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Assessment of the skin sensitising potency of the lower alkyl methacrylate esters

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ABSTRACT

There is continued interest in, and imperatives for, the classification of contact allergens according to their relative skin sensitising potency. However, achieving that end can prove problematic, not least when there is an apparent lack of concordance between experimental assessments of potency and the prevalence allergic contact dermatitis as judged by clinical experience. For the purpose of exploring this issue, and illustrating the important considerations that are required to reach sound judgements about potency categorisation, the lower alkyl methacrylate esters (LAM) have been employed here as a case study.

Although the sensitising potential of methyl methacrylate (MMA) has been reviewed previously, there is available new information that is relevant for assessment of skin sensitising potency. Moreover, for the purposes of this article, analyses have been extended to include also other LAM for which relevant data are available: ethyl methacrylate (EMA), n-butyl methacrylate (nBMA), isobutyl methacrylate (iBMA), and 2-ethylhexyl methacrylate (EHMA).

In addressing the skin sensitising activity of these chemicals and in drawing conclusions regarding relative potency, a number of sources of information has been considered, including estimates of potency derived from local lymph node assay (LLNA) data, the results of guinea pig assays, and data derived from *in silico* methods and from recently developed *in vitro* approaches. Moreover, clinical experience of skin sensitisation of humans by LAM has also been evaluated.

The conclusion drawn is that MMA and other LAM are contact allergens, but that none of these chemicals has any more than weak skin sensitising potency. We have also explored here the possible bases for this modest sensitising activity.

Finally, the nature of exposure to LAM has been reviewed briefly and on the basis of that information, together with an understanding of skin sensitising potency, a risk assessment has been prepared.

1. Introduction

It is now well established that contact allergens vary considerably (and by up to 5 orders of magnitude) with respect to their relative skin sensitising potency. As a result there has been considerable interest in the categorisation of chemical allergens with respect to potency (Kimber et al., 2001). However, although this is a legitimate aim, and a potentially very useful development, classification of chemical allergens in this way is not without problems. It is necessarily the case that relevant data should be available that provide a sound evidential basis for differential categorisation. However, it is appropriate, in addition, to distinguish carefully between potency and prevalence. That is, an important potential confounder is that there may be a lack of apparent concordance between estimates of potency derived from experimental assessment of skin sensitising activity and reports of prevalence of allergic contact dermatitis (ACD) that derive from clinical experience. To explore these issues, and to illustrate the important considerations that need to be addressed, the skin sensitising activity of methyl methacrylate (MMA) and other lower alkyl methacrylate esters (LAM) have been reviewed.

Methyl methacrylate is an α/β-unsaturated monomeric ester that is produced in relatively high volumes and used in a number of industrial applications and consumer products (ECETOC, 1995). This chemical forms part of a series of lower alkyl methacrylate esters (LAM) that includes as well as MMA, ethyl methacrylate (EMA), n-butyl methacrylate (nBMA), isobutyl methacrylate (iBMA) and 2-ethylhexyl methacrylate (EHMA). The chemical structures and key physico-chemical properties of the LAM considered in this

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article are provided in Table 1. The ability of MMA to cause allergic sensitisation has been considered previously. It is acknowledged that MMA has the potential to cause skin sensitisation resulting in ACD (Betts et al., 2006), but, although it is associated with respiratory irritation, the available evidence indicates that MMA fails to cause sensitisation of the respiratory tract and allergic asthma (Borak et al., 2011).

For purposes of this article the skin sensitising properties and potency of MMA will be reviewed using new and previously available data, and this analysis will be extended to embrace also a similar assessment of EMA, nBMA, iBMA and EHMA. For the purposes of exploring the assessment of potency for the purposes of classification, the LAM provide a relevant case study, not least – for example – because of the recent assessment of MMA by the American Conference of Government Industrial Hygienists (ACGIH). In 2013 the ACGIH published a draft notice of change that identified MMA as a potent skin sensitiser (ACGIH, 2013). Although, on the basis of further review, that assessment was rescinded, the original proposal does serve to illustrate the potential difficulties in deriving accurate assessments of skin sensitising potential when there are apparently inconsistent data available.

1.1. Skin sensitisation and allergic contact dermatitis: the importance of potency, hazard characterisation and risk assessment

Skin sensitisation resulting in allergic contact dermatitis is the most common manifestation of immunotoxicity in humans, and an important occupational health issue. In fact, there are many hundreds of chemicals that have been identified as having skin sensitisation potential sufficient to cause ACD (De Groot, 2008). Considerable progress has been made in developing a more detailed, but as yet incomplete, understanding of the cellular and molecular events that result in the acquisition and orchestration of skin sensitisation, and in the elicitation of ACD (Martin et al., 2011; Kaplan et al., 2012; Kimber et al., 2012; Ainscough et al., 2013). That increased understanding of the immunological and biochemical processes that cause skin sensitisation have, in turn, paved the way to improved methods for toxicological evaluation (Kimber et al., 2011). Naturally, the development of accurate risk assessments requires, in addition to effective hazard characterisation, a clear appreciation of likely considerations of exposure. The importance of exposure considerations in the context of LAM is explored later in this review.

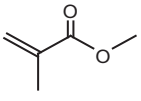
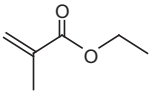
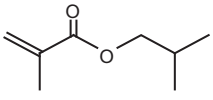
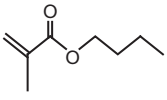
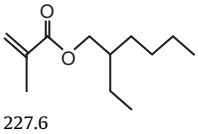
The initial approach to the identification of skin sensitisation hazards made use of guinea pig test methods in which activity was measured as a function of visual assessment of challenge-induced skin reactions in animals exposed previously to the test chemical. The guinea pig tests most thoroughly evaluated and most commonly used were the guinea pig maximisation test (GPMT) and the occluded patch test (Magnusson and Kligman, 1969; Buehler, 1965). These methods served the toxicology community well, but were subject to a variety of limitations, not least of which was the lack of an objective measure of sensitising potential. In an attempt to address some of those limitations the mouse local lymph node assay (LLNA) was developed in which skin sensitising chemicals are identified by their ability to provoke lymphocyte proliferative responses in lymph nodes draining the site of topical exposure to the test material (Kimber and Weisenberger, 1989; Kimber et al., 1989). The LLNA was evaluated extensively and was the subject of formal validation exercises. It is currently the preferred method for the identification of contact allergens and has been used extensively for this purpose. A detailed consideration of the LLNA is beyond the scope of this article, but there are several reviews available that document the development, validation, acceptance and practical application of this method (Kimber et al., 1994, 2002; Basketter et al., 2002; McGarry, 2007). Experience has shown that the LLNA provides a generally accurate and reliable way of identifying skin sensitisation hazards, and compared with the guinea pig tests that it largely superseded, offers a number of important advantages.

However, reliable hazard identification is only the first step in the toxicological evaluation of skin sensitisation potential. Although considerations of potency are germane for all classes of toxicants, this is of particular relevance for contact allergens that are known to differ by up to 5 orders of magnitude with respect to their relative skin sensitisation potency (Kimber et al., 2001).

Skin sensitisation potency is best defined in terms of the amount of chemical that is required to cause the acquisition of sensitisation; the more potent the chemical allergen the smaller will be the threshold exposure concentration required to induce skin sensitisation. Although, in some instances it is possible to derive estimates of sensitising potency from the results of guinea pig assays, this is not always the case since such methods are not normally configured to allow characterisation of dose–response relationships during the induction phase of skin sensitisation (Kimber et al., 2001).

In contrast, the LLNA has proven useful for characterisation of the relative potency of contact allergens. This is due to the fact that the end point used in the LLNA (proliferative responses by draining lymph node cells [LNC] provoked by local topical exposure to a contact allergen) is both causally and quantitatively related to the effectiveness with which skin sensitisation will be acquired (Kimber and Dearman, 1991; Kimber et al., 1999, 2012). The central event in the acquisition of skin sensitisation is the activation and clonal expansion of allergen responsive T lymphocytes within lymph nodes draining the site of exposure to the chemical allergen. Evaluation of proliferation by draining LNC induced by exposure to chemical provides a convenient measure of this, and thereby of the vigour and potency of the response (Kimber and Dearman, 1991; Kimber et al., 1999, 2012).

Table 1
Chemical structures and key physico chemical properties.

CAS no.	80-62-6	97-63-2	97-86-9	97-88-1	688-84-6
Chemical name	Methyl methacrylate (MMA)	Ethyl methacrylate (EMA)	Iso-butyl methacrylate (i-BMA)	n-Butyl methacrylate (n-BMA)	2-Ethylhexyl methacrylate (2-EHMA)
Structural formula					
Boiling point (°C)	100.36	118.2	163	155	227.6
Vapour pressure (hPa at 20 °C)	37	20	2.1	2.1	0.065
Water solubility (g/l @ 20 °C)	15.3	4.69	0.36 (25 °C)	0.47	0.003
Partition coefficient n-octanol/water (log value)	1.38	1.87	3.0	2.95	4.95