COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 07.02.2024

Substance name: methyl isothiocyanate
CAS number: 556-61-6
EC number: 209-132-5
Dossier submitter: Belgium

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
18.01.2024	Belgium	Taminco BV	Company-Manufacturer	1
Comment received				
The applicant, Taminco BV, would like to point out the necessity of an exchange of information between all relevant stakeholders of the active substance / plant protection product (PPP) process and the CLH process, in order to ensure that any evaluation is based on the latest available data set (see section “Information on the CLH process” of this webform: “If the substance is an active ingredient in a plant protection product (PPP) or biocidal product (BP), comments submitted in this consultation may be used in the PPP/BP processes, and, comments received for the PPP/BP processes may be used in the CLH process”). Hence the applicant assumes that any comments and supporting information submitted to EFSA in the public consultation phase and thereafter during the request for additional data will be made available by EFSA to ECHA and are as well taken into account in the CLH process by ECHA. The applicant will provide copies of the information referenced above to ECHA in case access will not be provided by EFSA. This relates to all hazard classes open for commenting. Comments on the PPP active substances metam-sodium (ISO) and metam-potassium (ISO) are submitted in the parallel consultation. Overall conclusions on hazard class are provided in the field “Comments on the open hazard classes”. A detailed feedback on specific hazard classes is provided as a public attachment (Taminco_Methyl_isothiocyanate_Comments). This public attachment includes both comments on the PPP active substances metam-sodium (ISO) and metam-potassium (ISO) and the main metabolite Methyl isothiocyanate (MITC) in one document. Parts regarding the PPP active substances metam-sodium (ISO) and metam-potassium (ISO) are greyed out. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Taminco_Methyl_isothiocyanate_Comments.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	Germany		MemberState	2
Comment received				
The classification proposal includes classifying the substance as Skin Corr. 1, H314 instead of Skin Corr. 1B, H314. According to Annex I Part 3 Chapter 3.3 section 3.3.2.2.2. of Regulation (EC) No. 1272/2008 (CLP Regulation), substances with a corrosive effect on the skin are also expected to cause serious eye damage (Category 1). In section 2.6.2.5.3 "Conclusion on classification and labelling for serious eye damage/eye irritation" of the CLH dossier also states that the substance is to be classified as Eye Dam, 1, H318. Since the hazard class serious eye damage/eye irritation is independent of the hazard class skin corrosion/skin irritation, a classification in both endpoints (Skin Corr. 1, H314 and Eye Dam. 1, H318) is required in this case. When labelling the substance, the hazard statement H318 is not indicated on the label due to redundancy (see also Guidance on the Application of the CLP Criteria, section 3.3.2.4 "Decision on classification"). Thus, in Table 65 of the CLH report in section 2.11.2.1 "Proposed harmonised classification and labelling according to the CLP criteria" in the rows "RMS proposal at renewal" and "Resulting Annex VI entry if agreed by RAC and COM" the codes Eye Dam. 1 and H318 are missing in the column "Classification".				

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	3
Comment received				
please find enclosed the comment relative of MITC (and below the most important ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

PHYSICAL HAZARDS

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	4
Comment received				
We know that MITC is corrosive to metals. 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 ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
18.01.2024	Belgium	Taminco BV	Company-Manufacturer	5
Comment received				
Vol. 1, 2.2.1., Summary of physical and chemical properties of the active substance, p. 46: Referring to RMS's note about the aggregate state of MITC relevant to the current submission, the applicant wants to emphasize that related to the use in crop protection, MITC as metabolite of metam is released as gas as the RMS states correctly. In pure form at room temperature, MITC is a solid, but for the applicant's use, this is not relevant. Vol. 1, 2.2.1.1.7 Self-reactive substances, p. 51: The applicant Taminco agrees that MITC contains unsaturations and that therefore not any doubts related to self-reactive properties of MITC can be removed. Nevertheless, assuming that in the application as a plant protection product, MITC is only formed as a gas after application, this classification point, which is relevant for the transport, handling and use of the substance as a solid, is not relevant for this submission. Vol. 1, 2.2.1.1.10 Self-heating substances, p. 53: Assuming that in the application as a plant protection product, MITC is only formed as a gas after application, this classification point, which is relevant for the transport, handling and use of the substance as a solid, is not relevant for this submission. Vol. 1, 2.2.1.1.15 Corrosive to metals, p. 56: The applicant Taminco agrees to the classification as Met. Corr. 1, H290 for MITC. No further information or experimental data is available. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Taminco_Methyl_isothiocyanate_Comments.pdf				

HEALTH HAZARDS – Acute toxicity

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	6
Comment received				
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. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
18.01.2024	Belgium	Taminco BV	Company-Manufacturer	7
Comment received				
Vol. 1, 2.6.2.1.3 Conclusion on classification and labelling for acute oral toxicity, p. 76: The applicant Taminco agrees with RMS on the endpoint and assessment of the single				

studies for acute oral toxicity and supports the proposed classification for MITC.
The applicant however disagrees with the ATE of 100 mg/kg for MITC as an experimental LD50 value is available that can be used for the calculation of mixture toxicity. Note (b) for Table 3.1.1 in Regulation (EC) 1272/2008 stipulates that the ATE for classification of a substance in a mixture is derived using the LD50/LC50 where available. The converted ATE values listed in Table 3.1.2 should only be used when only range data or acute toxicity hazard category information is available (point (d) of 3.1.3.3 of Regulation (EC) 1272/2008). This is not the case for MITC as an LD50 of 147 mg/kg bw was derived.
Vol. 1, 2.6.2.2.3 Conclusion on classification and labelling for acute dermal toxicity, p. 78: The applicant agrees with RMS on the endpoint and assessment of the single studies for acute dermal toxicity and supports the proposed classification for MITC.
The applicant however disagrees with the ATE of 1100 mg/kg for MITC as an experimental LD50 value is available that can be used for the calculation of mixture toxicity. Note (b) for Table 3.1.1 in Regulation (EC) 1272/2008 stipulates that the ATE for classification of a substance in a mixture is derived using the LD50/LC50 where available. The converted ATE values listed in Table 3.1.2 should only be used when only range data or acute toxicity hazard category information is available (point (d) of 3.1.3.3 of Regulation (EC) 1272/2008). This is not the case for MITC as an LD50 of 1290 mg/kg bw was derived.
Vol. 1, 2.6.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity, p. 82): the applicant agrees with RMS on the endpoint and assessment of the single studies for acute inhalation toxicity and supports the proposed classifications for MITC.
The applicant however disagrees with the ATE of 0.5 mg/L for MITC as an experimental LC50 value is available that can be used for the calculation of mixture toxicity. Note (b) for Table 3.1.1 in Regulation (EC) 1272/2008 stipulates that the ATE for classification of a substance in a mixture is derived using the LD50/LC50 where available. The converted ATE values listed in Table 3.1.2 should only be used when only range data or acute toxicity hazard category information is available (point (d) of 3.1.3.3 of Regulation (EC) 1272/2008). This is not the case for MITC as an LC50 of 0.54 mg/L was derived.
The applicant disagrees on the attribution of H335 based on the study from 1981 (B.6.8.1.1/03) as the use of “EUH071 – Corrosive to the respiratory tract” is proposed, thereby covering and taking precedence on H335.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Taminco_Methyl_isothiocyanate_Comments.pdf

HEALTH HAZARDS – Skin corrosion / irritation

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	8
Comment received				
Skin Corr. 1; H314 MLPC International agrees that a classification as Skin Corrosive Category 1 is appropriate. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

HEALTH HAZARDS – Serious eye damage / eye irritation

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	9
Comment received				
-				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf

HEALTH HAZARDS – Respiratory sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	10
Comment received				
- ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

HEALTH HAZARDS – Skin sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	11
Comment received				
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. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

HEALTH HAZARDS – Germ cell mutagenicity

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	12
Comment received				
- ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	Germany		MemberState	13
Comment received				
Increased rates of mutation (B.6.8.1.3.1/06-1) and chromosomal aberration (B.6.8.1.3.1/05) were evident in the in vitro studies. As with the parent compound metam sodium, we do not regard genotoxicity as a result of cytotoxicity, rather genotoxicity is seen together with cytotoxicity. The most probable MoA is an electrophilic attack of cellular components including DNA. This means damage to the DNA is going to occur at the same doses as cellular damage. Unless repaired, genotoxic damage is typically sustained in surviving cells and passed on to subsequent generations. Unlike metam sodium, however, there was little clear evidence of mutagenic/clastogenic/aneugenic potential in the in vivo studies and we thus support the DS's view that classification as Muta. 2 is not needed.				

HEALTH HAZARDS – Carcinogenicity

Date	Country	Organisation	Type of Organisation	Comment number
21.12.2023	United States of America		Individual	14
Comment received				
The nasal tumors observed in rats exposed to high concentrations of MITC are due to the confounding effects of excessive cytotoxicity and as such a classification for carcinogenicity is not warranted. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BG Comment_MITC_Carci_122123.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
18.01.2024	Belgium	Taminco BV	Company-Manufacturer	15
Comment received				
Vol. 1, 2.6.5.3 Conclusion on classification and labelling for carcinogenicity, p. 159: The applicant disagrees with the proposed classification for carcinogenicity in Category 2 (H351). Four GLP compliant and acceptable studies are available for MITC in rat and mouse by oral and inhalation route each. Mouse No carcinogenic potential of MITC was identified when the substance was administered in drinking water over a 2-year period to mice. No statistically significant and biologically relevant neoplastic findings were noted in male and female mice in a new 18-month whole body inhalation carcinogenicity study. The applicant is in accordance with the dossier submitter´s conclusion that “It was considered that there was insufficient evidence to indicate that MITC is carcinogenic in the CD-1 mouse”. In the 18-month whole body inhalation carcinogenicity study in mice there were no MITC exposure-related early deaths and there were no negative effects on survival in mice after 78 weeks exposure to 0, 1, 5, and 15 ppm. Treatment-related clinical findings were limited to ocular findings, including opacity, in the 15 ppm group at the detailed physical examinations. Body weight and body weight gain were significantly reduced throughout the exposure period (at 5 and 15 ppm) exceeding the Maximum Tolerable Dose (MTD) at 15 ppm (mean body weight reduction up to 21.4% and body weight gain reduction up to 52% of control). MITC exposure at 1 ppm did not result in any MITC-related nasal lesions. At 15 ppm non-neoplastic proliferative nasal lesions included squamous epithelial metaplasia, respiratory epithelial metaplasia, olfactory basal epithelial hyperplasia, transitional epithelial hyperplasia, respiratory epithelial hyperplasia, and Bowman’s gland hyperplasia. Non-neoplastic lesions in the nasal cavity as metaplasia of the respiratory epithelium and squamous metaplasia were considered indicative of irritating properties of MITC. At 15 ppm the MTD was exceeded based on the level of cytotoxicity, regenerative cell proliferation, hyperplasia, and metaplasia observed. Since there were no statistically significant neoplastic findings in males or females and a nasal neoplasm (benign papilloma) was found in only one MITC-exposed animal, there was insufficient evidence to indicate that MITC is carcinogenic in the CD-1 mouse. Rat No carcinogenic potential of MITC was identified when the substance was administered in drinking water over a 2-year period to rats. In the 2-year inhalation study, rats were exposed to 0, 0.5, 5 and 20 ppm MITC. No statistically significant effects on survival were noted for male or female rats in any group;				

however, MITC-related deaths did occur in the for both males and females in the 20 ppm group after inhalation exposure for one year and beyond. MITC-related causes of death included squamous cell carcinoma of the nose, anaplastic carcinoma of the nose, and lung lesions (necrotizing or suppurative inflammation secondary to MITC-related injury). 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 incidence of rales, laboured breathing and nasal discharge (clear and red) was significantly increased in both males and females of the highest dose group.
Body weights for males were reduced >10% from week 3 onwards and consistently >20% from week 33 males (even >30% from week 73). Body weights for females were reduced >10% from week 3 onwards and consistently >20% from week 47. At the end of the treatment period (week 103), body weights were 34% lower for males and 20% lower females, when compared to the control. Body weight gains for both males and females were reduced more >20% for throughout the entire treatment period (week 0-103), up to -46% for males and -27% for females. According to OECD TG 451/453 and Guidance Document No. 116 the highest dose level should induce toxicity, evidenced by for example slight depression of body weight gain (not more than 10%), but not severe toxicity, morbidity or death. OECD Guidance Document No. 19 defines a body weight decrease of more than 20% compared to control as a humane endpoint.
Based on mean body weights (-34% for males and -20% for females, compared to control) and cumulative body weight gains (-46% for males and -27% for females, compared to control) at the end of the treatment period, the highest concentration of 20 ppm clearly exceeded the MTD and is considered excessive.
Non-neoplastic MITC-related findings were not considered adverse in the 0.5 ppm group based on low incidence and/or severity (generally minimal to mild), presence in only 1-2 nasal levels or 1 laryngeal level and/or multifocal appearance. Non-neoplastic treatment-related findings which were considered adverse in the 5 ppm group were squamous metaplasia and olfactory epithelial degeneration in nasal tissues and epithelial hyperplasia and squamous metaplasia in the larynx (males only). Non-neoplastic nasal, laryngeal, tracheal and lung lesions were considered adverse in the 20 ppm group.
MITC exposure-related neoplasms were found in the 20 ppm group males and females and included malignant and benign nasal tumours and a single benign papilloma in the lung (1 male). Toxicologically significant local effects (portal of entry) were observed clinically in the eyes (opacity and bilateral keratitis in 20 ppm group) and microscopically in the nasal tissues, larynx, trachea, lungs, olfactory bulbs, and eyes.

Discussion
The non-neoplastic lesions present at the 20 ppm exposure level in rats are typical of those seen with contact irritants with high water solubility where nasal degeneration occurs and where penetration into the lungs is limited with a consequential limitation in pathology. Furthermore, in the larynx squamous metaplasia following a dose-response relationship was observed, which is also considered secondary to irritant properties. The degenerative changes at the 20 ppm exposure level include degenerative, inflammatory and regenerative changes. The extent of pathology, and the individual changes present at the 5 ppm exposure level are significantly abbreviated over that present at 20 ppm showing “hyperplasia of the respiratory epithelium (RE), squamous epithelium (SE) and transitional epithelium (TE), respectively in the nasal region, with squamous metaplasia”. At 0.5 ppm, the incidence of hyperplasia of respiratory epithelium, squamous epithelium and transitional epithelium, in the nasal region was comparable to controls for males; only the incidence of transitional epithelium hyperplasia was higher than the controls for the females. Hence the non-neoplastic changes, and the severity of those changes, show an expected dose-response relationship and it is only when compensatory adaptive changes are exceeded, (at 20 ppm), that cell replication required for regeneration, increases the risk of developing tumours which also supports a thresholdable nasal response to MITC.

Newly available mechanistic data is strengthening the conclusion above. In the study from 2020 (B.6.8.1.2.1/04) rats were exposed to concentrations of 0.5, 5, and 20 ppm MITC for 1 day, 5 days, 4 weeks, and 4 weeks with an additional recovery period.
All over, the main findings of this study in rats were:
• acute and subacute inhalation exposures to 5 and 20 ppm MITC caused dose-dependent effects including nasal histopathology and increased DNA synthesis/cellular replication in nasal epithelium,
• no nasal histopathology or increased epithelial DNA synthesis/cellular replication were present in rats exposed to 0.5 ppm, and
• MITC-induced DNA synthesis/epithelial cell proliferation was not sustained 4 weeks post-exposure indicating a return to normal epithelial cell turnover (no sustained increase in DNA synthesis and cell proliferation).
The results of this research study suggest that MITC-induced nasal tumours at high exposure concentrations were induced by transient nasal epithelial cell death with persistent regenerative epithelial cell proliferation and DNA synthesis (increased cellular turnover) with sustained inhalation exposures to MITC.
Along with increased epithelial cell proliferation, squamous metaplasia of TE and RE was a common finding in 20 ppm, but not 0.5 or 5 ppm, exposed rats at the end of the 20-day exposure. These proliferative non-neoplastic lesions in targeted intranasal sites of toxicity may be harbingers (pre-neoplastic lesions) of nasal cancers, especially squamous cell carcinomas, that develop in rats chronically exposed to high concentrations of MITC. As for the 2-year inhalation study in rats, the 20 ppm dose level was considered to clearly exceed the MTD, as the level of cytotoxicity, regenerative cell proliferation, hyperplasia, and metaplasia observed at 20 ppm clearly fulfil the criteria of causing unacceptable and excessive toxic effects.
In conclusion, the tumour formation in rats after inhalation of MITC is considered substance-related (with threshold), suggesting the following mode of action:
• Direct cytotoxicity of MITC in the nasal mucosa (e.g., degeneration, necrosis/apoptosis);
• Cell proliferation to compensate for MITC-induced cytotoxicity;
• Onset and persistence of squamous cell metaplasia as an adaptive response to the cytotoxic insult;
• Development of tumours, primarily squamous cell carcinomas.
This pattern of toxicity is further reasonable as MITC is known to have corrosive (cytotoxic) properties. Tumour formation was only observed in one of two inhalation studies at doses exceeding the MTD at sites of contact. No dose-response after gavage application was observed indicating that the concentration may be more important for the tumour formation than intrinsic properties of the substance. The lines of evidence described above can also be referred to in the CLP guidance, where following information is provided under “3.6.2.3.2 Additional considerations for classification:
j. The possibility of a confounding effect of excessive toxicity at test doses
Tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans. In addition, tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard.”
The proposed mechanism of tumour formation is generally relevant for humans, nevertheless a reduced sensitivity compared to rodents is assumed due to the anatomy of the nose/upper respiratory tract.
In the opinion of the applicant no classification for carcinogenicity is warranted for MITC. Although an increase in nasal tumours was observed at highest dose in rats and human relevance cannot be excluded, the applicant considers the following points being sufficient argumentation for non-classification (according to Annex I: 3.6.2.2.6 and the CLP guidance section 3.6.2.3.2 (j) (version 5, July 2017)):
• Tumour formation at top dose only (exceeding MTD)
• No dose-response relationship

• Tumour formation at site of contact only (nasal tissue)
• Suggested threshold mechanism (proposed effect of GSH-depletion)
• Only one species affected
Furthermore, the known corrosive (cytotoxic) effects of MITC are already considered by classification of MITC for acute toxicity, skin corrosion (Cat. 1) and STOT RE 1. In conclusion, no intrinsic hazard for carcinogenicity of MITC is expected and therefore no classification for carcinogenicity is warranted.
Comments to the single studies are provided in the attached commenting sheet for MITC ("Taminco_Methyl_isothiocyanate_Comments").

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Taminco_Methyl_isothiocyanate_Comments.pdf

Date	Country	Organisation	Type of Organisation	Comment number
06.12.2023	France		Individual	16
Comment received				
Independent expert opinion on the CLH proposal is given in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public comment on MITC Carcinogenicity_Dec2023.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	17
Comment received				
MLPC International does not consider the proposed classification of MITC as Carcinogenic Category 2 as appropriate. 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. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	United States of America	<confidential>	Company-Manufacturer	18
Comment received				
Public domain comments on the carcinogenicity hazard class can be found in the attachment 'MITC CLH Report - comments on carcinogenicity_Redacted' and the supporting position paper 'Mode of Action (MOA) for Nasal Tumors Induced by Methyl Isothiocyanate (MITC) in Sprague Dawley Rats_Redacted'. Both papers can be found in the zipped attachment 'MITC CLH report - comments on carcinogenicity and MOA paper_Redacted'. Confidential comments on the carcinogenicity hazard class can be found in the attachment 'MITC CLH Report - comments on carcinogenicity' and the supporting position paper 'Mode				

of Action (MOA) for Nasal Tumors Induced by Methyl Isothiocyanate (MITC) in Sprague Dawley Rats'. Both papers can be found in the zipped attachment 'MITC CLH report - comments on carcinogenicity and MOA paper'.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment MITC CLH report - comments on carcinogenicity and MOA paper_Redacted.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment MITC CLH report - comments on carcinogenicity and MOA paper.zip

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	United Kingdom	Health and Safety Executive	National Authority	19
Comment received				
MITC (Carcinogenicity) 'In the 2-year chronic and carcinogenicity study in rats (inhalation), nasal tumours are noted and a classification of Carc. 2 H351 Suspected of causing cancer is proposed based off these effects. However, the DS notes that these effects are only seen at doses exceeding the MTD. It is further noted that the MTD is derived based on low mean body weight and cumulative body weight gain (34% bw ; 47% bw gain). We think more detailed information from this study would be of use and we would welcome further discussion on the relevance of these nasal tumours which are only observed well in excess of the MTD on the classification for carcinogenicity.'				

HEALTH HAZARDS – Reproductive toxicity

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	20
Comment received				
- ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

HEALTH HAZARDS – Specific target organ toxicity - single exposure

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	21
Comment received				
- ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

HEALTH HAZARDS – Specific target organ toxicity - repeated exposure

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	22
Comment received				
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.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf

ENVIRONMENTAL HAZARDS – Hazardous to the aquatic environment

Date	Country	Organisation	Type of Organisation	Comment number
18.01.2024	Belgium	Taminco BV	Company-Manufacturer	23

Comment received

Vol.1, 2.9.2.4.1 Acute aquatic hazard, p. 641
Vol.1, 2.9.2.4.2 Long-term aquatic hazard (including bioaccumulation potential and degradation), p. 644
The applicant Taminco BV proposed an Acute and Chronic M-factor of 10 for the aquatic classification of Methyl isothiocyanate (MITC) in the submitted CLH report, as summarised in the following.
Acute aquatic toxicity data are available for fish, invertebrates, algae and aquatic plants. Aquatic invertebrates are the most sensitive trophic level. The acute aquatic toxicity data covers a wide range of taxonomic groups including crustaceans, insects, molluscs, flatworms and lumbricid worms. Therefore, a statistical extrapolation was done on the aquatic invertebrates data using the Species Sensitivity Distribution (SSD) approach. This resulted in a HC5 value of 0.01171 mg/L, based on which MITC should be classified as "Aquatic Acute 1" (H400) with an Acute M-factor of 10.
Chronic data are available for fish, invertebrates, algae and aquatic plants. Fish is the most sensitive trophic level, since the lowest chronic effect value is a 33-day EC10 of 0.00929 mg a.s./L for Pimephales promelas. Based on lack of rapid degradability and the fish chronic value below 0.01 mg/L, MITC should be classified as Aquatic Chronic 1 (H410) with a Chronic M-factor of 10.

The Rapporteur Member State (RMS) Belgium proposed an acute and chronic M-factor of 100 for the aquatic classification of MITC. The RMS used the deterministic approach for the acute aquatic classification (i.e., based on the lowest acute value: 48h-EC50 of 0.0038 mg/L for Hyalella azteca) and the surrogate approach for the chronic aquatic classification (i.e., based on lack of rapid degradability and on the lowest acute value for Hyalella azteca).

However, the applicant considers that M-factors of 10 are appropriate for the Acute and Chronic aquatic classification. MITC has a large dataset of acute data on aquatic invertebrates that meets the criteria for applying the SSD approach as defined in Guidance on Information Requirements and Chemical Safety Assessment (IR&CSA), Chapter R.10, as explained in the following paragraphs. Consequently, the HC5 value of 0.01171 mg/L for acute invertebrates should be used for the acute classification and the chronic classification should be based on fish, which is the trophic level with the lowest chronic value.

Further details are given in the attached commenting sheet for MITC ("Taminco_Methyl_isothiocyanate_Comments").

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Taminco_Methyl_isothiocyanate_Comments.pdf

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	United Kingdom	Health and Safety Executive	National Authority	24
Comment received				
Methyl isothiocyanate (MITC): Please could the CLH DS and RAC consider whether it is possible and relevant to use an SSD for the hazard classification of MITC given this substance appears data rich? Although algae are not the most sensitive species, we ask if the algal endpoints could be provided as mm since the measured concentrations of MITC declined is measured in all the algae studies.				

Date	Country	Organisation	Type of Organisation	Comment number
19.01.2024	France	MLPC International	Company-Manufacturer	25
Comment received				
MLPC is not agreed with the M= 100 factor ECHA note – An attachment was submitted with the comment above. Refer to public attachment 240119 CLH MITC MLPC comments.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
11.01.2024	Netherlands		MemberState	26
Comment received				
Thank you for sharing the CLH report with us. The report is well written and we agree with the CLH proposal for the environmental classifications. We agree with the proposed environmental classification but have a few general comments: - It seems not all information from the REACH registration dossier is taken into account. For example, on P. 324: It is reported that no relevant data on ready biodegradability is available for MITC. However, in the REACH registration dossier for MITC (EC no. 209-132-5), a OECD TG 301D study (2010) is provided. The study shows that MITC is not readily biodegradable (0%). Was this study not provided or left out for another reason? Perhaps it is worthwhile to include these studies as well. - p. 604-605 (Table 2.9.2.2-3): The study on Pseudokirchneriella subcapitata (CA8.2.6.1/09) is marked as key study for the chronic aquatic toxicity data on algae (72-h ErC10 of 0.076 mg/L). However, the acceptable study with S. costatum (p. 605) derived a lower chronic value (72-h ErC10 = 0.0351 mg/L). Why was this study not used as the key chronic algae study? -For the chronic aquatic classification is referred to a NOEC for P. promelas. Please note that for classification purposes, when available for the same study, the use of an EC10 is preferred over the use of a NOEC. The EC10 value of 0.00924 mg/L should therefore be used for the classification proposal.				

PUBLIC ATTACHMENTS
1. 240119 CLH MITC MLPC comments.pdf [Please refer to comment No. 3, 4, 6, 8, 9, 10, 11, 12, 17, 20, 21, 22, 25]
2. MITC CLH report - comments on carcinogenicity and MOA paper_Redacted.zip [Please refer to comment No. 18]
3. Taminco_Methyl_isothiocyanate_Comments.pdf [Please refer to comment No. 1, 5, 7, 15, 23]
4. Public comment on MITC Carcinogenicity_Dec2023.pdf [Please refer to comment No. 16]

CONFIDENTIAL ATTACHMENTS
1. MITC CLH report - comments on carcinogenicity and MOA paper.zip [Please refer to comment No. 18]
2. BG Comment_MITC_Carci_122123.pdf [Please refer to comment No. 14]