IEPR Publication Draft Summary

The European Chemical Industry Council (Cefic) Methacrylates Sector Group (MSG) and the Methacrylate Producers Association, Inc. (MPA) commissioned a workshop in October 2021 during which an independent Expert Panel discussed the hazard assessment of chemicals as respiratory sensitisers illustrated through a case study on MMA. The conclusions reached by the Panel and the manuscript that followed solely reflect the discussion, views and conclusions of the panel members.

The Expert Panel recognised the quantity and complexity of the toxicological, clinical and other data available on MMA and felt that in the short time available to them that they could not make a final conclusion on whether or not MMA should be classified as a respiratory sensitiser. Nevertheless, the Expert Panel recognised it significant that *" in those sectors in which there are anticipated high exposures to MMA for long periods of time (e.g. cast acrylic sheets industry and floor coating sector; Section 3.2.1), there have been no reports of OA caused by MMA"* and that *"information from the published literature indicates that dental technicians and nail beauticians may be exposed to a wide range of dusts and (volatile) chemicals and thus to much lower levels of airborne MMA than workers in the cast acrylic sheets industry or floor coating sector. …These mixed exposures could explain why OA was seen in the dental sector, but not in the other sectors."* The "*overall low incidence of OA in populations that may be exposed to MMA (see above) and the evidence that MMA is a weak dermal sensitiser"* was considered by the Expert panel as potential justification *"that the irritant MoA may be the most important mechanism for the development of respiratory effects caused by MMA".*

In consideration of the complexity of the evidence on MMA, the Expert Panel was motivated to make general recommendations including specifically the "*need for a framework to increase the consistency, objectivity and transparency in the regulatory assessment of respiratory sensitisers and associated uncertainties*". In their view, such framework should contain of a "*formal documentation of the weight-of-evidence for hazard classification both at the level of integration of individual studies within lines of evidence and across a broad range of data streams was agreed to be critical for such a framework*". Also, they propose the integration of all relevant data into a "*weight-of-evidence protocol against pre-defined considerations*" and the use of modified Bradford Hill considerations to assess causality. Furthermore, that regulatory "*conclusions should be based on transparent weighting of relevant data on the observed prevalence of occupational asthma in various studies taking into account all relevant information including*

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the range and nature of workplace exposures to the substance of interest, co-exposure to other chemicals and study quality". In this regard Cefic MSG and MPA draw a parallel between these recommendation and the existing requirements of the CLP guidance for classification for respiratory sensitisation.

Optional:

Reflecting upon the data available for MMA, the Expert Panel identified further aspects for such a weight-of-evidence assessment that are of specific relevance for MMA:

- The "*interpretation of results of human case reports and epidemiological studies for assessment of individual chemicals is often complicated by co-exposures to complex mixtures*", especially when the "*specific composition of the applied products* [in SIC[1] tests] *was not disclosed*";
- "*fundamental knowledge gaps* [in the underlying science e.g. in regard to the timing of asthmatic responses] *complicate, then, the assessment of whether a substance causes the development of OA as opposed to the aggravation of pre-existing or coincidentally acquired asthma*.";
- "*human studies may provide some information on respiratory hypersensitivity,* [however] *the data are frequently limited*" (citation of ECHA (2017a) Endpoint-Specific Guidance and referring to SIC tests), as, for example*, "it is not known to which specific substances workers were exposed since substance characterisation may be difficult to undertake in the clinical setting*" and "*SIC tests do not enable decisions to be made on whether a positive response is more likely due to an immune reaction or to irritation*";
- "*reliable information on the frequency (incidence) of reported effects in exposed populations was an important element for the assessment"*
- *For "asthmatic responses* [that] *are observed upon exposure to high levels of a respiratory irritant, it cannot be excluded with confidence that the asthmatic response indicates causation and not merely provocation*".
- "*considerations on the concordance of dose-response relationships across different data sources and lines of evidence* [and industry sectors] *also support the evaluation whether the effects observed in (selected) case reports are causally linked to exposure to the substance of interest*." (linked to the ECHA (2017a) guidance statement that "…*where there is reliable (e.g. supported by*

[1] Specific Inhalation Challenge test

medical surveillance reports) evidence that a large cohort of subjects has had opportunity for regular significant inhalation exposure to a substance for a sustained period of time in the absence of respiratory symptoms, or related health complaints, then this will provide reassurance within a WoE approach regarding the absence of a respiratory sensitisation hazard".