ADME / Metabolism			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.1.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s), p. 72	**Taminco:** Agrees with RMS conclusion. Applicant would also like to inform RMS that the final report, including the additional investigations on M1, M2 and M3, is available and can be submitted upon request. M1 was identified as an unknown dimeric species with a m/z of 203 and M3 was identified as carbonic acid. M2 was not ionisable and was therefore not further characterized.	

Acute toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.2.1, Acute toxicity – oral route (Table 20), p. 74	**Taminco:** The applicant would like to point out that in Table 20 a dose of 265 mg/kg bw/d is mentioned for the publication of Thompson (2002) instead of 260 mg/kg bw/d (fourth column).	
(2)	Vol. 1, 2.6.2.1.3 Conclusion on classification and labelling for acute oral toxicity, p. 76	**Taminco:** Agrees with RMS on the endpoint and assessment of the single studies for acute oral toxicity. Applicant supports the proposed classifications for metam and MITC. The applicant disagrees with the ATE of 500 mg/kg bw for metam and the ATE of 100 mg/kg for MITC. Further information is provided in column 3.	**Taminco:** Agrees with RMS on the endpoint and assessment of the single studies for acute oral toxicity. Applicant supports the proposed classifications for metam and MITC. The applicant disagrees with the ATE of 500 mg/kg bw for metam and the ATE of 100 mg/kg for MITC as experimental LD_{50} values are 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 LD_{50}/LC_{50}

Acute toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			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 metam and MITC: an LD_{50} of 896 mg/kg bw was derived for metam-sodium; an LD_{50} of 1000 mg/kg bw was derived for metam-potassium; and an LD_{50} of 147 mg/kg bw for MITC.
(3)	Vol. 1, 2.6.2.2.3 Conclusion on classification and labelling for acute dermal toxicity, p. 78	**Taminco:** Agrees with RMS on the endpoint and assessment of the single studies for acute dermal toxicity. Applicant supports the proposed classification for MITC. The applicant disagrees with the ATE of 1100 mg/kg for MITC. Further information is provided in column 3.	**Taminco:** Agrees with RMS on the endpoint and assessment of the single studies for acute dermal toxicity. Applicant supports the proposed classification for MITC. The applicant disagrees with the ATE of 1100 mg/kg for MITC as an experimental LD_{50} 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 LD_{50}/LC_{50} 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 LD_{50} of 1290 mg/kg bw was derived.
(4)	Vol. 1, 2.6.2.3 Acute toxicity – inhalation route (Table 24), p. 79	**Taminco:** Disagrees with RMS on the attribution of H335 based on the study from B.6.8.1.1/03 (1981) as the use of "EUH071 – Corrosive to the respiratory tract" is proposed, thereby covering and taking precedence on H335.	
(5)	Vol. 1, 2.6.2.3.3 Conclusion on classification and labelling	**Taminco:** Agrees with RMS on the endpoint and assessment of the single studies for acute inhalation toxicity. Applicant supports the	**Taminco:** Agrees with RMS on the endpoint and assessment of the single studies for acute inhalation toxicity. Applicant supports the proposed classifications for metam and MITC.

Acute toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	for acute inhalation toxicity, p. 82	proposed classifications for metam and MITC. The applicant disagrees with the ATE of 1.5 mg/L for metam and the ATE of 0.5 mg/L for MITC. Further information is provided in column 3.	The applicant disagrees with the ATE of 1.5 mg/L for metam and the ATE of 0.5 mg/L for MITC as experimental LD_{50} values are 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 LD_{50}/LC_{50} 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 metam and MITC: an LC_{50} of 2.54 mg/L was derived for metam-sodium, an LD_{50} of 3.04 mg/L for metam-potassium; and an LD_{50} of 0.54 mg/L for MITC.
(6)	Vol. 1, 2.6.2.4.3 Conclusion on classification and labelling for skin corrosion/irritation, p. 85	**Taminco:** Agrees with RMS on the endpoint and assessment of the single studies for skin irritation/corrosion. Applicant supports the proposed classifications for metam and MITC.	
(7)	Vol. 1, 2.6.2.5.3 Conclusion on classification and labelling for eye damage/eye irritation, p. 88	**Taminco:** Does not agree with the proposed classification as H318 for metam and MITC. Further information is provided in column 3.	**Taminco:** Does not agree with the proposed classification as H318 for metam and MITC as existing eye irritation studies are available supporting that no separate classification for eye irritation is warranted and thus that classification as H314 (also covering potential eye damage) is sufficient. Applicant agrees that, in case no animal data were available, the skin corrosive properties of both substances would be sufficient to classify them as H318 to avoid unnecessary animal suffering. This is however not applicable here as existing animal data from 1991 and 2002 are already available supporting non-classification for this hazard category. Additionally, according to Regulation (EC) 1272/2008 labelling as H318 can be omitted in case the substance is already classified as H314 (cfr. note under Table 3.3.5).

Acute toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(8)	Vol. 1, 2.6.2.6.3 Conclusion on classification and labelling for respiratory sensitisation, p. 89	**Taminco:** Applicant supports that a classification for respiratory sensitisation is not warranted.	
(9)	Vol. 1, 2.6.2.7.3 Conclusion on classification and labelling for skin sensitisation, p. 95	**Taminco:** Agrees with RMS on the endpoint and assessment of the single studies for skin sensitisation. Applicant supports the proposed classification.	
(10)	Vol. 1, 2.6.2.8 Phototoxicity, p. 96	**Taminco:** Agrees with RMS on the conclusion that a phototoxicity study for metam is "Not considered necessary, since a study on MITC (the main metabolite) was conducted". Applicant agrees that MITC is not phototoxic.	
(11)	Vol. 1, 2.6.2.9.3 Conclusion on classification and labelling for aspiration hazard, p. 96	**Taminco:** Agrees with RMS that aspiration hazard is not a relevant endpoint for metam and MITC.	
(12)	Vol. 1, 2.6.2.10 Specific target organ toxicity – single exposure (STOT SE) (Table 43), p. 98	**Taminco:** Does not agree with the derivation of the developmental NOAEL. For further detailed comments, please refer to comments 06-11 (reproductive toxicity, metam) and comments 13-19 (reproductive toxicity, MITC).	

Toxicology

Acute toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(13)	Vol. 1, 2.6.2.10.3 Conclusion on classification and labelling for STOT SE (specific target organ toxicity – single exposure), p. 105	**Taminco:** Agrees with RMS on the proposed classification for metam as STOT SE, Cat. 1 (H370) and as EUH071 for MITC.	

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.3.1 Specific target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.3.2.1/01), p. 107	**Taminco:** Generally, agrees with RMS on the assessment of the study, however, proposes a NOAEL of 0.088 mg/mL based on non-adverse effects observed at this dose level. Further information is provided in column 3.	**Taminco:** Generally, agrees with RMS on the assessment of the study. With regards to the effects seen in the bladder the applicant agrees with RMS that "Eosinophilic granules in epithelium" should not be disregarded, however also notes that the observation of "Eosinophilic granules in epithelium" is not following a clear dose-relationship with regards to incidence as well as severity. Furthermore, as no "Cystitis" or "Mucosal hyperplasia" was observed at 0.088 mg/mL, the effect is not regarded as "adverse". Indeed, this finding is listed in the Nonneoplastic Lesion Atlas of NTP. Similarly, some haematology parameters were only slightly affected (<10%, for haemoglobin or haematocrit), which may be explained through malnutrition/low water consumption. With regards to adversity, according to CLP guidance effects >10-20% are considered relevant.
(2)	Vol. 1, 2.6.3.1 Specific target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.3.2.2/01), p. 108	**Taminco:** Generally, agrees with RMS on the assessment of the study, however, proposes a NOAEL of 0.089 mg/mL based on non-adverse effects observed at this dose level. Further information is provided in column 3.	**Taminco:** Generally, agrees with RMS on the assessment of the study. It is acknowledged that metam-sodium seriously affected the food and water consumption at the highest dose of 0.443 mg/mL in both sexes, while the water consumption was also significantly reduced at 0.089 mg/mL in female rats. However, with regards to the NOAEL the applicant is of the opinion that the effect on body weight and body weight gain observed at 0.089 mg/mL should not be considered "adverse" as the effects were below or around 10%. Indeed, when the bodyweight change is directly compared with that of the control group, the effect is -5.7% for males and -10.8% for females. Similarly with regards to the haematological parameters, only statistically significant but biologically non-relevant changes were observed. The parameter "urinary volume" was also affected in the rat long-term study (B.6.5.1/01) but to some extent reversible when compared to the subchronic study. Similarly, specific gravity and protein content of the urine were only slightly

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			affected at this dose level. Effects on urinary volume and specific gravity relate to decreased water consumption, which, in the absence of an effect on bodyweight, cannot be considered adverse. Indeed, in the two-generation study in rats, RMS did not consider decreased water consumption as adverse and thus not for the parental NOAEL setting. Therefore, the NOAEL at 0.089 mg/mL is justified.
(3)	Vol. 1, 2.6.3.1 Specific target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.3.4.1/01), p. 109	**Taminco:** Disagrees with the setting of the NOAEL by RMS. Further information is provided in column 3.	**Taminco:** Disagrees with the setting of the NOAEL by RMS. The applicant is of the opinion that it is not appropriate to consider the changes in blood parameters of any biological and toxicological relevance since re-examination of the liver sections did not reveal a treatment-related effect on livers. Thus, changes on these blood parameters are not indicative for hepatotoxicity due to the absence of a histological correlation in the liver and also in other organs. The applicant proposes a systemic NOAEL of 45 mg/m³. The applicant considers the low dose of 6.5 mg/m³ as the local NOAEL. Clinical signs and histopathological findings were observed at the mid dose group in combination with reduced food consumption, which may also be influenced by the local effects.
(4)	Vol. 1, 2.6.3.1 Specific target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.3.3/01), p. 111	**Taminco:** Disagrees with the setting of the NOAEL 0.1 mg/kg bw based on hepatotoxicity, blood chemistry effects (kaolin-cephalin time or aPTT, ALT/AST/ALP), and associated histopathological liver findings (hepatocyte and Kupffer-cell pigmentation). Further information is provided in column 3.	**Taminco:** Disagrees with the setting of the NOAEL 0.1 mg/kg bw based on hepatotoxicity, blood chemistry effects (kaolin-cephalin time or aPTT, ALT/AST/ALP), and associated histopathological liver findings (hepatocyte and Kupffer-cell pigmentation). The liver enzyme induction was not statistically significant, was mainly driven by one animal, along with other findings: - Increase in ALT levels are indeed relevant but only in combination with AST levels. In this case, ALT was significantly increased starting from week 8 until week 52. However, AST was only slightly affected and even

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			slightly decreased in week 4 as well as rarely affected in week 13. Slight changes were observed in week 26 (+30.5%) and week 52 (+16.7%), which however do not reflect the highly increased ALT levels on week 26 (210.2%) to week 52 (279.2%). Additionally, no statistical significance was reached, which is quite comprehensible considering the high standard deviations starting from week 26. - The histopathological findings were slight telangiectasis with only one animal being affected, thus incidental, and pigmentation in liver hepatocytes and macrophages in two animals each. According to the goRENI database, pigments in the liver are of "incidental occurrence and secondary to cellular and erythroid breakdown products; lipid peroxidation of cellular membranes; altered heme metabolism.", along with the comment that "*A number of different pigments may be seen as an incidental finding within hepatocytes and Kupffer cells in rodents. Some of them may increase and/or accumulate after treatment. Definitive diagnosis of a specific pigment typically requires special stains.* " Thus, the pigmentations cannot be considered adverse or toxicologically relevant. - The kaolin-cephalin time or aPTT was shortly increased up to 14.9%, which however did not last long, and only slight changes were observed over time. Still, even a change of 14.9% compared to control values is not considered adverse or toxicologically relevant. - Physiologically normal values in dogs for aPTT are quite variable and various publications exist in the literature, such as Adhikari et al. (2019) reporting a range from 11 to 22 seconds. It is however noted that in the 90-day dog study adverse effects were observed already at 5 mg/kg bw/d, indicating organ damage. *Reference: Adhikari, R et al. (2019) Establishment of Reference Ranges for Coagulation Tests for Dogs in Sri Lanka. Journal of Pharmacology and Toxicology 7(1):1136.*

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(5)	Vol. 1, 2.6.3.1 Specific target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.8.1.2.1/01), p. 112	**Taminco:** Agrees with RMS assessment to set the local NOAEL to < 5 mg/m^3 = 0.005 mg/L (1.7 ppm) = 1.35 mg/kg bw/day. Disagrees with the setting of the systemic NOAEL of 5 mg/m³ by RMS. For further details please refer to column 3.	**Taminco**: With regards to the systemic NOAEL, the applicant is of the opinion that a systemic NOAEL of 20 mg/m^3 is appropriate. Body weight gain was reduced in males (-9 on day 28 to -18% on day 7) but increased in females (+1 on day 14 to +36% on day 21) and body weight was not significantly reduced in males and females. For males slight (<5%) but not statistically significant changes in body weight were observed. Furthermore, in females no difference was observed at all at 20 mg/m³. Clinical signs were indicative of local (irritating) effects and the animals of the 20 mg/m³ dose group constantly recovered between the exposure periods. Only in the 100 mg/m³ some clinical signs as ruffled fur or respiratory sounds were not fully reversible anymore with longer study duration. Clinical signs that persisted during the post-exposure period are still considered to be related to corrosive effects rather than to systemic toxicity (unkempt fur, respiratory sounds). The increase of neutrophils and leukocytes is associated to the inflammatory process in the respiratory tract. It is considered a systemic reaction to local damage. However, the applicant is of the opinion that this increase does not represent an adverse effect. Leukocytes generally have a wide range of a normal blood concentration. Neutrophil production may be increased up to 20-fold during infection/inflammation. The occurrence of atrophy of the olfactory epithelium can be considered secondary to the local effects and is thus not considered adequate to derive the systemic NOAEL, even more as the local effects and the local NOAEL are lower than the systemic one. A definition of local effects indicates that the point of contact should be considered when deciding on local or systemic effects: "*A local effect is an effect that is observed at the site of first contact, caused irrespective of whether a substance is systemically available. Observed systemic effects that are clearly secondary to causative local*

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			effects should be considered as part of the local effects, and not as primary ("true") systemic effects." JRC (2010) Risk Characterisation of local effects; Ispra, 05/03/2010; https://echa.europa.eu/documents/10162/983772/bpd_guid_guidance_risk_characterization_local_effects_working_document_2010_en.pdf/65ff2ff6-cd3d-48ba-a59e-6382e22c0794#:~:text=A%20local%20effect%20is%20an,or%20on%20the%20GI%20tract.
(6)	Vol. 1, 2.6.3.1 Specific target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.8.1.2.1/02), p. 113	**Taminco:** Disagrees with RMS assessment on NOAEL/LOAEL setting. For further details please refer to column 3.	**Taminco**: A reduction of body weights and body weight gain (mean/cumulative) is observed at all dose levels, especially in males. However, at 5 ppm the final body weight was reduced only by 7% (not statistically significant). Individual cumulative and mean body weight changes were reduced in males but mostly not statistically significant. Thymus weight was reduced but also lacking statistical significance and being comparable with HCD. No histopathological correlates were found indicating organ damage. Squamous metaplasia was observed in the larynx in one animal with minimal severity and without any other findings indicating inflammation. No other histopathological findings were reported at 5 ppm in the lung or nasal cavity. The effects observed at 5 ppm suggest a contribution of treatment but are not considered adverse and thus 5 ppm is considered a NOAEL rather than LOAEL.
(7)	Vol. 1, 2.6.3.1 Specific target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.8.1.2.1/03), p. 117	**Taminco:** Agrees with RMS assessment.	
(8)	Vol. 1, 2.6.3.1 Specific	**Taminco:** Agrees with RMS assessment for setting	**Taminco:** Agrees with RMS assessment for setting the local NOAEL. With

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.8.1.2.2/02), p. 114	the local NOAEL but disagrees with the setting of the systemic NOAEL. For further details please refer to column 3.	regards to the systemic NOAEL the applicant is of the opinion that the observations on haematology and coagulation parameters (APTT, neutrophils), increased liver and decreased thymus weight at 15 ppm do not represent adverse findings. For liver and thymus no histopathological correlates were reported, and no dose-response was observed for organ weights, which were also clearly within HCD. The observation of hepatocellular vacuolation in 2 females of the 15 ppm group and coagulative necrosis in one female of the 15 ppm group was considered incidental by the study director as they represented background lesions. Changes of APTT and neutrophil counts are considered incidental due to the values being generally within the HCD data, lacking a clear dose-response and without any histopathological correlates.
(9)	Vol. 1, 2.6.3.1 Specific target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.8.1.4.1/02), p.116	**Taminco:** Please refer to comment 4 (long-term toxicity and carcinogenicity, MITC)	
(10)	Vol. 1, 2.6.3.1 Specific target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.8.1.4.2/02), p.120	**Taminco:** Please refer to comment 6 (long-term toxicity and carcinogenicity, MITC)	
(11)	Vol. 1, 2.6.3.1 Specific target organ toxicity – repeated exposure (STOT RE) (Table 46 – B.6.8.1.2.2/01), p. 121	**Taminco:** Agrees with RMS that the isolated findings at mid dose level were not toxicologically relevant and that the NOAEL should be set at 0.4 mg/kg bw/d. For further details please refer to column 3.	**Taminco**: The applicant considers the effect on body weight (change) at the top dose as main effect for NOAEL derivation at 0.4 mg/kg bw/d. The change of aPTT at 0.4 mg/kg bw/d cannot be taken as adverse, as it was slightly higher without any statistical significance at one time point only in females, still within HCD. There was also no consistent pattern throughout the measured timepoints. After 6 weeks the values were statistically increased at 0.04 and 0.4 mg/kg bw/d but only very slightly

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			(<10%). After 13 weeks a slight increase was observed without any statistical significance. For both time points the data for 0.04 and 0.4 mg/kg bw/d were clearly within the HCD. Prolongation of aPTT is prone to various intrinsic adaptations (such as vitamin K deficiency and liver metabolism changes), indicating that the effect of direct protein interaction of MITC postulated by RMS might not be the sole reason. With regards to the effect of coarse liver texture the applicant agrees with the RMS that the isolated findings at the mid-dose are insufficient to confirm clear adversity at this dose-level. The applicant also considers remaining observations in the liver (e.g., vacuolation) not adverse in line with the Peer-Review Meeting in 2008 (PRAPeR 2008).
(12)	Vol. 1, 2.6.3.1.3 Conclusion on classification and labelling for STOT RE (specific target organ toxicity – repeated exposure), p. 130	**Taminco:** Agrees with RMS on the proposed classifications for metam and MITC as STOT RE, Cat. 1 (H372).	

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50a – B.6.4.1.1/01) (metam), p. 131	**Taminco:** Agrees with RMS assessment.	

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(2)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50a – B.6.4.1.1/02) (metam), p. 131	**Taminco:** The applicant generally agrees with the RMS. Further information is provided in column 3.	**Taminco:** In agreement with RMS, the study has some limitations also when compared to the current OECD TG 476, showing a very low spontaneous mutation frequency in the control. However, as the positive control provided reasonable results, the applicant is of the opinion that the data should be used as supplementary for the weight of evidence approach. Due to the fact that no dose-response was observed and increased incidences were only found in single experiments, mostly being within the spontaneous mutation frequency of 20 per million cells, the study results do not indicate a mutagenic potential of metam-sodium under the conditions applied. The RMS mentioned a positive response in two out of three experiments in the presence of metabolic activation and in one out of three experiments in the absence of metabolic activation. The applicant is of the opinion that although MF was increased, it was not statistically significant and did not follow a dose-response, thus ruling out a "positive" response in line with the OECD TG 476.
(3)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50a – B.6.4.1.1/03) (metam), p. 131	**Taminco:** Agrees with RMS on the general assessment and description of the study but disagrees with RMS' conclusion for the study result being "positive". Further information is provided in column 3.	**Taminco:** Agrees with RMS on the general assessment and description of the study but disagrees with RMS' conclusion for the study result being "positive". The applicant is of the opinion that the re-examination of the slides showing severe toxic effects on the chromosome morphology at 10 and 20 µg/mL (-S9) and at 40 µg/mL (+S9) prevented an accurate evaluation of the chromosome damaging potential. In the assessment from B.6.4.1.1/08 (1996b) the cytotoxicity was described as "*…overcondensation of the chromosomes, a diffuse, crinkly appearance to chromosomes, poor definition between the chromatids and separation of the chromatids*", which did prevent the correct analysis of chromosomal damage according to the author. The slight increase at 20 µg/mL (+S9) was only slightly outside the range of historical controls of the testing laboratory and is thus, considered of questionable biological significance. In conclusion, the applicant considers the study as

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			"equivocal".
(4)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50a – B.6.4.1.1/04) (metam), p. 131	**Taminco:** The applicant disagrees with the RMS on the final conclusion for the study as "weakly positive". In the opinion of the applicant the small increases of aberrant cells, although statistically significant, are not considered biologically relevant. Compared to the positive controls, the increase of aberrant cells after metam-sodium treatment was very low and clearly within the laboratory historical control range. Furthermore, the control incidence was very low (0-0.25%).	
(5)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50a – B.6.4.1.1/05) (metam), p. 132	**Taminco:** Agrees with RMS assessment.	
(6)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50a – B.6.4.1.2/01) (metam), p. 132	**Taminco:** Agrees with RMS assessment.	
(7)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50a – B.6.4.1.2/02) (metam), p. 132	**Taminco:** Agrees with RMS assessment and conclusion that the test is to be considered "positive" based on the criteria provided in the OECD TG 490. However, taking into account the contribution of glutathione depletion by metam-sodium, which contributes to cytotoxicity and is inversely correlated to mutation frequency in	

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		mouse lymphoma cells in general, and the fact that the mutation frequency was only increased at concentrations with a RTG <35% with a substantial increase only at RTG <10%, the biological relevance *in vivo* is questionable.	
(8)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50a – B.6.4.1.1/06) (metam), p. 132	**Taminco:** Agrees with RMS assessment.	
(9)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50a – B.6.4.1.1/07) (metam), p. 132	**Taminco:** Agrees with RMS assessment.	
(10)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50b –B.6.8.1.3.1/01) (MITC), p. 134	**Taminco:** Agrees with RMS assessment.	
(11)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50b –B.6.8.1.3.1/04) (MITC), p. 134	**Taminco:** Agrees with RMS assessment.	
(12)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50b	**Taminco:** Agrees with RMS assessment.	

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	–B.6.8.1.3.1/03) (MITC), p. 134		
(13)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50b –B.6.8.1.3.1/06) (MITC), p. 134	**Taminco:** Agrees with RMS assessment.	
(14)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50b –B.6.8.1.3.1/02) (MITC), p. 134	**Taminco:** Agrees with RMS assessment.	
(15)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 50b –B.6.8.1.3.1/05) (MITC), p. 134	Applicant has no copy of the respective study report and asked the owner of the data Kanesho Soil Treatment (KST) to comment. **KST:** RMS requested clarification on why the 4h+S9 conditions in Experiment 3 was not tested. Due to miscommunication with the CRO the pre-test was assumed to show clear genotoxicity. Therefore, it was assumed that only one condition had to be evaluated in the main test. A thorough review of all results after the main test was finished showed that the results were not as definite as originally communicated.	**Taminco:** The pilot study will be submitted by KST directly to clarify the problems while establishing a method for volatile compounds
(16)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 51a – B.6.4.2.1/01) (metam), p.	**Taminco:** Agrees with RMS' conclusion on the lack of genotoxicity in the *in vivo* MNT. Further information is provided in column 3.	**Taminco:** Agrees with RMS' conclusion on the lack of genotoxicity in the *in vivo* MNT. The applicant notes that, in agreement with the summary provided in the RAR, the systemic bioavailability of the test substance was demonstrated by clinical signs observed at 500 mg/kg bw and should

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	135		be further used in the weight of evidence assessment. Indeed, in the Appendix C "Examples of endpoints, which might contribute to the weight-of-evidence assessment" of the EFSA Scientific Opinion on "Clarification of some aspects related to genotoxicity assessment" (EFSA Journal 2017;15(12):5113) certain clinical signs of toxicity (CNS-related as well as clinical observations such as posture) are depicted as "lines of evidence of systemic bioavailability and consequently, lines of evidence of bone marrow exposure".
(17)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 51a – B.6.4.2.1/02) (metam), p. 135	**Taminco:** Agrees with the general assessment of the study results, however, is of the opinion that study results should be considered "negative". Further information is provided in column 3.	**Taminco:** The study results should be considered "negative", considering the following points: - No dose-response relationship was observed and, albeit being statistically significant, there was only a slight increase at the top dose occurring solely at 24 hours, i.e., one third of the sampling points. - The statistical significance of 95% in the Fisher's Exact test observed in the 600 mg/kg bw group at a sacrifice interval of 24 hours was found only in comparison of one dose group to the negative control. - No increases were seen at 6h or 48h after treatment. - This significance at a value of 0.9% aberrant cells excl. gaps is due to the low spontaneous rate of 0.1% aberrant metaphases excl. gaps and cannot reflect biological relevance, especially considering that 0.9% is within the range of HCD. When all three dose groups are compared to the negative control group, no statistical significance was attained.
(18)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 51a – B.6.4.2.2/01) (metam), p.	**Part 1, micronucleus test, bone marrow:** **Taminco:** Agrees with RMS assessment on genotoxicity. However, the applicant considers bone marrow exposure after oral application of	**Part 1, micronucleus test, bone marrow:** **Taminco:** Agrees with RMS assessment on genotoxicity. However, regarding the bioavailability of metam there is solid indication of the bone marrow cytotoxicity in the top dose animals, as

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	135	metam in rats has been sufficiently demonstrated. Further information is provided in column 3. **Part 2, Comet assay, stomach/liver:** **Taminco:** The applicant is of the opinion that the conclusion of the Comet assay should not be considered "positive". Further information is provided in column 3.	- the mean PCE/NCE ratio was decreased by 18%, with individual reductions ranging from 11% to 25%. Statistical analysis using a trend test supported this assumption that there is an effect on the PCE/NCE ratio at the top dose, and, - additionally, certain clinical signs that are relevant as lines of evidence for bone marrow exposure were observed in all metam-treated groups (lethargy as well as salivation). Indeed, according to the EFSA Scientific Opinion on "Clarification of some aspects related to genotoxicity assessment" (EFSA Journal 2017;15(12):5113) these are considered as sufficient evidence of bone marrow exposure (see section 3.2.1). Thus, considering all lines of evidence, bone marrow exposure after oral application of metam in rats has been sufficiently demonstrated. **Part 2, Comet assay, stomach/liver:** **Taminco:** The applicant is of the opinion that the conclusion of the Comet assay should not be considered "positive", due to the following reasons: - Increases of tail intensities were only observed at the top dose of 350 mg/kg bw in both liver and stomach tissue, being slightly above HCD. - A clear dose-response relationship was neither observed in liver nor in stomach, - in all animals of the top dose cytotoxicity was evident in liver (hypertrophy, necrosis, inflammation) and stomach (erosion/ulcer, oedema, inflammation, hyperplasia and hyperkeratosis). According to the OECD TG 489 (2016), "a test chemical is considered to be clearly positive [..] when <u>all</u> of the following criteria are met": - At least one test dose exhibiting statistically significant increase

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			compared with the concurrent negative control - A statistically dose-related increase is present - Any result is outside the distribution of the historical negative control data Thus, the conditions to conclude as "positive" were clearly not met. The OECD TG 489 additionally states that *"Increases in DNA migration in the presence of clear evidence of cytotoxicity should be interpreted with caution."* Indeed, the statistically significant increase was present at the highest top dose, where also cytotoxicity was noted. Still, applicant acknowledges the fact that the criteria for a clear negative result were not all met, and thus proposes to consider the study result as equivocal, which would be also in line with section 64 of the OECD TG 489, also considering that no biologically relevant increase of DNA damage was observed.
(19)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 51b –B.6.8.1.3.2/01) (MITC), p. 136	**Taminco:** Agrees with RMS assessment.	
(20)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 51b –B.6.8.1.3.2/02 and B.6.8.1.3.2/03) (MITC), p. 136	**Taminco:** Agrees with RMS assessment.	
(21)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 51b	**Taminco:** Agrees with RMS assessment.	

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	–B.6.8.1.3.2/05) (MITC), p. 136		
(22)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 51b –B.6.8.1.3.2/05) (MITC), p. 136	As both applicant and Kanesho Soil Treatment (KST) are co-owners of the study, KST was invited to provide comments. **KST:** One dose was chosen to be conducted with radiolabelled material to ensure proof of exposure in all tissues in question. There is no reason to believe that the different source should have any influence on the results.	
(23)	Vol. 1, 2.6.4 Summary of genotoxicity/germ cell mutagenicity (Table 51b –B.6.8.1.3.2/04) (MITC), p. 137	**Taminco:** Agrees with RMS assessment.	
(24)	Vol. 1, 2.6.4.1 Short summary and overall relevance of the provided information on genotoxicity/germ cell mutagenicity (metam), p. 139	**Taminco:** Agrees with RMS that classification in Category 1A or B is certainly not warranted. Furthermore, the applicant is of the opinion that no classification is warranted at all. For further details please refer to column 3.	**Taminco:** With regards to the proposed classification in Category 2, the applicant is of the opinion that there is not one single test available providing clear and unambiguously positive results for genotoxic properties of metam. Potential genotoxic effects observed in *in vitro* or *in vivo* studies were always accompanied by indication of cytotoxicity and consistently lacking a clear dose-response relationship. In addition, MITC, the main metabolite of metam formed by rapid degradation in animals, is devoid of a genotoxic potential and thus providing some supportive information for the weight of evidence of metam genotoxicity evaluation. The applicant is also of the opinion that the available *in vivo* somatic cell genotoxicity tests yield negative results and therefore classification for germ cell mutagenicity is not warranted. This was also suggested by the RMS in its statement under 2.6.4.2: "*As suggested here above and further discussed below, the genotoxicity*

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			package of metam indicated that, while there are some indications of interactions of metam with the genetic material the criteria for classification of this a.s. as Muta Category 2 are not fully met" and "*RMS notes that a positive gene mutation assay in the presence of clearly negative bacterial gene mutation assays could possibly reflect "false positive" results, especially in the case when the test article would cause severe cytotoxicity. This could be the case with metam, in which case this would constitute an important argument for no classification instead of classification as Muta. 2".* The applicant kindly asks RMS to revise the respective entry in the table under section 3.1.8 "Area(s) where expert consultation is considered necessary".
(25)	Vol. 1, 2.6.4.1 Short summary and overall relevance of the provided information on genotoxicity/germ cell mutagenicity (MITC), p. 140	**Taminco:** Agrees with RMS that MITC is devoid of genotoxic potential and should not be classified.	
(26)	Vol. 1, 2.6.4.3 Conclusion on classification and labelling for genotoxicity/germ cell mutagenicity, p. 144	**Taminco:** Does not agree with the proposed classification as Muta. 2 for metam and considers that a classification for germ cell mutagenicity is not warranted (please refer to comment 24). The applicant agrees with RMS that no classification is needed for MITC.	The applicant also kindly asks RMS to revise the respective entry in the table under section 3.1.8 "Area(s) where expert consultation is considered necessary".

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.5 Summary of long-term toxicity and carcinogenicity (Table 53a –B.6.5.1/01) (metam), p. 145	**Taminco:** Agrees with RMS assessment and conclusion on a long-term and carcinogenic NOAEL of 1.5 mg/kg bw/d. With regards to carcinogenicity the applicant is of the opinion that incidences of benign and malignant haemangiomatous tumours observed in rats were not considered treatment-related. Further information is provided in column 3.	**Taminco:** The incidence of haemangioma in treated groups was comparable to or lower than in the control group. The incidence of haemangiosarcoma was highest in mesenteric lymph nodes and slightly increased at mid dose for males and low dose for females, without attaining statistical significance or demonstrating a dose-response relationship. The incidence of mesenteric lymph node haemangiosarcoma at the other dose groups was comparable to the historical control data. When considering the combined incidence of haemangioma and haemangiosarcoma (at all sites), as suggested by NTP and the RMS, there is no statistically significant increase at any dose level and no clear dose-response relationship could be established. The relevance of the liver tumour formation is also questionable due to the lack of a dose-response relationship and being just slightly, but not statistically significantly, above HCD data. The liver tumours were only observed in one species and the hepatoblastoma was observed in one animal of the intercurrent group only. Though the incidences just slightly deviated from the HCD data, considering that hepatoblastoma represents a rare tumour type, it is acknowledged that the findings were outside the HCD range. In view of the overall results obtained in this carcinogenicity study, a carcinogenic potential of metam-sodium is considered low. Respective reference in the RAR (Metam RAR_08_Volume_3CA_B-6_2023-07-25): Table B.6.5.1/01-10 (page 309) and Table B.6.5.1/01-11a (page 310).
(2)	Vol. 1, 2.6.5 Summary of long-term toxicity and carcinogenicity (Table 53a –B.6.5.2/01)	**Taminco:** Disagrees with the effect level setting of the RMS. The applicant is of the opinion that the systemic effects at the low dose should be considered a NOAEL.	**Taminco:** The relevance of the increased amounts in the epithelial cells especially at the low dose group is questionable. For "eosinophilic cytoplasmic inclusion, epithelium, total" indeed an increased incidence was observed at the low dose group but only in females. They are

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	(metam), p. 145	Further information is provided in column 3.	however not associated with adverse or neoplastic effects and specific for mice. There is some evidence that they represent test substance incorporation into the cells, which would explain the increased incidence in the treated animals in general. However, no further lesions were observed in the bladder that were affected at the low dose. Furthermore, "mononuclear cell infiltration total" was higher in the control group (63% of animals affected) than in the treatment groups (48%, 40%, 53%). With regards to neoplastic lesions the applicant proposes a carcinogenic NOAEL of 0.019 mg/mL (1.9 mg/kg bw/d). There is no clear dose-response relationship for the incidence of angiosarcoma (all sites), also showing a lower incidence for females at the low dose compared to the control. Only at the top dose a statistically significant increase was observed (in males only). It should be noted that the current study duration of 104 weeks is longer than recommended for a mouse carcinogenicity study (78 weeks) and that 92.6% of the angiosarcoma in this group were detected after 78 weeks of treatment. In addition, as the incidences of angiosarcoma are quite variable with regards to respective target organs, the overall incidence considering all organs should be treated with caution. For example, although the incidence of angiosarcoma in the liver is within HCD and no dose-response relationship is observed, these incidences in combination with their absence in the control group contribute to the assessment of total angiosarcoma incidence in all organs and indicate a higher incidence also at the low dose. In the view of the applicant this should be considered biasing the overall outcome. The sites with the highest angiosarcoma incidence were spleen and liver. Albeit the increase being not statistically significant, the incidence of spleen angiosarcoma was outside the historical control data for males at the mid and high dose. It should also be noted that those for the control

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			group was at the upper limit of the HCD. For females, the incidence of spleen angiosarcoma was within HCD for all dose groups. For liver angiosarcoma, the incidence at the highest dose group in males was slightly outside the HCD but without any statistical significance or a clear dose-response relationship. The incidence of liver angiosarcoma in females was within HCD for all dose groups. The single lesions in the urinary bladder (cell carcinoma, cell papilloma) may be attributed to metam treatment, as non-neoplastic inflammatory lesions were also consistently observed in this study. However, the non-neoplastic inflammatory lesions were not considered adverse at the low dose. A possible correlation between the bladder tumours and the more frequent bladder anomalies is unknown in this case, though it is plausible that a mechanism to compensate tissue damage involving hyperplasia and immune infiltration is part of an adaptive response possibly leading to neoplasia, especially as the tumours were only observed in the high dose animals. Thus, the applicant considers the low dose a NOAEL for systemic and carcinogenic effects. With regards to classification as Carc. Cat. 2, the applicant is of the opinion that there are more reasons why a classification is not mandatory but acknowledges the fact that some uncertainty exists with regards to the rare tumour observed or single incidences above HCD. Respective reference in the RAR (Metam_RAR_08_Volume_3CA_B-6_2023-07-25): Table B.6.5.2/01-9 (page 324). Additional HCD data (see below) can be submitted on request:

Non-neoplastic lesion	Male	Female
HCD, Spleen extramedullary	1.7% - 21.8%	1.7% - 48.3%

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			haematopoiesis total | | | HCD, Mononuclear cell infiltration | 0 – 14.5% | 3.4 – 58.2% HCD, Eosinophilic cytoplasmic inclusion epithelium | 0% | 0% HCD, Liver fat vacuolation | 0% - 3.3% | 1.67% - 21.8% HCD, Liver areas of hepatocyte necrosis | 0% - 5% | 0% - 7.3% HCD, Adrenals cortical ceroidosis total | 1.8% - 96.7% | 0% - 61.7% HCD, Epididymis mononuclear cell infiltration total | 0% - 15% | Not applicable HCD, Testis atrophy moderate | 0% - 87.3% | Not applicable
(3)	Vol. 1, 2.6.5 Summary of long-term toxicity and carcinogenicity (Table 53b –B.6.8.1.4.1/01) (MITC), p. 146	**Taminco:** Agrees with RMS to set a NOAEL of 10 ppm based on mainly the reduced body weight of male rats at 50 ppm in combination with histopathological and haematological alterations. No indication for carcinogenicity was observed. For further details please refer to column 3.	**Taminco:** With regard to the comment by RMS that the analytical verification of the test material in the drinking water showed deficiencies, the applicant agrees that the impact of the uncertainty is acceptable, as explained by the RMS on p. 646 of the RAR B6: if an average recovery of 88% (validation results) would have to be applied as a correction, the NOAEL of about 0.44 mg/kg bw/d would recalculate to about 0.39 mg/kg bw/d, which is equivalent to the most relevant NOAEL in the dog (gavage) study, which is also 0.4 mg/kg bw/d.

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	Vol. 1, 2.6.5 Summary of long-term toxicity and carcinogenicity (Table 53b –B.6.8.1.4.1/02) (MITC), p. 146	**Taminco:** Agrees with RMS assessment to set the systemic NOAEL to 5 ppm based on decreased body weight (gain), haematology and clinical chemistry parameter modifications, and organ weight effects at 20 ppm. Agrees with RMS assessment to set the carcinogenic NOAEL to 5 ppm (15 mg/m^3) mainly based on the occurrence of nasal tumours at 20 ppm. Disagrees with the setting of the local NOAEL and considers that classification for carcinogenicity not warranted. For further details refer to column 3.	**Taminco:** Agrees with the RMS' conclusion that the high dose of 20 ppm (60 mg/m^3) exceeded the MTD. With regards to the local NOAEL the applicant disagrees and is of the opinion that based on the low incidence combined with minimal to mild severity, effects observed in the larynx or trachea are not adverse at 0.5 ppm in agreement with the study director. Moderate to severe laryngeal squamous metaplasia should be considered adverse, whereas minimal to slight effects can be regarded as non-adverse.* The local NOAEL should therefore be set at 0.5 ppm (1.5 mg/m^3). Classification for carcinogenicity is not warranted due to the following reasons: As the carcinogenic effects were only noted in the lifetime rat bioassay at doses clearly exceeding the MTD, the finding is considered an indication of a confounding effect of excessive cytotoxicity. The lack of a dose-response relationship and the presence of a threshold clearly supports this assumption. The non-neoplastic lesions are typical of those seen with contact irritants with high water solubility where nasal degeneration occurs. These data are supported by the information from B.6.8.1.2.1/04 (2020). As the tumour formation was only seen in one of two inhalation studies but not in drinking water studies and only at concentrations above the MTD, it is considered that classification as Carc. Cat. 2 is not warranted. Reference is also made to 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*

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			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." 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 covering dose levels or concentrations equivalent to those leading to tumour formation. 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. Overall, no classification for carcinogenicity according to CLP is warranted for MITC. *: Kaufmann et al. (2009) 1st International ESTP Expert Workshop: "Larynx squamous metaplasia". A re-consideration of morphology and diagnostic approaches in rodent studies and its relevance for human risk assessment, Experimental and Toxicologic Pathology, Volume 61, Issue 6, 2009, Pages 591-603; https://doi.org/10.1016/j.etp.2009.01.001
(5)	Vol. 1, 2.6.5 Summary of long-term toxicity and carcinogenicity (Table 53b –B.6.8.1.4.2/01) (MITC), p. 147	**Taminco:** Agrees with RMS to set a NOAEL of 20 ppm based on clinical signs, reduced body weight and body weight gain, slight effects on blood and changes in organ weight at 80 ppm. No indication for carcinogenicity was observed.	
(6)	Vol. 1, 2.6.5 Summary of long-term toxicity and	**Taminco:** Agrees with RMS assessment to set the systemic NOAEL to 1 ppm (3 mg/m³) and a	**Taminco:** Agrees with RMS assessment to set the systemic NOAEL to 1 ppm (3 mg/m³) based on persistent lower mean body weight and body

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	carcinogenicity (Table 53b –B.6.8.1.4.2/02) (MITC), p. 147	carcinogenicity NOAEL of 15 ppm (45 mg/m³). The applicant also agrees with the RMS that the dose of 15 ppm is considered to exceed the MTD. Disagrees with the setting of the local NOAEL and considers that the local NOAEL should be set at 1 ppm (3 mg/m³). For further details please refer to column 3.	weight gain and lower food consumption as well as lower spleen weight and a carcinogenicity NOAEL of 15 ppm (45 mg/m³). The applicant also agrees with the RMS that the dose of 15 ppm is considered to exceed the MTD. With regards to the local NOAEL, the applicant agrees with RMS that treatment related effects based on respiratory and transitional epithelial hyperplasia were observed. These effects are typically observed in rodents exposed to irritants. However, as the severity was comparable to the control group and no further effects as metaplasia or necrosis/ulceration in combination with general inflammatory areas were observed, the applicant is of the opinion that these effects may not be adverse but rather adaptive at this dose level. Therefore, the applicant is of the opinion that the local NOAEL should be set at 1 ppm (3 mg/m³).
(7)	Vol. 1, 2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity (metam), p. 155	**Taminco:** Based on a weight of evidence, classification as "Carc 2 (H351: Suspected of causing cancer)" is meaningful considering some uncertainties for the haemangioma/haemangiosarcoma formation.	
(8)	Vol. 1, 2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity (MITC), p. 157	**Taminco:** The applicant would like to highlight that a possible MoA for MITC carcinogenicity is elaborated under Vol.3 CA B.6.8.2.1b. For further details please refer to column 3.	**Taminco:** Additionally in the study from B.6.8.1.2.1/04 (2020), rats were exposed to concentrations of 0, 0.5, 5, and 20 ppm MITC for 1 day, 5 days, 4 weeks (5 days/week), and 4 weeks (5 days/week) with an additional 4-week recovery period. 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

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			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 was 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 20 ppm was considered to be above the MTD, as the level of cytotoxicity, regenerative cell proliferation, hyperplasia, and metaplasia observed at 20 ppm does clearly fulfil the criteria of causing unacceptable toxic effects. In conclusion, the tumour formation in rats after inhalation of MITC is considered substance-related (with threshold) based on local cytotoxic effects and resulting cell regeneration and was observed above the MTD only.
(9)	Vol. 1, 2.6.5.2 Comparison with the CLP criteria regarding	**Taminco:** In the opinion of the applicant no classification for carcinogenicity is warranted for MITC.	**Taminco:** 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

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	carcinogenicity (MITC), p. 157	For further details please refer to column 3.	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.
(10)	Vol. 1, 2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity (MITC), p. 157-159	**Taminco:** The applicant would like to highlight that point (e) refers to angiosarcomas in both sexes which seems to be a copy/paste error from metam. Additionally point (j) makes references to nasal tumours observed at dose**s** (indicating more than one dose was affected), which is however, not correct as nasal tumours were only observed at the top dose.	
(11)	Vol. 1, 2.6.5.3 Conclusion	**Taminco:** Agrees with the proposed classification	

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	on classification and labelling for carcinogenicity, p. 159	as Carc. Cat. 2 (H351) for metam taking into account some uncertainties for the haemangioma/haemangiosarcoma formation. The applicant does not agree with the proposed classification as Carc. 2 for MITC and considers that a classification for carcinogenicity is not warranted (please refer to comment 9).	

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 56a –B.6.6.1.2/01) (metam), p. 160	**Taminco:** Agrees with RMS to set the following effect levels: • Parental toxicity NOAEL: 0.03 mg/mL (4.0 mg/kg bw/d) • Offspring toxicity NOAEL: 4.0 mg/kg bw/d • Reproduction toxicity NOAEL: 12.3 mg/kg bw/d.	
(2)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 56b – B.6.8.1.5.1/01) (MITC), p. 161	**Taminco:** Agrees with RMS assessment to set the parental NOAEL to 10 ppm based on lower mean body weight and body weight gain. Agrees to set the reproductive toxicity/fertility and developmental NOAELs to >50 ppm as no adverse effects were observed at the top dose. For further details please refer to column 3.	**Taminco:** The applicant agrees with RMS assessment to set the parental NOAEL to 10 ppm based on lower mean body weight and body weight gain. Agrees to set the reproductive toxicity/fertility and developmental NOAELs to >50 ppm as no adverse effects were observed at the top dose. The fertility indices of the F0 animals were not considered a treatment-related effect as no dose response was observed and this potential effect was not consistent within different generations. In other generations (e.g., F1) the fertility index was 100% in the high dose group compared to 96% of the control group. With regards to the request for HCD on hydrocephaly findings in the timeframe of 5 years around the reference study, the applicant did reach out to the laboratory. However, no HCD are available for the respective study within the respective timeframe. With regards to the calculated intake of test substance the applicant agrees with RMS that considering an average recovery of 60%, the re-calculated intake would be 0.43 instead of 0.71 mg/kg bw/day, which is equivalent to the NOAEL of 0.4 mg/kg bw/day obtained in the dog study. The impact of the uncertainty is therefore considered acceptable. The applicant cannot certainly confirm that the poor recovery has been taken into account for the test substance intake.

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(3)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 56b – B.6.8.1.5.1/02) (MITC), p. 161	**Taminco:** Agrees in general with RMS assessment to set the parental NOAEL to 5 ppm, the offspring NOAEL to 20 ppm and the reproductive toxicity NOAEL to 5 ppm. Further details and remarks are provided in column 3. NOAEL values for reproductive toxicity as listed in Table 56b should be adapted to 5 ppm. The reference for the study B.6.8.**4**.5.1 should be replaced by B.6.8.**1**.5.1.	**Taminco:** Agrees with RMS assessment to set the parental NOAEL to 5 ppm, the offspring NOAEL to 20 ppm and the reproductive toxicity NOAEL to 5 ppm. Due to the slight variation and being within the respective HCD, effects on oestrous cycle and gestation length at 20 ppm were not considered adverse and thus in accordance with the former evaluation as "not toxicologically relevant" in the post-approval addendum. Considering the effect on the vaginal patency at 20 ppm, a concentration of 5 ppm is considered justified for the reproductive toxicity NOAEL. An increase in the oestrous cycle length for F_0 (4.5 days) and F_1 (4.9 days) females was noted at the highest dose of 20 ppm. These values were however within the range of historical control data (mean 4.5 days; range 4.0-5.8 days) and attributable to two females in F_0 with longer oestrous cycles (6.3 and 8.0 days) and two females in F_1 (7.3 and 10.3 days). Therefore, the slight prolongation in oestrus cycle length at 20 ppm was not considered to be of toxicological relevance. This is also in agreement with the conclusion in the post-approval addendum of September 2016 in which the RMS agreed that the slight prolongation in oestrous cycle length can be regarded as not toxicologically relevant and additionally noted that the mean oestrous cycle length of the study control was on the lower side of the HCD with several animals even below the control range. Longer gestation lengths were also noted for F_0 females (22 days) at the highest dose of 20 ppm. These values were however within the range of historical control data (mean: 22.0 days; range: 21.5-22.3 days) and the observation did not occur in F_1 females, the slightly longer gestation length was therefore not attributed to test item exposure. This is also in agreement with the conclusion in the post-approval addendum of September 2016 in which the RMS agreed with the conclusion from the

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			study report and additionally noted that the individual gestation lengths of the F_0 females at 20 ppm did not exceed the HCD (all females had a gestation length of 22 days at 20 ppm), nor the gestation lengths observed for the concurrent control (gestation length was 21-22 days). The RMS additionally asked for further information on ovary primordial follicle counts for all dose groups. The applicant has an expert statement available concluding on the relevance of the higher primordial follicle count (PFC) in the high dose group, which can be provided upon request. In summary, the mean PFC in the high dose group, although statistically significantly different from control, is not an indication of adversity (i.e., follicular depletion), and therefore, does not require further assessment of the low and mid-dose group animals. This conclusion is further driven home by the fact that the mean PFC value in the high dose group was well within the HCD range, and therefore, unlikely to be indicative of a biologically relevant change. Moreover, no other indications of ovarian or reproductive toxicity were observed in the OECD 416 inhalation study of MITC (B.6.8.1.5.1/02, 2014).
(4)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 56b – B.6.8.1.5.1/03) (MITC), p. 161	**Taminco:** Agrees with RMS assessment. **Reference to be adapted to** B.6.8.**1**.5.1/03 instead of B.6.8.4.5.1/03	
(5)	Vol. 1, 2.6.6.1.1 Short summary and overall relevance of the provided information on adverse effects on sexual function	**Taminco:** Agrees with RMS that both metam and MITC did not show adverse effects on sexual function as well as fertility and should not be classified accordingly.	

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	and fertility – generational studies, p. 207		
(6)	Vol. 1, 2.6.6.2 Summary of reproductive toxicity (Table 59a –B.6.6.2.1/01) (metam), p. 209	**Taminco:** Agrees with RMS to set the maternal toxicity NOAEL at 10 mg/kg bw/d based on reduced body weight, body weight gain and food consumption at ≥40 mg/kg bw/d. With regards to the developmental toxicity NOAEL the applicant is of the opinion that 10 mg/kg bw/d is still applicable in alignment with the former evaluation. For further details please refer to column 3.	**Taminco:** Agrees with RMS to set the maternal toxicity NOAEL at 10 mg/kg bw/d based on reduced body weight, body weight gain and food consumption at ≥40 mg/kg bw/d. With regards to the developmental toxicity NOAEL the applicant is of the opinion that 10 mg/kg bw/d is still applicable in alignment with the former evaluation. The effects observed (ossification delay, variations) are considered secondary to treatment. Maternal bw during GD 0-20 was reduced by 7.1% and most prominently body weight gain during early gestation periods was reduced by 21.3% (GD 6-8). Furthermore, with respect to CLP criteria these effects are not considered adverse (CLP guidance, 2017, Annex I: 3.7.2.4.3, see column 3). This is supported by the fact that the data were only partly and slightly above HCD. Besides, several variations were reduced at 10 mg/kg bw/d compared to controls, thus further questioning the relevance of the effects observed. Please also note that the two affected litters displaying incomplete ossification of the metatarsal bones had both decreased bodyweight gains of -11% compared to the control mean group. Thus, it is obvious that the incomplete ossification was due to the systemic maternal toxicity. RMS' has stated that the litter incidence is the most relevant statistical unit. Thus, from that point of view the slight increase of 0.4% of incomplete ossification of metatarsal bones in the low dose animals compared to control animals cannot be considered toxicologically relevant. Additionally, it is important to note that even the control animals had higher incidences than the historical control data.

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			CLP guidance, 2017, Annex I: 3.7.2.4.3: *"Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1. However, when a substance is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects.* ***Classification is not necessarily the outcome in the case of minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity."*** [emphasis added]
(7)	Vol. 1, 2.6.6.2 Summary of reproductive toxicity (Table 59a –B.6.6.2.1/02) (metam), p. 209	**Taminco:** Agrees with RMS that the doses of 5, 20 and 60 mg/kg bw/d were adequate for the full developmental toxicity study in the rat. With respect to tentative NOAEL values the applicant would agree with the RMS to propose them at < 20 mg/kg bw/d (reduced maternal and foetal weight) for maternal toxicity and developmental toxicity.	
(8)	Vol. 1, 2.6.6.2 Summary of reproductive toxicity (Table 59a –B.6.6.2.1/03) (metam), p. 209	**Taminco:** Agrees with RMS to keep the maternal NOAEL at 5 mg/kg bw/d based on reduced body weight (gain) and clinical signs observed at 20 mg/kg bw/d. For the developmental NOAEL the applicant	**Taminco:** The applicant is of the opinion that a classification is not warranted based on the effects observed. Variations/retardations (odontoid: unossified; cervical vertebrae (2nd): centrum not ossified; calcaneum: not ossified; thoracic vertebrae (5th and $10\text{-}13^{th}$): centrum partially ossified) are not *per se* considered adverse effects according to

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		disagrees and considers the lowest dose of 5 mg/kg bw/d as the appropriate NOAEL. The variations/retardations are not considered adverse with regards to CLP criteria and were observed at incidences within HCD (at 5 and 20 mg/kg bw/d). According to the applicant, the effects observed do not represent specific developmental effects relevant for classification that were observed in the absence of maternal toxicity and thus, classification for Category 2 for reproductive toxicity is not warranted. Further information is provided in column 3.	the CLP regulation and were furthermore observed within HCD values. A dose-dependent increase due to metam-sodium exposure cannot be excluded, however, is considered a secondary effect of maternal toxicity and with an increase in an extent comparable to that of the maternal toxicity. Furthermore, the applicant supports maintaining the developmental NOAEL at 5 mg/kg bw/day, as the developmental effects observed at 5 mg/kg bw/day are not considered adverse due to co-occurrence with systemic toxicity. Only some parameters were increased slightly and/or significantly compared to the control, however concerned only minor skeletal defects or variations. They were also consistently within HCD data. In addition, several parameters related to skeletal effects were decreased when compared to control. In conclusion, the NOAEL for maternal and developmental toxicity is considered 5 mg/kg bw/day. According to the applicant, the effects observed do not represent specific developmental effects relevant for classification that were observed in the absence of maternal toxicity and thus, classification for Category 2 for reproductive toxicity is not warranted. The applicant kindly asks RMS to revise the respective entry in the table under section 3.1.8 "Area(s) where expert consultation is considered necessary".
(9)	Vol. 1, 2.6.6.2 Summary of reproductive toxicity (Table 59a –B.6.6.2.2/01-02) (metam), p. 209	**Taminco:** Agrees with RMS to keep the developmental NOAEL at 20 mg/kg bw/d based on clear foetotoxicity at 40 mg/kg bw/d. The applicant is also suggesting a maternal NOAEL of 20 mg/kg bw/d. Further information is provided in column 3.	**Taminco:** Agrees with RMS to keep the developmental NOAEL at 20 mg/kg bw/d based on clear foetotoxicity at 40 mg/kg bw/d. The applicant is also suggesting a maternal NOAEL of 20 mg/kg bw/d. There were differences in body weight gain being increased or decreased during various periods during gestation at 20 mg/kg bw/d compared to the control. However, no clear trend was observed and the slight, not

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			statistically significant reduction of 8% at GD 8-20 was not observed at the end of the study (GD 4-30). When considering the complete gestation period (GD 4-30), the body weight gain was even increased up to 17% at 20 mg/kg bw/d compared to the control.
(10)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 59a –B.6.6.2.2/03) (metam), p. 210	**Taminco:** Agrees with RMS to keep the maternal NOAEL at 5 mg/kg bw/d based on reduction in body weight and food consumption at 20 mg/kg bw/d. The applicant disagrees with lowering of the developmental NOAEL and supports to maintain it at 20 mg/kg bw/d. The applicant is of the opinion that no classification for reproductive toxicity is warranted for metam-sodium based on the effects observed in this study in the presence of maternal toxicity. Further information is provided in column 3.	**Taminco:** Four groups of 20 presumed pregnant NZW rabbits received metam-sodium at dose levels of 0, 5, 20 and 60 mg/kg bw/d by gavage from GD 8-20. Clear evidence of maternal toxicity was seen at 20 and 60 mg/kg bw/d dose levels of metam-sodium as shown by dose-related reductions in bodyweight gain and food consumption during dosing period. Thus, the NOAEL for maternal toxicity was considered to be 5 mg/kg bw/day. Evidence for foetotoxicity was observed at 60 mg/kg bw/day by reduced foetal weights. Considering the CLP criteria, the increased incidence of single skeletal minor defects or variants at 20 mg/kg bw/d is not considered adverse. This is supported by additional HCD showing that incidences of "Cervical Vertebrae - transverse process partially ossified 7th; Lumbar vertebrae - transverse processes fully ossified 3rd; Odontoid – partially ossified; Vertebral column – 27 presacral vertebrae" at 20 mg/kg bw/day were all covered. Furthermore, the total incidence of minor skeletal defects was even lower (-13%) at 20 mg/kg bw/d compared to the control group. The NOAEL for developmental toxicity should therefore remain at 20 mg/kg bw/d. The level of maternal toxicity at 60 mg/kg bw/d most likely exceeded the MTD and was associated with increased embryonic lethality. The absolute number of major abnormalities was increased at 60 mg/kg bw/d because of the decreased number of viable foetuses. Specific defects included cleft palate which is uncommon in control NZW rabbits in the performing laboratory but was also seen incidentally at a low incidence in the control group. The incidence of major defects was

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			slightly increased and outside the HCD for the finding cleft palate in the high dose group. There are several reasons to assume that these defects are not direct teratogenic effects caused by metam-sodium but were rather incidental or secondary to general systemic toxicity exceeding the MTD. The effects observed (meningocele, cleft palate) are known to be sensitive to developmental delays, which normally include also ossification delays. In conclusion, the NOAEL for developmental toxicity was considered 20 mg/kg bw/day. It has been shown that dosing with various chemicals at sufficiently high doses on any single day between GD 10 and 12 was enough to induce cleft palate development in rabbits (Buser and Pohl, 2018*). In an evaluation of 234 studies, it was shown that typical maternal toxicity-associated foetal malformations were exencephaly, encephalocele, micro- or anophthalmia, and fused ribs in hamsters and defective (fused, missing, or extra) ribs, vertebrae, and sternebrae, ex-, an-, or microphthalmia, and cleft palate in rats and rabbits (Khera, 1985**). These malformations occurred at low frequencies, generally with no readily apparent dose-response relationship. Presumptive evidence indicates that embryo-foetal deaths, and the above-mentioned foetal malformations in experimental animals, which in published literature are presently attributed to chemical induction for a large number of chemicals, may be a consequence of maternal toxicity per se. This is also considered true for metam-sodium, as the slightly increased incidences were observed at the high dose only without any dose-relationship, but in the presence of general toxicity (reduced FC and BWG, reduced number of live foetuses, reduced foetal weight). In addition, it is obvious that defects were not uniformly distributed over the foetuses, as only single foetuses were affected bearing up to 10 different effects. Furthermore, it has to be noted that hydrocephaly and spina bifida meningocele were

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			observed in the control but not in the treated groups. During the treatment phase (GD 8-20), food consumption of the high dose dams (60 mg/kg bw/d) ranged from between 23.9 to 70.4% lower than the corresponding controls, with a final reduction in bodyweight gain (d9-d20) of 22.1% compared to the control group. Furthermore, body weight loss was observed in the treated animals of the high dose group immediately after beginning of treatment. The initial body weight (before dosing) was only reached at GD 15-16. Thus, there is no doubt that during this period the MTD was clearly exceeded and a developmental delay leading to the findings of meningocele and cleft palate in this rabbit developmental toxicity study is considered highly likely. Indeed, even the most prominent effect (reduction of food consumption of 70.4% during GD 8-11) was observed during GD 10-12, right after the early differentiation phase, which has also been previously described by Buser and Pohl (2015) as the sensitive period for meningocele and cleft palate induction in rabbits. The applicant is of the opinion that no classification for reproductive toxicity is warranted for metam-sodium based on the effects observed in this study in the presence of maternal toxicity. The applicant kindly asks RMS to revise the respective entry in the table under section 3.1.8 "Area(s) where expert consultation is considered necessary". Respective reference in the RAR (Metam_RAR_08_Volume_3CA_B-6_2023-07-25): Table B.6.6.2.2/03-7 (page 392). Additional HCD data (see below) can be submitted on request: Minor foetal effects | Male | Female HCD (foetal incidence) [%]

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Cervical Vertebrae, transverse process partially ossified 7th	0 – 8.43	0 – 4.48
Lumbar vertebrae transverse processes fully ossified 3rd	2.63 – 63.64	2.25 – 67.80
Sternebrae : present, 7th	0 – 1.2	0
Sternebrae : not ossified, 5th	1.85	0 – 16.42
Sternebrae : partially ossified 2nd	0 – 2.63	0—2.38
Odontoid partially ossified	2.78 – 51.32	1.05 – 70.00
Vertebral column, 27 presacral vertebrae	14.6 – 48.5	

* : Buser et al. (2018) Windows of sensitivity to toxic chemicals in the development of reproductive effects: an analysis of ATSDR's toxicological profile database. Int J Environ Health Res. 2018 Oct;28(5):553-578. doi: 10.1080/09603123.2018.1496235.

**: Khera KS. Maternal toxicity: a possible etiological factor in embryo-fetal deaths and fetal malformations of rodent-rabbit species. Teratology. 1985 Feb;31(1):129-53. doi: 10.1002/tera.1420310115.

***: Buser MC, Pohl HR. Windows of Sensitivity to Toxic Chemicals in the Development of Cleft Palates. J Toxicol Environ Health B Crit Rev. 2015;18(5):242-57. doi: 10.1080/10937404.2015.1068719.

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(11)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 59a –B.6.6.2.2/04) (metam), p. 210	**Taminco:** Agrees with RMS to keep the maternal NOAEL at 10 mg/kg bw/d based on reduction in body weight gain. The applicant disagrees with lowering of the developmental NOAEL and is of the opinion that it should remain at 10 mg/kg bw/d based on increased number of dead implantations and decreased number of live foetuses at higher doses. According to the applicant, the effects observed do not represent specific developmental effects relevant for classification and thus, classification in Category 2 for reproductive toxicity is not warranted. Further information is provided in column 3.	**Taminco:** The effects observed at 10 mg/kg bw/d were not consistent and not considered adverse. Pre- and post-implantation loss was either decreased or increased when compared to the vehicle control and was within HCD at 10 mg/kg bw/day. Similarly, intra-uterine deaths were increased or decreased when compared to the vehicle control but also within HCD at 10 mg/kg bw/day. No effect was observed on number of implantations, live foetuses and foetal weight. In accordance with the other developmental toxicity studies (rat/rabbit) effects on preimplantation loss was not consistent (no clear dose response). The pre-implantation loss is higher in the control animals, suggesting that treatment with metam-sodium may reduce implantation loss at an early stage but lead to a higher incidence later (post-implantation loss). One of the reasons might be due to a transient increase of cellular GSH concentrations due to metam-sodium treatment. Although the number of early intra-uterine deaths was higher at the low dose of 10 mg/kg bw when compared with the control (6 and 1), the incidence for intermediate and late intra-uterine deaths combined was lower in the control group (1 vs 3 in control). Due to this inconsistency, intra-uterine deaths (in total) at 10 mg/kg bw were considered similar to those in the control group. The absent maternal toxicity at 10 mg/kg bw/d is in accordance with the absence of relevant skeletal variations or retardations. With regards to anomalies there are several reasons to assume that these defects are not direct teratogenic effects caused by metam-sodium but were rather incidental or secondary to general systemic toxicity exceeding the MTD (see Vol. 3, B.6.6.2.2/03). The effects observed at high doses after metam-sodium exposure (e.g., meningocele, cleft palate) are known to occur in case of developmental delays, which also include ossification delays. These malformations occurred at low frequencies, generally with

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			no readily apparent dose-response relationship. Presumptive evidence indicates that embryo-foetal deaths, and the above-mentioned foetal malformations in experimental animals, which in published literature are presently attributed to chemical induction for many chemicals, may be a consequence of maternal toxicity *per se*. This is also considered true for metam-sodium, as the slightly increased incidences were only observed at the high dose without any dose-relationship, but in the presence of general toxicity, i.e., reduced FC, reduced body weight gain (down to 29% of the control) and reduced number of live foetuses. Other observations as *spina bifida*, meningocoele, gall bladder agenesis or *truncus arteriosus communis* are rare findings. However, additional HCD data show that they still occur also in control animals even if at low percentages. According to the applicant, the effects observed do not represent specific developmental effects relevant for classification and thus, classification in Category 2 for reproductive toxicity is not warranted. The applicant kindly asks RMS to revise the respective entry in the table under section 3.1.8 "Area(s) where expert consultation is considered necessary". Respective reference in the RAR (Metam_RAR_08_Volume_3CA_B-6_2023-07-25): Table B.6.6.2.2/04-2 (page 399); Table B.6.6.2.2/04-3 (page 400). Additional HCD data (see below) can be submitted on request: Foetal and litter effects: Female HCD (foetal incidence) [%] Pre-implantation losses: 14.6 ± 18.8 (range 6.5 – 28.5) Post-implantation losses: 11.7 ± 17.4 (range 3 – 23.1)

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			Intra-uterine deaths: 11.6 ± 17.3 (range 3 – 23.1) Vertebral column Spina bifida (foetal): (Breeder data) HCD: 0% (N=6451 foetuses examined in vehicle controls); 0.03% (N=19383 foetuses examined in vehicle controls + unaffected dosages) (2.4% of total malformations) Gall bladder agenesis: (Breeder data) HCD: 0.5% (N=1975 foetuses examined in vehicle controls); (range 0-1.4% per study) Truncus arteriosus communis: (Breeder data) HCD: 0.05% (N=1975 foetuses examined in vehicle controls); (range 0-3% per study)
(12)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 59b – B.6.8.1.5.2/01) (MITC), p. 211	**Taminco:** Agrees with RMS assessment.	
(13)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 59b – B.6.8.1.5.2/03) (MITC), p. 211	**Taminco:** Agrees with RMS assessment to set the maternal NOAEL to 4.13 ppm (12.39 mg/m^3) and disagrees with the NOAEL setting for developmental effects. For further details please refer to column 3.	**Taminco:** Agrees with RMS assessment to set the maternal NOAEL to 4.13 ppm. With regards to the developmental NOAEL the applicant disagrees and is of the opinion that the incidence of a major blood vessel variation and reduced ossification of the 13th rib are no adverse effects, and the developmental NOAEL should therefore be set at ≥12.11 ppm.

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			The occurrence of blood vessel variations is a background lesion with different incidences within various species. It is observed more often in rabbits than rats, however, it is also observed in rats at low incidences. Ossification delay in the presence of maternal toxicity is also observed quite frequently. Reduced ossification of the 13th rib was observed in all groups, including control, above HCD (% litter). No dose-response was observed and thus a direct test substance related effects is questionable. The HCD data show that these lesions occur also spontaneously, although at low incidences and are often affected by general toxicity and/or malnutrition. Indeed, according to the DevTox database the visceral finding is listed as a variation (Carotid artery – Branching variation) and incomplete ossification is considered a grey zone. While it is not clear whether this corresponds to the reduced ossification of the 13th rib, it is still to be considered that this finding is clearly not listed as malformation. In the table below selected numerical values of the effects discussed in column 2 are presented. Considering the CLP criteria, the applicant is of the opinion that the effects discussed and presented in the table below do not constitute adversity.

Group	**Dosage level (ppm)**			
	0	**1**	**4**	**12**
Number of foetuses/litters	***404 / 25***	***394 / 25***	***392 / 25***	***364 / 23***
Number with skeletal malformations	1/1	0/0	2/1	0/0
Number viscerally examined	***404 / 25***	***394 / 25***	***392 / 25***	***364 / 23***
Renal papilla not developed and/or distended ureter	3/3	2/2	5/1	3/2
Major blood vessel variation	0/0	0/0	0/0	**1/1 0.27%/ 4.3%**

Reproductive toxicity

No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			Vessels malpositioned, **HCD (% per litter)** **(0-0.3%)** ***Number skeletally examined*** ***404 / 25*** ***394 / 25*** ***392 / 25*** ***364 / 23*** Sternebra malaligned (slight or moderate) 3/3 1/1 2/2 2/2 14th rudimentary rib 25/11 51/14 30/11 8/5 Reduced ossification of the 13th rib 2/2 0.5%/ 8% 3/2 0.8%/ 8% 1/1 0.3%/ 4% **5/4 1.4%/ 17%** Reduced ossification of the 13th rib, **HCD (% per litter)** **0.7% (0-2.3%)** Vertebral centra not fully ossified 2/2 2/1 2/1 2/2 7th cervical rib 1/1 2/1 1/1 2/2 Sternebra #5 and #6 unossified 4/3 3/3 2/2 4/4 25 presacral vertebrae 1/1 3/1 0/0 1/1 14th full rib 1/1 1/1 1/1 0/0 27 presacral vertebrae 0/0 1/1 0/0 0/0 Results expressed in absolute number of foetuses /litters, or in %.
(14)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 59b – B.6.8.1.5.2/02) (MITC), p. 211	**Taminco:** Agrees with RMS assessment.	
(15)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 59b – B.6.8.1.5.2/07) (MITC), p. 211	**Taminco:** Agrees with RMS assessment.	
(16)	Vol. 1, 2.6.6 Summary of reproductive toxicity	**Taminco:** Agrees with RMS assessment to set the maternal NOAEL to 5 ppm and disagrees with the	**Taminco:** Agrees with RMS assessment to set the maternal NOAEL to 5 ppm based on mortality, moribundity, body weight losses, decreased food

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	(Table 59b – B.6.8.1.5.2/06) (MITC), p. 211	setting of the NOAEL for developmental effects. For further details please refer to column 3.	consumption, and maternal macroscopic findings at 15 ppm. The effects at 15 ppm were however not considered adverse with regards to developmental toxicity. The slightly altered litter parameters (e.g., decrease of foetal viability or increased early resorption) as well as single developmental findings (e.g., omphalocoele, vertebral centra anomaly, irregular ossification of 6th sternebra) were observed mainly in one pup of dam No. 64824. This animal suffered from general toxicity affecting body weight and body weight changes and did not consume food between days 7 and 11, a critical window for skeletal development during which amongst others primitive streak and early differentiation occurs. Indeed, low to absent food consumption was also observed in three other litters (64997, 65025 and 65026), which had to be euthanized due to welfare reasons, thus confirming the excessive maternal toxicity. Overall, the applicant is of the opinion that the developmental NOAEL should be set to 15 ppm.
(17)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 59b – B.6.8.1.5.2/06) (MITC), p. 211	**Taminco:** RMS changed the incidence from 0 to 1 for the highest dose (fetuses and litters) in Table B.6.8.1.5.2/06-8 for external variations. Based on the study report, this is not correct and should remain 0. Please refer to Table S15 of the study report for which the extract is added in column 3.	TABLE S15 AN INHALATION PRENATAL DEV. TOX. STUDY OF MITC IN RABBITS SUMMARY OF FETUSES AND LITTERS WITH VARIATIONS [ABSOLUTE NO.] PAGE 1 DAY 29 FETUSES / LITTERS DOSE GROUP: 1 2 3 4 / 1 2 3 4 NUMBER EXAMINED EXTERNALLY: 197 183 174 138 / 24 22 22 18 NUMBER WITH FINDINGS: 0 0 0 0 / 0 0 0 0
(18)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 59b – B.6.8.1.5.2/05) (MITC), p. 211	**Taminco:** Agrees with RMS assessment that 10 ppm can be regarded a LOAEL in the study due to the consistent lower food consumption, body weight as well as body weight gain. At 5 ppm the body weight was comparable with the control group animals and only food consumption and body	

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		weight gain were lowered showing generally high variations. Thus, the applicant is of the opinion to set the LOAEL to 10 ppm rather than 5 ppm.	
(19)	Vol. 1, 2.6.6 Summary of reproductive toxicity (Table 59b – B.6.8.1.5.2/04) (MITC), p. 211	**Taminco:** Agrees with RMS assessment.	
(20)	Vol. 1, 2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development (metam), p. 215	**Taminco:** The applicant is of the opinion that a classification of metam-sodium for reproductive toxicity (Cat. 2, H361d) is not warranted. Effects observed were linked to severe maternal toxicity and not considered adverse at low doses with less maternal toxicity. Furthermore, the additional classification proposals for STOT-SE Cat. 1 and STOT-RE Cat. 1 are considered sufficient to also cover potential developmental defects triggered by general toxicity.	**Taminco:** The applicant is of the opinion that no classification for reproductive toxicity (Cat. 2, H361d) is warranted for metam-sodium. The frequency of the defects observed is very low and there is clear evidence from each developmental toxicity study (and the 90-day repeated-dose toxicity study in rats) that they occurred in presence of distinct maternal toxicity (manifesting as effects on food consumption and body weight parameters), at the same level(s) as those at which these foetal defects are also observed. Furthermore, the pattern for the occurrence of these defects is the same in all studies: • Observed at highest dose only (in the presence of distinct systemic toxicity) • No dose-relationship • Clear threshold for defects (in all studies) • Defects observed are known to be sensitive to maternal/foetal general toxicity Consequently, these findings are not considered relevant for classification purposes (teratogenicity). According to Annex I: 3.7.2.4.3 and the CLP guidance section 3.7.2.2.1.1 (version 5, July 2017, page 401) *Classification is not necessarily the outcome in the case of minor*

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity". Furthermore, classification in Category 2 for reproductive toxicity should be considered when *"Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects".* In the opinion of the applicant, the clear foetotoxic effects observed in various studies were always linked to maternal toxicity. The foetotoxic effects included foetal mortality (reduced live foetuses) and reduced foetal weight and were linked to reduced gravid uterus weight and increased post-implantation loss. Furthermore, the classification of metam-sodium as STOT-RE Cat. 1 is sufficient to also cover potential developmental defects triggered by general toxicity observed at doses not lower than those that have been basis for STOT-RE Cat. 1 classification. The anomalies or malformations reported were only observed at the highest, severely maternotoxic doses and are known to be sensitive to severe systemic toxicity. In conclusion, classification in Category 2 for reproductive toxicity is not warranted. The applicant kindly asks RMS to revise the respective entry in the table under section 3.1.8 "Area(s) where expert consultation is considered necessary".
(21)	Vol. 1, 2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development (MITC), p. 221	**Taminco:** Agrees that MITC is devoid of potential to cause developmental toxicity and should not be classified accordingly.	

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(22)	Vol. 1, 2.6.6.4 Conclusion on classification and labelling for reproductive toxicity, p. 221	**Taminco:** Does not agree with the proposed classification as Repr. 2 for metam and considers that a classification for reproductive toxicity is not warranted (please refer to comment 20). The applicant agrees that no classification is warranted for MITC.	

Neurotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.7 Summary of neurotoxicity (Table 65a–B.6.7.1/01) (metam), p. 223	**Taminco:** The applicant agrees with the RMS that study is conducted at high dose levels, and that it is difficult to differentiate between direct and indirect effects on the nervous system. However, the applicant is of the opinion that due to the lack of specific evidence for neurotoxicity (including histopathological findings) the data are not sufficient to conclude on a NOAEL/LOAEL for neurotoxicity. Further information is provided in column 3.	**Taminco:** The RMS states that changes in (loco)motor activity or hindlimb extensor strength are observed at dose levels (50 mg/kg bw), which did not show overt systemic toxicity and thus the effects should be considered potentially neurotoxic. The applicant agrees that based on this study data alone it is difficult to exclude the neurotoxic effects. The observed effects, i.e. (loco)motor activity or hindlimb extensor strength, are also sensitive to systemic toxicity and can be induced for example by body weight effects or general bad health condition. Considering the general toxicity of metam at the day of exposure and the slightly lower body weight gain from day 0 to 7, a relationship between the general health condition of the animals and the activity of the rats cannot be excluded. Besides it is important to note that the type of method chosen is highly dependent on the test device as well as proficiency of the lab technician and, given that the motor activity was measured only once, it is highly likely that these readings are not robust. The applicant is of the opinion that the former NOAEL for neurotoxic effects of >1500 mg/kg bw is still applicable.

Neurotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(2)	Vol. 1, 2.6.7 Summary of neurotoxicity (Table 65a–B.6.7.1/02) (metam), p. 223	**Taminco:** Agrees with RMS conclusion on acute neurotoxicity (acetylcholinesterase parameter) NOAEL of 1500 mg/kg bw	
(3)	Vol. 1, 2.6.7 Summary of neurotoxicity (Table 65a–B.6.7.1/03) (metam), p. 223	**Taminco:** Agrees with RMS conclusion.	
(4)	Vol. 1, 2.6.7 Summary of neurotoxicity (Table 65b–B.6.8.1.6/01) (MITC), p. 223	**Taminco:** Agrees with RMS assessment that no NOAEL for local or portal of entry effects of MITC can be established based on nasal effects at ≥20 ppm. Disagrees with RMS on the NOAEL setting for neurotoxicity and systemic effects. For further details please refer to column 3.	**Taminco:** Agrees with RMS assessment that no NOAEL for local or portal of entry effects of MITC can be established based on nasal effects at ≥20 ppm. With regards to an acute neurotoxicity NOAEL the applicant agrees with the RMS that the findings observed at 80 ppm could be confounded by high systemic toxicity (80 ppm ≙ 40% of the LC_{50}) of MITC. However, the applicant is questioning if the effects at 80 ppm should be considered adverse as the incidence of axonal degeneration was only slightly increased for lumbar ventral root fibers as well as peroneal, sciatic, sural and tibial nerve (mostly in one sex only). In contrast the axonal degeneration was higher in spinal (both sexes) and tibial nerve (males) of the control animals or showed generally high incidences (4/6) in males of the control group for sciatic nerve. With regards to a systemic toxicity NOAEL the applicant is of the opinion that the liver weight loss in the satellite group may be due to acute stress as indicated by the study director. This effect was not observed in the core group and was considered a transient effect not relevant for systemic NOAEL setting. The NOAEL for systemic toxicity should therefore be set at 40 ppm.

Neurotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(5)	Vol. 1, 2.6.7 Short summary and overall relevance of the provided information on neurotoxic effects, p. 224	**Taminco:** Agrees with RMS conclusion. The existing developmental studies and the overall most relevant NOAEL are sufficient to cover a potential developmental NT effect, also taking into consideration that neurotoxic effects are probably not the most critical effects of metam/MITC, and therefore no further study need to be conducted on neither metam nor MITC.	

Further toxicological studies			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.8 Summary of other toxicological studies (minor metabolites and relevant impurities), p. 226	**Taminco:** Agrees with RMS conclusion.	
(2)	Vol. 1, 2.6.8 Summary of other toxicological studies (immunotoxicity) (B.6.8.1.7/01) (MITC), p. 228	**Taminco:** Agrees with RMS assessment to set the NOAEL for systemic and immunotoxicity at ≥10 ppm (30 mg/m³; 13 mg/kg bw/d).	
(3)	Vol. 1, 2.6.8 Summary of	**Taminco:** Agrees with RMS conclusion that there is	**Taminco:** Agrees with RMS conclusion that there is no overt

Further toxicological studies			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	other toxicological studies (immunotoxicity) (metam), p. 229	no overt immunotoxicity of metam or MITC. Further information is provided in column 3.	immunotoxicity of metam or MITC. A possible effect on cellular immunity by metam at doses which are not excessively toxic cannot be excluded. However, the available data especially from cell signalling experiments are complex to evaluate and a definite conclusion is difficult. Furthermore, it has been shown that Natural Killer cell (NK cells) cytotoxic activity (part of the cellular immunoreaction) is depending/sensitive to the redox balance (GSH levels and GSH:GSSG ratio). Therefore, it cannot be excluded that the reduced cellular response (decreased NK cell cytotoxicity) is secondary to metam toxicity. The applicant is of the opinion that no further testing is necessary as the changes related to the immune system are presumably not due to primary/specific effects of metam. In addition, a sufficiently high MoS exists against the proposed reference values exists indicating that the potential risk of immunotoxicity is sufficiently covered by the existing studies to agree on an acceptable risk for this endpoint. No untoward effects were observed in long-term studies whereby opportunistic infections would have indicated a compromised immunity of the animals. *: Allen M, Bailey C, Cahatol I, Dodge L, Yim J, Kassissa C, Luong J, Kasko S, Pandya S, Venketaraman V. Mechanisms of Control of Mycobacterium tuberculosis by NK Cells: Role of Glutathione. Front Immunol. 2015 Oct 5;6:508. doi: 10.3389/fimmu.2015.00508. Bailey CP, Figueroa M, Gangadharan A, Lee DA, Chandra J. Scaffolding LSD1 Inhibitors Impair NK Cell Metabolism and Cytotoxic Function Through Depletion of Glutathione. Front Immunol. 2020 Sep 17;11:2196. doi: 10.3389/fimmu.2020.02196. Millman AC, Salman M, Dayaram YK, Connell ND, Venketaraman V. Natural killer cells, glutathione, cytokines, and innate immunity against Mycobacterium tuberculosis. J Interferon Cytokine Res. 2008

Further toxicological studies			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			Mar;28(3):153-65. doi: 10.1089/jir.2007.0095.
(4)	Vol. 1, 2.6.8 Summary of other toxicological studies (supplementary studies on the active substance) (Goldman, J.M. et al. (2007) –B.6.8.2.3/02), p. 233	**Taminco:** Agrees with RMS conclusion. Due to the slight variation and being within the respective HCD, effects on oestrous cycle and gestation length at 20 ppm were not considered adverse and thus in accordance with the former evaluation "not toxicologically relevant" in the post-approval addendum.	**Taminco:** An increase in the oestrous cycle length for F_0 (4.5 days) and F_1 (4.9 days) females was noted at the highest dose of 20 ppm. These values were however within the range of historical control data (mean 4.5 days; range 4.0-5.8 days) and attributable to two females in F_0 with longer oestrous cycles (6.3 and 8.0 days) and two females in F_1 (7.3 and 10.3 days). Therefore, the slight prolongation in oestrus cycle length at 20 ppm was not considered to be of toxicological relevance. This is also in agreement with the conclusion in the post-approval addendum of September 2016 in which the RMS agreed that the slight prolongation in oestrous cycle length can be regarded as not toxicologically relevant and additionally noted that the mean oestrous cycle length of the study control was on the lower side of the HCD with a number of animals even below the control range.

Toxicological endpoints for risk assessment			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.10.1 Toxicological endpoint for assessment of risk following long-term dietary exposure (ADI), p. 254	**Taminco:** Agrees with proposed ADI for metam and MITC.	
(2)	Vol. 1, 2.6.10.2 Toxicological endpoint for assessment of risk	**Taminco:** Agrees with proposed ARfD for metam and MITC.	

Toxicological endpoints for risk assessment			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	following acute dietary exposure (ARfD), p. 254		
(3)	Vol. 1, 2.6.10.3 Toxicological endpoint for assessment of occupational, bystander and residents risks (AOEL), p. 254	**Taminco:** Agrees with proposed AOEL for metam. Applicant does not agree with the proposed AOEL of 0.004 mg/kg bw/d for MITC and proposes an AOEL of 0.0112 mg/kg bw/d instead. Further information is provided in column 3.	**Taminco:** Agrees with proposed AOEL for metam. Applicant does not agree with the proposed AOEL of 0.004 mg/kg bw/d for MITC and proposes an AOEL of 0.0112 mg/kg bw/d instead. The applicant's proposal is based on a NOAEC of 5 ppm (15 mg/m³) (corresponding to a NOAEL of 1.12 mg/kg bw/day) for maternal toxicity in the rabbit developmental toxicity study with AF=100 (inhalation route). Clinical signs of toxicity were evident in females of the 15 ppm group which were largely characterized by local (portal of entry) effects. Females that died or were euthanized in extremis prior to the scheduled necropsy were noted with dark red areas of the lungs, dark red discoloration of the lungs, firm lungs, lungs not fully collapsed, and white or thick white contents of the trachea or stomach. A statistically significantly lower mean food consumption and corresponding statistically significantly reduced mean body weight gains during gestation days 7 – 29 were also noted in females exposed at 15 ppm. The effects were considered secondary to local irritating effects and following general bad health condition. The AOEL of 0.0112 mg/kg bw/day is considered sufficiently conservative. In the respective rabbit developmental toxicity study after oral gavage a NOAEL of 3 mg/kg bw/day was observed. Similarly, in the rat developmental toxicity study after oral gavage and after inhalation a NOAEL of 3 and 0.8 mg/kg bw/day was observed, respectively. In the rat 90-day inhalation study a NOAEC of 3 and 45 mg/m³ (equivalent to 0.8 and 12.2 mg/kg bw/day) was observed for local and systemic effects, respectively. In the long-term and carcinogenicity studies in rats and mice the NOAEL/NOAEC values were comparable or even higher after oral or inhalation exposure than for the subchronic studies. The applicant kindly asks to revise the relevant entry under 3.1.1.4

Toxicological endpoints for risk assessment			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			"Impact on human health – ADI, AOEL, ARfD".
(4)	Vol. 1, 2.6.10.4 Toxicological endpoint for assessment of occupational, bystander and residents risks (AAOEL), p. 254	**Taminco:** Does not consider setting of an AAOEL for metam relevant. The applicant proposes to set the AAOEL for MITC at 0.0112 mg/kg bw/d. Further information is provided in column 3.	**Taminco:** Does not consider setting of an AAOEL for metam relevant considering that application by drip irrigation in combination with the recommended personal protective equipment precludes the risk of exposure to the formulated product. Additionally, the active metabolite MITC is the compound of interest for the operator, worker, bystander and resident risk assessments. The applicant proposes to set the AAOEL for MITC at 0.0112 mg/kg bw/d based on a NOAEC of 5 ppm (15 mg/m³) (corresponding to a NOAEL of 1.12 mg/kg bw/day) for maternal toxicity in the rabbit developmental toxicity study with AF=100. The same endpoint from the rabbit developmental toxicity study is also applicable for acute exposure of the operator, worker, bystander and resident. The applicant kindly asks to revise the relevant entry under 3.1.1.4 "Impact on human health – ADI, AOEL, ARfD".

Endocrine disrupting properties			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.10 Endocrine disrupting properties, p. 767	**Taminco:** Agrees with RMS conclusion. The applicant would like to inform RMS about the finalization of the following studies, which can be submitted upon request: • *In vitro* androgen transactivation assay (OECD TG 458) • *In vivo* Hershberger assay (OECD TG 441) • *In vitro* H295R steroidogenesis assay (OECD TG 456) • *In vitro* aromatase assay (human recombinant) (OPPTS 890.1200)	

Classification and labelling – Aquatic hazard			
No.	Column 1 Reference to assessment report	Column 2 Comment	Column 3 Further explanations
(1)	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	**Taminco:** 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. See further details in column 3.	**Taminco:** 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

Classification and labelling – Aquatic hazard			
No.	Column 1 Reference to assessment report	Column 2 Comment	Column 3 Further explanations
			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. The use of the SSD presented in support of the aquatic invertebrate acute risk assessment for MITC meets the minimum data requirements of the CLP criteria that would allow the use of the statistically derived HC5 value in place of the lowest, deterministic endpoint for *Hyalella azteca*. The IR&CSA, Chapter R.10 states that data for at least 8 'taxonomic groups' are required to use SSD confidently. The IR&CSA guidance does not, however, define what level of taxonomy is intended by this statement. In addition, the guidance relates to deriving an overall aquatic PNEC covering all tested species, rather than an endpoint for a specific group i.e. acute aquatic invertebrates. While the guidance does provide a list of 8 example taxonomic groups, these include algae, higher plants and animals including fish, and the list also allows duplicates within some higher taxonomic groups, and there is no consistency in the taxonomic levels of the suggested groups. The SSD submitted in support of the MITC acute aquatic invertebrate risk assessment was generated according to the EFSA 2013 aquatic risk assessment guidance. While this guidance requires data for at least 8 test species to allow use of an SSD in risk assessment, it does not allow the inclusion of non-relevant taxa, as it is required that the SSD used in risk assessment refinement represents the most sensitive group. To this end, various Crustacean species are included in the SSD as these are most sensitive, in addition to members

Classification and labelling – Aquatic hazard			
No.	Column 1 Reference to assessment report	Column 2 Comment	Column 3 Further explanations
			of other groups such as rotifers, molluscs, annelid worms, flatworms and insects, to represent the broad spectrum of activity of MITC as a soil sterilant. No data on algae, higher aquatic plants, fish or amphibians are included however, as these are not considered to represent the most sensitive groups. Therefore, it is necessary to define a meaningful 'taxonomic group' to allow an assessment of the adequacy of the existing SSD data for CLH purposes i.e. assess whether the data represent 8 meaningful taxonomic groups. The taxonomy of animals follows a hierarchical system, with Phylum being the highest level of organisation (an example is shown below for humans). Kingdom: Animalia (animals) Phylum: Chordata (presence of notochord) (Sub-phylum: Vertebrata (presence of backbone)) Class: Mammalia (mammals) Order: Primates (lemurs, galagos, tarsiers, monkeys, apes, humans) Family: Hominidae (hominids, human-like apes) Genus: Homo Species: sapiens The different Phyla represent very broad taxonomic groupings of animals, and within each of these are various Classes. It can be seen from the above example that all mammals fall into one Class. A Class is therefore a very broad grouping of evolutionarily-related but not necessarily similar

Classification and labelling – Aquatic hazard			
No.	Column 1 Reference to assessment report	Column 2 Comment	Column 3 Further explanations
			animals. For example, the Mammalia includes organisms as diverse as whales and dolphins, mice, bats, elephants, armadillos, bears, platypuses, and sloths. These represent very different life histories, methods of reproduction, diet, habitat etc. A Class is therefore considered a practicable and very conservative level of organisation for differentiating organisms into 'taxonomic groups'. The toxicity data included in the aquatic invertebrate SSD for MITC represent 8 different Classes, as outlined in the table below. The table below takes a consistent level of taxonomy (Class) as the basis for a different 'taxonomic group', in contrast to the IR&CSA Chapter R.10 guidance, and thus demonstrates that the MITC SSD satisfies the criteria for use of the SSD in CLP. Table 1. Summary of taxonomic Classes of existing MITC aquatic invertebrate acute toxicity data (Classes underlined).

Test species	**Taxonomic group name**	**Taxonomic level**	**Cumulative count of 'taxonomic groups' (equivalent here to 'Class') present in MITC aquatic invertebrate SSD**
	Arthropoda	***Phylum***	
	Crustacea	***Sub-phylum***	

Classification and labelling – Aquatic hazard						
No.	Column 1 Reference to assessment report	Column 2 Comment	Column 3 Further explanations			
			Daphnia magna	Branchiopoda Anomopoda	Class Order	1
			Thamnocephalus platyurus	Branchiopoda Anostraca	Class Order	
			Hyalella azteca	Malacostraca Amphipoda	Class Order	2
			Asellus aquaticus	Malacostraca Isopoda	Class Order	
			Leptocheirus plumulosus	Malacostraca Amphipoda	Class Order	
			Crangonyx pseudogracilis	Malacostraca Amphipoda	Class Order	
			Americamysis bahia	Malacostraca Mysida	Class Order	
				Hexapoda	***Sub-Phylum***	
			Chironomus riparius	Insecta Diptera	Class Order	3
				Rotifera	***Phylum***	
			Brachionus calyciflorus	Eurotatoria Ploima	Class Order	4
				Mollusca	***Phylum***	
			Crassostrea virginica	Bivalva Osteidae	Class Order	5
			Potamopyrgus antipodarum	Gastropoda Littorinimorpha	Class Order	6
				Annelida	***Phylum***	
			Lumbriculus variegatus	Clitellata Lumbriculida	Class Order	7
				Platyhelminthes	***Phylum***	
			Dugesia tigrina	Tubellaria	Class	8

Classification and labelling – Aquatic hazard			
No.	Column 1 Reference to assessment report	Column 2 Comment	Column 3 Further explanations
			Tricladida Order It is clear, therefore, that the existing SSD acute aquatic invertebrate toxicity data for MITC represents both a broad range of taxonomy and life history, with a focus on the most relevant (sensitive) species, while also including data for 8 separate taxonomic Classes. The data is therefore considered to fulfil the requirements of the IR&CSA Chapter R.10 guidance on use of SSDs in CLP.