COMPILED COMMENTS ON CLH CONSULTATION

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

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Last data extracted on 27.11.2023

Substance name: [ethylenebis[nitrilobis(methylene)]]tetrakisphosphonic acid, calcium sodium salt
CAS number: 85480-89-3
EC number: 287-370-9
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
24.11.2023	United Kingdom	Italmatch Chemicals SpA	Company-Manufacturer	1
Comment received				
The most characteristic property of EDTMP-H is its ability to complex metals (7. Physicochemical properties, in the CLH report). As per the CLH report, we are here commenting only Germ cell mutagenicity and carcinogenicity (see the attached report). ECHA note – An attachment was submitted with the comment above. Refer to public attachment EDTMP.zip				

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2023	France		MemberState	2
Comment received				
The justification for read-across from EDTMP-H and EDTMP-Na is agreed upon.				

HEALTH HAZARDS – Germ cell mutagenicity

Date	Country	Organisation	Type of Organisation	Comment number
24.11.2023	United Kingdom	Italmatch Chemicals SpA	Company-Manufacturer	3
Comment received				
The attached response and supporting expert documents contain a thoughtful explanation on why EDTMP-H needs no classification hazard for mutagenicity. ECHA note – An attachment was submitted with the comment above. Refer to public attachment EDTMP.zip				

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2023	France		MemberState	4

Comment received
France supports DS's assessment. Regarding clastogenicity, it is agreed that valid in vitro and in vivo data is missing to allow a firm conclusion. Another limitation of the in vivo mammalian bone marrow chromosome aberration test is the use of corn oil as vehicle which is surprising for such a hydrophilic compound (LogKow: - 4.1). Is there any explanation for the use of corn oil? Regarding bone marrow exposure, based on the results reported in TK data, blood levels seem very low suggesting a very low bone marrow exposure if any. Therefore, no classification for mutagenicity based on inconclusive data is considered more appropriate.

HEALTH HAZARDS – Carcinogenicity

Date	Country	Organisation	Type of Organisation	Comment number
21.11.2023	France		MemberState	5
Comment received				
France supports the proposal for classification Carc. 1B based on increased incidences of malignant tumours (osteosarcomas) observed in both sexes in a well conducted OECD TG 453 study carried out with EDTMP-Na in SD rats, supported by another study where SD rats were tested with a mixture EDTMP-Na and NaF. The absence of osteosarcoma in the mouse study does not weaken the evidence considering the low doses tested in this species (no effects on mortality, bodyweight and food consumption in any of the two doses tested). France generally agrees with the DS's assessment of the different factors taken into consideration for classification purposes. Regarding the putative MoAs as mentioned in page 25 (j) uncertainties remain on clastogenic potential due to non-reliable tests, this point should also be reported in the last column of table 11 dedicated to MoA. Regarding potency, in the key rat study, osteosarcomas were already observed before dosage of high-dose group was increased (from 150 to 333 mg/kg bw/d) and a T25 of 80 mg/kg bw/day is obtained if a dosage of 150 mg/kg bw/d is taken into account. Lower T25 values were also obtained in the "coexposure" study (i.e.: 50 and 62.5 mg/kg bw/d). Moreover, evidence of high malignancy, metastasis, and a short latency period are suggestive of potential genotoxic events and clastogenic potential has not been correctly investigated. In view of the uncertainties linked to the proposed T25 value and considering all the available data, France considers that a medium potency (with a general concentration limit of 0.1%) is more appropriate than the proposed SCL for low potency.				

Date	Country	Organisation	Type of Organisation	Comment number
24.11.2023	United Kingdom	Health and Safety Executive	National Authority	6
Comment received				
'We note that the DS has classified for Carc. 1B for EDTMP-H and its salts. However, would the DS/RAC be able to explain what additional toxicological data/weight of evidence justification the registrant is referring to in the registration dossier (under carcinogenicity summary):				

'Toxicological data are conclusive in some animals (rats) at high doses but not sufficient for classification in humans. Additional toxicological data and weight of evidence to justify this non-classification are reported in supporting document attached in Section 13.'

It would be useful to have this 'supporting document' available for the overall assessment.'

Date	Country	Organisation	Type of Organisation	Comment number
24.11.2023	United Kingdom	Italmatch Chemicals SpA	Company-Manufacturer	7
Comment received				
The attached response and supporting expert documents contain a thoughtful explanation on why EDTMP-H needs no classification hazard for carcinogenicity. Our position is summarised starting on page 6, with further details on the following pages. ECHA note – An attachment was submitted with the comment above. Refer to public attachment EDTMP.zip				

Date	Country	Organisation	Type of Organisation	Comment number
24.11.2023	Sweden		MemberState	8
Comment received				
The Swedish CA considers that the evidence presented in the dossier for [Ethylenebis[nitrilobis(methylene)]]tetrakisphosphonic acid, calcium sodium salt (CAS No. 85480-89-3) is sufficient to classify the substance as Carc. 1B. The Swedish CA agrees that a higher concentration limit is justified.				

HEALTH HAZARDS – Specific target organ toxicity - repeated exposure

Date	Country	Organisation	Type of Organisation	Comment number
24.11.2023	United Kingdom	Italmatch Chemicals SpA	Company-Manufacturer	9
Comment received				
Regarding Specific target organ toxicity – repeated exposure, we agree on the conclusion reported in the CLH report: "Severe effects mainly related to the bone have been observed after chronic oral EDTMP-H/-Na administration in rodents. However, effective dose levels (LOAELs) are above the guidance values that would warrant classification as STOT RE 1 or 2. Therefore, no classification as STOT RE is proposed for EDTMP-H." (11.10.3 Conclusion on classification and labelling for STOT RE. Page 26 of the CLH report). It should be noted that, among the 287 CLP notifications in the database, there are 7 notifications for H373, 'May cause damage to organs through prolonged or repeated exposure.' The explanation of why CLP notifications should be disregarded is presented in the attached document. Furthermore, we understand these CLP self-classifications for STOT-RE are thus historic and should be superseded by the subsequent REACH registrations. ECHA note – An attachment was submitted with the comment above. Refer to public attachment EDTMP.zip				

Date	Country	Organisation	Type of Organisation	Comment number

21.11.2023	France		MemberState	10
Comment received				
It is agreed that bone is the target organ. In the 2-year rat study (study report, 1985), osteosclerosis in femur, rib and sternum was observed from 50 mg/kg bw/d in females and at 150/333 mg/kg bw/d in females. The effective doses (ED) are clearly above the extrapolated guidance value (GV) for STOT RE 2 (i.e. 12.5 mg/kg bw/d for 2-year exposure according to Haber's rule) and no bone effect was observed at the low dose tested (i.e. 15 mg/kg bw/d). In the 2-year mouse study (study report, 1986d), statistically significant increase in fibrous osteodystrophy and increase in alkaline phosphatase levels were observed in females from the lowest tested dose (15 mg/kg bw/d), which is close to the extrapolated GV for STOT RE 2. For this species the ED is above the GV but no NOAEL could be set. According to CLP guidance, interpolation is required to determine whether the effects expected at or below the GV would warrant classification. Fibrous osteodystrophy was already observed in control females (23/85 (27 %)) versus 37/81 (46 %); 35/85 (41 %) in 15 and 75 mg/kg bw/d respectively. Is there any information on the severity of the lesions in the different groups? Regarding the increase of alkaline phosphatase levels could you please indicate the magnitude of the changes? Depending on the severity of the above mentioned effects STOT RE 2 could be warranted. Regarding the 6-month dog study bone effects are observed from 50 mg/kg bw/d which could trigger STOT RE 2, however it seems that the animals are coexposed to tetracycline which may represent a confounding factor. Overall, no firm conclusion can be drawn on STOT RE classification pending a more complete information on the effects observed in mice.				

PUBLIC ATTACHMENTS
1. EDTMP.zip [Please refer to comment No. 1, 3, 7, 9]