

October 1, 2022

## General Comments

While we as **European Aliphatic Isocyanates Producers Association ALIPA** appreciate the opportunity to contribute to the classification and labelling procedure for 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (IPDI), we would like to emphasize our disagreement with the conclusion drawn by the Dossier submitter BAuA (Federal Institute for Occupational Safety and Health) regarding the endpoints skin corrosion, skin sensitization and the additional labelling as 'corrosive to the respiratory tract' (Specific target organ toxicity – single exposure).

## Comments on the open hazard classes:

### Acute toxicity:

We agree with the proposal of the dossier submitter (DS) to modify the classification from Acute Tox. 3 with H331 to Acute Tox. 1 with H330.

### Skin corrosion/irritation:

Regarding the Acute Dermal Irritation / Corrosion study OECD TG 404 (Hüls AG, 1984a). The report states that no further information is given in addition to the single sentence: "*Necrosis formation after an exposure time of 4 hours, but not after 3 minutes.*" and that neither in the experimental procedure nor in the results table a three-minute exposure and/or observation is further documented. We agree that this observation should be discussed in more detail in the text or displayed in the table. However, we do not agree that this sentence is not assignable. This short passage undoubtedly states that there has been an observation after 3 minutes without any findings in terms of necrosis. The absence of necrosis might be the reason for this poor documentation. Nevertheless, the poor documentation is no reason to leave the content out of consideration. A negative observation after 3 minutes excludes a classification as Skin corr. 1A, a differentiation between subcategories 1B and 1C is not possible due to missing reading after 1 hour.

Regarding the OECD 435 Corrositex™ study we acknowledge the deficiencies in the study design and study performance (strong corrosive substance as positive control rather than medium corrosive substance; precipitation in the chemical detection system (CDS) instead of color change; unclear differences in color change after use of confirmation reagent for the test- and reference substance). The study cannot be used stand alone for subcategorization of the substance. We just partly agree with the DS that the overall assessment of the study is not reliable. The study should be regarded as reliable with restrictions because the test substance obviously passed the barrier and reacted with the CDS by a precipitation reaction instead of the required color change. The substance did not lead to an effect on the CDS within 60 min, therefore the study at least contradicts a classification as a strong corrosive substance.

In general, we agree with the DS that *in vivo* data demonstrate that 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is corrosive to the skin and needs to be classified adequately. We also agree that Sub-Category 1A is not appropriate and the distinction between 1B/1C is not feasible due to the reading interval at that time.

However, a Category 1 without subcategorization corresponds to an over classification since other legislations may equal Category 1 with Subcategory 1A. Such classification may lead to strong restrictions, e.g., in transportation sector, which is not appropriate for IPDI since Subcategory 1A can be excluded. Facing the discrepancy between available (pre) CLP animal data and modern CLP hazard criteria and a poor applicability of in vitro methods with this substance we claim for a subcategorization. 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate should be classified as Corrosive Subcategory 1B (1A is not appropriate) taking precautionary principles into account instead of Category 1 without subcategorization.

**Serious eye damage/eye irritation:**

We agree with the proposal of the DS.

**Skin sensitization:**

We agree with the DS that the available results are clearly positive indicative of sensitizing properties of IPDI. However, we doubt that data are sufficient for a clear discrimination between subcategories. Available animal data is not in accordance with modern criteria for classification and data on experience with human has no information on exposure or a poor documentation.

The result of the Local Lymph Node Assay (LLNA; pre-guideline study with minor deviations from OECD 429 guideline) of IPDI, a known respiratory sensitizer with corrosive properties, point to a high potency (correlate to sub-category 1A). The LLNA reveals positive results for skin sensitizers but also for respiratory sensitizers and it cannot be conclusively evaluated whether the indicated potency directly relates to skin sensitization. Furthermore, the LLNA may be over-predictive for irritants as concluded by ICCVAM in its report of 2011 (NIH Publication No. 10-7512; <http://iccvam.niehs.nih.gov/methods/immunotox/LLNA-app/TMER.htm>): *“LLNA cannot be considered a stand-alone assay to determine skin sensitization potency categories. ... Among the 21 substances that produced a LLNA EC3 ≤ 2 %, 67 % (14/21) were correctly identified as strong sensitizers, but 33 % (7/21) were incorrectly overclassified as strong skin sensitizers based on available human test data.”*

The Guinea Pig Maximization Test (GPMT) and Buehler Test (BT) assays have been developed for the assessment of sensitization potential in terms of yes or no and not for determination of potency. Even though there are nowadays criteria defined in Annex I to Regulation (EC) No 1272/2008 (CLP), these values cannot have been considered in the study design and are thus less appropriate to distinguish between categories 1A and 1B. The DS stated that “The results of the guinea pig maximization test fulfil the criteria for classification to Sub-Category 1B. IPDI was not tested at ≤ 1 % intradermal induction dose in the guinea pig maximization test. Therefore, a classification for Sub-Category 1A cannot be excluded “. We agree with that conclusion but want to add that ECHAs Guidance on the Application of the CLP Criteria (2017) recommends applying Category 1 instead of a Category 1B in case a Category 1A cannot be excluded. This would be particularly important if only data from certain tests are available showing a high response after exposure to a high concentration, but lower concentrations have not been tested.

We acknowledge that the results from the Buehler test (epicutaneous, occlusive induction; 5 % (w/v) and epicutaneous, occlusive, challenge 1 % (w/v); 80 % animals showed positive response) are indicative for Sub-Category 1A.

Human data will normally take preference over animal data. The potency of a chemical can in some cases be evaluated by comparison of the incidence of skin sensitization in the human population with the exposure situation (see e.g., Schlede et al. 2003). Schlede et al. (2003) evaluated IPDI mainly based on the available human data to be a proven human sensitizer not with high but moderate frequency in humans. Geier and Schubert (2021)

concluded that IPDI is a highly reactive substance and generated results are doubtful due to instable patch test preparation.

Overall, as the data on potency of IPDI are limited and human and animal data are not fully consistent we conclude, that the available data currently do not allow a solid assessment of the potency. The DS already described the broad discrepancy between SCL based on the LLNA and based on the BT. Consequently, also a deviation of a specific concentration limit is doubtful.

According to Annex I to Regulation (EC) No 1272/2008 (CLP) paragraph 3.4.2.2.1.1 “skin sensitizers shall be classified in Category 1 where data are not sufficient for sub-categorization.”, we conclude a classification of IPDI in Category 1 of hazard class “skin sensitization” in combination with the generic concentration limit of  $\geq 1\%$  to be appropriate.

**Specific target organ toxicity – single exposure:**

We agree with the DS that based on the CLP regulation including the Guidance on CLP and the proposed classification as Skin Corr. Category 1 (or like we propose Skin Corr. Category 1B), Acute Tox. Category 1 for inhalation as well as Resp. Sens. Category 1, the Classification “STOT-SE” should be modified from Category 3 to “not classified” because classification STOT SE 3 is also implicit with the aforementioned classifications. However, we disagree with the DS regarding additional labelling as ‘corrosive to the respiratory tract’. In the acute inhalation toxicity study (Bayer, 1995) macroscopic examinations revealed that animals showed symptoms like nose/muzzle with red incrustations, mucous membrane of the nose with reddening, pleural cavity filled with liquid, lung less collapsed emphysematous, and spongy. Thus, local irritating effects are evident whereas no histological examinations were conducted discriminating between local irritation and corrosion to the respiratory tract. Consequently, effects on the respiratory tract are not sufficiently examined to justify additional labelling.

**ALIPA** represents the European manufacturers of aliphatic isocyanates, the main raw materials used for high-quality protective and decorative coating systems for modern adhesive systems and for specialties like elastomers. More information on diisocyanates, their applications and ALIPA’s product stewardship initiatives can be found on the [ALIPA website](http://www.alipa.org).