SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Dipotassium tetraborate

EC No 215-575-5

CAS No 1332-77-0

Evaluating Member State(s): Lithuania

Dated: 7 November 2018

Evaluating Member State Competent Authority

Environmental Protection Agency
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Year of evaluation in CoRAP: 2017

Lithuania concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Dipotassium tetraborate was originally selected for substance evaluation in order to clarify concerns about:

- Reprotoxicity
- Consumer use
- Exposure of workers
- High RCR
- Wide dispersive use

During the evaluation another concern was identified. The additional concern was: respiratory irritation.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

For dipotassium tetraborate there are no other completed/ongoing processes.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	X
Identification as SVHC (authorisation)	-
Restrictions	-
Other EU-wide measures	-
No need for regulatory follow-up action at EU level	-

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

According to the evaluation of the eMSCA, the registered substance fulfills the criteria for classification as Repr. 1B, H360FD "May damage fertility. May damage the unborn

child". The eMSCA therefore suggests a new entry in Annex VI of Regulation (EC) 1272/2008 in order to cover reproductive toxicity as specified below.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not yet applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the Member State. A commitment to prepare a REACH CLP Annex VI dossier will be made via the Registry of Intentions.

Table 3

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
CLH dossier for inclusion the substance in Annex VI of the CLP. Dipotassium tetraborate could fit into the preliminary plan to assess a group of boron compounds for harmonised classification in reproductive toxicity.	Preliminary assessment of boron compounds could start in 2019 but it depends on the available resources and prioritizations.	Depending on the outcome of the assessment of boron compounds candidates and on the most appropriate grouping approach Dipotassium tetraborate could be included in Sweden's plan to assess boron compounds for harmonised classification.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Dipotassium tetraborate was originally selected for substance evaluation in order to clarify concerns about:

- Reprotoxicity
- Consumer use
- Exposure of workers
- High RCR
- Wide dispersive use

During the evaluation another concern was identified. The additional concern was: respiratory irritation.

Table 4

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Toxicity to reproduction	Reprotoxic effects confirmed, harmonised C&L process to be initiated.
Consumer use	Concern not substantiated. No further action.
Exposure of workers, high RCR, wide dispersive use	Operational conditions and risk management measures are adequately described for all the exposure scenarios. Nevertheless evaluation of the available information shows that in some exposure scenarios there may be potential risk for workers as well as for the environment as some uses' RCRs are close to 1.

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, dipotassium tetraborate was included on the Community rolling action plan (CoRAP) for evaluation in 2017. The Competent Authority of Lithuania was appointed to carry out the evaluation. The substance evaluation commenced on 21 March 2017.

Environmental protection agency (EPA) is designated as a national Competent Authority to perform the tasks allotted to the competent authorities under Regulation (EC) No 1907/2006 in cooperation with the Ministry of Health/National Public Health Centre. EPA is responsible for environmental assessment and coordination of evaluation meanwhile National Public Health Centre is responsible for human health assessment. In addition EPA consulted with State Labour Inspectorate regarding exposure of workers.

The evaluation was targeted to human health hazards and exposure. As environmental evaluation was not the main focus thus the assessment of environmental hazards was not carried out.

The main source of information for the evaluation was the original data/information submitted within REACH registration (IUCLID dossiers, Chemical Safety Reports (CSRs)).

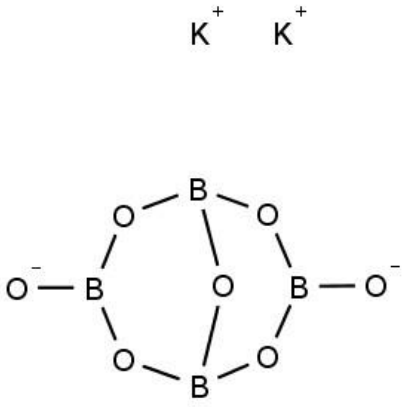
7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	Dipotassium tetraborate
EC number:	215-575-5
CAS number:	1332-77-0, 12045-78-2
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	$B_4K_2O_7$
Molecular weight range:	233.4358
Synonyms:	dipotassium bicyclo[3.3.1]tetraboroxane-3,7-bis(olate); dipotassium tetraborate, anhydrous; Potassium tetraborate; Potassiumtetraborat Tetrahydrat.

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Solid (100%)
Vapour pressure	If the melting point is above 300 °C vapour pressure study does not need to be conducted

	(according to Annex VII, section 7.5, column 2 of Regulation No. 1907/2006)
Melting point	500 °C
Water solubility	16.32 % w/w (calculated from the titration for boric oxide)
Partition coefficient n-octanol/water (Log Kow)	The study does not need to be conducted if the substance is inorganic (according to Annex VII, section 7.8, column 2 of Regulation No. 1907/2006)
Flammability	Non flammable (100%)
Explosive properties	Non explosive
Oxidising properties	-
Granulometry	The d50 was shown to be 25.057 µm. Coefficient of variation for d50 was less than 3 %; d10 and d90 were less than 5 %
Stability in organic solvents and identity of relevant degradation products	Not applicable
Dissociation constant	pKa 9.08 at 20 °C

7.5. Manufacture and uses

7.5.1. Quantities

Table 8

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☒ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 9

USES	Use(s)
Uses as intermediate	Formulation of borate PVA solutions; Production/Import; Manufacture of new chemicals using borates.
Formulation	Production of low alkali glass; Formulation into photographic solutions; Formulation of borates into industrial fluids; Formulation of paints and coatings; Manufacture of flux mixtures and pastes; Industrial use of industrial fluids; Formulation into detergents;

	Formulation of borates in fertilizers; Formulation into cement; Formulation into analytical reagents; Formulation of borates in adhesives.
Uses at industrial sites	Industrial use of fluxes for (Precious) Metal smelting; Industrial use of adhesives; Industrial use of photographic solutions; Industrial/Professional use of welding, brazing or soldering rods; Laboratory use of analytical reagent; Manufacture of new chemicals using borates; Production of low alkali glass; Industrial use of cement; Industrial use of industrial fluids; Industrial use of paints and coatings; Formulation of borates PVA solutions; Use of borates in metal treatment (plating, passivation, galvanising, cleaning, etc.); Production/Import; Industrial use of borates in closed nuclear system; Industrial use of flux pastes for coating brazing and welding rods.
Uses by professional workers	Professional use of detergents; Professional use of paints and coatings; Professional use of photographic solutions; Professional use of fertilizers.
Consumer Uses	Consumer use of detergents; Consumer use of articles containing adhesives; Consumer use of fertilizers; Consumer use of automotive fluids.
Article service life	Industrial use of flux pastes for coating brazing and welding rods; Production of low alkali glass; Indudtrial use of fluxes for (Precious) Metal smelting; Consumer use of articles containing adhesives.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Currently no harmonised classification available.

7.6.2. Self-classification

- In the registration(s):

- Repr. 2, H361: Suspected of damaging the unborn child. (d)

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

- Repr. 1B, H360: May damage fertility or the unborn child. (FD)
- Repr. 1A, H360: May damage fertility or the unborn child.
- Eye Irrit. 2, H319: Causes serious eye irritation.

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Justification of read-across method:

In the plasma of mammals and in the environment (physiological and acidic pH) dipotassium tetraborate as other simple inorganic borates such as boric acid, potassium pentaborate, potassium tetraborate, disodium tetraborate decahydrate, disodium tetraborate pentahydrate, boric oxide and disodium octaborate tetrahydrate (hereinafter – borates) would predominantly exist as un-dissociated boric acid [$B(OH)_3$]. As borates dissociate to form boric acid, which can be considered to exist as undissociated boric acid in aqueous solutions, results from one substance can be transferred to also evaluate another substance on the basis of boron equivalents. For comparative purposes, borates are expressed in terms of boron (B) equivalents based on the fraction of boron in the source substance on a molecular weight basis (WHO, 1998). Since the systemic effects and some of the local effects can be traced back to boric acid, results from one substance can be transferred to also evaluate another substance on the basis of boron equivalents. Therefore read-across between the different borates can be done in the human health assessment. Conversion factors are given in the Table 10 below.

Table 10

CONVERSION FACTORS OF BORATES		
Substance name	**Formula**	**Conversion factor for equivalent dose of B (multiply by)**
Boric acid (CAS no.: 10043-35-3; EC / List no.: 233-139-2)	H_3BO_3	0.1748
Boric oxide (CAS no.: 1303-86-2; EC / List no.: 215-125-8)	B_2O_3	0.311
Disodium tetraborate anhydrous (CAS no.: 1330-43-4, 1303-96-4, 12179-04-3; EC / List no.: 215-540-4)	$Na_2B_4O_7$	0.2149
Disodium tetraborate pentahydrate (CAS no.: 12179-04-3; EC / List no.: 601-808-1)	$Na_2B_4O_7 \bullet 5H_2O$	0.1484
Disodium tetraborate decahydrate (CAS no.: 1303-96-4; EC / List no.: 603-411-9; borax)	$Na_2B_4O_7 \bullet 10H_2O$	0.1134
Disodium octaborate tetrahydrate (CAS no.: 12280-03-4; EC / List no.: 602-894-3)	$Na_2B_8O_{13} \bullet 4H_2O$	0.2096

Dipotassium tetraborate (anhydrous) (CAS no.: 1332-77-0, 12045-78-2; EC / List no.: 215-575-5)	$B_4K_2O_7$	0.1415
Dipotassium tetraborate (tetrahydrate) (CAS no.: 12045-78-2; EC / List no.: 601-707-2)	$K_2B_4O_7 \bullet 4H_2O$	0.1415
Potassium pentaborate (anhydrous) (CAS no.: 11128-29-3; EC / List no.: 234-371-7)	B_5KO_8	0.244
Potassium pentaborate (tetrahydrate) (CAS no.: 12229-13-9; EC / List no.: 602-489-1)	$B_5KO_8 \bullet 4H_2O$	0.1843

Absorption of borates via the oral route is nearly 100 % but dermal absoption is very low in humans. Boric acid is mainly excreted rapidly in the urine and has low potential for accumulation.

Since dipotassium tetraborate as other borates dissociate to form boric acid in aqueous solutions, they too can be considered to exist as un-dissociated boric acid under the same conditions. Additional support for this derives from studies in which more than 90 % of administered doses of inorganic borates are excreted in the urine as boric acid. Absorption of borates via the oral route is nearly 100 %. For the inhalation route also 100 % absorption is assumed as worst case scenario. Dermal absorption through intact skin is very low with a percent dose absorbed of 0.226 ± 0.125 in humans. Using the % dose absorbed plus standard deviation (SD) for boric acid, a dermal absorption for borates of about 0.5 % can be assumed as a worse case estimate.

In the blood boric acid is the main species present and is not further metabolised. Boric acid is distributed rapidly and evenly through the body, with concentrations in bone 2 - 3 higher than in other tissues. Boric acid is excreted rapidly, with elimination half-lives of 1 h in the mouse, 3 h in the rat and < 27.8 h in humans, and has low potential for accumulation. Boric acid is mainly excreted in the urine.

7.9.2. Acute toxicity and Corrosion/Irritation

Acute toxicity

According to a reliable with restrictions acute oral toxicity key study with dipotassium tetraborate, oral LD_{50} value (male rat) of 3690 mg/kg was obtained (Unpublished report 8, 1975). Another (OECD 401) key study (Klimisch score 1) with borate analogue (disodium tetraborate anhydrous) indicated LD_{50} oral (male rat) > 2500 mg/kg (Unpublished report 24, 1996). However, a previous OECD 401 supporting study (Klimisch score 1) with the same borate analogue indicates LD_{50} value for male rat >250 mg/kg and for female rat >2000 mg/kg (Unpublished report 27, 1995). All other supporting studies rated Klimisch 1 with borate analogues (disodium tetraborate pentahydrate and disodium tetraborate decahydrate) clearly indicate LD_{50} oral values of > 2000 mg/kg (Unpublished report 9, 1985; Unpublished report 1, 1961; Weir RJ & Fisher RS, 1972). The eMSCA conclucion is based on key study on dipotassium tetraborate which indicates low toxicity by oral route with LD_{50} of 3690 mg/kg.

The realiable studies on acute dermal toxicity were done only with two borate analogues (disodium tetraborate pentahydrate and disodium tetraborate decahydrate). Both of them indicate LD_{50} dermal >2000 mg/kg (Unpublished report 9 and 10, 1985). Based on read-accros MSCA concluded that dipotassium tetraborate has low toxicity by dermal route (LD_{50} dermal >2000 mg/kg.)

Two realiable acute inhalation studies (Unpublished report 20, 1994) with one borate analogue (disodium tetraborate pentahydrate) were performed at concentrations above 2000 mg/m^3 . According to the key study (Klimisch score 1) LC_{50} inhalation was >2,04 mg/L (air, 4 h) and according to the supporting study (Klimisch score 2) LC_{50} inhalation was >2,03 mg/L (air, 4 h). In both studies no lethal effect at limit dose was observed. As discriminating concentration (dose) was indicated >2000 mg/m^3 and no lethal effect at limit dose was observed. eMSCA considers dipotassium tetraborate based on read–accross as not acute toxic by inhalation route.

Corrosion/Irritation

Skin:

Three reliable *in vivo* studies on skin irritation were performed. The key study (Klimisch score 2) with borate analogue (potassium tetraborate) indicates no irritation to rabbits (Unpublished report 7,1973). Overall irritation score for intact and abraded skin was 0 of max. 8, time point 48 h. The other key study (Klimisch score 2) with borate analogue (disodium tetraborate pentahydrate) as well indicates no irritation (Unpublished report 11, 1985). Erythema / Edema score was 0 of max. 4, time not specified. A supporting study (Unpublished report 11, 1985), although performed with a different borate analogue (disodium tetraborate decahydrate), also indicates same results as the previous one. As adequate data from *in vivo* skin irritation studies was available no *in vitro* studies are needed. Overall, eMSCA assumes that dipotassium tetraborate based on read-across should be considered as not corrosive / irritant to skin.

Eye:

Numerous non-human studies on eye irritation were presented by registrants. All of them have been done with borate analogues. The results of the key study (OECD 405, Klimisch score 1) with borate analogue (dipotassium tetraborate (tetrahydrate)) clearly indicate no irritation effects to eyes (Unpublished report 28, 2013). No irritation was observed in any animal throughout the study for iris lesions. Conjunctival redness scores were 1.0 for all animals, and conjunctival chemosis scores ranged from 0.7 to 1.0. No signs of any ocular irritation were present at 14 days after dosing (initial testing) or 7 days after dosing (confirmatory testing). Two equivalent or similar to OECD 405 supporting studies (Klimisch score 1/2) with two different borate analogues(disodium tetraborate pentahydrate and disodium tetraborate decahydrate) support the conclusion on non irritant to eyes (Unpublished report 26, 2000 and Unpublished report 14, 1989). However, three supporting studies indicated irritation effects. An equivalent or similar to OECD 405 study (Klimisch score 2) with borate analogue (disodium tetraborate pentahydrate) indicated moderate irritation in unwashed eyes (Unpublished report 25, 1996). Another study rated Klimisch score 1 (EPA, Pesticide Assessment Guideline) with borate analogue (disodium tetraborate decahydrate) indicated high irritation, however as this irritation arises from the glassy nature of the crystals of the substance it is deemed not relevant for classification (Unpublished report 12, 1985). Another study rated Klimisch score 1 (EPA, Pesticide Assessment Guideline) with borate analogue (disodium tetraborate pentahydrate) indicates irritation however does not provide relevant data to support conclusion (Unpublished report 13, 1985e). As *in vivo* studies were available, no *in vitro* study was carried out. Although registrants provide numerous exposure-related observations on eye irritation in humans, the eMSCA did not asume this information as relevant as these observations did not provide sufficient evidence on eye irritation. Taking into account information provided above, eMSCA concluded that dipotassium tetraborate based on read-across does not need to be considered as causing serious eye damage or irritantion to eyes.

Respiratory tract:

Six exposure-related observations on respiratory irritation in humans were provided by the registrant in the CSR with borate analogues (boric acid, boric oxide, sodium borate, disodium tetraborate pentahydrate, Borax). The eMSCA considered as not relevant four of these observations as information in them did not provide sufficient evidence on respiratory tract irritation. Furthermore, no respiratory irritation studies with dipotassium tetraborate have been conducted.

Other two exposure-related observations with borate analogues on respiratory irritation in exposed workers showed upper respiratory tract irritation. Adverse effects were observed including nasal and eye irritation, throat irritations, cough, breathlessness, etc (Garabrant DH, et al., 1984; Unpublished report 16, 1991; Hu X, et al., 1992; Wegman DH, et al., 1994; Woskie SR, et al., 1993, 1994; Woskie SR, et al., 1998). Overall, borates act as mild sensory irritants, indicated by the effects observed in humans however, the actual mechanism has not yet been determined. Based on read-across eMSCA assumes that dipotassium tetraborate should be considered as respiratory irritant.

7.9.3. Sensitisation

Skin

Although no skin sensitisation study was available for dipotassium tetraborate however two studies according OECD 406 guidline (Buehler method) were performed with borate analogues (disodium tetraborate pentahydrate and disodium tetraborate decahydrate). Both of this studies (rated Klimisch score 1) indicated no skin sensitisation in animals (Unpublished report 21 and 22, 1994). In addition exposure-related observations in humans were reported for borate analogue (boric acid) also indicating no skin sensitisation (Bruze, M, et. all, 1995). Therefore the eMSCA considers based on read-across that dipotassium tetraborate is not a skin sensitiser.

Respiratory tract:

As in the CSR no data were provided on the respiratory sensitising property of dipotassium tetraborate or other borate analogues, the eMSCA was unable to evaluate this particular hazard. Based on lack of information eMSCA can not conlude on respiratory sensitisation.

7.9.4. Repeated dose toxicity

Most subchronic and chronic studies, which were carried out in rats, mice and dogs, showed that boron, boric acid, and other borates, under physiological conditions, can cause adverse haematological effects such as reduced red cell volume and haemoglobin values and toxicity to testis (testicular atrophy). Notwithstanding that borates can cause adverse haematological effects the main target organ of boron toxicity is the testis. There was no clear evidence for testicular damage in studies of highly exposed workers in Turkey and China and no available data which supports that boric acid may cause reproductive and developmental effects in humans (Robbins, et al., 2008, 2010; Scialli, et al., 2010).

Additionally, there was no information available for dipotassium tetraborate regarding repeated dose toxicity (STOT RE). Read-across to dipotassium tetraborate was applied, using data of boric acid and other borates (borax). Furthermore, according to the fact that borates will predominantly exist as undissociated boric acid under physiological conditions, the toxicological properties of borates are expected to be similar. Human data on accidental or intentional poisoning incidents with boric acid and sodium borate reflected symptoms of acute poisoning which were deemed not valid for STOT RE assessment. The majority of sub-chronic and chronic studies on boric acid and other

borates in rats and mice revealed testicular atrophy in males and the effects occured generally at relatively high doses. The estimated LOAEL value in studies on boric acid was 58,5 mg B/kg bw/day (Unpublished report 2 and 3, 1966). Since dipotassium tetraborate is proposed to be classfied for effects on reproductive toxicity, the effects on testis will not be considered under STOT RE. Consequently the eMSCA is of the opinion that classification for toxicity to reproduction is more appropriate than STOT RE.

7.9.5. Mutagenicity

Several *in vitro* mutagenicity studies were performed with borate analogues (boric acid and borax). With borate analogue (boric acid) the first key study, equivalent or similar to OECD Guideline 471, on bacterial reverse mutation (Klimisch score 1) clearly indicated a negative result (Unpublished report 19, 1991). The second key study, equivalent or similar to OECD Guideline 476, on mammalian cell gene mutation (Klimisch score 1) also clearly indicated a negative result (Unpublished report 18, 1991). All supporting studies on gene mutation with borate analogue (oric acid) confirm the negative results (Benson W H, et al., 1984; Yahagi, et al., 1975; Haworth S, et al., 1983; NTP, 1987a).

With borate analogue (boric acid) two supporting in vitro mammalian chromosome aberration studies were conducted. One of them equivalent or similar to an internal NTP protocol, which generally complies with OECD guidelines (Klimisch 1), indicated a negative result (NTP, 1987a) although another study (Klimisch 2) indicates a positive result for lymphocytes where chromosome aberrations were present at all tested concentrations and positive observation on cytotoxicity (Arslan M, Topaktas M & Rencuzogullari E., 2008). Furthermore, two supporting studies in vitro mammalian chromosome aberration tests (both Klimisch score 2) with borate analogues (boric acid and borax) were provided with indication of negative results (Turkez H, et al., 2007; Geyikoglu F & Turkez H, 2008). Also with boric acid and borax were provided three supporting in vitro mammalian cell micronucleus studies (Klimisch score 2) with indication of negative results (Turkez H, et al., 2007; Geyikoglu F & Turkez H, 2008; Turkez H., 2008).

The key study with borate analogue (boric acid) on sister chromatid exchange in mammalian cells (Klimisch score 1) as well indicated a negative result (NTP, 1987b). Supporting studies (Klimisch score 1/2) on DNA damage and/or repair with borate analogues (boric acid and borax) confirm the negative results (Unpublished report 15, 1991; Turkez H., 2008; Turkez H, et al., 2007; Arslan M, Topaktas M & Rencuzogullari E., 2008; Geyikoglu F & Turkez H, 2008). However, one sister chromatid exchange assay in mammalian cells (Klimisch score 2) with borax solution indicated positive results for human lymphocytes and positive observation on cytotoxicity (Pongsavee M, 2009).

In vivo as a key study was performed one micronucleus assay (Klimisch score 1). The result was negative (Unpublished report 17, 1991).

As the data from in vitro and in vivo key studies with borate analogues showed no evidence for genotoxicity, the eMSCA concludes based on read-across that dipotassium tetraborate does not require classification as a mutagen.

7.9.6. Carcinogenicity

One study, equivalent or similar to OECD Guideline 451 (Klimisch score 2), on carcinogenicity in mouse after oral administration with borate analogue (boric acid) was performed (NTP, 1987b). The results showed no evidence of carcinogenicity. In addition registrant considers that in long term feeding studies with boric acid and disodium tetraborate decahydrate in both rats and mice, no carcinogenic effects were observed (Unpublished report 2 and 3, 1966; Weir RJ and Fisher RS, 1972). However,

this cannot be verified by eMSCA as particular studies and results were not available in the dossier, nor were results of 2-year studies in rats and dogs which were mentioned by the registrant as well in the CSR.

Overall, the eMSCA conclusion is based on the carcinogenicity study in mouse after oral administration with borate analogue (boric acid) (NTP, 1987b). Based on read across the eMSCA concluded that dipotassium tetraborate does not require classification as a carcinogen.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Based on read-across from other tested borates such as boric acid eMSCA suggests to classify dipotassium tetraborate for reproductive toxicity with Repr. 1 B, H360FD (May damage fertility. May damage unborn child). A number of animal studies were conducted with analogue boron compounds, mainly boric acid. No multigeneration studies on fertility nor developmental studies with dipotassium tetraborate itself were provided. The eMSCA supports a read across approach using data on boric acid and disodium tetraborate decahydrate.

A clear evidence of adverse effects on both fertility and development is demonstrated in animal studies. In a three generation study in rats, which were treated with boric acid equivalent to 0, 5.9, 17.5 and 58.8 mg B/kg bw/day (Unpublished report 4 and 5, 1966). The clear testicular atrophy, reduced fertility at the top dose levels in males was discovered (LOAEL (P): 58.5 mg B/kg bw/day). In a breeding study of boric acid in Swiss mice the three administered doses were 26.6, 111.3 and 220.9 mg B/kg bw/day (Fail PA, et al., 1991). A dose-related effect on the testis such as reduced sperm motility (seminiferous tubule degeneration, decreased sperm count) was observed. LOAEL (F0, F1) was 27 mg B/kg bw/day, fertility was partially reduced at 111 and disapeared at 221 mg B/kg bw/day. Based on the total weight of evidence, toxicity data from four different species (mice, rats, rabbits and dogs) provided clear evidence of an adverse effect of borax on sexual function, fertility and development in the absence of other toxic effects. Thus studies of reproductive toxicity in rats and mice demonstrate that boron impairs fertility through effects on testes, such as testicular atrophy and degeneration of seminiferous tubules at doses equal to and above 26 mg B/kg bw/day (Unpublished report 6, 1966; Weir RJ and Fisher RS, 1972; Fail PA, et al., 1991). A multigeneration study in the rat (Unpublished report 6, 1966) gave a NOAEL for fertility in males of 17.5 mg B/kg bw/day. NOAEL of 9.6 mg B/kg bw/day was derived for developmental toxicity based mainly on skeletal malformations in the rat (Unpublished report 23, 1994).

A variety of human information on borates' toxicity to reproduction were provided by registrants as well. No evidence of reproductive toxicity was observed in epidemiological studies. However, having in mind methodological limitations and the fact that exposure levels in human studies were meaningfully lower (highest average daily boron exposure was 125 mg B/day, i.e. approximately 1.8 mg B/kg bw/day (Scialli, et al., 2010)) than NOAELs for laboratory animals, the eMSCA considers that human information can not disprove the abovementioned animal data on toxicity to reproduction.

Therefore, eMSCA does not support the classification proposed by registrants (Repr. 2 H361d) but considers that dipotassium tetraborate should be classified as Repr. 1B, H360FD "May damage fertility. May damage the unborn child."

7.9.8. Hazard assessment of physico-chemical properties

Dipotassium tetraborate has no explosive properties and is a not highly flammable solid.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The eMSCA concluded that DNEL(s) provided by the registrants are acceptable.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

Based on the available data, the eMSCA concludes that dipotassium tetraborate requires a classification Repr. 1B, H360FD "May damage fertility. May damage the unborn child."

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

Dipotassium tetraborate is described to be found in various commercial products, such as detergents, washing and cleaning products, fertilizers, automotive fluids, photo chemicals, coating and paints, ink and tonner. Thus having wide dispersive and consumer uses. Workers of the relevant industry are exposed to dipotassium tetraborate through various processes. The evaluating MSCA concluded that the inhalation exposure estimates presented in the registration data may underestimate the potential for exposure and therefore a potential concern for inhalation exposure for workers remains.

7.13. Risk characterisation

The eMSCA concludes that borates may have potential risk for workers, as for discharging big bags into vessels as well as for packaging into big bags (without personal protective equipment) RCRs are above 1 and also for some other uses RCR for long-term inhalation exposure is above 1. Furthermore for some uses RCR is close to 1, e.g. PROC 7 Using cleaning solutions, General maintenance activities. The highest risk arising from these two uses is for consumers. Therefore, the registrants are recommended to consider further refinement of the inhalation exposure estimates and consumer uses for which RCRs are close to 1. Despite that some uses as well have RCRs slightly below 1 for environment, the evaluation of environmental hazards was not carried out as being outside the scope of this substance evaluation.

7.14. References

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7.15. Abbreviations

DNEL	Derived no-effect level
eMSCA	Evaluating Member State Competent Authority
PROC	Process category
QSAR	Quantitative Structure-Activity Relationship models
RCR	Risk characterisation ratio

SVHC Substances of very high concern