Regulatory Toxicology and Pharmacology 98 (2018) 171–183

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

A quantitative risk assessment for skin sensitizing plant protection products: Linking derived No-Effect levels (DNELs) with agricultural exposure models

Olivier Sanvido[a,*], Kaspar Schmid[a], Rex E. FitzGerald[b], Nicolas Roth[b], Martin F. Wilks[b], Peter Bormann[c], Nancy B. Hopf[d]

[a] State Secretariat for Economic Affairs, Holzikofenweg 36, CH-3003, Bern, Switzerland
[b] University of Basel, Swiss Centre for Applied Human Toxicology, Missionsstrasse 64, CH-4055, Basel, Switzerland
[c] Federal Office for Agriculture, Schwarzenburgstrasse 165, CH-3003, Bern, Switzerland
[d] University of Lausanne, Institute for Work and Health (IST) , Route de la Corniche 2, CH-1066, Epalinges-Lausanne, Switzerland

ARTICLE INFO

Keywords:
Chemical skin sensitizers
Allergic contact dermatitis
Plant protection products
Quantitative risk assessment
Derived No-Effect level (DNEL)
Agricultural operator exposure model

ABSTRACT

Chemical skin sensitizers produce allergic contact dermatitis, which is one of the most frequent occupational diseases associated with chemical exposures. Skin exposure is the major route of exposure when using plant protection products (PPPs). Therefore, skin sensitization is an important factor to be addressed during the regulatory risk assessment of PPPs. The main regulatory decision criterion considered when performing risk assessment for skin sensitizers is the dose applied. The equally important criteria "potency of the substance" is insufficiently considered by two potency categories as potency may vary up to five orders of magnitude. "Frequency of exposure" to the skin sensitizer is not considered at all. Consequently, an improved risk assessment methodology is essential to adequately assess health risks from skin sensitizers, especially for agricultural operators using PPPs. A quantitative risk assessment (QRA) approach for addressing PPPs sensitizing potential is proposed here. This QRA combines a methodology to derive a substance-specific threshold for skin sensitizers, a Derived No-Effect Level (DNEL), and an agricultural exposure model used for assessing chronic health risks of PPPs. The proposed QRA for skin sensitizing PPPs is a clear improvement over current risk assessment to ensure the safe use of skin sensitizers in an occupational context.

1. Introduction

Chemical skin sensitizers are known to produce allergic contact dermatitis, which is one of the most frequent occupational diseases associated with exposure to chemicals (Diepgen and Coenraads, 1999; McDonald et al., 2006). Allergic contact dermatitis progresses in two stages as commonly observed with other forms of allergy. After a single exposure to a skin sensitizer during an initial induction phase, sensitization to the allergen is acquired. Subsequent exposures to the same skin sensitizer elicit the actual allergic reaction (elicitation phase) (see Appendix A1 for further information on the scientific background of skin sensitization). Allergic responses to skin sensitizers are driven by the amount of substance applied per area of exposed skin (expressed in $\mu g/cm^2$) and referred to as external dose, by the potency of the skin sensitizer (i.e. its electrophilic reactivity), and by the frequency of exposure to the skin sensitizer (Friedmann, 2007; Kimber et al., 2008; Paramasivan et al., 2010). Yet, the main regulatory decision criterion currently considered in the EU when performing a risk assessment for skin sensitizing chemicals is the classification of a substance or mixture as skin sensitizer. The actual amount of substance reaching the skin is not considered for current risk assessment. According to the EU Regulation for Classification, Labelling and Packaging (CLP), a mixture containing a skin sensitizer is not considered having skin sensitizing properties if the concentration of the skin sensitizer in the mixture is below defined concentration limits of 0.1% or 1% (see Appendix A2 for further information on the classification criteria used in the EU CLP Regulation). However, this concentration-based approach does not sufficiently address potency, especially for strong sensitizers, since sensitization after exposure to strong sensitizers can occur at far lower concentrations than set forth in the CLP Regulation (Liden, 2008). Similarly, frequency of exposure is completely disregarded. Consequently, an improved risk assessment methodology for skin sensitizers is needed to adequately consider these three factors: dose, potency, and frequency of exposure to the skin sensitizers. All three are important in

* Corresponding author.
E-mail addresses: olivier.sanvido@seco.admin.ch (O. Sanvido), kaspar.schmid@seco.admin.ch (K. Schmid), rex.fitzgerald@unibas.ch (R.E. FitzGerald), nicolas.roth@unibas.ch (N. Roth), martin.wilks@unibas.ch (M.F. Wilks), peter.bormann@blw.admin.ch (P. Bormann), Nancy.Hopf@hospvd.ch (N.B. Hopf).

https://doi.org/10.1016/j.yrtph.2018.07.022
Received 3 May 2018; Received in revised form 23 July 2018; Accepted 25 July 2018
Available online 29 July 2018

determining occurrence of sensitization. Ideally, a quantitative risk assessment (QRA) methodology would combine a quantitative model comparing predicted exposures to the specific skin sensitizer with an endpoint that has been derived considering these three influencing factors.

A number of authors have proposed QRA approaches for skin sensitizing chemicals, primarily focusing on cosmetic and household products and on the risk for consumers of such products (Api et al., 2008; Felter et al., 2002; Griem et al., 2003; ter Burg et al., 2010). Since the EU banned animal testing of cosmetic ingredients in 2013 (including tests for skin sensitization), considerable efforts have been and are being made in the cosmetic and fragrance industry to update skin sensitization QRA (Basketter and Safford, 2016; SCCS, 2017). Common to all these approaches is the aim to derive a quantitative endpoint to protect non-allergic individuals against skin sensitization. This endpoint is either called “No Expected Sensitizing Induction Level (NESIL)” (Api et al., 2008) or “Acceptable Non-Sensitizing Area Dose (ANSAD)” (Griem et al., 2003). Apart from focusing on risks for consumers, publications so far have concentrated on the scientific basis of skin sensitization; and appropriate use of uncertainty factors or sensitization assessment factors (SAFs) for deriving an endpoint, below which no sensitization occurs. Derived quantitative endpoints have so far not been combined with an exposure assessment, thus estimates for the likelihood of exposure to skin sensitizers have not been provided. The exposure assessment is a pre-requisite in order to perform a risk assessment where both the hazard of the substance is characterized as well as the exposure to the substance are considered.

The present study aims at developing a QRA methodology for plant protection products (PPPs) which is an important group of skin sensitizing chemicals since skin exposure is the most significant route of entry when using PPPs (Anderson and Meade, 2014; Baldi et al., 2006; Macfarlane et al., 2013). Quantitative methodologies are available for chemicals (ECHA, 2012), biocides (ECHA, 2017) and cosmetics (Api et al., 2008; Basketter and Safford, 2016; Felter et al., 2002; Griem et al., 2003; SCCS, 2017; ter Burg, 2006). For PPPs, currently only a qualitative or hazard-based approach is implemented, which consists of wearing personal protective equipment (PPE) while using sensitizing products or dilutions. The QRA approach presented here uses a methodology to derive a substance-specific threshold for skin sensitizers, a Derived No-Effect Level (DNEL) (ECHA, 2012). The DNEL explicitly includes potency and frequency of exposure being two important determinants of skin sensitization. Subsequently, the third determinant being the actual amount of substance reaching the skin is considered by using the DNEL in an agricultural exposure model used for assessing the chronic risks of PPPs to agricultural operators[1] during the approval process of PPPs. The advantage of such an agricultural exposure model is that the estimated systemic PPP exposure is compared to a systemic endpoint. By doing this the maximum amount of PPP to which an operator may be exposed per day without any adverse health effects to be expected (Acceptable Operator Exposure Level, AOEL) can be defined. While the AOEL covers subacute and partially subchronic effects, it does not cover local skin effects such as irritation and sensitization. Hence, an endpoint reflecting skin sensitizing risk such as a DNEL is needed.

The approach presented here may help to improve the risk assessment for skin sensitizing chemicals. In addition, it addresses appropriate exposure scenarios in the risk assessment. This will eventually lead to a better protection of operators using PPPs regularly. The proposed approach will be discussed considering both the toxicological as well as the cumulative and occupational exposure assessment perspective.

[1] The term “operator” is used here according to EFSA (2014) to denominate persons who are involved in activities relating to the application of a plant protection product.

2. Skin sensitizing plant protection products

Plant protection products (PPPs) aim at protecting plants from damaging influences such as weeds, fungi or insects. They are primarily used in the agricultural sector but also in forestry, horticulture, amenity areas, and private gardens to protect crops or desirable or useful plants. Given that PPPs are biologically active, they do not only have the desired plant protecting effects but also drawbacks, such as potential toxicity to humans and other non-target species in the environment. PPPs therefore undergo an authorization process in most countries where the manufacturer is required to assess the risks to human health and the environment prior to putting a product on the market (EC, 2009; PSMV, 2010). The risk assessment data have to be submitted by the manufacturer to governmental agencies. The appropriate authorities assess the data and eventually decide whether the health risks associated with the PPP use are acceptable and market approval can be granted. Assessing the PPP's potential to induce skin sensitization is a data requirement for placing on the market in the EU and in Switzerland (EC, 2013). Among the 1134 PPPs authorized by April 2018 in Switzerland, 323 products (i.e. 28.5%) were classified as being skin sensitizers (FOAG). They contained chemical active substances or adjuvants and co-formulants possibly being skin sensitizers.

PPP applications on agricultural crops are typically divided into four clearly separated tasks: (1) mixing and loading the PPP into a tank; (2) applying diluted PPP with spray equipment; (3) rinsing and cleaning the spray equipment; and (4) re-entering previously treated crops. The level of PPP exposure varies between these four tasks. Mixing and loading are usually tasks associated with the highest exposure because agricultural operators are handling the concentrated product. In addition, accidental spills of the concentrated product may lead to direct local skin exposure. Exposure during spraying of the diluted PPP greatly vary depending on the spray equipment used. Field crops such as cereals, potatoes, and sugar beets are predominantly sprayed with tractor-mounted boom sprayers or self-propelled sprayers. The operator often sits in a closed cabin, which significantly reduces exposure to the diluted PPP. Closed cabins may not, however, be available in all cases. Other crops such as grapes, stone or pome fruits are sprayed with tractor-mounted broadcast air-assisted sprayers. The tractors used in orchards and vineyards are usually smaller than those used in field crops and may not always include a closed cabin. Where the terrain is too steep to use machinery, operators use knapsack sprayers or backpack mist blowers. Hand held equipment is likewise used in greenhouses to spray certain vegetables such as tomatoes and cucumbers, as well as for spraying ornamental plants. Especially with hand-held equipment, exposure to the diluted product can be higher than when using a tractor-mounted spraying equipment (Baldi et al., 2006, 2012). In addition, agricultural operators are exposed to contaminated surfaces on the spraying equipment during rinsing and cleaning operations. They may also come in contact with sprayed plant material following application of PPPs during pruning and harvesting activities. Apart from the factor determined by the characteristics of the equipment described above, a number of other factor determine the level of exposure during the three tasks described. An obvious factor is exposure time, which depends on the length of the tasks performed. Spraying operations usually last several hours while mixing, loading, rinsing, and cleaning are usually shorter; about 15–20 min (Baldi et al., 2006). In addition to intensity (exposure level) and duration (exposure time), another factor is the number of tasks performed over one working day (daily frequency) such as mixing and loading tasks needed to refill empty tanks. A further crucial factor is the type of protective clothing or equipment worn by the agricultural operators. Especially for skin sensitizing PPPs, exposure is clearly influenced by the area of unprotected skin as the concentrated or diluted PPP can deposit on bare arms or legs. Finally, an additional important factor is the frequency of exposure to PPPs over a growing season (seasonal frequency). In agriculture, the seasonal frequency is related to the crops grown on the