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ScienceDirect
Regulatory Toxicology and Pharmacology 52 (2008) 3–23
Regulatory Toxicology and Pharmacology
www.elsevier.com/locate/yrtph

Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients

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Received 16 July 2007
Available online 24 October 2007

Abstract

Based on chemical, cellular, and molecular understanding of dermal sensitization, an exposure-based quantitative risk assessment (QRA) can be conducted to determine safe use levels of fragrance ingredients in different consumer product types. The key steps are: (1) determination of benchmarks (no expected sensitization induction level (NESIL)); (2) application of sensitization assessment factors (SAF); and (3) consumer exposure (CEL) calculation through product use. Using these parameters, an acceptable exposure level (AEL) can be calculated and compared with the CEL. The ratio of AEL to CEL must be favorable to support safe use of the potential skin sensitizer. This ratio must be calculated for the fragrance ingredient in each product type. Based on the Research Institute for Fragrance Materials, Inc. (RIFM) Expert Panel's recommendation, RIFM and the International Fragrance Association (IFRA) have adopted the dermal sensitization QRA approach described in this review for fragrance ingredients identified as potential dermal sensitizers. This now forms the fragrance industry's core strategy for primary prevention of dermal sensitization to these materials in consumer products. This methodology is used to determine global fragrance industry product management practices (IFRA Standards) for fragrance ingredients that are potential dermal sensitizers. This paper describes the principles of the recommended approach, provides detailed review of all the information used in the dermal sensitization QRA approach for fragrance ingredients and presents key conclusions for its use now and refinement in the future.

Keywords: Quantitative risk assessment; Dermal sensitization; Fragrance ingredients; NESIL; SAF; AEL; CEL

1. Introduction

Although some substances in common use today may have the potential to cause dermal sensitization, they can be formulated into consumer products at safe levels. This is also the case for fragrance ingredients.

IFRA provides the fragrance industry with risk management strategies on the use of fragrance ingredients includ-

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0273-2300/$ - see front matter © 2008 Published by Elsevier Inc.
doi:10.1016/j.yrtph.2007.10.008

ing those ingredients identified as contact allergens. Historically they achieved this through the establishment of Standards based on no-effect concentrations and translated these as maximum limits that were applied equally to all types of skin contact products with different limits only for non-contact products.

More recently, significant developments have been incorporated in the way dermal sensitization risk assessments are conducted for fragrance ingredients (Gerberick et al., 2001). The general toxicological principles of quantitative risk assessment can be applied here, since it is known that the induction of dermal sensitization is also a threshold based phenomenon (Kimber et al., 1999; Robinson et al., 2000). With this and based on an understanding of the chemical, cellular, and molecular principles of dermal sensitization, it is possible to conduct an exposure-based quantitative risk assessment (QRA) to determine safe use levels of fragrance ingredients in a variety of consumer product types.

This paper describes the principles of the approach for fragrance ingredients in consumer products and provides detailed review of all the areas and information used. There will be other publications that demonstrate the implementation by providing practical examples for individual fragrance ingredients.

1.1. Review of dermal sensitization risk assessment methodologies for recommendation of the QRA approach for fragrance ingredients

The safety assessment of chemicals that possess the ability to cause sensitization by skin contact have traditionally been done using an ad hoc comparative risk assessment technique (Robinson et al., 1989).

It is only recently that the principles of exposure-based risk assessment, as an extrapolation of quantitative risk assessment methods that are widely accepted in general toxicology, have also been applied to induction of skin sensitization. Several papers (Farage et al., 2003; Felter et al., 2002, 2003; Gerberick et al., 2001; Griem et al., 2003; Robinson et al., 2000) have been published supporting the use of alternative and potentially better quantitative risk assessment approaches.

For the purpose of this review, two key methods were considered in detail (Gerberick et al., 2001; Griem et al., 2003) in the evaluation of a common approach to risk assessment for fragrance ingredients that are contact allergens. Both methods are based on the same fundamental principles and have significant common elements that were used as a starting point to define the refined risk assessment methodology for fragrance ingredients based on the induction of dermal sensitization.

The key refinements that have been introduced in this paper are the establishment of known benchmarks [weight of evidence no expected sensitization induction level (NESIL)] and the determination of uncertainty factors (sensitization assessment factors). As with any risk assessment, exposure is an essential element of the risk assessment process. Elements addressed here are the appropriate dose metric and how to prioritize exposure data from different sources. All of these refinements are described in detail in this review and clear guidance is provided on their use within this dermal sensitization risk assessment approach.

1.1.1. QRA methodology for fragrance ingredients

It is implicit that the conduct of a dermal sensitization QRA is necessary only for those fragrance ingredients identified as dermal sensitizers. The skin sensitization QRA approach for fragrance ingredients follows the same four fundamental steps as identified for general toxicology risk assessment. These four steps are outlined below for dermal sensitization.

Hazard identification. This involves the use of experimental data to determine the skin sensitization potential of the fragrance ingredient. Typically this would involve a murine Local Lymph Node Assay (LLNA), but may also involve the use of other assays such as the guinea pig maximization test or Buehler guinea pig test. Criteria that are used to define a dermal sensitizer and a non-sensitizer have been published in ECETOC (2003).

Dose–response assessment or hazard quantification. The dose–response for induction of skin sensitization is typically determined in the first instance using animal assays such as the LLNA. Confirmatory human assays such as the Human Repeat Insult Patch Test (HRIPT) may also be subsequently conducted to provide substantiation of the NOEL. Relative skin permeability and integrity are also considered in this section.

Exposure assessment. Exposure to the fragrance ingredient is determined using habits and practice data for consumer product use and human parameters data.

Risk characterization. The data from the previous steps are used to determine an acceptable exposure level to a fragrance ingredient against which the real life consumer exposure to that fragrance ingredient in a specific product type can be compared. The acceptability or unacceptability of real life exposures can then be determined accordingly.

In developing a quantitative risk assessment method for skin sensitization of fragrance ingredients, based on the above recommended approach, some new terms have been adopted and are presented below. The new terms are ''No Expected Sensitizing Induction Level'' (NESIL) and ''Sensitization Assessment Factors'' (SAFs) that replace no observed effect level (NOEL) and uncertainty factors, respectively. These terms have been adopted to take into account unique elements of quantitative risk assessment for skin sensitization.

1.2. Hazard identification

1.2.1. Animal data

Historically, there are several animal models that have been used to determine the potential for a fragrance ingre-