Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Trimethyl borate

EC Number: 204-468-9
CAS Number: 121-43-7

CLH-O-0000007155-76-01/F

Adopted

15 September 2022

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

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Substance name: Trimethyl borate
EC number: 204-468-9
CAS number: 121-43-7
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Germany		MemberState	1
Comment received				
The DE CA appreciates the CLH proposal prepared by the NL CA. Scientific data relevant for boron, boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate regarding reproductive toxicity have already been reviewed by RAC in the past (RAC, 2014b, RAC, 2014d, RAC, 2014c, RAC, 2019) and the relevant information was adopted in the current dossier. In addition to this information, new studies on effects of boric acid on fertility that were published recently have been included in the dossier. Furthermore, available information on reproductive toxicity of methanol are included and discussed in the dossier as well. Concerning toxicokinetics and read-across, it is noted that the sentence "According to the REACH registration dossier, trimethyl borate is rapidly (too fast to measure) hydrolysed into boric acid and methanol in water under physiological conditions (Steinberg et al., 1957)." may be somewhat confusing, as hydrolysis in water does not represent physiological conditions (similar sentence used in section 3 of the dossier). Furthermore, and in closer inspection of the respective study, hydrolysis of trimethyl borate was not tested in 'pure water' in this study but rather under 'conditions of possible applications'. In the respective publication (https://pubs.acs.org/doi/pdf/10.1021/ie50566a023), the following is reported: "Water at 21°C (Heterogeneous). In order more closely to approximate actual conditions of possible applications of the boric acid esters, the esters were subjected to hydrolysis by agitation in water. A solution of 50 mL of water, 5 grams of mannitol, 4 drops of phenolphthalein, and one half the amount of 0.2457 or 0.1130 N sodium hydroxide necessary to neutralize the boric acid resulting from complete hydrolysis was added to a weighed sample of ester. The mixtures were agitated, and the time for fade of the indicator was recorded as the half time. Compensation for the liberated phenols (runs 53, 54, and 59) with additional base did not				

materially change the half times".
As these study conditions do not reflect any physiological conditions, clarification may be helpful. It seems as if there is no further information on hydrolysis of the substance (or behaviour in artificial biological fluids) available in the scientific literature and the registration dossier. In addition, no data on toxicokinetics, repeated-dose toxicity, or reproductive toxicity of the substance are available. Conclusions on the appropriateness of the proposed read-across from data of boric acid and methanol are therefore difficult, although read-across from boric compounds to boric acid (and methanol in this case) generally seems plausible and was already accepted by RAC for other borates.
In this regard, it might be helpful if the basic assumptions underlining the applied read-across were further elaborated on (e.g. by adding information on other/similar borate compounds).

Acute toxicity:
Not addressed in the present dossier, although trimethyl borate has a minimal classification for acute dermal toxicity, Cat. 4*, H312. It would have been beneficial, if this hazard class and the ATE had been included in the dossier in order to allow for a final conclusion on the acute dermal toxicity of the substance.

Specific target organ toxicity – single exposure:
Not addressed in the present dossier. However, due to the harmonised classification of methanol as STOT SE 1, H370, and the applied read-across from methanol for the hazard class reproductive toxicity, it is questioned why this endpoint is not addressed in this CLH report.

Dossier Submitter's Response

We thank DE CA for their comments.

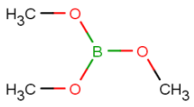
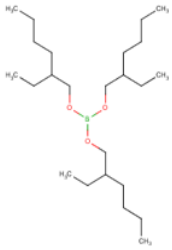
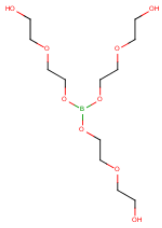
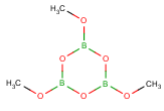
Hydrolysis of trimethyl borate and read-across
We agree that conditions to measure hydrolysis of trimethyl borate in water (at 21 °C) used by Steinberg et al. (1957) cannot be defined as physiological. However, this study demonstrates that trimethyl borate is rapidly hydrolysed when dissolved in water. Data from handbooks (likely based on other primary sources) confirm this; according to the Merck index online[1] '*trimethyl hydrolyses in the presence of water to methanol and boric acid*', and according to Sax's Dangerous Properties of Industrial Materials[2] '*trimethyl borate decomposes in water'*. There is no data available showing trimethyl borate is not hydrolysed under physiological conditions in the presence of water.

Read-across from boric acid to other borates and between borates has been applied in other CLH dossiers and was accepted by RAC (e.g. disodium octaborate, anhydrate; disodium octaborate tetrahydrate; diboron trioxide; tetraboron disodium heptaoxide, hydrate). In addition, similar chemical and toxicological properties of boric acid and other borates are expected on a mol boron/litre equivalent basis when dissolved in water or biological fluids at the same pH and low concentration as stated experts of the World Health Organization & International Programme on Chemical Safety (1998)[3]. A judgement of the European Court of Justice further supports the use read-across for assessment of borates.[4] In addition, registrants have proposed read-across for trimethyl borate based on data for methanol and boric acid.

[1] https://www.rsc.org/Merck-Index/monograph/m11152/trimethyl%20borate?q=unauthorize
[2] https://onlinelibrary.wiley.com/doi/10.1002/0471701343.sdp50588
[3]https://apps.who.int/iris/bitstream/handle/10665/42046/9241572043_eng.pdf?sequence=1&isAllowed=y
[4] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?isOldUri=true&uri=CELEX:62010CJ0015

A comparison of the structure, hydrolysis and physicochemical properties of trimethyl borate, tris (2-ethylhexyl)orthoborate (another alkoxy borate), tris[2-(2-hydroxyethoxy)ethyl] borate and triboron trimethyl hexaoxide (two ethoxylated borates) has been made in the table below. Data from OECD 111 (hydrolysis as a function of pH) is available in the ECHA online registration dossier for the latter three substances. This comparison demonstrates that rapid hydrolysis (<10 min) of these borate esters take place at different pH, temperatures and buffer compositions. Therefore, it is considered likely that trimethyl borate will also hydrolyse under such conditions.

Table: Summary of physicochemical properties for trimethyl borate, tris(2-ethylhexyl) orthoborate, tris[2-(2-hydroxyethoxy)ethyl] borate and triboron trimethyl hexaoxide

Property	Trimethyl borate[5]	Tris(2-ethylhexyl) orthoborate[6]	Tris[2-(2-hydroxyethoxy)ethyl] borate[6]	Triboron trimethyl hexaoxide[6]
EC number	204-468-9	219-581-9	615-244-9	203-016-8
Structure				
Hydrolysis	Half time too fast to measure (in water at 21°C, pH unknown; Steinberg and Hunter, 1957)	Complete hydrolysis (<10 min; OECD 111) at pH 1.2 (37°C), 7 (water; 20°C), and 4, 7, 9 (25°C) Half time 70 sec (in water at 21°C, pH unknown; Steinberg and Hunter, 1957)	Complete hydrolysis (<10 min; OECD 111) at pH 1.4, 4, 7 and 9 at 20°C	Complete hydrolysis (<5 min; OECD 111) at pH 6 (pH at start)
Physical state at 20°C and 101.3 kPa	Liquid	Liquid	Liquid	Liquid
Melting/freezing point	-31 °C	-20.2°C	> -35°C at 1013 hPa	-57.1°C at 1013 hPa

[5] As stated in the CLH proposal for trimethyl borate
[6] As stated in the ECHA online registration dossier, unless stated otherwise

Boiling point	68.2 - 68.6 °C	273°C	> 250°C	Reaction and/or decomposition of the test item was observed. Boiling of the test item was not observed below the temperature at which reaction and/or decomposition started
Relative density	0.91	0.859	1.06	1.22
Water solubility	Data waived	<3.15 x 10-5 g/L (based on boric acid and 2-ethylhexanol)	Spontaneous hydrolysis of the test substance in diethylene glycol and boric acid after contact with water. ~1000 g/L based on hydrolysis products	Technically not feasible. Hydrolytically instable and breaks down in methanol and boric acid in water.

Based on this information together, rapid hydrolysis of trimethyl borate in the presence of water is considered highly likely under physiological conditions. There is sufficient evidence to justify read-across from trimethyl borate based on its hydrolysis products, in line with other borates and performed in other regulatory contexts.

Acute toxicity and specific target organ toxicity – single exposure:
The classification of Acute tox and a corresponding ATE-value is challenging for trimethyl borate in our opinion. This is mainly because of the hydrolysis product methanol. The data for methanol in animal studies is not representative to humans, as also mentioned in this CLH proposal. However, the registrant uses the read-across from methanol for the acute toxicity (category 3) and specific target organ toxicity – single exposure (STOT-SE, category 1) classification for trimethyl borate for inhalation, oral and dermal routes.

For the dermal and inhalation routes trimethyl borate could possibly also hydrolysis rapidly in boric acid and methanol but this needs proper argumentation. Therefore, read-across for both hydrolysis products would be required for all three routes (oral, dermal, inhalation).

We estimate that this will take a substantial amount of time. Furthermore, CMR criteria are the main focus of CLP. The same arguments are true for STOT-SE. Therefore we prefer not to reassess the Acute tox 4 classification (and the corresponding ATE-value) and/or assess a STOT-SE classification for trimethyl borate.

RAC's response

RAC considers the read-across of data on boric acid and methanol to trimethyl borate as valid. Please see RAC Opinion for further information.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2021	Germany		MemberState	2
Comment received				

Fertility

The DE CA supports the proposed classification of trimethyl borate as Repr. 1B, H360F, and a GCL due to the medium potency. Nevertheless, there are some points particularly with respect to the applied read-across that need clarification (for details please see "General comments").

There is no information available on the reproductive toxicity of trimethyl borate itself. The DS has proposed read-across from data on boric acid and methanol based on the assumption that trimethyl borate is quickly hydrolysed into these two substances. Accordingly, the DS states that after oral or inhalation exposure, complete hydrolysis is expected in the body. Again, the DE CA notes that this was not demonstrated for the substance in any study, but remains an assumption based on a single study showing fast hydrolysis under unphysiological conditions (Steinberg and Hunter, 1957) and information on other borates.

Information on boric acid and borates

RAC confirmed the recently proposed classification of boric acid and multiple borates as Repr. 1B, H360FD (RAC, 2019). The data for classification of trimethyl borate for fertility effects do not differ from this previous data set, except for some few additional and more recent studies, which confirm the prior findings. Treatment-related effects in animals included impairment of fertility through effects on the testes (e.g. testicular atrophy and seminiferous tubule degeneration). Additionally, a new sub-acute study (Aktas, 2020) suggests that oxidative stress may be a cause of the observed effects in testicular tissue, supporting previous data. Moreover, several recent epidemiological studies reported increased levels of boron in semen, blood and/or urine in males exposed to boron through environment and/or occupation, which however did not correlate with fertility parameters. As the daily exposure levels to boron were well below the LOAELs observed in animal studies, RAC previously concluded that the available human data on fertility and sexual function do not contradict the animal data.

Information on methanol

In chronic studies in rats and mice, some fertility effects were observed, including significant increase of testicular interstitial hyperplasia (rats), testicular adenomas and sarcomas of the uterus (both in rats) and testicular atrophy and reductions in relative and absolute weight of testis (in mice). Additional repeated-dose toxicity studies with methanol in various species (oral and inhalation) yielded contradicting findings, as several reported some adverse fertility effects, while others did not. No adverse effects on sexual function and fertility were observed in non-human primates. No relevant human data are available. It is noted that currently there exists no harmonised classification of methanol for the hazard class reproductive toxicity, and the DS is of the opinion that the limited effects of methanol observed in animals do not warrant classification in Cat. 1B. Overall, and in agreement with previous evaluations of RAC, the DE CA agrees with the DS that the effects on fertility parameters observed particularly after exposure to boric acid and boron justify classification of trimethyl borate as Repr. 1B, H360F. Due to the

medium potency estimated for trimethyl borate, the use of a GCL as proposed by the DS is supported.

Severe toxicity and mortality due to the simultaneous methanol exposure (in addition to the other hydrolysis product boric acid) could mask the effects on fertility of boric acid at high doses/concentrations. However, as the human ED10 for trimethyl borate calculated by the DS (i.e. 40 mg/kg bw/d) is below the minimal lethal dose of methanol in humans (300 – 1000 mg/kg bw), the reprotoxic effects induced by boric acid are considered relevant for classification.

Developmental Toxicity

The DE CA supports the proposed classification of trimethyl borate as Repr. 1B, H360D, with a GCL.
As with fertility, there is no information available on the developmental toxicity of trimethyl borate itself, and read-across from data on boric acid and methanol is proposed. Specific comments on the applied read-across from boric acid and methanol can be found under section "General Comments".

Information on boric acid and borates

The numerous available developmental toxicity studies in animals with boric acid and borates have been evaluated by RAC in the past. RAC confirmed the proposed classification of boric acid and multiple borates as Repr. 1B, H360FD (RAC, 2019). Developmental abnormalities included enlargement of lateral ventricles in the brain and agenesis and shortening of the 13th rib in the absence of maternal toxicity (at doses ≥ 76 mg boric acid/kg bw/d). Lower doses of boric acid tested in another study (up to 11 mg/kg bw/d), did not yield any adverse developmental effects, except for slight reductions in mean foetal body weight (up to -7 %). Data from human studies did not indicate boron-induced adverse developmental effects.

Information on methanol

RAC previously concluded that classification of methanol based on animal studies is not warranted because methanol will result in severe toxicity and mortality in humans at lower doses, before methanol-induced developmental toxicity is expected (RAC 2014). Therefore, the data of methanol are not considered relevant for classifying trimethyl borate for developmental toxicity. In addition, differences in developmental toxicity upon exposure to methanol in rodents and non-human primates suggest a different mechanism responsible for methanol-induced developmental toxicity in rodents and non-rodents. Available human data further have to be interpreted with caution due to the limited number of cases, co-exposure to other substances, and/or a limited number of patients tested.

Overall, and in agreement with previous evaluations of RAC regarding boric acid and numerous borates, the DE CA is of the opinion that classification of trimethyl borate as Repr. 1B, H360D, is justified, if the read-across can be considered acceptable. Due to the medium potency estimated for trimethyl borate, the use of a GCL as proposed by the DS is supported.

The DS calculated an estimated LOAEL for developmental toxicity in humans (i.e. 32 mg/kg bw/d), which is below the minimal lethal dose of methanol in humans (300 – 1000 mg/kg bw). Thus, developmental toxicity in humans induced by boric acid is expected to occur at lower doses than the lethal dose of methanol underlining the need for

classification for developmental toxicity. **Effects on or via Lactation** The DE CA concurs with the conclusion of the DS that classification of trimethyl borate is not justified due to insufficient data. As with fertility and developmental toxicity, there is no relevant data available testing the effects of trimethyl borate itself. Specific comments on the applied read-across from boric acid and methanol can be found under section "General Comments". There is one study available in which rather small amounts of boric acid were detected in milk, but no details are reported in the dossier. With respect to methanol effects on/via lactation, one available study reported methanol-induced adverse lactational effects in rats at the high dose (4 % methanol in drinking water), including decreased body weight gain and neurodevelopmental toxicity. No details on maternal toxicity were reported. The DS states that it is "unknown whether this mechanism of adverse effects in rodents is relevant to humans, seen the difference in metabolism of methanol in rodents and humans". No further data was provided in the dossier. Overall, the DE CA is of the opinion that the available data are insufficient to justify classification of trimethyl borate for effects on or via lactation, although adverse effects upon lactational exposure cannot be excluded.
Dossier Submitter's Response
The DS would like to point out that the human ED_{10} for fertility for trimethyl borate mentioned by the DE CA is for methanol (40 mg/kg bw/d) and not for trimethyl borate. The estimated human ED_{10} is 43 mg trimethyl borate /kg bw/d, with a simultaneous estimated exposure to methanol of 40 mg/kg bw/d. Similarly, the estimated human LOAEL for developmental toxicity is 32 mg trimethyl borate/kg bw/d, with a simultaneous estimated exposure to methanol of 30 mg/kg bw/d. The DS agrees with DE CA that there is insufficient data available to justify classification of trimethyl borate for effects on or via lactation.
RAC's response
Noted.