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Risk Assessment of residual monomer migrating from acrylic polymers and causing Allergic Contact Dermatitis during normal handling and use

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ABSTRACT

Acrylic, Poly Methyl Methacrylate (PMMA) based polymers are found in many industrial, professional and consumer products and are of low toxicity, but do contain very low levels of residual monomers and process chemicals that can leach out during handling and use. Methyl Methacrylate, the principle monomer is of low toxicity, but is a recognized weak skin sensitizer. The risk of induction of contact allergy in consumers was determined using a method based upon the Exposure-based Quantitative Risk Assessment approach developed for fragrance ingredients. The No Expected Sensitization Induction Level (NESIL) was based on the threshold to induction of sensitization (EC3) in the Local Lymph Node Assay (LLNA) since no Human Repeat Insult Patch Test (HRIPT) data were available. Categorical estimation of Consumer Exposure Level was substituted with a worst case assumption based upon the quantitative determination of MMA monomer migration into simulants. Application of default and Chemical-Specific Adjustment Factors results in a Risk Characterization Ratio (RCR) of 10,000 and a high Margin of Safety for induction of Allergic Contact Dermatitis (ACD) in consumers handling polymers under conservative exposure conditions. Although there are no data available to derive a RCR for elicitation of ACD it is likely to be lower than that for induction.

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1. Introduction

Plastics play an important role in every aspect of modern life from health and well-being, nutrition, accommodation and transportation to safety and security, communication, leisure activities and innovation. Plastics are involved in every phase of food production, storage and preparation and regulations have been established to control the substances used in their manufacture

and/or levels of harmful substances that can migrate from them. In most other areas of application restrictive regulation has not been considered necessary to date and it remains the responsibility of the manufacturer/supplier to ensure safety in use.

Poly Methyl Methacrylate (PMMA) is a high production volume plastic with a global market of almost 3 million tons in 2011 (CEH, 2012). Although the majority of Methyl Methacrylate (MMA) monomer production is used by industry to manufacture acrylic based polymers (acrylic sheeting, moulding compounds, surface coatings, acrylic latexes (emulsions), lacquers, enamels, resins impact modifiers and processing aids) some finds its way into professional or skilled trade applications, such as the construction, dental and medical industries (MPA, 2013). While residual level of monomers in acrylic polymers is typically regulated according their intended end-use such as food contact, dental, medical etc., there are many other types of acrylic-based polymers handled by consumers in everyday life in the form of finished articles, coatings etc., and therefore there is potential for more widespread consumer dermal exposure.

In studies in animals, MMA is of low acute toxicity by all routes. It is a skin and respiratory irritant but only a weak irritant to the eyes. MMA is a weak skin sensitizer, but there is no convincing evidence that it is a respiratory sensitizer in humans (Borak et al.,

Abbreviations: ACD, Allergic Contact Dermatitis; AEL, Acceptable Exposure Level; AF, assessment factor; AOO, acetone-olive oil; CEE, categorical exposure estimate; CEL, Consumer Exposure Level; CES, carboxylesterases; CSAF, Chemical-Specific Adjustment Factors; DDEF, Data Derived Extrapolation Factors; EC3, effect concentration 3%; EF, Extrapolation Factor; HRIPT, Human Repeat Insult Patch Test; HMT, Human Maximization Test; LLNA, Local Lymph Node Assay; MHC, major histocompatibility complex; MMA, Methyl Methacrylate; MOS, Margin of Safety; NESIL, No Expected Sensitization Induction Level; NOEL, no-observed effect level; OECD, Organisation for Economic Cooperation and Development; PMMA, Poly Methyl Methacrylate; POD, Point of Departure; REACH, registration evaluation assessment of chemicals; RCR, Risk Characterisation Ratio; QRA, Quantitative Risk Assessment; SAF, Sensitization Assessment Factor; WHO, World Health Organisation; WoE, Weight of Evidence.

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2011). In repeat dose studies in rodents, general signs of toxicity were noted at high doses including degenerative and necrotic lesions in liver, kidney, brain, and atrophic changes in spleen and bone marrow. MMA is clastogenic at high doses *in vitro* with strong toxic effects but this potential is not expressed *in vivo*, and there is no relevant concern for carcinogenicity in humans and animals. It has no effect on developmental toxicity, teratogenicity, embryotoxicity or fetotoxicity (OECD, 2007). In terms of safeguarding consumer health from residual MMA monomer migrating from acrylic polymers, the potential to cause Allergic Contact Dermatitis (ACD) during the handling of acrylic-based polymer products is the lead health effect of potential concern.

2. Objectives

Exposure-based Quantitative Risk Assessment (QRA) of fragrance ingredients present in consumer products and known to cause ACD has been described previously (Api et al., 2008) and although QRA of food additives, or substances migrating from plastics in contact with food, is well established both at national and international levels (e.g., FDA, 1977; EU, 2012); to our knowledge the QRA of substances migrating from polymers and causing ACD during consumer handling of polymer products has not been reported.

The key steps in the Exposure-based QRA of fragrance ingredients include the determination of benchmarks (No Expected Sensitization Induction Level or NESIL); the application of Sensitization Assessment Factors (SAF); and the estimation of Consumer Exposure Levels (CEL) associated with product use. This paper describes the application of a comparable approach to that developed for fragrances to address very low levels of allergenic monomers potentially migrating from acrylic polymers during handling by consumers.

3. Mode of Action of MMA in the development of Allergic Contact Dermatitis

The general processes that result in the development of sensitization comprises as key events the penetration into the skin of the (pro)haptens and potential interaction with activating/deactivating enzymes, reaction of haptens with skin protein to form antigen, antigen encounter and recognition, antigen processing and transport, and antigen presentation (IPCS, 2012).

MMA is a low molecular weight (100.12 g/mol) organic chemical that is readily absorbed through the skin giving it ready access into the viable layers of the epidermis (CEFIC, 1993; Betts et al., 2006). MMA itself is unlikely to be a complete antigen due to its low molecular weight. The metabolic fate of MMA has been established (Bratt and Hathway, 1977) and since the intact esters can conjugate via vinylogous additive reactions, metabolic activation is not thought to be required for MMA to become antigenic. Skin however is rich in carboxylesterases (CES) and has been shown to be a significant site for local metabolism of topically applied chemicals (Imai et al., 2013). Since the first step of MMA metabolism is hydrolysis of the ester bond by non-specific CES to form methacrylic acid and methanol, neither of which is a recognized contact sensitizer, metabolism is likely to be the mechanism of detoxification following dermal exposure (Jones, 2002). MMA, like other acrylic and methacrylic esters, is a Michael acceptor electrophile and as such is capable of reaction with tissue nucleophiles via Michael addition on the electrophilic C_β of the α,β-unsaturated carboxyl group (Freidig et al., 1999; Greim et al., 1995; McCarthy et al., 1994). MMA is likely therefore to form covalent adducts with carrier proteins, that can subsequently be recognized as antigenic hapten-protein complexes (Natsch and Emter, 2008; Roberts et al., 2008; Roberts and Aptula, 2008; Smith and Hotchkiss, 2001; OECD, 2012).

4. Summary of contact allergy data on MMA

Numerous *in vivo* animal studies have been performed to characterize the potential of MMA to cause skin sensitization.

There have been a large number of contact allergy tests in MMA in animals reported in the literature including 12 Maximization tests, 2 Buehler tests, 2 Freund's complete adjuvant tests, 2 Split adjuvant tests, 4 Polak tests and one Draize in guinea pigs; as well as 2 ear sensitization tests and 3 Local Lymph Node Assays (LLNAs) in mice. These have collectively been described by ECETOC (1995) and Borak et al. (2011). In a representative Guinea Pig Maximization Test (GPMT), using an intradermal induction concentration of 5% Methyl Methacrylate, topical induction with 100% and challenge with 1% and 5%, showed a 10% and a 50% positive sensitisation rate, respectively (Cavelier et al., 1981). Results from other Maximization tests showed positive reactions for 50–100% MMA as well as non-sensitising responses. The reported negative results appear to be mainly due to lower MMA concentration or volatile vehicles being used. Non-adjuvant tests gave negative responses.

Three LLNAs have been reported with MMA. In an early version of the LLNA, MMA caused no increase in proliferation of lymphocytes in the draining lymph nodes of guinea pigs after topical application of MMA in acetone-olive oil (AOO) when measured by a microscopic cell-counting method (Bull et al., 1985). More recently, Betts et al. tested MMA in CBA/Ca mice using a method consistent with OECD guideline 429 (OECD, 2002). In one test MMA was dissolved in acetone, and in the other MMA was dissolved in an AOO mixture. MMA was weakly positive in both assays, with EC3 values of 60% (w/v) and 90% (w/v), respectively (Betts, 2004; Betts et al., 2006).

There are multiple case reports of contact allergy to MMA in certain occupational environments (orthopaedic surgeons, dentists and dental technicians and skilled trades using sealants) where frequent and prolonged unprotected skin contact with monomer containing preparations could occur. Single cases were also reported in some medical, dental and cosmetic applications (EU RAR, 2002; OECD, 2007). A critical review of the available literature indicated that repeated exposure to undiluted MMA may lead to skin sensitisation in susceptible persons but that the prevalence is relatively low and cross reactivity to other methacrylates, reactions to impurities, stabilizers, etc. may contribute. No clinical studies equivalent to the Human Repeat Insult Patch Test (HRIPT) have been reported with MMA so the dose–response or No Observed Effect Level (NOEL) for induction of skin sensitization in humans has not been established.

5. The approach

Historically, regulatory assessment of skin sensitisation has exclusively been aimed at the qualitative identification of a substance as an allergen, with the end result being classification either as a sensitizer or non-sensitizer.

More recently, it has been established that the induction as well as elicitation of dermal sensitisation is a threshold phenomenon (Kimber et al., 1999; Robinson et al., 2000). This, in principle, enables a quantitative approach for the Risk Assessment (QRA). Such an approach has been developed for fragrance ingredients in consumer products, but can also be applied to other substances.

The first step in the QRA is the determination of the benchmark (No Expected Sensitization Induction Level or NESIL) as described initially for fragrance ingredients (Api et al., 2008) and critically reviewed by National Institute for Public Health and the Environment (ten Burg et al., 2010) and the WHO (IPCS, 2012).

Ideally, a NESIL would be based on a HRIPT tests done in classical design using several different induction doses and thus being

appropriate for determination of a dose–response curve and a No-Observed Effect Level (NOEL). This however is not available for MMA and conducting such a study is not justifiable for a recognized contact allergen on ethical grounds.

Despite there being numerous guinea pig tests with MMA, methods such as the Buehler Assay or the Guinea Pig Maximisation Test (GPMT) provide relatively poor information with regard to sensitisation potency since they do not incorporate a dose–response analysis, and activity is measured as frequency of responses rather than as severity of responses (Basketter et al., 1996, 2005a; Loveren et al., 2008). Therefore these data will not be used for establishing a Point of Departure (PoD) for the QRA. The data will be used, however, in a Weight of Evidence (WoE) approach together with the available human data for MMA to inform on the consistency of the database and on the potency of MMA in humans and hence the reliability of the PoD.

There are 2 reliable LLNAs available for MMA, each using a different vehicle and with at least 3 different doses sufficient to provide a dose–response curve for induction of sensitisation and the determination of an EC3 value, the effective concentration of a chemical leading to a 3-fold increase in proliferation of lymph node cells compared to non-exposed controls (Basketter et al., 1999). Therefore we will use the EC3 values from these studies as the PoD for deriving the NESIL for MMA. Differences between in exposure conditions and the way in which animals and humans respond will be accounted for by using Sensitisation Assessment Factors (SAFs) as detailed below.

6. The Point of Departure (PoD) for MMA

As described above, MMA was weakly positive in both Local Lymph Node Assays, with EC3 values of 90% (w/v) and 60% (w/v), respectively (Betts, 2004; Betts et al., 2006). Since it is the dose per unit area of a chemical that determines the level of sensitisation (Friedmann et al., 1983), these EC3 values have to be recalculated as dose per unit (skin) area in $\mu\text{g}/\text{cm}^2$.

An estimate of the amount applied in a single application during epidermal induction can be made based on the following assumptions: mouse ear assumed to be 1 cm^2 area; volume used in the studies by Betts and in the guideline LLNA is 25 μL (Garcia et al., 2010; OECD, 2002).

Assuming the density of the liquid is 1, a conversion factor to be applied to the EC3 (%) of 250 is calculated by converting 25 $\mu\text{L}/\text{cm}^2$ into $\mu\text{g}/\text{cm}^2$. The EC3 (%) is then converted to EC3 ($\mu\text{g}/\text{cm}^2$) as shown in the formula below:

$$\text{EC3}[\%] * 250[\mu\text{g}/\text{cm}^2\%] = \text{EC3}[\mu\text{g}/\text{cm}^2]$$

For EC3 values of 90% (w/v) and 60% (w/v), respectively this results in an EC3 of $2.25 \times 10^4 \mu\text{g}/\text{cm}^2$ and $1.5 \times 10^4 \mu\text{g}/\text{cm}^2$.

7. Data extrapolation: Sensitization Assessment Factors (SAFs)

In line with established procedures for other areas of toxicological Risk Assessment such as non-cancer endpoints, the use of uncertainty factors is also accepted in immunotoxicity Risk Assessment. The overall factors are based on various subfactors depending on the regulatory framework and/or the scope and purpose of the Risk Assessment. Uncertainty factors applied to hypersensitivity generally include interspecies, intraspecies, matrix, use and duration/frequency factors and may include database uncertainty factors (IPCS, 2012). Although very conservative generally applicable values for the individual factors exist, in order to prevent over-conservatism by combining various subfactors, chemical specific numerical values for each factor (generally ranging from 0.1 to 10) have to be derived on a case-by-case basis.

7.1. Reliability of the POD

MMA has been shown to be a “weak” skin sensitizer in two independent OECD guideline 429 Local Lymph Node Assays (LLNA) in CBA/Ca mice requiring 60% (w/v) MMA monomer in acetone or 90% (w/v) MMA monomer in AOO (acetone: olive oil vehicle in a 4:1 ratio) to give a positive allergenic response in the mouse (Betts et al., 2006).

The LLNA study (Betts et al., 2006) has been conducted equivalent to an OECD Guideline 429 study (Skin Sensitisation: Local Lymph Node Assay) as described by Kimber and Basketter, 1992. Although there was no information on compliance with GLP, the publication gives a thorough and detailed documentation of materials, methods and results from which the study can be judged as being reliable without restrictions. Concerning the dose response relationship, exceeding the minimum requirements of the most recent version of the OECD guideline 429, 5 concentrations have been tested and the two tests conducted with two different vehicles gave results that were in the same order of magnitude. When using a semi-quantitative approach, both results would lead to classification of MMA as a weak sensitizer.

The negative result obtained in the earlier study by Bull et al. is consistent with the findings of Betts and co-workers if one takes into account that the microscopic cell-counting method employed is less sensitive than the ^3H TdR incorporation method and the level of stimulation observed by Betts only doubled the EC3 cut-off with acetone (7.3%), and barely exceeded it in the case of AOO (3.6%). Overall it may be concluded that the data in the LLNA are internally consistent.

For the LLNA, it has been proposed that a vehicle-based mean EC3 value can be used to derive a NESIL (Api et al., 2008). Use of a vehicle-weighted mean, rather than the lowest EC value, could be justified, because LLNA EC3 values, when tested repeatedly, tend to vary within a factor of 2–3 from the mean value, and the variability of the EC3 value caused by different vehicles leads to uncertainty in the Risk Assessment that is taken into account in setting the matrix assessment factor (IPCS, 2012). By giving preference to the study with the lowest EC3 value we ensure a high level of conservatism is maintained.

The other available contact allergy data on MMA although unsuitable for deriving a NESIL can be used in a weight-of-evidence approach to inform on the reliability of the POD.

In terms of the available test data in the guinea pig, MMA has showed some positive reactions following induction with 50–100% monomer in Maximization tests with typically negative results at lower concentrations when non-Maximization protocols were used. Overall this is indicative of a weak sensitizing potential that is consistent with the EC3 value determined in the LLNA.

The available clinical data appear inconsistent at first glance with some papers reporting a high prevalence of ACD in some medical, dental and cosmetic applications (EU RAR, 2002; OECD, 2007). However, in-depth review of these reports reveals a relatively low overall prevalence in exposed individuals handling the liquid monomer (Betts et al., 2006).

Altogether the data in animals and humans are consistent in indicating a weak sensitizing potential for MMA and point to a high level of confidence in the POD. Thus for the reliability of the POD an assessment factor of 1 is considered appropriate.

7.2. Assessment factors to address uncertainties in inter- and intra-species variability

There has been a long-standing practice of using default assessment factors to address uncertainties in inter- and intra-species extrapolation in human health Risk Assessments with the application of a total AF of 100 to the NOAEL observed in animal

experiments to calculate a safe dose for the general population (Renwick, 1991, 1993; Renwick and Lazarus, 1998; U.S. EPA, 1988, 1993). In the last two decades there has been the development of Data Derived Extrapolation Factors (DDEF) by the World Health Organization (WHO) in 1994 and their guidance on the development of Chemical-Specific Adjustment Factors (CSAFs) in 2005. More recently there has been the release of the European Chemicals Bureau's Technical Guidance Document for Risk Assessment (ECB, 2003); the European Chemicals Agency's Guidance on information requirements and chemical safety assessment (ECHA, 2012) and U.S. EPA's drafting of guidance for applying quantitative data to develop data-derived extrapolation factors for interspecies and intraspecies extrapolation (US EPA, 2011).

In context with this shift in paradigm we have endeavored to develop chemical-specific assessment factors to address uncertainties in inter- and intra-species variability.

7.2.1. Inter-species response variability

An interspecies uncertainty factor of 1 is conventionally applied when the POD is derived from human data – for example, HRIPT results for induction of skin sensitization. Using dose response information from an LLNA for derivation of the NESIL differences in sensitivity between mice and humans will have to be taken into account by using appropriate inter-species SAF.

For systemic toxicity (non-cancer endpoints) historically an assessment factor of 10 has been used to extrapolate from laboratory animals to humans (Renwick and Lazarus, 1998; WHO, 1994). However, it is generally accepted that this only applies to the extrapolation from rats to humans as it is comprised of two sub-factors, a factor of 4 to account for toxicokinetics (basically allometric scaling between the rat and humans) and a further 2.5, mainly for toxicodynamics (Renwick, 1991, 1993). For extrapolation from the mouse to humans an allometric scaling factor of 7 would apply (ECETOC, 2005). In contrast, for local toxicity endpoints such as skin irritation, no assessment factor was typically applied (ECB, 2003; ECETOC, 2003, 2005).

For contact sensitisation, when using mouse LLNA data, a somewhat different approach is proposed:

Systemic toxicokinetic differences (e.g., allometric differences) are not considered to play an important role in the development of ACD since access of topically applied MMA to the target tissue (the skin) does not involve systemic circulation, and due to the short half-life of MMA within the body, it is unlikely to survive long enough to be recirculated to the skin. However, local toxicokinetic differences, associated with differences in skin penetration, and toxicodynamic differences, associated with local metabolism, may be important.

With regard to skin penetration, there is no data on the relative permeability of mouse-ear and human palm skin to MMA. There is, however, *in vitro* data showing that separated human abdominal epidermis is 12.5 times less permeable than separated rat dorsal/flank epidermis to C_{14} radiolabelled MMA (453 ± 44.5 compared with 5688 ± 223 ; $\mu\text{g cm}^{-2}\text{h}^{-1} \pm \text{SEM}$; Jones, 2002) and the use of data generated in rodents as a surrogate for humans is generally considered conservative because the skin of mice and rats tend to show greater permeability to chemicals compared with that of humans, with a 3- to 10-fold higher penetration often being reported (Barber et al., 1992; Boogaard et al., 2000).

In term of comparative morphology there are obvious differences between mouse ear skin and human palm skin. Skin thickness in humans ranges from 521 μm (eyelid) to 1977 μm (back) with the palms (1394 μm) being on the upper end of this range, and comparable to that of the soles of the feet at 1565 μm (Lee and Hwang, 2002). Palm skin also has a higher proportion of epidermis than in other regions being comprised predominantly of stratum corneum, which is the principal barrier against hydro-

philic and lipophilic chemicals. In contrast the epidermal thickness of 1–9 month old NMRI mice was calculated to be between 10 and 15 μm (Kietzmann et al., 1990). Furthermore, the presence of hair follicles in mouse-ear skin, but in human-palm skin, might further enhance the penetration of lipophilic chemicals like MMA.

Although there is no specific data on the relative permeabilities of the two skin types to MMA, it appears highly unlikely that human skin will be more permeable than mouse-ear skin.

As described earlier, MMA undergoes local metabolism by tissue CES within the skin and this is likely to be the main mechanism of detoxification of dermally applied MMA. However, as non-specific CES are ubiquitous in both mouse and human skin (Jones, 2002) significant interspecies differences are not to be expected.

The biological process that takes place for the immune system to respond to sensitisers is considered a practically similar process across mammalian species and the mouse is considered a good model for contact allergy in humans. It has further been shown in a number of studies that mouse EC3 data when compared with human NOELs from HRIPT tests in general closely correlate. On this basis, the LLNA EC3 value has been suggested as a surrogate NOEL in QRA by different authors (Basketter et al., 2000, 2005b; Gerberick et al., 2001; Griem et al., 2003; Schneider and Akkan, 2004; Api et al., 2008) although there appears to be no consensus on the need for, or magnitude of, an assessment factor for intraspecies difference.

European Chemicals Agency (ECHA) guidance supporting registration of chemicals under REACH recognizes that EC3 data generally correlate well with human skin sensitisation thresholds derived from historical predictive testing; however they go on to state that cases exist where this correlation is poor with the two values differing by 10-fold or more. Therefore ECHA recommends use of a default SAF of ten for interspecies variation, unless there is evidence (e.g., from a close analogue) of good correlation between the EC3 and human NOAEL/LOAEL, in which case the interspecies AF could be lowered. Griem et al. (2003) evaluated a large data set of >30 different chemicals for which both human and LLNA-data was available and on the basis of comparable potency information proposed an Extrapolation Factor (EF) of 3. API and coworkers did not include a SAF for interspecies differences for fragrance ingredients (API et al., 2008).

On the basis that human palm skin is very likely to be less permeable than mouse ear skin and that metabolism is unlikely to be a moderating factor in the case of MMA, an interspecies Af of 1 is considered appropriate. The degree of confidence in this assessment is moderate to high, particularly bearing in mind that the lowest value from the LLNA data is used and additional testing in animals and available human data is supporting the very low potency.

7.2.2. Intra-species variability

This uncertainty factor is used to address the variability in responses between individuals and protect particular sensitive subpopulations such as children or elderly people.

Although it is now well understood that thresholds exist for both the induction and the elicitation of allergic responses, such as those of Allergic Contact Dermatitis, it must also be appreciated that for any given allergen, these thresholds are not absolute values (Basketter et al., 2002). Differences in individual sensitivity may be due to the condition of the skin at the site of contact or individual differences in skin metabolism as these are relevant factors which modulate the intradermal bioavailable dose of the allergen (Felter et al., 2002). Additional factors that might contribute to the inter-individual variation in sensitivity could be related to all individual molecular steps leading finally to the clinical

apparent contact dermatitis. These steps include in addition to skin bioavailability and metabolism, hapten formation (covalent binding to proteins), epidermal inflammation via keratinocyte cell signalling, dendritic cell activation and T cell proliferation as explained in detail in diverse reviews (Gerberick et al., 2008; Karlberg et al., 2008; Basketter and Kimber, 2010; Adler et al., 2011). It is usually assumed that a default assessment factor of 10 is sufficient to protect the larger part of the population, including e.g., children and the elderly. For systemic toxicity, the use of a default factor of 10 for the general population is currently suggested by regulatory agencies and expert groups (WHO, 2005; OECD, 2010; US EPA, 2011; ECHA, 2012).

A default value of 10 was also considered adequate to account for individual susceptibility differences for the induction of skin sensitisation (Felter et al., 2002, 2003).

The intraspecies uncertainty factor can be subdivided into toxicokinetic and toxicodynamic components. Furthermore, the default value may be replaced by CSAFs when chemical specific human toxicokinetic and toxicodynamic data are available.

In the case of MMA, we have to recognize that some information exists on skin permeability, metabolism and protein-reactivity that might suggest that toxicokinetic variability will likely be low. Overall there is insufficient data upon which to propose a CSAF and therefore the default AF of 10 is considered appropriate.

7.3. Matrix and differences in use pattern

This uncertainty factor is intended to account for differences in vehicle or product form (matrix) between experimental conditions used to determine the EC3/NOEL and real-life use situations. This approach has originally developed for fragrance substances that are usually formulated into a complex product matrix, which might contain irritants or penetration enhancers (API et al., 2008).

According to Api et al. there are three key parameters for consideration when extrapolating from the controlled experimental situation to the real life scenario. They are site of contact, dermal integrity, and occlusion.

The site of contact in the respective experimental setting (LLNA) is the mouse ear whereas the typical site of consumer contact with plastic articles is the palm of the hands. In the LLNA the mice were exposed topically on the dorsum of both ears to 25 μ l of various concentrations of MMA in acetone or in an acetone/olive oil vehicle daily for 3 consecutive days. Acetone disrupts the organization of the lipid bilayer by selectively removing lipids from intercellular lipid domains. Using acetone as a vehicle results in a substantial reduction of the barrier function of the skin and therefore enhance skin absorption for many substances (Tsai et al., 2001). In the other LLNA study a mixture of acetone olive oil was used as a vehicle. Olive oil has low volatility and would provide a lipophilic reservoir on the skin surface aiding partitioning of MMA into the stratum corneum and possibly retarding volatilisation. In contrast, consumer exposure would typically involve intimate contact between skin on the palms of the hands and the polymer product, perhaps in the presence of sweat, for periods of between several minutes to several hours. This combined with the previously established conclusion that human palm skin is likely to be considerably less permeable to MMA than mouse ear skin would indicate that the experimental scenario in the LLNA is conservative of human exposure and an overall factor of 1 is sufficiently conservative to account for differences in use pattern.

It is however, recognized that for the calculation of the consumer exposure, a 24 h continuous contact with no evaporation was assumed and that more realistically the contact with plastic products will be intermittent and of much shorter duration. Thus a factor of 1 will be extremely conservative.

8. Risk Assessment

Calculation of the risk quotient.

The two key elements for assessing the risk are the Acceptable Exposure Level (AEL) and the comparison of that AEL to the Consumer Exposure Level (CEL).

8.1. Consumer Exposure Level (CEL)

Acrylic PMMA (Poly Methyl Methacrylate)-based polymers are produced by industry using one of three free-radical initiation polymerization processes i.e. bulk polymerization, emulsion polymerization and solution polymerization (MPA, 2013).

Bulk or mass polymerization is the most common industrial polymerization process and includes the manufacture of both acrylic sheets and pellets (often referred to as resins). Cell cast acrylic (PMMA) sheets typically contains 0.05–0.3% residual monomer whereas extruded acrylic (PMMA) sheets contain 0.1–0.9% and are used in the form of articles in windows, lighting, security, safety, signage, retail displays and many other applications. Bulk polymerized polymers are also extruded into pellets and contain 0.1–0.9% residual monomer and are used by industrial processors in injection molding, compression molding and extrusion processes to make acrylic articles for lighting, displays, signage, optical and other applications.

Emulsion polymerized polymers contain 0.01–0.05% residual monomer and are supplied in the form of solid latex particles or liquid latexes or emulsions and used in the manufacture of water-based adhesives and paints, as well as coatings for paper and textiles.

Solution polymerized polymers typically contains 0.1–0.9% residual monomer and are supplied as a polymer pellet, or in solvent for the manufacture of varnishes, adhesives and coatings.

Although the handling of unprocessed acrylic sheets, polymer pellets, emulsions and solvent-based polymer solutions is typically restricted to industrial manufacturers and processors, some consumers potentially could have frequent and daily contact with end-processed and formulated acrylic polymers in the form of articles (kitchenware and utensils, reading glass lenses, LCD TV and mobile phone screens etc.), as coatings on household or personal items (paper and textiles etc.), or formulated into cleaning (polishes and waxes etc.) and Do-It-Yourself (water-based decorative paints and corks etc.) products.

While acrylic polymers typically will only represent a small portion of a formulated consumer product, in the case of solid acrylic articles and surface coatings the acrylic polymer is likely to represent the primary, if not only, surface that consumers will be contacting on a routine basis. As such consumer handling of acrylic articles and acrylic coated products and exposure to residual acrylic monomers migrating from these polymers could represent a significant contribution to overall consumer exposure.

Franz and Brandsch reported extensive kinetic studies on the migration of acrylic monomers (Methyl Acrylate, Ethyl Acrylate, Butyl Acrylate, Methyl Methacrylate and n-Butyl Methacrylate) from 11 representative acrylic polymers (produced by bulk (cast sheet and pellets) and emulsion polymerization processes) using CEN (European Committee for Standardization) methods for the testing of food contact materials (CEN, 2004). Migration into standardized simulants for saliva, sweat, aqueous foods, fatty foods and dry foods at 3 different temperatures (20 °C, 40 °C, 60 °C) was measured and the diffusion coefficients of the monomers in the polymer and the partition coefficients between polymer and contact media were determined. Migration of MMA and other acrylic monomers from acrylic materials used for rigid plastics applications (bulk polymerized polymers) was described as being

extremely low with migration from acrylic polymer resins used for coating applications (emulsion polymerized polymers) being somewhat higher, but still very low when compared with other typical polymers used for manufacture of food packaging materials. Specifically, migration of residual acrylic (including MMA) monomer from acrylic plaques into aqueous systems including saliva and sweat simulant, as well as the skin contact simulant Tenax[®], obeys Fickian laws of diffusion and was less than 15 µg/dm² (0.15 µg/cm²) over the first 24 h of contact at ≤40 °C (Franz and Brandsch, 2013).

Considering the wide variety of acrylic articles and formulated products available to consumers and the potential impact of different life-styles and activity patterns it was decided to assume 24 h continuous exposure as a worst case scenario for this assessment. Accordingly a Consumer Exposure Level (CEL) of 15 µg/dm² (0.15 µg/cm²) was established.

8.2. Acceptable Exposure Level (AEL)

The AEL is determined by dividing the Weight of Evidence (WoE) NESIL by the total SAF. Whereas the WoE NESIL was derived from the EC3 level derived from mouse LLNA as discussed above, the SAF_{total} is determined by the multiplication of all relevant individual SAFs. Individual SAF have been assigned for the quality of the database, for interspecies differences, for human inter-individual variability, for matrix effects and for use characteristics.

$$\text{SAF}_{\text{total}} = \text{SAF}_{\text{quality}} \times \text{SAF}_{\text{interspecies}} \times \text{SAF}_{\text{inter-individual}} \times \text{SAF}_{\text{matrix}} \times \text{SAF}_{\text{use}}$$

Skin sensitisation specific AFs		
SAF for quality of database	1	Reliable and well documented experimental data available
SAF for interspecies differences	1	EC3 derived from mouse LLNA
Inter-individual SAF	10	Default AF for general population
SAF for vehicle or matrix effects	1	Matrix/vehicle used during animal testing already reflects a worst-case situation
Use SAF	1	Skin contact with plastic products will likely be intermittent and of short duration
SAF total	10	

After calculation of the SAF_{total}, the AEL was calculated according to the following equation (Api et al., 2008):

$$\text{AEL} = \text{WoE NESIL} / \text{SAF}_{\text{total}}$$

WoE NESIL	1.5 × 10 ⁴ µg/cm ²
SAF total	10
AEL = NESIL/SAF	1.5 × 10 ⁴ /10
AEL	1500 µg/cm ² /day

The AEL is expressed in terms of dose/unit/day area. This Acceptable Exposure Level for human general population is then compared to the expected Consumer Exposure Level under normal conditions of use. In the originally developed QRA for fragrance ingredients for consumer products, the CEL (expressed as dose/unit area/day) is a measure of exposure under intended and foreseeable conditions

of use (but not abuse) and takes account of the frequency of use, habits, and practices (e.g., how consumers use the product), duration of use and amount of product used per application/use (Api et al., 2008). For MMA as discussed above, migration of residual acrylic (including MMA) monomer from acrylic plaques into diverse simulants including saliva and sweat simulant, was less than 0.15 µg/cm² over the first 24 h of contact at ≤40 °C (Franz and Brandsch, 2013). This measured value was taken as a worst-case for a scenario of 24 h continuous skin contact with polymerised plastic articles and thus also taking into account any possible aggregate exposure from the use of different products during the day. Additional factors that might possibly lower the exposure to human skin during use such as evaporation of MMA or rapid intradermal detoxification by CES as discussed above have not been taken into account for the Risk Assessment thus also ensuring the worst-case approach.

8.3. Risk Characterisation Ratio (RCR)

AEL	1500 µg/cm ² /day
CEL	0.15 µg/cm ² /day
RCR (AEL/CEL)	10,000

The Risk Characterisation Ratio (RCR) is derived by dividing the Acceptable Exposure Level (AEL) by the Consumer Exposure Level (CEL). The RCR of 10,000 indicates a high Margin of Safety i.e. the measured rate of MMA being leaching over a 24 h period is many times lower than the Acceptable Exposure Level despite the conservative nature of the exposure assessment.

9. Discussion

The ability of chemicals to cause Allergic Contact Dermatitis (ACD) is a common toxicological property of both naturally occurring and industrial manufactured substances and to illustrate this point more than 4000 environmental (natural and synthetic) chemicals have been identified as potential contact allergens (De Groot et al., 2008). This has to be appreciated in the context of an estimated 15–20% of the general population of Western Europe and North America suffering from contact allergy caused by one or more substance (Thyssen et al., 2007; Peiser et al., 2012).

Society has, therefore, perhaps to recognize that many of the conveniences considered necessary for modern life and that we routinely take for granted, come at a non-zero risk. Often that risk is very low-to-practically zero and does not require consideration, but on occasion that risk may not be considered acceptable. On the other hand, product de-selection on the basis of inherent hazard where there is no risk to health would deprive society of beneficial products. Many fragrance materials, both naturally occurring and man-made, are contact allergens and the fragrance and consumer product industry has refined Quantitative Risk Assessment (QRA) approaches tailored for the wide variety of personal care and consumer products on the market thereby ensuring appropriate risk/benefit considerations are taken before they are brought to market.

In the case of many polymer plastics that are not specifically regulated by end-use regulations or standards, there has perhaps been a general assumption that due to their high molecular weight and the fact that they are often in the form of articles, that they are safe. Certainly in the majority of cases this assumptions hold true, but despite this there has been concern over the safety of plastics and this has led to some calls for their restriction on the grounds of the inherent hazard of the monomers used in their manufacture

(Lithner et al., 2011). Since in the case of many polymeric substances it is the chemical reactivity of the monomers themselves that not only enable them to react and form polymers, but also react with biological tissues, their toxicological properties often go hand-in-hand with their utility to industry. It is important, therefore, to develop QRA approaches, such as that described in this paper, to reassure consumers and stakeholders that these products are indeed safe and their continued use is justified.

The approach adopted here is based upon that developed for fragrance materials. The two main adaptations are the inclusion of a quantitative exposure estimate, to account for the release of monomers from the polymer matrix, and the use of additional adjustment factors, to address reliability of the Point of Departure (PoD), and interspecies differences between mice and humans. Where possible we have developed Chemical-Specific Adjustment Factors (CSAFs) in-line with guidance on best practices.

In developing the approach we have consciously adopted a tiered process to the quantification of individual safety factors whereby very conservative assumptions were made during the first tier of assessment, with a view to refining these as and when necessary. As it turned out the Margin of Safety (MOS) at the first tier was so large that further refinement and the development of less conservative, more realistic, assessment factors was not necessary. It is envisaged, however, that this may not always be the case and that possibly in other situations some refinement of these assumptions may be required before an acceptable MOS can be achieved.

By applying an overall Sensitisation Assessment Factors (SAF) of 10 to the lowest EC3 value determined in a guideline LLNA study, an AEL of 1500 $\mu\text{g}/\text{cm}^2/\text{d}$ was derived.

In terms of the exposure assessment we recognized that it was extremely difficult to be precautionary but sufficiently realistic at the same time. This problem has already been recognized for consumer products with dispersive uses and for fragrance ingredients, such as citral, an exposure estimation mostly based on use categories is usually performed. Since we were aware of data indicating extremely low migration of monomer from polymers we decided to adopt a very conservative approach assuming extreme worst case. In this scenario consumer contact with the polymer article would be assumed to be continuous for 24 h, without loss by evaporation or metabolism by CES within the skin.

The exposure assessment was therefore taken as the measured amount of residual acrylic monomer migrating from acrylic polymer product into aqueous systems including saliva and sweat simulant, as well as the skin contact simulant Tenax[®], over 24 h i.e., 15 $\mu\text{g}/\text{cm}^2$. A more realistic use scenario for handling plastic products would perhaps be repeated exposures of much shorter duration throughout the day.

9.1. Risk characterization

The resulting Risk Characterization Ratio (RCR), or the Acceptable Exposure Level (AEL) divided by the Consumer Exposure Level (CEL), of 10,000 indicates a high Margin of Safety for the induction of contact allergy resulting from the handling of acrylic articles, despite the conservative nature of the exposure assessment. More realistically the RCR for consumer handling of acrylic articles may be many orders of magnitude higher than that this.

While this high RCR indicates a low concern for ACD developing during consumer handling of acrylic articles, it has to be recognized that the threshold to elicitation of contact allergy usually occurs at considerably lower levels than that for the induction of allergy (Felter et al., 2002). As the NOEL for elicitation is typically established in humans (IPCS, 2012) and this has not been established for MMA, the Margin of Safety will likely be lower for individuals that are already sensitized to MMA. Notwithstanding this,

the high Margin of Safety demonstrated for the induction of contact allergy combined with the conservative nature of the exposure assessment would suggest that the risk of elicitation during consumer handling of acrylic articles would also be low.

Conflict of interest

Dr. Pemberton reports personal fees from Methacrylate Producers Association, during the conduct of the study and from outside the submitted work. Dr. Lohmann reports personal fees from Methacrylate Producers Association, during the conduct of the study.

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