C COUCHARRIERE
MLPC International

209 avenue Charles Despiau
40370 Rion des Landes
France
T +33 (0)5 58 57 02 00

European Chemicals Agency
FI-00121 Helsinki Finland

Date : February 19. 2024

Comments on the CLH report 'Proposal for Harmonized Classification and Labelling based on Regulation (EC) No 1272/2008 (CLP Regulation), MITC methylisothiocyanate (CAS 556-61-6).

Please find below the comment of MLPC International concerning the classification of MITC methylisothiocyanate (CAS 556-61-6).

First at all, we want to precise to be a manufacturer of MITC still 1984 and having register it under the REACH regulation. The dossier can be available using the weblink:
https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/11490

1- Phys-Chem :

Corrosion to the metal:

We confirm that no test was done for MITC, considering it as a pure solid, and according to our REACH dossier should be consider as "No classification due to a lack of data'". Nevertheless, we concede that the corrosion study for metals should have been carried out because MITC is a solid which can become liquid during transport (melting point of MITC equals 39°C , thus < 55°C.

We know that MITC is corrosive to metals (the state of our installations shows this). However, we know how to manufacture it, transfer it, store it, etc. The risks on our installations are therefore already known and controlled. We also know this for transport. All is under control.We can not realize the UN C1 test considering the inflammable liquid propertie and the the test temperature higher to the flash point due to the inflammability risk , but we are agreeing on the H290 classement

2- Toxicology:

Acute Tox. 3; H301
MLPC International agrees that a classification as Acute Toxic Category 3 is appropriate for the oral route.

Acute Tox. 2; H330
MLPC International agrees that a classification as Acute Toxic Category 2 is appropriate for inhalation.

Acute Tox. 4; H312
MLPC International agrees that MITC shall be classified as Acute Toxic via the dermal route of exposure.

Skin Corr. 1; H314
MLPC International agrees that a classification as Skin Corrosive Category 1 is appropriate.

Skin Sens. 1; H317
MLPC International agrees that a classification as Skin Sensitiser Category 1 is appropriate.

EUH071
MLPC International agrees that a note as EUH071 is appropriate.

STOT RE 1; H372 (inhalation)
MLPC International agrees that a classification as STOT RE; H372 (Causes damage to the upper respiratory tract through prolonged or repeated exposure by inhalation) is appropriate.

Carc. 2; H351
MLPC International does not consider the proposed classification of MITC as Carcinogenic Category 2 as appropriate.
Studies are available evaluating the carcinogenicity of MITC in rats and mice via the oral (drinking water) and inhalation routes of exposure. MITC was not considered as carcinogenic when tested in mice by both routes of exposure, and in rats via the oral route of exposure.

The Member State Competent Authority (MSCA) considered the findings from a 2-year inhalation chronic study in rats as warranting a classification as Carcinogenic Category 2. MITC was administered for a period of 104 weeks via whole-body inhalation exposure for 6 hours per day to 3 groups of Sprague-Dawley rats, control animals were included. Exposures were performed using a standard 5-day per week inhalation study regimen. Target exposure concentrations were 0.5, 5, and 20 ppm.

Treatment-related deaths occurred in the 20 ppm group males and females. These deaths were considered secondary to squamous cell carcinoma of the nose, anaplastic carcinoma of the nose, and lung lesions (necrotising or suppurative inflammation induced by treatment-related injuries). Treatment-related clinical findings were primarily observed in the 20 ppm group males and females. Higher total occurrence and/or number of animals with rales, laboured respiration, clear and/or red nasal discharge, and red material around the nose (males only) were reported, likely related to the corrosive properties of the test substance. Eye opacities were observed in a relatively small number of 20 ppm group males and females. Thin appearance, associated with lower body weight and food consumption, also had a higher occurrence and incidence in the 20 ppm males and females. The only exposure-related palpable masses were located on or near the nose in 20 ppm group males and

females. Neoplastic findings were found in the 20-ppm group and included malignant and benign nasal tumours and a single benign papilloma in the lung.
According to the MSCA, MITC is eligible for classification as Carcinogenic Category 2 based on the above-mentioned findings. Please find below why MLPC International does not consider this proposed classification as appropriate.

According to the OECD Guidance Document (GD) 116, the concept of the Maximum Tolerated Concentration (MTC) is well-establish, and conventionally defined as the highest concentration to produce toxic effects without causing death and to decrease body weight gain by no more than 10% relative to controls (OECD 2002, GD No. 35). The MTC is often used in the assessment of a chronic toxicity or a carcinogenicity study to decide whether the top concentration tested was adequate to give confidence in a result. Excessive toxicity at the top concentration level (or any other concentration level) may compromise the usefulness of the study and/or quality of data generated. In particular, the testing of substances at potentially irritating or corrosive concentrations should be avoided, as administering such substances could result in severe pain and tissue damage at site of contact, which would compromise both animal welfare and the integrity of the study.

The highest concentration investigated (20 ppm) resulted in a significant reduction in bodyweight gain (-47% when compared to control animals) and bodyweight (-34% when compared to control animals) in animals. These findings are indicative of distress in the animals. Following the criteria laid down in OECD GD 116 and OECD GD 35, this concentration-level of 20 ppm is above the MTC, thus compromising the interpretability of the data generated at this concentration-level.

In this occurrence, tumours were limited to site of contact and neighbouring tissues, in presence of severe local toxicity at a concentration clearly above the MTC. Below this MTC, no relevant treatment-related systemic adverse effects were reported and the NOAEC for systemic toxicity was 5 ppm. The NOAEC for local effects was 0.5 ppm, based upon increased incidences of squamous metaplasia and olfactory epithelial degeneration in the nasal epithelium, and epithelial hyperplasia and squamous metaplasia on the larynx. No neoplastic findings were recorded below the MTC.

The Mode Of Action (MOA) for point of contact tumours observed in the rat bioassays that is best supported by available data involves increased cell replication and regenerative proliferation. These tumours were only reported in rats following a lifelong exposure, at a concentration above the MTC, which induced severe pain and tissue damage at site of contact.

The nasal tumours observed at the highest concentration investigated are of questionable relevance to human health risk assessment, given that such exposure level is much higher than would be tolerated by humans. Consequently, the potential of MITC to pose a substantial cancer risk is implausible. Human health risk assessment for MITC must rely on non-cancer, precursor endpoints observed at the site of contact (e.g. irritation, inflammation, hyperplasia, metaplasia) and occurring at concentrations lower than the MTC.

MLPC International agrees that MITC shall be classified as EUH 071 and STOT RE 1; H372 via inhalation. The objective of this classification is to prevent MITC from inducing tissue damage at the site of contact via inhalation. Since the effects leading to the precursor lesions will be prevented from occurring, classification of MITC as a Carcinogen is not relevant and would only be redundant.

ARKEMA

3- Ecotoxicology

Aquatic Acute 1, H400 - M-factor=100

MLPC International did review the aquatic toxicity data submitted for MITC. The Rapporteur Member State (RMS) BE uses the worst-case approach to determine the acute M-factor. The justification is available on page 641 of the CLH report. The acute aquatic toxicity data on *Hyalella Azteca* (EC50 of 0.0038 mg MITC/L), the most sensitive species, lead to an acute M-Factor equal to 100. RMS BE uses this data instead of considering the large data set available for the three standard trophic levels on MITC allowing an SSD approach. Instead the approach currently used is appropriate for data-poor substances, such as new substances. The relevance of this worst-case approach is therefore questionable.

MLPC International considers that an approach using the Species Sensitivity Distribution (SSD), as allowed by REACH, CLH and PPP regulations, might be more appropriate in such case to perform the risk assessment and to determine the classification of MITC. Indeed, some species are more sensitive to substances due to differences in their physiology, behaviours, or geographic distributions etc. than others. On the other hand, when the substance toxicity has been studied using a broader range of aquatic species, as is the case for MITC, the SSD can provide a protective approach for a large range of species. SSD derived from acute toxicity data can protect 95% of the species by setting a HC5. When used correctly, this statistical approach can therefore give a greater statistical confidence to the risk assessment compared to the assessment factor approach as used by the RMS BE. This statistical approach must be based on reliable and large dataset. These conditions appear to be met based on the information provided in the CLH report and therefore the SSD approach can be used for classification purposes,

Indeed, this SSD approach is addressed in the Guidance on the Application of the CLP Criteria Version 6.0 – January 2024 (page 504), "There are some circumstances where it may not be appropriate to use the lowest toxicity value as the basis for classification. This will usually only arise where it is possible to define the sensitivity distribution with more accuracy than would normally be possible, such as when large datasets are available. Such large datasets should be evaluated with due caution". As indicated in the section 4.1.3.2.4.1 of the same guidance document (page 504) "In case of very large data sets meeting the criteria for applying the Species Sensitivity Distribution (SSD) approach (see IR&CSA, Chapter R.10), statistical techniques (e.g. HC5 derivation) can be considered to estimate the aquatic toxicity reference value for classification (equivalent to using the lowest EC50 or NOEC), in a weight of evidence approach."

Depending on the regulations, and as observed in the literature, the required parameters to build a SSD strategy may vary (species number, acute versus chronic toxicity etc.).

The CLP guidance refers to the IR&CSA Chapter R.10, Among the basic considerations outlined in Section R.10.3.1.3 of the document, the following requirements seem to be too restrictive. For example, only long-term studies are concerned. Furthermore, the minimal information requirement is important *"Confidence can be associated with a PNEC derived by statistical extrapolation if the database contains at least 10 NOECs (preferably more than 15) for different species covering at least 8 taxonomic groups."*.

The application conditions described in the CLP and Chapter R.10 guidances differ from those addressed in the section 8.4 of the EFSA Guidance. For example, the minimum number of acute toxicity data required is 8 (see section 8.4.2). As described page 678 in the CLH report,

TAMINCO did indicate to apply the SSD approach based on acute invertebrates toxicity data following this 2013 guidance on the tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. Despite the absence of robust justification included in the CLH report related to the SSD application, this approach is relevant.

Aquatic Chronic 1, H410 - M-factor=100

MLPC International did review the aquatic toxicity data submitted for MITC. The RMS BE does use a worst-case approach to determine the chronic M-factor. The acute toxicity data on *Hyalella azteca*, the most sensitive species, was used and lead to a chronic M-Factor equal to 100. This approach is driven by the fact that no chronic toxicity data is available on *Hyalella azteca*.

The RMS quoted the CLP table 4.1.0(b)(iii) to justify its classification approach. This table is mentioned in the second step of the tiered approach for chronic classification described in the figure 4.1.1 of the CLP regulation. This second step applies to substances for which adequate chronic data are available for one or two trophic levels. Acute and chronic data must in that case be compared to cut-off values and the most stringent classification must be applied. However, reliable chronic toxicity data on MITC are available for the three trophic levels. In this case, the first step of the tiered approach applies. CLP table 4.1.0(b)(i) and CLP table 4.1.0(b)(ii) must be used in this case, depending on the substance rapid degradation.

Furthermore, in the Guidance on the Application of the CLP Criteria Version 6.0 – January 2024, page 507, it is stated that adequate chronic toxicity data are preferred to define the long-term hazard category.

When applying the first step of the tiered approach, the M-factor associated to the aquatic chronic classification is 10 as MITC cannot be considered as rapidly degradable following the conditions described in the CLH guidance.