Regulatory Toxicology and Pharmacology 83 (2017) 104–108

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Commentary

Quantitative risk assessment for skin sensitization: Success or failure?

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ARTICLE INFO

Article history:
Received 27 July 2016
Received in revised form
15 November 2016
Accepted 17 November 2016
Available online 18 November 2016

Keywords:
Skin sensitization
Quantitative risk assessment
Contact allergy

ABSTRACT

Skin sensitization is unique in the world of toxicology. There is a combination of reliable, validated predictive test methods for identification of skin sensitizing chemicals, a clearly documented and transparent approach to risk assessment, and effective feedback from dermatology clinics around the world delivering evidence of the success or failure of the hazard identification/risk assessment/management process. Recent epidemics of contact allergy, particularly to preservatives, have raised questions of whether the safety/risk assessment process is working in an optimal manner (or indeed is working at all!). This review has as its focus skin sensitization quantitative risk assessment (QRA). The core toxicological principles of QRA are reviewed, and evidence of use and misuse examined. What becomes clear is that skin sensitization QRA will only function adequately if two essential criteria are met. The first is that QRA is applied rigourously, and the second is that potential exposure to the sensitizing substance is assessed adequately. This conclusion will come as no surprise to any toxicologist who appreciates the basic premise that "risk = hazard x exposure". Accordingly, use of skin sensitization QRA is encouraged, not least because the essential feedback from dermatology clinics can be used as a tool to refine QRA in situations where this risk assessment tool has not been properly used.

1. Introduction

Many hundreds of chemicals have been shown to cause skin sensitization associated with allergic contact dermatitis (ACD). In common with other forms of allergy, ACD develops in two phases. In the first of these, the induction phase, skin exposure of a subject to an appropriate concentration of a contact allergen will result in specific immunological priming and the acquisition of skin sensitization (contact allergy). If the sensitized subject is exposed subsequently, at the same or a different skin site, to the same chemical allergen then the second or elicitation phase will be initiated. This is associated with the elicitation of an accelerated and more vigorous secondary immune response resulting in a local cutaneous inflammatory reaction that is described clinically as ACD (Kimber and Dearman, 1997).

There remains an important need to understand the hazards and risks associated with exposure to chemicals that have the potential to cause skin sensitization. For hazard identification there are available validated *in vivo* and *in vitro* methods. The use of these methods to evaluate chemicals for the presence or absence of skin sensitizing potential is beyond the scope of this article and will not be explored further. The focus here is rather the assessment of the risk of skin sensitization. It is important to emphasise that it is the risk for the induction of skin sensitization (rather then the risk of eliciting a reaction in a previously sensitized subject) that is the primary purpose of the safety evaluation process. Risk can be defined most simply as the likelihood that, under a given set of circumstances, a hazard will translate into a meaningful adverse health effect.

Potency is inversely proportional to the amount of chemical required to initiate the pathway leading ultimately to an adverse event. That is, the lower the level of exposure required to induce an effect, the more potent the chemical. In the context of this article potency of a contact allergen describes the amount of chemical required to cause the acquisition of skin sensitization, and the relevant dose metric is the amount of chemical experienced per unit area of skin, e.g. $\mu g/cm^2$. An understanding of skin sensitizing potency is particularly important because it has been established that contact allergens vary by up to 5 orders of magnitude with respect to their relative skin sensitizing potency (Gerberick et al., 2005; Kern et al., 2010).

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http://dx.doi.org/10.1016/j.yrtph.2016.11.020
0273-2300/

The pattern of exposure takes into consideration the dose of chemical, the medium in which it is experienced, and the site, duration and frequency of contact. If these variables are understood it is possible, using the QRA approach, to establish whether certain conditions of exposure to a specified chemical allergen will result in the acquisition of sensitization. The QRA seeks to determine whether, and to what extent, anticipated patterns of exposure (in an occupational setting or among consumers) will be below the estimated threshold for induction of skin sensitization based on an understanding of sensitizing potency.

It is timely now to consider the value of the QRA paradigm, and the extent to which this provides a basis for accurate assessment of the risk of inducing skin sensitization. In this article the principles and practice of the QRA methodology will be considered, including the relevance of safety factors incorporated into the risk assessment process. In addition, evidence regarding the effectiveness of the QRA system will be reviewed and conclusions drawn about the general applicability of the method for evaluating risks of inducing skin sensitization.

2. Elements of QRA

Based upon the familiar tenet of toxicology that 'the dose makes the poison' a guiding principle is that risk is the product of hazard and exposure. However, until approximately the end of the last century risk assessment for skin sensitization had been conducted rather differently (reviewed in Basketter et al., 1996). That changed with the availability of a robust method for assessing accurately the skin sensitizing potency of contact allergens (Basketter et al., 2007). That approach was based on evaluation of dose-response relationships in the validated mouse test, the local lymph node assay (LLNA) (Kimber and Basketter, 1997). It was found that estimates of skin sensitizing potency as measured using the LLNA, correlated closely with clinical assessments of potency by practicing dermatologists, and the results of the Human Repeated Insult Patch Test (HRIPT) (e.g. Gerberick et al., 2001a,b; Basketter and McFadden, 2012; Api et al., 2015). Despite the inevitable variability associated with biological assays such the LLNA (e.g. Hoffmann, 2015), the ability to measure with confidence relative skin sensitization potency, and the assurance that such measurements are relevant to humans, permitted the adoption of a classical approach to risk assessment for skin sensitizing chemicals that incorporated the following features:

1. A no effect level is derived from the predictive toxicology work
2. Appropriate safety factors are used to adjust the no effect level
3. The adjusted level is compared with the human exposure level

For the purposes of skin sensitization QRA, the no effect level derived from the toxicology assessment has been given a specific term - no expected sensitization induction level (NESIL) - where it is important to remember that this value is based on a weight of evidence approach using all available data followed by confirmatory HRIPT to establish the NESIL, and is not directly relevant to the end user. It is important to note that HRIPT testing is not an option for some regions. In such cases, small consumer studies may be employed to gain confirmation of the risk assessment before larger scale marketing of the ingredient evaluated.

In the original manifestation of QRA, three safety factors, termed Sensitization Assessment Factors (SAFs) were applied to the NESIL: a factor of 10 for human variability; a factor of between one and 10 to accommodate the uncertainty associated with differing exposure matrices; a factor also between one and 10 to accommodate other possible exposure conditions or characteristics not included in the actual exposure assessment for the end-user. Comprehensive details of this first iteration of skin sensitization QRA were published several years ago (Robinson et al., 2000; Gerberick et al., 2001a,b; Griem et al., 2003; Felter et al., 2002, 2003; Api et al., 2008; Api and Vey, 2008).

One essential element of skin sensitization risk assessment is that it is intended only to address the induction of skin sensitization (commonly termed contact allergy in humans). The sole intention is therefore to prevent induction. Where contact allergy has already been induced, then an entirely different process is necessary to establish safe exposure limits, and that is not a part of this commentary paper - which is not to say that defining safe exposure limits for the elicitation of contact allergy, i.e. allergic contact dermatitis, is unimportant, it is, but it is not part of QRA.

3. Highlights of QRA

In response to critical commentary concerning the original QRA approach, for example by the European Union Scientific Committee for Consumer Products (SCCS) (http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_135.pdf), the scientific principles underpinning this risk assessment method have been again subjected to detailed review (Basketter and Safford, 2016). The review resulted in proposals for some changes to the safety assessment factors as well as providing support for the inclusion of aggregated exposure assessment for the end user. Collectively those changes have resulted in a revised and updated QRA process.

3.1. Skin sensitization QRA in action

As already mentioned, the underlying principles of skin sensitization QRA are entirely congruent with the general principles and practice of toxicology. Furthermore, the aim of the risk assessment process is always to avoid the induction of skin sensitization in humans. Consequently, it is necessary to examine not only whether QRA follows standard toxicology principles, but also whether there is evidence that it is operationally effective. Several publications have exemplified the use of QRA, including for transition metal allergens (Basketter et al., 2003), for many preservative chemicals (Basketter et al., 2008, 2010) as well as for a number of fragrance sensitizers (Gerberick et al., 2001a,b; Corea et al., 2006; Api and Vey, 2008; Basketter et al., 2015). All these examples have followed the original version of QRA and demonstrate, via retrospective analysis, that its rigorous application should lead to levels of exposure that are below those required for the acquisition of skin sensitization. Skin sensitization QRA has also been applied in the same manner to a substantial number of frequent sensitizers, leading to extensive revision of industry guidelines (Api and Vey, 2008). Nevertheless, there is good evidence that the frequency of contact allergy at least to fragrances and preservatives has not declined significantly, judging by clinical data up to the end of 2015 (Basketter et al., 2015; Basketter and Corsini, 2016; Schwensen et al., 2015; 2016). Of course, making an impact on the frequency of contact allergy in humans where there is a substantial existing population of individuals that are already sensitized is challenging, just as is any such demonstration of effects at an epidemiological level. What has caused particular disappointment though is that the introduction into the marketplace of a new preservative, methylisothiazolinone, has led to substantial epidemic of contact allergy (Schwensen et al., 2015, 2016). These matters have certainly been a key driver for the critical examination of the whole skin sensitization QRA process.

3.2. How is QRA best used?

Risk assessment in skin sensitization is founded on general