Regulatory Toxicology and Pharmacology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

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

Mark A. Pemberton [a,*], Barbara S. Lohmann [b]

[a] Systox Ltd, Wilmslow, Cheshire, UK
[b] CFCS-Consult GmbH, Essen, Germany

ARTICLE INFO

Article history:
Received 2 April 2014
Available online xxxx

Keywords:
Acrylic polymer
PMMA
Methyl Methacrylate
Residual monomer
Migration
Risk Assessment
Allergic Contact Dermatitis
Consumer exposure
Skin sensitization

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.

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.

* Corresponding author. Address: Systox Ltd, 84 Hazelwood Rd, Wilmslow, Cheshire, UK. Fax: +44 (0)1625 548059.
E-mail address: markpemberton@systox.com (M.A. Pemberton).

http://dx.doi.org/10.1016/j.yrtph.2014.05.013
0273-2300/

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)hapten and potential interaction with activating/deactivating enzymes, reaction of hapten 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

Please cite this article in press as: Pemberton, M.A., Lohmann, B.S. Risk Assessment of residual monomer migrating from acrylic polymers and causing Allergic Contact Dermatitis during normal handling and use. Regul. Toxicol. Pharmacol. (2014), http://dx.doi.org/10.1016/j.yrtph.2014.05.013