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June 5, 2013

Dr. Terry Gordon
Chair, ACGIH TLV Committee
1330 Kemper Meadow Drive
Cincinnati, Ohio 45240, USA

RE: 2013 Draft Documentation for Methyl Methacrylate (CAS 80-62-6)

Dear Dr. Gordon:

I am writing on behalf of the Methacrylate Producers Association, Inc. (MPA) regarding the proposed notations for Methyl Methacrylate (MMA). MPA's members are: Arkema Inc., Dow Chemical Company, Evonik Cyro LLC, and Lucite International.

The draft documentation for MMA is both comprehensive and a reasonably balanced reflection of the extensive literature that has been published to date on this chemical. Furthermore, the threshold limit values (TLVs) being proposed are consistent with values recently set by the European Union SCOEL (Scientific Committee on Occupational Exposure Limits) and the publication by Pemberton et al., 2013. In this regard, we express support for the draft documentation prepared by the Committee.

However, two statements have been made that are not supported by a wider evaluation of the literature. In our opinion, these statements could lead to misunderstanding by your intended audiences. We respectfully request that you reconsider these statements in light of the information provided below.

1) **The RSEN notation recommended for MMA is not justified based upon the available literature.**

While the draft documentation recognizes that "data supporting MMA as a pulmonary sensitizer are less unequivocal", it goes on to state that a RSEN notation is thought to be appropriate as a number of studies have identified a late asthmatic reaction following exposure, which would suggest more than a simple irritant response (citing Savonius et al, 1993; Pickering et al., 1986 and Seppalainen and Rajaniemi, 1984; Kennes et al., 1981).

In this regard, we would like to bring to the attention of the committee the recent publication by Borak et al., 2011. This exhaustive review of the literature on exposure to MMA and PMMA and respiratory effects, including asthma, addresses the papers cited by ACGIH. The main author of this publication is a Clinical Professor of Epidemiology & Public Health and Clinical Professor of Medicine at Yale University who is certified in Internal Medicine, Occupational Medicine, and Toxicology. This publication found sufficient scientific grounds to conclude that MMA is not causally related to the development of asthma. Rather, the effects reported in the literature are more consistent with primary irritation--in some cases possibly provoking pre-existing asthmatic conditions. Furthermore, this conclusion is consistent with several significant regulatory reviews on MMA including the following:

In January 2001, the OECD (Organization for Economic Co-operation and Development) completed its Screening Inventory Dataset (SIDS) Initial Assessment Report (SIAR) for MMA concluding that "There is no convincing evidence that methyl methacrylate is a respiratory sensitizer in humans." The review panel consisted of medical, toxicological and regulatory experts from the governmental agencies of the member OECD countries (Australia, Austria, Belgium, Canada, Czech republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Korea, Norway, Poland, Portugal, Slovak Republic, Spain, Sweden, Switzerland, The Netherlands, UK, USA) as well as from the European Commission, UNEP, and WHO.

In April 2001, the European Union finalized its Risk Assessment for MMA. This six-year risk assessment reviewed published and unpublished (company confidential) studies/reports on MMA, and in Chapter (section) 4.1.2.5 concluded that "no convincing evidence was found that MMA acts as a respiratory sensitiser in humans". The review panel consisted of the leading medical and toxicological experts of the Competent Authorities in the European Union as well as the World Health Organisation. The report was also reviewed and approved by an independent panel of International Peer Scientists/Professors/clinicians comprising the Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE). The review specifically addressed asthma and concludes: "The literature reports isolated cases of asthma in the context of MMA exposure. Substance-specific broncho-constriction or delayed asthmatic responses respectively were confirmed only in very few cases. Asthmatic reactions seem to be restricted to exposure levels which primarily result in respiratory tract irritation".

In 2002, Health Canada (HC) actually reversed the 1996 decision to classify MMA as a respiratory sensitizer (which required all products containing MMA, or MMA residues (polymers etc.); to be labelled "Contains a respiratory sensitizer"). This decision was based upon the conclusion that, "on balance, there is insufficient evidence at this time to regard MMA as a respiratory sensitizer". Accordingly HC has removed MMA from their list of known respiratory sensitizers.

From 2001 to 2004, an advisory committee for California OSHA considered whether to list several chemicals, including MMA, as airborne contaminants in the workplace and, if so, what should be permissible exposure limits. Minutes for the advisory committee meetings show that the committee reviewed whether the data indicated that MMA was a respiratory sensitizer. Ultimately, however, while sensitization was found to be a concern for other chemicals reviewed by the advisory committee, there was no such finding for MMA, as shown by the Initial Statement of Reasons for the proposed rule, now codified at 8 CCR 5155, Table AC.

Accordingly, we respectfully request that you reconsider your decision to add the RSEN notation for MMA since this is not justified based upon the available literature.

2) MMA should not be regarded as a "potent" skin sensitizer.

The draft documentation makes the conclusion that MMA is considered a "potent" skin sensitizer (citing Magnusson and Mobacken 1972a & 1972b and Samitz and Shumunes 1969). Of the available clinical literature, the three papers cited in the documentation are not informative in establishing that MMA is a potent sensitizer as summarized below.

Since it has been established that methacrylates cross-react in individuals sensitized to other methacrylates (Dempsey, 1982; Mathias et al., 1979; Fisher, 1980), it is not possible to conclude that the contact allergy observed in the first of the reports by Magnusson and Mobacken was caused by MMA. Specifically, the thread-locking fluid (threadlocker) involved in the clinical cases reported in 1972 are polyglycol dimethacrylate-based products and do not contain MMA. Dempsey (1982) demonstrated cross reactivity to MMA in individuals sensitized to these types of anaerobic sealants. Hence, although a positive challenge result was obtained with MMA the causative allergen was most certainly the dimethacrylate.

In the clinical cases involving Dycril printing plates also reported in 1972, the photocure acrylic monomer used in this product is a cross-linkable multifunctional (di/tri-vinyl type) acrylic monomer. Although the monomer is confidential and has not been identified to date (Morris and English, 2000; Livesley et al., 2002), it is likely that in the early years after product introduction it was Pentaerythreitol triacrylate (Davidson, 1993) and perhaps only more recently triethylene glycol diacrylate (Chanda and Roy, 2008). More significant, however, is the observation that the author reported negative challenge reactions with MMA and the four other acrylates studied concluding that "the allergen consisted of an acrylic monomer not known to us" i.e. not MMA. Hence, not only is MMA not a multifunctional monomer and therefore unsuitable for use in such applications, but also no cases of contact allergy to MMA were actually cited in the paper.

Finally, the third publication by Samitz and Shmunes (1969) is more of a general overview and does not cite any data on the prevalence of MMA induced contact allergy. Indeed, the authors describe the composition of self-curing resins only in general terms as "created by inducing polymerization in a mixture of MMA monomer and polymethyl methacrylate powder with an organic peroxide and an accelerator" and went on to cite Magnusson (1958) and his conclusion that "many cases of supposed methacrylate sensitivity were actually due to additives in dentures such as hydroquinone, benzoyl peroxide, dimethyl-p-toluidine and dyes". Hence, the publication by Samitz and Shmunes is far from persuasive that MMA is a potent sensitizer in humans.

We appreciate that the database on contact allergy due to MMA is extensive and somewhat conflicting. In general, MMA is confirmed as being a skin sensitizer in animals. In humans, MMA is a recognized contact allergen and contact dermatitis has been reported in workers that handle the liquid monomer, such as dental technicians. Cross reactivity to other methacrylates has also been reported.

However, the number of case studies reported in the literature is relatively small compared with the total number of individuals that work in these industries, leading to the conclusion that although MMA is a recognized skin sensitizer it is not a potent allergen.

In this regard, we respectfully draw to the attention of the committee the publication by Betts et al., (2006). Betts and co-workers reported studies on the potency of MMA to induce contact allergy in the Local Lymph Node Assay (LLNA) and reviewed prevalence data for published clinical studies on contact allergy due to MMA in humans (i.e. Rustemeyer and Frosch, 1996 (also as Peiler et al., 1996); Schnuch and Geier, 1994 and Kiec-Swierczynska, 1996). Based upon the low potency of MMA to induce allergy in the LLNA assay (greater than 60% MMA required to induce allergy) and in observing that there was a positive bias to inclusion of sensitized individuals in the test cohort used in these studies, thereby overstating actual prevalence, Betts and co-workers concluded that MMA "has only a relatively weak potential to cause the acquisition of skin sensitization". This conclusion is consistent with the findings of the registration of MMA under the REACH (Registration, Evaluation and Authorization of Chemicals) Regulation within the EU and the current classification of MMA under CLP and GHS.

Therefore, while we agree that a SEN notation is warranted, we respectfully request that you reconsider your decision to cite MMA as a "potent" skin sensitizer, since this is not supported by the available data.

Sincerely,

Elizabeth K. Hunt
Executive Director, MPA

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