e.g. Aerts et al., 2017; Gameiro et al., 2014; Herman et al., 2019, 2021; Jong et al., 2007; Schnuch et al., 2011; White et al., 2007; Zirwas et al., 2017). This has resulted in significant changes in the way in which products are formulated and labelled in order to minimize the development of new cases of contact allergy and protect those individuals who are already sensitized (EC-SCCS and SCCS, 2012; IFRA Standards). Clear product labelling allows individuals with existing allergies to make an informed choice at the time of purchase (EC, 2008; INCI; Basketter et al., 2015b). Furthermore, safety evaluation based on proper understanding of allergenic potency in combination with accurate estimation of exposure can be used to determine suitable thresholds for formulation, a process that should prevent new cases occurring (Api et al., 2008, 2020; Basketter et al., 2008; Garcia-Hidalgo et al., 2018; Gilmour et al., 2019, 2022; Marcelis et al., 2022).

The concept of a quantitative risk assessment (QRA) framework to prevent the induction of skin sensitization was developed over two decades ago by a dermatologist and consumer goods industry partnership (Robinson et al., 2000; Gerberick et al., 2001; Felter et al., 2003). The fragrance industry adopted QRA in 2008 and used its conclusions to update their guidance on safe exposure levels (Api et al., 2008; Api and Vey, 2008). Since that time, the underlying principles have been critically reviewed by EU regulators, academia and dermatologists, leading to a series of international interdisciplinary discussions over several years (EC-SCCS and SCCS, 2018 and 2021; https://ideaproject.info). By

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this means, QRA has been revised to a second version, incorporating additional understanding of exposure estimation and clarifying areas of uncertainty (Api et al., 2020; Basketter and Safford, 2016). This updated quantitative risk assessment approach (QRA2) has also been extended to products with unintended skin contact which are marketed to the general public and/or professional users, and has been endorsed in multiple EU technical guidance documents, for example within the REACH Regulations and for Biocidal products (ECHA, 2012, 2017). It is this most recent version, QRA2, which has been applied in the material that follows. However, it is worth noting that one essential difference between the original QRA and QRA2 is the requirement to assess aggregated exposures from multiple product use. Whereas this is very relevant to products such as cosmetics, it does not apply to the resident and bystander scenario. Other differences between the original QRA and QRA2 have been fully detailed already (Api et al., 2020).

Although having been developed specifically for fragrance chemicals, the underlying principles of QRA2 can be extended to any scenario in which skin exposure to a contact allergen occurs, providing adequate scientific data are available for expert judgement. In addition, the adoption of QRA2 by other industries is not unexpected, as risk based approaches are superior to traditional hazard based approaches for the protection of human health (e.g. Basketter, 2008, 2023; Basketter et al., 2015a). In recent years, there has been concern in some quarters about the potential induction of skin sensitization from pesticides which has prompted certain European regulators to request registrants of plant protection products (PPPs), to address bystanders and residents who may become inadvertently exposed to 'spray drift' or airborne droplets, following professional application of PPPs in the field. In the European Union (EU), one of the primary roles of Regulation (EC) 1107/2009 (EC, 2009a), the regulation for approval and marketing of PPPs, is to ensure an adequate degree of protection for humans. Registrants must demonstrate that exposure towards PPPs placed on the market does not result in "unacceptable" risk for human health, by comparison with a suitably derived toxicological reference value that accounts for any uncertainty or variability. Currently however, although the risk associated with systemic toxicity is routinely considered, risk for skin sensitization is not commonly addressed in a quantitative manner. Rather, PPPs are qualified based on test outcomes as sensitizers or non-sensitizers, which may have regulatory consequences in the target region (Corvaro et al., 2017).

Historical cases of ACD have been reported for individuals in occupational settings mostly when using a concentrated pesticidal product (Chatzi et al., 2006; Koch, 1996; Lisi, 1992; Sharma et al., 2018). Occasionally, cases occur also from contact with diluted pesticide solutions (i.e., in the market format adapted for non-professionals) or residues on the plants (Bruynzeel et al., 1993, 1995; Bruynzeel and van Ketel, 1986; Lensen et al., 2011). More recently, specifically in the United Kingdom (UK, 2022) and Germany, concern for the bystander and resident has been expressed by the regulatory agencies with respect to pesticide formulations classified as skin sensitizers under Regulation (EC) 1272/2008, the regulation considering the Classification, Labelling and Packaging (CLP) of products, which is the European implementation of the Globally Harmonized System, when the product exceeds classification thresholds (EC, 2009a). The associated precautionary phrases triggered under Classification, Labelling and Packaging (CLP) inform the professional user of the product's hazard properties and associated Personal Protective Equipment (PPE) recommendations which need to be followed to offer suitable protection against the hazard. However, a risk-based approach may be warranted for other populations who need to be considered as "uninformed" about PPP use in their vicinity and cannot be expected to take action to avoid/limit exposure.

In the absence of suitable technical guidance for PPPs, the European Chemical Agency (ECHA) Biocides guidance has been adopted by regulators and industry for conducting skin sensitization risk assessments (ECHA, 2017; Sanvido et al., 2018). Although the exposure scenarios differ considerably, the fundamental principles are still relevant and can be adapted accordingly providing sufficient data are available. However, further consideration of the uncertainties and parameters specific to the application of PPPs are warranted to ensure the risk assessment approach for skin sensitization is deployed appropriately (Jowsey et al., 2019).

In light of the above, the scope of the current paper is to review critically the existing risk assessment methodology for skin sensitization established by the consumer goods industry and examine how this can be tailored to PPPs. A case study for the bystander and resident is presented to illustrate how this can be achieved in practice. Remaining areas of uncertainty are also discussed, along with existing and future challenges.

2. Method

The primary aim of the risk assessment approach for skin sensitizers must be to prevent the primary induction of skin sensitization. Success at this level should ensure that it is unnecessary to protect against elicitation responses. It is important that this is achieved, because the concentration of a contact allergen required for the primary induction of immunological memory is typically higher than the concentration required subsequently to elicit a response in pre-sensitized individuals, particularly if the skin is damaged (Allenby and Basketter, 1993; Corea et al., 2006).

The key elements in the risk assessment process for skin sensitization are similar to those used for systemic toxicity, and have been recently summarised (Api et al., 2020).

- In QRA2, A threshold for the induction of sensitization, i.e., point of departure (PoD), is determined for the contact allergen using dose-response data from assays designed to provide an estimate of potency. In the context of skin sensitization, this PoD is termed the NESIL, or 'No Expected Sensitization Induction Level' and is considered equivalent to a No Observed Effect Level (NOEL) for induction from a Human Repeat Insult Patch Test (HRIPT) (Politano and Api, 2008). For mixtures, a NESIL is determined on a per ingredient basis, considering the high specificity of the immune adverse outcome.
- The NESIL is then adjusted downwards to estimate an Acceptable Exposure Level (AEL), specific for a substance deployed in an exposure scenario of interest. To achieve this, the threshold is divided by a series of Sensitization Assessment Factors (SAFs) to account for areas of uncertainty regarding the appropriateness of the derived PoD for the AEL set for the target population, including inter-individual differences, vehicle/matrix effects and exposure considerations. Each SAF is assigned a value from 1 to 10 depending on the degree of uncertainty, and the overall SAF is calculated as the product of the individual SAFs (Api et al., 2020).
- An estimate of skin exposure is made for the population of concern. A clear understanding of the nature of exposure and formulation composition is key to derive a realistic and representative estimate.
- The exposure estimate is compared to the AEL. An unacceptable risk of induction of skin sensitization is assumed if the AEL is exceeded.

This approach is explained in detail in the following text, using a theoretical case study for PPPs. The scientific principles of the QRA approach, particularly the underlying assumptions behind the SAFs, have recently been reviewed and the reader is referred to these updates for further detail (Basketter and Safford, 2016; Api et al., 2020). The aim of the current article is to demonstrate how this framework can be adapted from consumer products to PPPs, specifically for bystander and resident exposure, where regulatory requests for assessments have been made, but guidance for these assessments is missing.

2.1. Derivation of the NESIL

The NESIL for a sensitizing substance, i.e., the PoD for QRA2, is equivalent to the threshold in an HRIPT for the induction of skin sensitization, but is normally derived from non-human experimental data (Lee et al., 2022; Natsch and Gerberick, 2022). The generation of new HRIPT data is often not considered acceptable, either for ethical and/or regulatory reasons, particularly in the EU (Basketter, 2009). However, existing historical human data (from the testing of individual substances) provides valuable insight on induction thresholds and is taken into consideration as part of a weight of evidence approach with information from more recent *in vivo, in vitro* and *in silico* data (Api et al., 2020). The following sub-sections detail how a NESIL is derived for agrochemicals.

2.1.1. Current global testing requirements for PPPs and testing methods

The test method currently required/accepted in most jurisdictions in pesticide regulation is the Local Lymph Node Assay (EC, 2009a; US-EPA, 2003), considered as the "gold standard". Here a test item induced dose response of lymph node cell proliferation is measured and an EC3 value (see section 2.1.3) derived, which relates to Key event 4 of the OECD approved adverse outcome pathway for skin sensitization (OECD, 2014). The EC3 allows hazard characterization, i.e., the determination of potency. It is to be noted that the LLNA was validated for individual chemicals; thus, in principle at least, it can be considered acceptable for pesticide active ingredients, but as with all other predictive tests for skin sensitization, it has not been validated for hazard or potency characterisation of mixtures.

Guinea pig tests may be accepted in some regulatory areas or required specific circumstances and have historically been used to assess skin sensitization hazard of pesticide active ingredients and PPPs. These tests were not validated and, although hazard classes can be established based on arbitrary thresholds indicated in classification schemes (based on induction concentration), the assays are not designed to provide potency information (Basketter et al., 2005a). Guinea pig assays are therefore not considered suitable for establishing a PoD for QRA.

Although available, non-animal approaches (OECD TG 442C, OECD TG 442D, OECD TG 442E, OECD TG 497) to assess skin sensitization hazard (OECD 2018; OECD 2021a; 2021b, OECD, 2014) are not yet formally implemented into data requirements to assess pesticide active ingredients, they may be used and accepted by regulatory bodies (Strickland et al., 2022 and 2022).

2.1.2. Applicability domain of traditional and non-animal testing methods for NESIL derivation in agrochemical active substances and mixtures

When a PoD selection for an active ingredient is to be determined, risk assessors should consider how well the experimental model(s) predict human responses for the chemical space of interest. In terms of *in vivo* data, evidence from the LLNA can be reliably used for active substances based on the validation dataset and decades of experience with this assay. The ability of the assay to deliver an estimate of the relative potency of an identified skin sensitiser has already been mentioned. As is the case with guinea pig assays, non-animal methods for skin sensitization are still limited in their ability to assess relative potency of skin sensitization, albeit efforts are ongoing to develop appropriate methodologies (e.g. Gradin et al., 2021; Reynolds et al., 2022).

2.1.3. Proposed NESIL derivation

As discussed above, the NESIL for any individual sensitizing substance is derived solely from toxicological assays, which for PPPs indicates the current reference test, the LLNA (OECD, 2010a). This assay identifies the potential of a material to induce contact sensitization and provides an estimate of its sensitizing potency. The derived endpoint is the proliferative response in the draining lymph nodes of mice exposed to the test substance topically on the ears. Substances that elicit a 3-fold or greater proliferative response (i.e., the threshold stimulation index (SI) in the case of the classical radiolabel-based LLNA) compared to control animals are considered to be potential skin sensitizers (OECD, 2010a). With regard to the other OECD test guideline non-radioactive LLNA methods (OECD, 2010b; OECD, 2018a,b) a corresponding threshold could, in theory, be derived. The concentration of a substance which gives a 3-fold response in the LLNA, compared to control animals, is known as the EC3 value. It is normally obtained by linear interpolation of the points in the dose response curve which lie just above and below the 3-fold response (OECD, 2010a). Other approaches based on dose-response modelling, which may also extrapolate an appropriate threshold concentration and prevent additional testing if the EC3 cannot be interpolated, are theoretically possible but have no regulatory acceptance; linear extrapolation, with limits, may be used (Ryan et al., 2007).

The utilization of induction thresholds in QRA aligns with the approach recognized in the scientific literature on toxicology, as implemented by multiple industries and within EU technical guidance (ECHA, 2017; Kimber et al., 2017; Sanvido et al., 2018; Soo Lim et al., 2018; Ezendam et al., 2018; Goebel et al., 2019; Marcelis et al., 2022).

Comparisons of LLNA and human experimental thresholds have been made for a range of substances of varying potency (Api et al., 2015; Basketter et al., 2005b, 2008; Gerberick et al., 2001; Greim and Rühl, 2003; Schneider and Akkan, 2004). These analyses demonstrated good concordance between EC3 values and HRIPT NOELs, and the former is therefore used to directly predict the NESIL for QRA (Basketter et al., 2018). Although a distinct portion of chemicals evaluated are fragrance and other cosmetic ingredients, it should be noted that the ability of the LLNA to test the sensitizing potential of pesticides has been validated by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM and ICCVAM, 2010; ICCVAM and ICCVAM, 2011). Therefore, it is reasonable to conclude that a similar process can be extended to pesticides.

The key exposure metric in QRA is dose per unit area of skin, unlike systemic toxicity risk assessment which relies on total systemic exposure. For skin sensitization, extensive data from historical human patch tests and investigative animal studies have shown that it is the threshold of the contact allergen within a fixed area of skin rather than total dose which drives both induction and elicitation responses (Upadhye and Maibach, 1992; Api et al., 2008; Kimber et al., 2008). Therefore, the NESIL, AEL and exposure estimates are expressed as μg substance/cm^2 skin.

2.2. Application of SAFs

2.2.1. Inter-individual or human variability SAF

The standard risk assessment approach for systemic toxicology relies on an uncertainty factor of 10 to account for variability within the human population, which was subsequently subdivided into chemical specific adjustment factors to account for differences in kinetics and dynamics (Bhat et al., 2017; Meek et al., 2002; Renwick, 1993). For skin sensitization, susceptibility to the induction of contact allergy may vary within the general population. This has been subject to detailed consideration including an evaluation of the induction dose-response relationship from historical human studies, diagnostic clinical observations and occupational data although the two latter sources, based on elicitation thresholds, cannot be interpreted quantitatively (Basketter and Safford, 2016). The authors concluded that, when accounting for variability within the human population for doses below the NESIL, a value of 10 is considered sufficient. This also aligns with the 10-fold uncertainty factor recommended by ECHA for human variability for local effects (ECHA, 2012) and the Biocides guidance for sensitization risk assessment (ECHA, 2017). A SAF of 10 is used consistently across all product categories by the consumer products industry for human variability in induction thresholds (Api et al., 2008, 2020), and also seems appropriate for the current case study.

2.2.2. Inter-species variability

It is prudent at this point to briefly consider any inter-species differences in QRA, particularly as the point of departure often relies on murine data. Although an uncertainty factor for differences between the test species and humans is standard for systemic toxicity risk assessment, it is not a prerequisite for sensitization QRA (Basketter and Safford, 2016; Api et al., 2020). SAFs for inter-species differences have been proposed in the public literature (Bil et al., 2017; ECHA 2017; Sanvido et al., 2018) but as previously mentioned (section 2.1), good correlation between mouse and human experimental thresholds has been demonstrated through studies on varying substances and potency thresholds. In a detailed evaluation of the existing literature, it was concluded that there was no need for a generic SAF to account for inter-species differences for the induction of skin sensitization unless the safety assessor had existing knowledge that the underlying chemistry indicated otherwise (Basketter et al., 2018).

The mechanism of action for skin sensitization is well characterized and shown to be similar between mouse and humans, indeed the mouse has been the main mammalian surrogate model for immunology research for several decades. In contrast, many systemic endpoints carry more uncertainty in kinetics and dynamics warranting the application of an additional uncertainty factor. As the LLNA EC3 is used to directly predict a HRIPT NOEL for QRA, any variability between species (whether kinetic or dynamic) would already be accounted for in this extrapolation, negating the need to account for uncertainty.

2.2.3. Vehicle/matrix effects SAF

This SAF encompasses differences between the test vehicle used in the experimental assay(s) and the matrix or formulation to which the individual is exposed. To some degree, this will depend on whether the product formulation has been tested (thus including all co-formulants) or the active ingredient alone. Used correctly, the LLNA should be conducted on individual substances in a relatively simple vehicle or test solvent (OECD, 2010a, 2010b). An additional SAF would then be applied to account for differences in the product matrix that could enhance the induction of sensitization in the exposed population. For example, some consumer products contain co-formulants which may result in skin irritation, either deliberately (e.g., low concentration acids in face creams designed to provide a mild chemical peel) or inadvertently (surfactant-based cleaning products). The influence of skin irritation has been discussed (Basketter and Safford, 2016), and though this field requires further elucidation, the role of inflammatory mediators such as cytokines present in irritated, inflamed skin cannot be overlooked (Gilmour et al., 2019). Although irritation has not been investigated in the context of PPPs, it should be acknowledged that perhaps 30% of neat formulations (as sold) may well be irritant in nature and classified as such under the CLP regulation (Corvaro et al., 2017). However, whilst the operator (wearing personal protection where recommended on the product label) will utilise the concentrated product for mixing and loading tasks, for the bystander and resident, the spray solution to which they may be exposed through drift will be composed of the PPP greatly diluted with water according to the specific label instructions, rendering co-formulants of no toxicological concern for QRA purposes.

Further, the influence of the matrix is accounted for in the other part of the risk assessment equation, i.e. when estimating the skin exposure to the pesticide active ingredient Skin absorption can be accounted for by conservative default values (EFSA, 2017) or experimentally derived for the pesticide active ingredient within the matrix of the PPP of concern.

For the purposes of this case study, the active substance rather than the product formulation was tested in the LLNA, so composition differences between the LLNA test vehicle and the spray solution were considered. The test solvent was 1% Pluronic L92 surfactant in distilled water, a commonly used aqueous-based vehicle for PPPs, selected for its low irritancy profile and skin wetting characteristics (Ryan et al., 2002; McGarry, 2007; Boverhof et al., 2008). In comparison, the PPP as sold was classified for skin irritation under the CLP regulation, indicating a difference in irritation profiles between the test solvent and the concentrated product. However, for the bystander and resident, spray drift exposure is to the PPP significantly diluted in large volumes of water by the operator prior to application, resulting in a 100-fold dilution of the neat product (see section 3.3. for calculation details). In addition to the active substance, all co-formulants would also undergo the same 100-fold dilution which would logically serve to minimize any irritant potential associated with the concentrated product. Notably, both the test solvent in the LLNA and the drifting spray would be primarily aqueous.

An evaluation of the SAFs assigned to consumer products indicates values of 0.3–3 are applied for matrix differences, the latter being used for products with increased irritation potential (Api et al., 2020). Due to the high degree of dilution of the pesticide spray solution and the similarity in vehicles with the LLNA, a SAF of 1 was assigned for vehicle/matrix effects in the case study.

2.3. Exposure considerations

This takes into consideration the variability associated with the frequency and duration of exposure, whether the site of exposure becomes occluded, and whether the exposed skin site(s) has existing inflammation (the latter aspect is not incorporated into human variability). Each of these parameters may influence the possibility of inducing sensitization and are therefore evaluated for the specific exposure situation.

2.3.1. Frequency/duration of exposure SAF

Frequency and duration of exposure can influence the likelihood of developing a contact allergy, particularly if exposure occurs over extended periods of time (Basketter and Safford, 2016; Api et al., 2020). However, it is important to remember the context under which this SAF was designed. The original QRA process was defined for contact allergens in consumer products intended for direct, frequent application to the skin (Api et al., 2008). For example, skin contact to cosmetics can occur up to several times a day over a number of years, regardless of season. Conversely, bystanders and residents may experience incidental exposure to spray drift when the PPP is applied by the operator according to the frequency specified on the product label. Although this will vary between products, it will typically be limited to <6 exposures during the spraying season each year. As an illustration, an extreme scenario might involve multiple (8 or more) foliar applications of a fungicide in vineyards. However, the likelihood of an individual being incidentally exposed to spray drift during each of these events would seem very low. More typically, PPPs are applied once or twice per season.

In the QRA process, the notional HRIPT NOEL is directly extrapolated from the standard LLNA, and for QRA purposes termed the NESIL. However, considering that a HRIPT utilises nine (semi)occluded 24h exposures over a 3-week period, it clearly represents a substantial exaggeration of exposure compared to bystander and resident exposure scenarios (Politano and Api, 2008). Thus, whilst it may not cover the typical long-term use of consumer products for which a SAF of 3 was considered appropriate, a frequency/duration SAF of 1 is considered more than sufficient for spray drift due to infrequent exposure and limited duration.

2.3.2. Occlusion

For skin sensitization, occlusion refers to the covering of skin with an impermeable barrier after exposure has occurred. It is recognized that full occlusion affects several physiological parameters in the skin, including increased hydration, temperature and irritation, thus enhancing the induction phase (Basketter and Safford, 2016; Api et al., 2020). The HRIPT employs a series of exposures with (semi)occlusive patches to exaggerate the sensitization response. This, in turn, will

provide additional conservatism when extrapolating to the majority of consumer products where most exposures are not under occlusion, with a few exceptions (e.g., deodorants applied to underarms). Although a SAF of less than 1 could be employed when extrapolating from the experimental situation (HRIPT) to exposures resulting from consumer products (to account for lower occlusion), this was deliberately avoided to provide additional conservatism in the approach (Api et al., 2020). For the PPP QRA case study for bystanders and residents, a SAF of 1 was therefore considered adequate as exposure will not be under full occlusion for the bystander or resident, who, as a conservative assumption are taken to be lightly clothed (EFSA, 2014, 2022).

2.3.3. Skin site and condition SAF

The skin site SAF takes into consideration specific areas of the body that may be predisposed to developing contact dermatitis due to existing skin irritation/inflammation. In their review of the published literature, Basketter and Safford noted little evidence of different skin sites being more susceptible to developing sensitization than others, although it has been suggested that induction may be enhanced at sites with existing inflammation due to the presence of inflammatory mediators (Basketter and Safford, 2016; Gilmour et al., 2019). The cosmetics industry has assigned a SAF of 10 for products contacting the intimate regions of the body or areas likely to already have inflammation, e.g., the axillae due to shaving, perspiration, and humidity (Api et al., 2020). A lower SAF of 3 has been assigned to most cosmetic and household products likely to contact the face, hands and legs during use. For products with incidental, limited exposure where direct skin contact is not intended, a SAF of 1 has been assigned. This category includes products which may infrequently contact the hands, such as shoe polish and candles. Also included are aerosol air fresheners and electrical insecticides, where airborne droplets are generated which may result in skin contact (supplementary data to Api et al., 2020; RIVM, 2021; RIVM, 2006).

Given these considerations, since exposure to spray drift for the bystander and resident results only in incidental skin contact, a SAF of 1 is considered most representative for this scenario.

2.3.4. Relevance of skin availability for exposure estimation

Although skin penetration is an important parameter for the exposure and risk assessment of other systemic endpoints, the available evidence indicates that it is not a significant factor for skin sensitization (reviewed in Basketter and Safford, 2016). The induction process will indeed depend on the allergen reaching the viable epidermis to form a protein-hapten complex as the initial step for induction. However, the subsequent reaction within the relevant compartments of the skin is key rather than penetration of the allergen through the skin and into the systemic circulation (Cumberbatch et al., 1993; Basketter and Safford, 2016; Fitzpatrick et al., 2017a, 2017b).

Surprisingly, in a classic series of clinical studies, substantial disruption to the skin barrier, even its removal, has been shown to have little influence on the induction of sensitization, with any real impact being due to inflammation (Kligman, 1966). Consequently, it has been concluded that enhanced penetration per se should not influence the choice of SAF (Api et al., 2020). Furthermore, as indicated above and applied below the exposure estimation for PPP already accounts for skin penetration.

Notwithstanding those considerations regarding skin penetration, there is one further aspect that could be applied to refine further the estimation of exposure. In QRA2, thought is given to whether a sensitiser remains on the skin or is washed off (Api et al., 2020). For the accidental exposure that may occur with residents/bystanders, it is pertinent to consider what information might be derived from the standard manner in which pesticide active ingredients are assessed (OECD, 2004; EFSA, 2017). In brief, the dose penetrating through the skin is determined, together with the residue dose within the skin and the external dose that can be removed from the skin by washing (after the 24h exposure period). This last item, the material that can be removed by washing could offer a further insight into the true exposure concentration, in $\mu g/cm^2$, adding a further potential refinement to QRA2 calculations.

3. Case study

A QRA for the bystander and resident is presented below for a theoretical pesticide, active ingredient X, formulated into a PPP at 400 g/L. In this case study, the key elements presented in the previous section are considered in a stepwise approach.

It was assumed that experimental potency data were available for the active substance, and a suitable PoD can be derived. SAF values are carefully assigned for individual areas of uncertainty and used to extrapolate the experimentally derived threshold to an AEL for the actual exposure event. Exposure to spray drift is then estimated using information provided in the product label or Good Agricultural Practice (GAP) table (a summary of appropriate use conditions), which included any restrictions for the operator during application (Table 1).

The exposure estimate is finally compared to the AEL to identify any risk of inducing contact allergy in a bystander or resident following exposure to active ingredient X via spray drift.

3.1. Derivation of the NESIL

As the EC3 is usually expressed as an applied concentration (%), it needs to be converted to $\mu g/cm^2$ for QRA. For the case study, as a theoretical example, the LLNA on the active ingredient X results in an EC3 of 1.8%, meaning it would be classified as a strong skin sensitiser (i.e. it is clearly lower than the threshold of 2%, but not so far below that it would represent a more extreme sensitiser that would be atypical for PPPs). The percentage EC3 can be converted to a dose per unit area by taking the experimental dose volume of 25 μl from the LLNA, the estimated application area of 1 cm^2 for the mouse ear and using a conversion factor of 250 (Basketter et al., 2005a). The NESIL for active ingredient X is therefore 1.8 x 250 = 450 $\mu g/cm^2$.

3.2. Derivation of the AEL

To use the NESIL in risk assessment, it must be converted into an AEL for the wider population by applying SAFs specific to a described exposure scenario. The values assigned to the SAFs, described previously in section 2.2, are summarised below (Table 2). The overall SAF is calculated as the product of the individual values, therefore accounting for all areas of uncertainty when extrapolating from an experimental NOEL to bystander and resident exposure.

The AEL is subsequently determined by dividing the NESIL by the overall SAF:

AEL = 450 $\mu g/cm^2$ / 25, i.e. 18 $\mu g/cm^2$

The AEL represents a safe exposure threshold or benchmark tailored to the population of concern, below which the chance of developing a contact allergy to its relative tested item is highly unlikely. The AEL is later compared to exposure estimates for the bystander and resident.

3.3. Exposure estimation for the bystander and resident

To complete the QRA for skin sensitization in unprotected persons, a relevant estimate of exposure is needed. Exposure assessment methodologies for bystanders and residents are most advanced in the EU with the EFSA guidance (2014 and revised in 2022) providing approaches for various spray application scenarios. This case study considers exposure to spray drift resulting from the use of vehicle mounted boom sprayers, typically used for broadacre crops and the EFSA guidance which uses data from the BREAM (Bystander Resident Exposure Assessment Model) project, where mannequins placed at varying distances downwind of the sprayer were used to determine the total volume of spray deposited on

Table 1
Use directions for a theoretical plant protection product containing active ingredient X.

Crop	Type of application	Application		Application rate		Additional information
		Method	Number of applications per year	Maximum application rate (g a.i. X/ha)	Water volume (L/ha)	
Cereals	Professional field use	Low crop, tractor mounted boom spray	3 (10 days apart)	800	200 to 400	No buffer zone or drift reduction technology required

Table 2
SAFs proposed for Bystander and Resident exposure to PPPs.

SAF	Value	Rationale
Inter-species	2.5	No scientific rationale (see section 2.2.3), but a value of 2.5 is required by ECHA Technical Guidance
Inter-individual	10	Standard value used in QRA
Vehicle/matrix effects	1	Exposure is to an aqueous matrix
Exposure considerations:	–	
- Frequency/ duration	1	Both are very low, <6 times per year
- Occlusion	1	Significant exposure only occurs on uncovered skin
- Skin condition/ site	1	Value adopted generally in QRA for infrequent skin exposure
Overall SAF	**25**	

simulated adult and child bystanders. Spray drift exposures typically decrease with increasing distance from the sprayer (buffer) and for this case study data for 2m were selected as no buffer zone was specified in the GAP. EU guidance dictates that high percentiles are taken from relevant datasets with 75th percentiles being used for longer term exposures (resident) and 95th percentiles for short term or acute exposures (bystander) (EFSA, 2014, 2022). The indicative skin exposure values to spray drift are presented for an adult and child below (Table 3).

Exposures to spray drift were converted to a dose per unit area by dividing the measured volumes above by the total body surface area. The expert group of the European Chemicals Agency has published a summary of body surface areas for different age groups, based on the US EPA Exposure Factors Handbook, 2011 (HEAdhoc recommendation no. 14, 2017) in which total body surface areas of 4800 cm^2 and 16600 cm^2 have been derived for toddlers and adults, respectively. These surface areas are also used in the risk assessment of PPPs for systemic toxicity in the EU (EFSA, 2022). Spray volume per unit area of skin is presented in Table 4 below.

Combining the highest application rate (g a.i./ha) and the lowest water volume (L/ha) on the product label, thus giving the highest in-use concentration, provides an exposure estimate that is protective for all potential application scenarios, known as the 'critical' GAP. Bystander and resident exposure was calculated using the highest application rate of 2 L of product per hectare. With a product concentration of 400 g a.i./L of product, this equates to an application rate of 800 g a.i. per hectare treated. The lowest water volume in the range (200 L/ha) was selected to determine the highest concentration that could be applied in the field, as shown in the following.

Maximum in use spray concentration = Max. use rate (a.i.)/Min. water volume = 800 g a.i./ha ÷ 200 L/ha = 4 g a.i./L = 4 μg a.i./μL.

This conservative figure for in use dilution concentration was used to calculate the predicted skin loading (Table 5). Exposure values were expressed as μg active/cm^2 of skin for direct comparison with the AEL to inform the risk characterisation.

Table 3
Skin exposure to spray drift for unprotected persons.

Skin exposure (mL spray dilution – 75th p. spray volumes for residents)		Skin exposure (mL spray dilution – 95th p. spray volumes for bystanders)	
Adult	Child	Adult	Child
0.47	0.33	1.21	0.74

Table 4
Skin exposure to spray drift per unit area of skin.

Skin exposure (μl spray/cm^2 – 75th p. spray volumes)		Skin exposure (μl spray/cm^2 – 95th p. spray volumes)	
Adult	Child	Adult	Child
0.0283	0.0688	0.0729	0.1542

The generic spray drift values above were then refined using the in-use concentration of the active substance to determine potential exposure to active substance X for each age group in the same units (μg/cm^2) as the AEL.

3.4. Risk characterisation

The risk of induction of sensitization following bystander and resident exposure to chemical X in spray drift is determined by comparing exposure estimates to the AEL (Table 6). No unacceptable risk from exposure to skin sensitizers is assumed, when the % exposure in relation to the AEL is <100%.

Resident and bystander exposure was markedly less than the AEL for all cases, with the highest ratio being 0.034 for the child bystander, equivalent to 3.4% of the AEL. The second highest ratio was for a child resident, but again, exposure was very low at only 1.5% of the AEL. Consequently, the likelihood of inducing contact allergy to chemical X in either bystanders and/or residents is negligible. As a note of caution, reverse engineering this quantitative approach to indicate maximum possible use levels, in use spray concentrations, or the most potent sensitiser that could, in theory, be used safely should be approached with caution, particularly until there is greater confidence derived from experience of use of the approach.

4. Discussion

It has long been recognized that PPPs which contain skin sensitizing ingredients have the potential to lead to ACD, particularly in occupational settings (see Introduction). Accordingly, their labelling and use is associated with appropriate warnings and recommendations regarding the use of PPE to minimize skin contact. However, in normal use there is the possibility that inadvertent exposure may occur in residents and/or bystanders. This paper endeavours to address how such a risk can be characterised, such that manufacturers and regulators can make informed decisions regarding skin safety.

In the present case study, the most recent adaptation of a quantitative approach to skin sensitization risk assessment, QRA2, has been taken as a basis for evaluation of resident and bystander safety (Api

Table 5
Skin exposure to active ingredient X from spray drift.

Skin exposure (μg active X/cm^2 – 75th % ile)		Skin exposure (μg active X/cm^2 – 95th % ile)	
Adult	Child	Adult	Child
0.1132	0.2752	0.2916	0.6168

Table 6
Ratio of resident and bystander exposure to the AEL following treatment of cereals with active ingredient X.

Exposed person	Skin exposure (μg active X/cm^2)[a]	Ratio of skin exposure: AEL[b]	Skin Exposure as a % of the AEL
Resident - child	0.2752	0.015	1.5
Resident - adult	0.1132	0.006	0.6
Bystander - child	0.6168	0.034	3.4
Bystander - adult	0.2916	0.016	1.6

[a] All exposure calculations are for application to cereals with 800 g a.i. X/ha and a minimum water volume of 200 l/ha.
[b] Based on an AEL of 18 μg a.i./cm.^{2}.

et al., 2020). QRA2 is already in widespread use by the cosmetics, household products and fragrance industries (e.g. Basketter et al., 2008; Fukushima et al., 2022; Marcelis et al., 2022). It has received a good degree of support recently from its annual review at the European Commission (https://cdn2.assets-servd.host/selective-koala/production/images/IDEA-Ann-Rev-Key-Conclusions-2911-2022-Final.pdf). One key conclusion from this event states *"State of the art (quantitative) risk assessment continues to be seen as the only scientifically defensible approach to ensuring safe use of fragrance materials. The successful development and application of QRA2 by industry marks a significant milestone in this context."* Importantly, the core principles of QRA2 can readily be adapted for evaluation of PPPs, applying safety assessment factors to a sensitization threshold value (NESIL) based on the potency of a sensitizing ingredient. As shown herein, application of an aggregate SAF of 25 to the NESIL for a strong sensitiser (i.e. a substance with an LLNA EC3 value of <2%) leads to a very considerable margin of safety (more than an order of magnitude). Of course, this is in part due to the very low and infrequent levels of exposure which a bystander or resident would, in reality, experience. Plus, it is entirely consistent with the absence of evidence of a clinical problem in this inadvertently exposed population (see Introduction).

The SAFs adopted in the present work have followed precisely the logic applied to QRA2 and to its implementation to fragrances used in cosmetics and household products (Api et al., 2020). Nevertheless, there may be a degree of concern that the overall SAF at 25 is low - typical values are often in the region of 100–300 for other industries, but this reflects the specific nature of the exposure scenario. In the present example (i.e., with active ingredient X in a PPP), even such high values would still fail to indicate a risk to bystanders/residents. Furthermore, it is very reasonable to argue that the approach taken herein is in reality highly conservative. This is particularly the case since the exposure scenarios for cosmetics and household products that are associated with higher SAFs also correspond with product categories that lead to repeated, and often multiple, daily exposure, with many cases involving direct application to skin. This is in complete contrast to the very occasional, ad hoc, exposures foreseen for PPPs for this population and serves to highlight the importance of careful consideration of all aspects of the exposure scenario in the risk assessment process.

Ultimately, it is anticipated that the NESIL used as the starting point for the risk assessment of skin sensitizing actives in PPPs will be derived from non-animal methods, such as those currently being developed in relation to cosmetic and other chemical safety evaluation (Gradin et al., 2021; Reynolds et al., 2022). Until then, it is recommended that the considered application of QRA2 to resident/bystander exposure to PPPs, as detailed in the present work, represents current best practice.

Conflict of interest for all authors and reviewers

The authors and/or reviewers listed immediately below declare the following financial interests which may be considered as potential competing interests:

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Data availability

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