

Editorial

Risk assessment failures of chemicals commonly used in consumer products

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The choice between a diversity of consumer products is a characteristic of the modern life style and for the well-being of the population. The development of consumer products correlates closely with the development of human culture. With increasing sophistication of the products and industrialized mass production during the last century, a multitude of new chemicals have been introduced on the mass market that come into intensive contact with human skin.

Skin contact with low molecular weight, either natural or man-made chemicals may lead to contact sensitization and allergic contact dermatitis. The main risk factors for induction and elicitation of allergic contact dermatitis are the inherent sensitizing potential of a chemical and the skin exposure concentration (dose per unit area), skin barrier function, presence of penetration-enhancing factors, and time. Genetic factors have some significance for the risk of contact sensitization but are not as clearly documented.

Industry has made efforts to develop methods to predict the skin sensitization potential of new chemicals (1). The efforts have undoubtedly had a major impact on excluding a number of contact sensitizing chemicals from consumer products or making them appear in restricted concentrations. Notwithstanding this apparent success, industry's risk assessment of preservatives used in consumer products, particularly cosmetics, represents a long list of failures, starting with formaldehyde, formaldehyde releasers, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and methyldibromoglutaronitrile. However, preservatives that can prevent growth of microorganisms are chemically reactive and thus often relatively allergenic chemicals.

The paper in this issue of *Contact Dermatitis* by Wilkinson et al., based on patch testing of more than 80,000 patients over a decade, illustrates the

problem with the present risk assessment procedure. For the 'old preservatives' a certain stable level in the frequency of contact allergy seems to develop. But even a patch test frequency of 1–2% may represent 100,000 new cases of contact dermatitis diagnosed by EU dermatologists. Such data only represents the tip of the iceberg and population-based incidence data on contact allergy indicates a much wider problem (2, 3). It is questionable whether a 1–2% sensitization rate among patch tested patients can be considered an acceptable level. The acceptance of such a level is probably not up to doctors/dermatologists to decide. The rise in frequency of contact allergy to methyldibromoglutaronitrile from 1990 to 2000 is worrying and questions the effectiveness of industry's risk assessment and risk management of cosmetic ingredients.

The introduction and legal adoption of methyldibromoglutaronitrile in cosmetic products and other consumer products, which has led to the current high frequency of contact allergy to methyldibromoglutaronitrile, was based on the following studies.

One of the established methods to identify contact allergens, the guinea pig maximization test (GPMT) failed in 11 studies to demonstrate an allergenic potential for methyldibromoglutaronitrile (4). Bruze et al. (5) could not demonstrate any sensitizing capacity of methyldibromoglutaronitrile but pointed out that there was a reason for re-evaluation if future patch testing in humans demonstrated a different sensitizing capacity. Our studies (6) showed 3/15 positive test animals compared to 0/15 controls. However, the difference was not statistically significant. In the same review (4) 7 human repeated insult patch tests (HRIPT) were reported negative.

However, in other animal models using multiple topical applications, i.e. the cumulative contact enhancement test (CCET) and the local lymph node assay (LLNA), a clear positive response was ob-

tained (6). It was suggested that multiple topical applications seem to be required to induce sensitization to methyldibromoglutaronitrile and may explain the positive outcome of the CCET and the LLNA, while the GPMT, with only 1 topical application, failed. The negative HRIPTs (4), however, do not support this explanation and alternatives should be looked for. This chemical is labile in biological systems in the presence of sulfhydryl groups and/or it might be a pro-hapten (6). On predictive testing in animal models an allergenic potential is sometimes indicated (hazard identification) but there are no clinical cases of dermatitis reported from this particular chemical. This disagreement is usually explained by a minimal or zero exposure in man, while exposure in the experimental animals is greatly exaggerated with injections and the use of adjuvant, and the method used is then claimed to be too sensitive. The opposite is rarely reported but an example often quoted is clonidine, where there is a vast experience of cases of contact allergy in man, while it was very hard to identify the drug as a contact allergen in animal models (7).

Further examples of risk assessment failures are represented by various fragrance constituents which had been classified as 'safe' based on predictive tests but turned out to be sensitizers in humans after regular use (8).

The risk assessment procedure can and should be improved. Understanding of the basic biology of induction and elicitation of allergic contact dermatitis has increased significantly in recent years. Understanding of the importance of dose/unit area both for sensitization and elicitation is important for the undertaking of risk assessment and risk management. Industry often refers to HRIPT (human repeated insult patch test) as clinical studies for sensitization risk (1). HRIPT is not a clinical study but represents a human experimental exposure model using a limited number of healthy volunteers. The panel differs significantly from those who develop allergic contact dermatitis from consumer products. Patch testing is usually performed with products 'as is' and not with appropriate/adequate concentrations of suspected ingredients. The value of HRIPT to predict clinical outcome parameters is limited. Based on the outcome of animal experiments, HRIPT studies, and exposure assessment, industry has developed a risk assessment strategy. This risk assessment, as illustrated in the section on exposure-based risk assessment in a recent paper (1), is based partly on theoretical considerations, and partly on experimental grounds. Evidence-based final risk assessment of the safety of consumer product chemicals needs to include human epidemiological data, diagnostic patch test data, and population-based studies.

Further, it needs to be based on experimental elicitation studies in patients sensitized by consumer products and the effect of avoiding exposure in clinical studies.

It is well documented that restriction of skin exposure to chemicals is a feasible and extremely effective way to prevent allergic contact dermatitis, as illustrated by the effect of reducing hexavalent chromium in cement and nickel release from metallic items designed to be in prolonged skin contact (9).

Therefore, in addition to ensuring improvement to premarket risk assessment, it is also necessary to start both an academic and a political process to improve the current risk assessment and risk management procedure for evaluation of ingredients in cosmetic products. Contact sensitizing chemicals or new chemicals introduced in cosmetics should not be permanently approved until a sufficient database on human clinical endpoint parameters for the final risk assessment and risk management has been established.

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