

Harmonised classification and labelling consultation

[ethane-1,2-diylbis[nitrilobis(methylene)]]tetrakisphosphonic acid

EDTMP-H

EC number: 215-851-5 | CAS number: 1429-50-1

This submission is made by Italmatch Chemicals SpA on behalf of the members of the Phosphonates Consortium, namely:

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Introduction

On 25th September 2023, ECHA published the proposal submitted by BAuA for a harmonized classification for [\[ethane-1,2-diylbis\[nitrilobis\(methylene\)\]\]tetrakisphosphonic acid \(EDTMP-H\), EC 215-851-5, CAS 1429-50-1](#) to be classified as Carc. 1B, H350 according to CLP. Germ cell mutagenicity, Carcinogenicity and Specific target organ toxicity - repeated exposure are the hazard classes that are open for consultation.

This substance has a REACH registration dossier and the lead registrant (LR) is Italmatch Chemicals S.p.A. The CLP classification in the REACH registration dossier is only: H319: Causes serious eye irritation. The CSR contains the full justification on why no other hazard statements have been assigned to this substance.

In addition to the acid form of EDTMP, BAuA also submitted identical CLH proposal for the related salts, listed below:

- [ethylenebis[nitrilobis(methylene)]]tetrakisphosphonic acid, calcium sodium salt, EC# 287-370-9, CAS# 85480-89-3
- [ethylenebis[nitrilobis(methylene)]]tetrakisphosphonic acid, potassium salt, EC# 251-910-1, CAS# 34274-30-1
- [ethylenebis[nitrilobis(methylene)]]tetrakisphosphonic acid, sodium salt, EC# 244-742-5, CAS# 22036-77-7

To avoid the submission of additional documents, the information presented in this document is equally applicable to all four substances listed above.

Italmatch Chemicals S.p.A. (IT) is a member of the Phosphonates Consortium, which is supporting numerous Phosphonates in the REACH review programme. Other members of the Consortium who have contributed to this submission, are Aquapharm Chemicals Pvt. Ltd (India), Giovanni Bozzetto SpA (IT), Henkel AG & Co. KG (DE) and Zschimmer & Schwarz Mohsdorf GmbH & Co. KG (DE). The Consortium has consulted known experts to provide additional information on the concern that is reported in the proposal for Harmonised Classification and Labelling.

The opinions of the experts are fully reported as Annexes to this document, establishing the scientific basis in response to the proposal for a new harmonized classification of EDTMP-H. The CVs of the experts are also included to demonstrate their expertise in this field.

Here below, we summarize the main inputs related to the CLH proposal for Harmonised Classification and Labelling for EDTMP-H. The full text of the expert opinions constitutes the main reference.

CLP notifications

The study on rats and mice that are included in the registration dossiers of these substances were available to the importers and manufacturers of this substance (Calvin et al., 1988). We understand that some notifiers did not investigate the results of this study in detail before notification and this is the reason why some CLP notifications in the past expressed the classification as STOT RE (H373- bone, blood). However, this topic was extensively discussed within the SIEF (Substance Information Exchange Forum) for the substance, and in the end, all members of the SIEF agreed with the conclusions that are reported in the REACH registration dossier. Accordingly, EDTMP-H was registered without the STOT-RE classification. No member opted out from the need to have a different CLP classification. We understand these CLP self-classifications for STOT-RE are thus historic and are superseded by the subsequent REACH registrations.

Identified Uses

The consortium confirms that the uses are those reported in the REACH registration dossiers.

Data Sources

There are no additional toxicological studies. The EDTMP-H consortium is committed to update the REACH registration dossier as soon as additional information is available. There is a study on the stability constant of EDTMP-H complexing several metals. The latter is not yet in the registration dossier for EDTMP-H and the other phosphonate of that study. It will be our commitment to update the registration dossier with no undue delay.

Physicochemical properties

EDTMP-H is non-volatile in both acidic and neutralized forms and stable over a wide pH range (pH 1-13) and at elevated temperatures or moderate pressures.

The stability of EDTMP-H (and other polyamino(polymethylenephosphonates) is mainly based on the existence of Phosphorus-Carbon covalent bonds which leads to resistance to chemical hydrolysis, thermal decomposition and even to the action of phosphatases. The dissociation energy of P-C bonds is about 70 kcal/mol which is essentially like a P-O bond but requires a much higher activation energy (Quinn et al., 2007).

Chemical reactivity of EDTMP-H is dominated by reaction of the acid with bases to form salts and there are no structural moieties that can lead to alkylation, thus the reactivity towards other organic substances, in particular those being regarded as nucleobases, is nil.

EDTMP-H and its salts undergo further modification degradation only under the influence of different modes of energy:

- a) Application of high temperature (> 120°C) in an autoclave will lead to degradation of the substance and release of ortho-phosphate.
- b) Irradiation with UV-light or daylight in diluted aqueous solutions leads to cleavage of the molecule releasing iminobis(methylenephosphonic acid) and further degradation products.

In the latter case, it has been shown that EDTMP-H is first split by a C-N cleavage reaction to imino bis(methylenephosphonic acid) and ethylamine bis(methylene phosphonic acid). These intermediates are finally degraded via aminomethylene phosphonic acid to CO₂ (Kuhn et al. 2017). It must be stated here that none of these intermediates exhibits an alkylating potential. A homologue of EDTMP-H, Diethylentriaminepenta(methylene phosphonic acid) (DTPMP), degrades in the same way under both UV and daylight, while the highest degradation rates were found for pure water solution without alkaline earth metals present, suggesting the hypothesis that the complexation of Calcium and/or Magnesium by aminomethylenephosphonates increases their molecular stability (Kuhn et al. 2022). Based on the structural similarity, it can be concluded that the same applies for EDTMP-H.

Chelation properties

Chelation is an essential property to mask transition metals and prevents them from initiating Redox reactions leading to several ways of radical formation (Fenton-like reactions). This is of utmost importance in industrial applications but also in biological systems by inhibiting oxidative stress.

EDTMP-H can complex multivalent dissolved metal ions in aqueous solution. Each phosphonate group contains two dissociable protons. The phosphonate could be coordinated in the fully dissociated form or in the monoprotonated form. Thus, protonated complexes, with the proton localized on the non-coordinated phosphonate oxygen atom, are typical for phosphonate complexes. Additional protonation might occur of the non-coordinated nitrogen atoms in aminomethylenephosphonates (Kubicek, 2022).

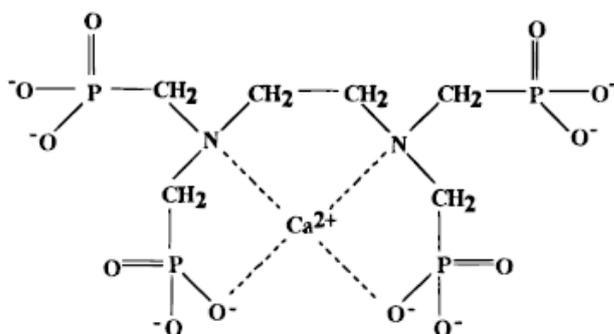


Figure 1 Structure of the EDTMP-H complex with Ca^{2+}

The so-called conditional complex formation constants are a very useful tool to describe the chemical equilibrium between a free metal ion and a chelated metal ion depending on the pH value of the aqueous solution. These constants have been re-evaluated by the consortium with modern analytical techniques. For the most abundant multivalent cations in organisms, Calcium and Magnesium, the complex formation constants under typical biological conditions are highlighted below:

EDTMP									
pH	Cu(II)	Zn(II)	Ni(II)	Co(II)	Ca(II)	Mg(II)	Fe(III)	Na(I)	K(I)
3	6.3	3.4	3.6	2.7	2.1	2.1	12.5	0.4	0.4
4	7.8	4.7	4.8	3.9	2.4	2.5	13.0	1.5	1.5
5	9.6	6.3	6.1	5.4	2.9	3.1	13.7	2.3	2.3
6	11.6	8.4	7.6	7.3	3.6	3.8	13.8	2.7	2.6
7	13.6	10.5	9.0	9.3	4.6	4.5	13.6	2.9	2.9
8	15.5	11.5	10.3	11.3	5.7	5.2	13.2	3.3	3.3
9	17.3	11.4	10.6	12.2	6.8	5.8	12.3	3.5	3.5
10	18.1	11.0	9.7	12.1	7.9	6.5	10.8	3.7	3.7
11	15.7	17.4	14.2	16.5	9.0	7.8	8.7	3.9	3.9

Table 1: Conditional stability constants of mononuclear complexes (25°C , $I = 0.1 \text{ M NMe}_4\text{Cl}$) adapted from Kubicek, 2022.

Figure 2: Complexation of Calcium and Magnesium with EDTMP-H can afford two complexes with different stoichiometries: EDTMP-H:Ca = 1:1 and 1:2.

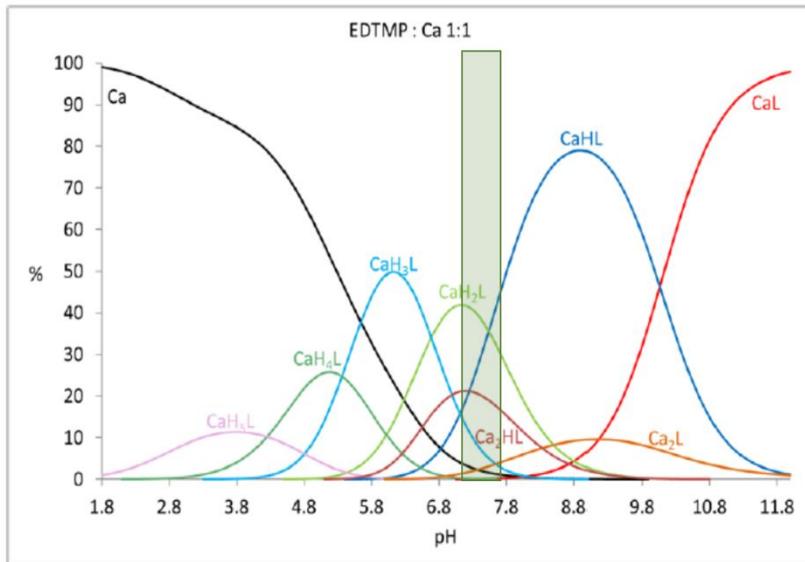


Figure 2a: Abundance of Ca-EDTMP-H complexes as function of pH ($c_L = 4 \text{ mM}$, $c_M = 4 \text{ mM}$ (ratio 1:1) (the green bar illustrates a broader range of physiological conditions) adapted from Kubicek, 2022.

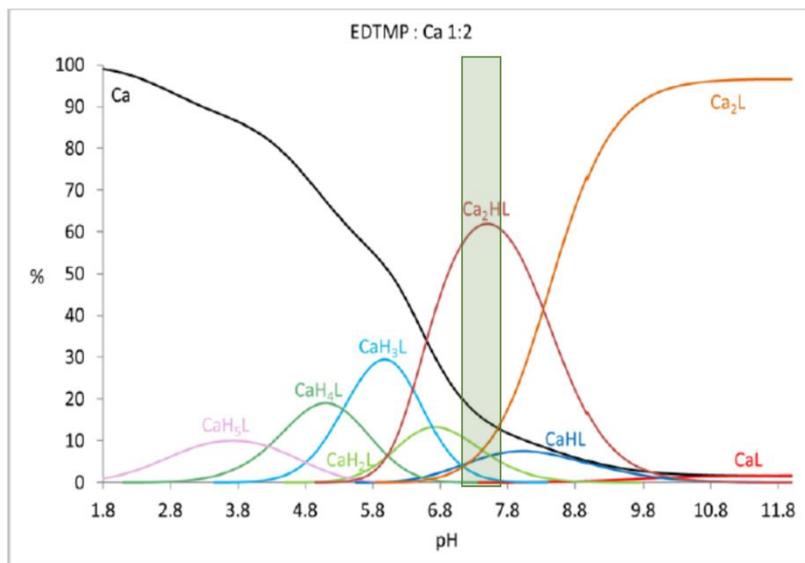


Figure 2b: Abundance of Ca-EDTMP-H complexes as function of pH or 8 mM (ratio 1:2), $25 \text{ }^\circ\text{C}$, $I = 0.1 \text{ M}$ NMe₄Cl) adapted from Kubicek, 2022. (The green bar illustrates a broader range of physiological conditions)

Adsorption

EDTMP-H has a high affinity to adsorb on surfaces of minerals, mainly on Alkaline earth based minerals or hardly soluble substances like Calcite, Gypsum, Struvite and Apatite to name a few. Due to this adsorption on the pre-formed (small) crystal of a hardly soluble alkaline earth salt, its further growth is retarded and the crystal shape is modified by continuous rearrangements of the growing sites. In particular, hydroxyapatite is of high biological importance. The strength of adsorption on hydroxyapatite has been investigated mainly in the direction of inhibiting its crystallization under defined conditions which allows a conclusion to be drawn on the interactions between mineral surfaces and the corresponding phosphonate (Zieba et al., 1996).

Justification for read-across

There is no additional comment.

Toxicokinetics (ADME)

There is no available human toxicokinetic study with EDTMP-H. However, EDTMP-H is used for drug purposes as a vehicle for ¹⁵³Sm against bone metastases (Lexidronam), demonstrating the high affinity of EDTMP-H for the bone matrix.

All available oral and intravenous toxicokinetic studies reveal a high affinity of EDTMP-H-H/Na to the bone with detected bone tissue concentrations of up to 2.8 % of the administered dose with the iv administration, mainly in femur and tibia with a long half-life of up to 27 d (repeated dosing in rats).

Absorption was observed to be less in rat oral feeding studies compared to rat oral studies performed using gavage (similar dose levels).

Germ cell mutagenicity

The LR in agreement with the co-registrants regarded the available studies relevant in a Weight of Evidence approach and sufficient to conclude that EDTMP-H does not raise a concern for mutagenicity. To update the dossier, we are committed to repeating a test on this substance according to OECD TG 487: In Vitro Mammalian Cell Micronucleus Test; or OECD TG 473: In Vitro Mammalian Chromosomal Aberration Test.

Carcinogenicity studies and their overall relevance

The expert opinion from [REDACTED] brings useful insights on the reliability of the three studies, providing details on why the available studies cannot be considered for the classification of EDTMP-H as a carcinogen.

1. Combined repeated dose and carcinogenicity study; EDTMP-Na, EC No. 244-742-5 (EDTMP-H adjusted with sodium hydroxide to pH 7.0 – 7.4), study report 1985; ECHA's dissemination site 001 (ETDMP-H)
2. Subchronic and chronic toxicity study, oral; EDTMP-H, EC No. 215-851-5; Calvin et al, 1988
3. Carcinogenicity, oral; mixture of EDTMP-Na, EC No. 244-742-5 (EDTMP-H) adjusted with sodium hydroxide to pH 7.0 – 7.4 and sodium fluoride), study report 1986c; ECHA's dissemination site 003 (ETDMP-H)

In summary, the Study #1 cannot be considered for the classification of EDTMP-H as a carcinogen due to the following reasons:

- The cancer-causing effects are directly related to toxic behavior of EDTMP-H that has only been observed at high doses.
- There is no observable dose-response relationship.
- No other tumors have been reported in any other site.

In Study #2, the compound induced tumors in the pancreatic islets. The authors believe that the results of this study should not be considered due to the extremely low incidence in the controls compared to historical controls.

Study #3 was conducted with a mixture of EDTMP-H and sodium fluoride. The results are compromised by the high mortality of animals during the treatment period at the two highest doses tested, leading to a significantly reduced number of surviving animals. It is therefore believed that the tumors obtained at these doses are a consequence of excessive toxicity. The administration of substances at doses approaching the maximum tolerated dose (MTD) is believed to stimulate regenerative growth, thereby increasing the likelihood of mutagenicity and, consequently, secondary carcinogenicity induced by toxic regenerative response.

Moreover, [REDACTED] points out that the bone anomalies found in the experimental studies most likely do not represent osteosarcomas, but rather other forms of benign tumors such as osteomas or osteodystrophies. This is the result of osteoclast activity disturbed by high and repeated dose of EDTMP-H that is reducing the rate of bone resorption leading to reactive response from the neighboring osteoblasts. Only physiopathology of the cells would have revealed the real nature of the tumors, but this was not performed in 1985. However, all other considerations on the possible mechanism of EDTMP-H on the homeostasis of $Fe^{2+/3+}$ and Ca^{2+} lead to the conclusion that EDTMP-H does not have a carcinogenic effect on rats. This evidence is clear in all animal studies, which can be used in a weight of evidence approach with no need to perform a new in vivo study.

Based on the above findings, these studies are clearly neither reliable, nor acceptable for confirming carcinogenicity properties according to CLP. Therefore, they should not be used as evidence in the classification of EDTMP-H as a carcinogen.

Comparison with the CLP criteria

According to the opinion of the experts, the available studies for EDTMP-H are conclusive, and their results do not require classification of EDTMP-H as a carcinogen. This is the consequence of the analysis of the animal studies, including against all of the factors that are listed in Annex 3.6.2.2.4 of the CLP Regulation.

There is an increased incidence of tumor, either benign or not, in only one study, whose compliance with actual OECD TG 451 is questionable. A second study is of lower relevance as the substance was administered with NaF which confounds the result. The incidence of the tumor is not exceptionally high and there is no recording of tumors in other sites.

There is no evidence of carcinogenicity. In only one experiment are there suspicious findings that can be explained as non-neoplastic lesions. The key study has no data on the characterisation of osteosarcoma, whose presence is reported only as a visual assessment of the morphology of bones in the sacrificed animals. Other findings come from a study where EDTMP-H was administered with NaF, which is a substance with known toxicity, as demonstrated in a study that was performed by administering only NaF that gave very similar outcomes. The neoplastic potential is not demonstrated, and the activity was recorded only in particular types of bones, the growing ones, and it is not a generalized effect. Based on historical controls, the incidence of osteosarcoma in SD rats is in the range 1.11-2.67%.

a) Tumor type and background

The animal studies report the occurrence of osteosarcoma in only one study at high doses. There is no certainty that it is osteosarcoma as it could also be another form of benign tumor. Any results must anyway be considered in full context which includes the fact that it is a common malignant tumor in this species, where bones are growing for the whole life cycle. After analyzing the possible activity of EDTMP-H in the organism, it can be concluded that the evidence in the available animal studies is not biologically relevant.

b) Multi-site responses

The osteosarcoma was not recorded on multi-sites, but only on growing bones. Other findings were not considered metastasis of the osteosarcoma. Taking into account the high prevalence of osteosarcoma to generate metastasis, this fact can be considered unusual and confirms that there is no multi-site response in animal studies.

There is no evidence of osteosarcoma generated in humans from exposure to carcinogenic substances. Alkylating agents can induce osteosarcoma, but in conjunction with many other types of tumors. From a chemical point of view, EDTMP-H has no possibility to act as an alkylating agent.

c) Progression of lesions to malignancy

The effect measured in other organs are not related to metastasis of the osteosarcoma. In the study where osteosarcoma was detected, the highest administered dose was increased from 150 mg/kg/day to 333 mg/kg/day as a consequence of a detected increase level of alkaline phosphatase. However, the serum level of alkaline phosphatase did not further change, even in animals where osteosarcoma was detected, demonstrating the non-malignancy of the tumors.

d) Reduced tumor latency

Tumors in rats that were detected at the Maximum tolerated dose could be non-specific and leading to positive responses that are not indicative at lower exposure levels.

e) Whether responses are in single or both sexes

The incidence of osteosarcoma-like effects was found in males at high and mid dose. The occurrence in females is only at high doses, with minor biological relevance. The low chemical reactivity of EDTMP-H leads to the exclusion of hormonal activity and the difference between the sexes are explained only by the higher rate of bone growth in males, the situation that enhance the activity of EDTMP-H in the perturbation of metal homeostasis and with direct effect on the generation of anomalous masses at the level of the bones.

f) Whether responses are in a single species or several species

The only study with concerning results is performed on rats. There is another study on mice, but the administered dose was lower and not comparable with the study performed on rats. The conclusion is that either the mice are not sensitive to EDTMP-H or that the effect of EDTMP-H is threshold based and cannot be considered a carcinogenic mechanism.

g) Routes of exposure

The unusual results were recorded only after administration by gavage. Studies performed with the substance administered in the diet did not result in a detectable effect, probably due to a much lower absorbance. We confirm that there is no study performed by either dermal or inhalation route.

h) Comparison of absorption, distribution, metabolism and excretion between test animals and humans

We agree that there is no reason to consider that the metabolism and excretion between test animals and humans are different, even if there is no evidence in humans.

Absorption is usually different in humans and rats, but this difference probably has little impact. Distribution can be more different, considering the chelating property of EDTMP-H and the increased incidence on animals' bones that are continuously growing.

i) The possibility of a confounding effect of excessive toxicity at test doses

There is already a recorded effect at high doses, as demonstrated by the high mortality. The difference between females and males is consistent. High tumors were already evident but the lack of concomitant increase of PTH demonstrates that the incidence of tumors at high dose is not consequence of a real carcinogenic effect. The incidence of effects on bones is not surprising by analyzing the effect of EDTMP-H in the organism.

j) Mode of action and its relevance for humans

Available studies lead to the conclusion that EDTMP-H is not genotoxic. To update the dataset, the study to demonstrate the absence of chromosomal aberration will be repeated.

The possible mode of action of EDTMP-H is through its binding capacity, that can reduce the normal level of Ca²⁺ in the plasma, leading to clinical symptoms of hypocalcemia with benign bone growth outside the skeleton (Cortes and Gosain, 2006, Diercks et al., 1996). EDTMP-H can also bind iron, inducing anemia by enhancing iron excretion, preventing iron utilization and depleting iron stores.

Dr. Rosemann listed possible etiology for the promotion of osteosarcoma in humans. Growth hormones can be associated to a higher prevalence, but this is due to the fact that bone growth is generally linked to the risk of osteosarcoma (Gianferante et al., 2023). Hormones that do not influence growth are not associated with the development of osteosarcoma. Alkylating chemicals can have an effect, but in this case, the risk of malignancy is generalized and not selective for osteosarcoma. From a chemical point of view, EDTMP-H cannot be regarded as an alkylating agent.

There is strong evidence that the mechanism of tumour formation is not relevant for humans. Animal experiments on osteosarcoma are probably (only) partially transferable to humans. However, they are carried out time and again, sometimes in the absence of more suitable, better models. It should be noted that the epidemiology of osteosarcoma in different animal species is very heterogeneous and, in some cases, is also very different from that in humans (Guijarro 2014).

The fact that the rat is not a good model for human osteosarcoma has prevented the possibility to develop an effective drug to cure such a rare human cancer. This situation could be solved through the availability of a suitable in vitro model, but research in this area is still limited.

The incidence of osteosarcoma in humans is low. [REDACTED] explains that it varies with various genetic, biological and external influencing factors. The use of non-radiolabeled aminomethylene phosphonates and hydroxy-bisphosphonates has so far not been associated with the incidence of this tumor in humans, despite extensive studies on its occurrence.

Summary

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
Rats, Sprague-Dawley, ♂ and ♀	Treatment related increased incidence of osteosarcoma or benign bone tumors; incidence is above historical control incidence	No; Osteosarcoma or benign bone tumors as the only treatment related tumour type observed	High mortality incidence at the dose generating bone tumors in animals. No metastasis have been detected	Yes; first tumors evident after 35 weeks (♂)	Osteosarcoma identified in ♂ and ♀, but the latter not in a statistical meaning rate	Yes, as demonstrated by the high mortality rate	Studies performed with oral (gavage) application	Mode of action: unknown. Possible contributions by inhibitory effects on bone resorption. No data to demonstrate relevance to human

In summary, the available data for EDTMP-H-H/Na are sufficient to exclude the concern for carcinogenicity. None of the CLP criteria is fulfilled because osteosarcoma was detected only in animals at toxic level.

Prevalence was high but not unusual in SD rats. The available data do not permit to conclude that rats had malignant osteosarcoma.

Osteosarcoma in humans has a different etiology and there is no demonstration that the possible mechanism of EDTMP-H can be translated to cause the same effect in humans.

The non-genotoxic carcinogenicity property of EDTMP-H can be further assessed by performing a new study according to the protocol of one of the Cell Transformation Assays (CTAs), based on their ability to induce malignant cell oncotransformation. CTAs, supported by mechanistic information, has been included in the Integrated Approach to Testing and Assessment (IATA) for non-genotoxic carcinogens (Jacobs et al., 2016, Jacobs et al., 2020, Colacci et al., 2023). Among them, BALB/c 3T3 CTA represents a good model to highlight chemical-induced perturbations in the microenvironment and is a critical step in oncotransformation. The EDTMP-H consortium is open to performing this new study if the RAC deems that it can be useful to disperse all concern about the carcinogenicity properties of EDTMP-H.

Conclusion on classification and labelling for carcinogenicity

The substance should not be classified as carcinogenic.

In support of this conclusion, the group also commits to conducting the following studies:

- OECD TG 487: In Vitro Mammalian Cell Micronucleus Test; or OECD TG 473: In Vitro Mammalian Chromosomal Aberration Test
- Cell Transformation Assays (CTAs), specifically BALB/c 3T3 CTA

Specific concentration limits for Category 1 carcinogens

The CLH report suggests a specific concentration limit of 1% in spite of the proposed classification as Carc. 1B, that should require a specific concentration limit of 0.1%. This is the admission that the effect recorded in animals has a high threshold. The clear mismatch between the proposed classification and the concentration limit demonstrates that EDTMP-H has not the typical activity of a carcinogenic substance.

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