**Committee for Risk Assessment**

**RAC**

Annex 1

**Background document**

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

# Boric acid, Diboron trioxide, Tetraboron disodium heptaoxide hydrate, Disodium tetraborate anhydrous, Orthoboric acid sodium salt, Disodium tetraborate decahydrate and Disodium tetraborate pentahydrate

CLH-O-0000001412-86-300/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

**Adopted**

**20 September 2019**

# CLH report

# Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

# International Chemical Identification:

Boric acid [1]; Diboron trioxide [2]; Tetraboron disodium heptaoxide, hydrate [3]; Disodium tetraborate, anhydrous [4]; Orthoboric acid sodium salt [5]; Disodium tetraborate decahydrate [6]; Disodium tetraborate pentahydrate [7]

**EC Numbers: 233-139-2 [1]; 234-343-4 [1]; 215-125-8 [2]; 235-541-3 [3]; 215-540-4 [4;6;7]; 237-560-2 [5]**

**CAS Numbers: 10043-35-3 [1]; 11113-50-1 [1]; 1303-86-2 [2]; 12267-73-1 [3]; 1330-43-4 [4]; 13840-56-7 [5]; 1303-96-4 [6]; 12179-04-3 [7]**

**Index Numbers: 005-007-00-2 [1]; 005-008-00-8 [2]; 005-011-00-4 [3;4;5]; 005-011-01-1 [6]; 005-011-02-9 [7]**

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# CONTENTS

## 0. BACKGROUND INFORMATION

The present proposal for harmonised classification and labelling concerns several existing entries in Annex VI of the Regulation (EC) No 1272/2008 (CLP Regulation). The borates covered in the proposal are harmonised as toxic to reproduction for both developmental and fertility effects, i.e. Repr. 1B (H360FD). They also have various specific concentration limits (SCLs) (table 0 below) which were set based on the developmental effects of the boron moiety (B) using an approach proposed by BauA (1998). Later this approach have been challenged and the committee for risk assessment (RAC) have removed SCLs set by the approach for a number of substances (see for example RAC opinions on NMP[1] and N,N-dimethylacetamide (DMAC)[2]).

The classification of mixtures containing substances classified for reproductive toxicity and of substances containing impurities, additives or constituents classified for reproductive toxicity is based on the concentration of the reproductive toxic component(s). Table 3.7.2 of Annex I to CLP contains generic concentration limits (GCLs) above which classification for reproductive toxicity is required. The GCL is 0.3% (w/w) for reproductive toxicants in Category 1A and 1B.

The RAC concluded in March 2014 on the classification of two octaborates[3,4] as Repr. 1B (H360FD) with a GCL of 0.3% w/w. A proposal for a revised harmonised classification of boric acid submitted in September 2013 did not include a suggestion to revise the SCL and it was therefore not addressed by the RAC. However, in the opinion for boric acid[5] the RAC notes that a GCL of 0.3% would apply if the concentration limit had been addressed. Hence, the objective of the present CLH proposal is to harmonise the seven borates with a GCL of 0.3% w/w. The reason for combining the borates in one CLH-report is that the data and argumentation is the same for all the substances.

Experimental data and information on the borates included in the present CLH proposal originate from the publically disseminated REACH Registration Dossiers (ECHA 2018a;b;c) and the Assessment Reports under the Biocide Products Regulation, BPR (ECHA 2011a;b;c;d;e). Two of the borates covered by the proposal i.e. tetraboron disodium heptaoxide, hydrate and orthoboric acid, sodium salt have not been registered under REACH nor have they been evaluated under BPR, but they have been notified by 55 and 584 notifiers[6], respectively.

[1] https://www.echa.europa.eu/documents/10162/355b86c1-5a0f-f104-0931-8ffdce4e1cbd

[2] https://www.echa.europa.eu/documents/10162/a435d3fc-a05f-b558-3f51-9aff166f2de0

[3] https://www.echa.europa.eu/documents/10162/7d740d8c-5cd5-872b-5da2-e549983a9ff9

[4] https://www.echa.europa.eu/documents/10162/658b802c-1ca3-663e-4bd4-437369d715de

[5] https://www.echa.europa.eu/documents/10162/4db9bc68-844e-c557-8914-ab491743d471

[6] C&L inventory accessed Nov 1, 2018

Table 0: Borates covered by the present CLH proposal

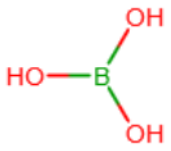
| **Entry in CLP (Index number)** | **Chemical name(s)** | **CAS** | **EC** | **Existing specific concentration limit (SCL) (% w/w)** | **Proposed generic concentration limit (GCL) (% w/w)** |
|---|---|---|---|---|---|
| 005-007-00-2 | boric acid | 10043-35-3<br>11113-50-1 | 233-139-2<br>234-343-4 | 5,5 | 0,3 |
| 005-008-00-8 | diboron trioxide | 1303-86-2 | 215-125-8 | 3,1 | 0,3 |
| 005-011-00-4 | disodium tetraborate, anhydrous; boric acid, disodium salt | 1330-43-4 | 215-540-4 | 4,5 | 0,3 |
| | tetraboron disodium heptaoxide, hydrate | 12267-73-1 | 235-541-3 | 4,5 | 0,3 |
| | orthoboric acid, sodium salt | 13840-56-7 | 237-560-2 | 4,5 | 0,3 |
| 005-011-01-1 | disodium tetraborate decahydrate; borax decahydrate | 1303-96-4 | 215-540-4 | 8,5 | 0,3 |
| 005-011-02-9 | disodium tetraborate pentahydrate; borax pentahydrate | 12179-04-3 | 215-540-4 | 6,5 | 0,3 |

# 1. IDENTITY OF THE SUBSTANCES

## 1.1 Names and other identifiers of the substances

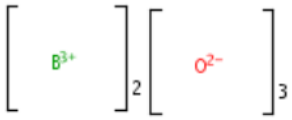
### 1.1.1 Annex VI Index No. 005-007-00-2

**Table 1: Substance identity and information related to molecular and structural formula of boric acid (CAS No: 10043-35-3; 11113-50-1)**

| | |
|---|---|
| **Name(s) in the IUPAC nomenclature or other international chemical name(s)** | Boric acid |
| **Other names (usual name, trade name, abbreviation)** | Optibor<br>orthoboric acid |
| **ISO common name (if available and appropriate)** | Not available |
| **EC number (if available and appropriate)** | 233-139-2; 234-343-4 |
| **EC name (if available and appropriate)** | Boric acid |
| **CAS number (if available)** | 10043-35-3; 11113-50-1 |
| **Other identity code (if available)** | Not available |
| **Molecular formula** | H3BO3 |
| **Structural formula** |  |
| **SMILES notation (if available)** | B(O)(O)O; OB(O)O |
| **Molecular weight or molecular weight range** | 61.831 g/mol |
| **Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)** | Not applicable |
| **Description of the manufacturing process and identity of the source (for UVCB substances only)** | Not applicable |
| **Degree of purity (%) (if relevant for the entry in Annex VI)** | Not relevant |

### 1.1.2 Annex VI Index No. 005-008-00-8

**Table 2: Substance identity and information related to molecular and structural formula of diboron trioxide (CAS No: 1303-86-2)**

| | |
|---|---|
| **Name(s) in the IUPAC nomenclature or other international chemical name(s)** | Diboron trioxide |
| **Other names (usual name, trade name, abbreviation)** | Anhydrous boric acid<br>boric oxide<br>borium oxide<br>Boroglas<br>Boron oxide<br>Boropowder |
| **ISO common name (if available and appropriate)** | Not available |
| **EC number (if available and appropriate)** | 215-125-8 |
| **EC name (if available and appropriate)** | Diboron trioxide |
| **CAS number (if available)** | 1303-86-2 |
| **Other identity code (if available)** | Not available |
| **Molecular formula** | B2O3 |
| **Structural formula** |  |
| **SMILES notation (if available)** | O=BOB=O |
| **Molecular weight or molecular weight range** | 69.6182 g/mol |
| **Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)** | Not applicable |
| **Description of the manufacturing process and identity of the source (for UVCB substances only)** | Not applicable |
| **Degree of purity (%) (if relevant for the entry in Annex VI)** | Not relevant |

### 1.1.3 Annex VI Index No. 005-011-00-4

**Table 3: Substance identity and information related to molecular and structural formula of tetraboron disodium heptaoxide, hydrate (CAS No: 12267-73-1)**

| | |
|---|---|
| **Name(s) in the IUPAC nomenclature or other international chemical name(s)** | Tetraboron disodium heptaoxide, hydrate |
| **Other names (usual name, trade name, abbreviation)** | - |
| **ISO common name (if available and appropriate)** | Not available |
| **EC number (if available and appropriate)** | 235-541-3 |
| **EC name (if available and appropriate)** | Tetraboron disodium heptaoxide, hydrate |
| **CAS number (if available)** | 12267-73-1 |
| **Other identity code (if available)** | Not available |
| **Molecular formula** | Na2B4O7·xH2O |
| **Structural formula** | * |
| **SMILES notation (if available)** | [Na+].[Na+].O.O=BOB([O-])OB([O-])OB=O |
| **Molecular weight or molecular weight range** | 219.24 g/mol |
| **Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)** | Not applicable |
| **Description of the manufacturing process and identity of the source (for UVCB substances only)** | Not applicable |
| **Degree of purity (%) (if relevant for the entry in Annex VI)** | Not relevant |

*no definite structural formula is available for describing the complexity of the structure of these substances, including metastable structures, hydrated and hydroxylated forms.

**Table 4: Substance identity and information related to molecular and structural formula of disodium tetraborate, anhydrous (CAS No: 1330-43-4)**

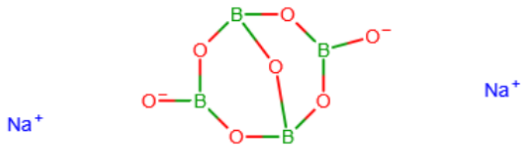
| | |
|---|---|
| **Name(s) in the IUPAC nomenclature or other international chemical name(s)** | Tetraboron disodium heptaoxide, anhydrous |
| **Other names (usual name, trade name, abbreviation)** | Borax<br>Borax anhydrous<br>Borax Dehybor<br>Dehybor<br>Etibor-48<br>PYROBOR Dehydrated borax<br>sodium borate anhydrous |
| **ISO common name (if available and appropriate)** | Not available |
| **EC number (if available and appropriate)** | 215-540-4 |
| **EC name (if available and appropriate)** | Tetraboron disodium heptaoxide, anhydrous |
| **CAS number (if available)** | 1330-43-4 |
| **Other identity code (if available)** | Not available |
| **Molecular formula** | Na2B4O7 |
| **Structural formula** |  |
| **SMILES notation (if available)** | [B]1(O[B]2O[B](O[B](O1)O2)[O-])[O-].[Na+].[Na+] |
| **Molecular weight or molecular weight range** | 202.22 g/mol |
| **Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)** | Not applicable |
| **Description of the manufacturing process and identity of the source (for UVCB substances only)** | Not applicable |
| **Degree of purity (%) (if relevant for the entry in Annex VI)** | Not relevant |

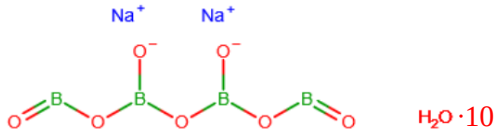
**Table 5: Substance identity and information related to molecular and structural formula of orthoboric acid sodium salt (CAS No:13840-56-7)**

| | |
|---|---|
| **Name(s) in the IUPAC nomenclature or other international chemical name(s)** | Orthoboric acid, sodium salt |
| **Other names (usual name, trade name, abbreviation)** | - |
| **ISO common name (if available and appropriate)** | Not available |
| **EC number (if available and appropriate)** | 237-560-2 |
| **EC name (if available and appropriate)** | Orthoboric acid, sodium salt |
| **CAS number (if available)** | 13840-56-7 |
| **Other identity code (if available)** | Not available |
| **Molecular formula** | $BH_3O_3 \cdot xNa$ |
| **Structural formula** | * |
| **SMILES notation (if available)** | [Na+].B([O-])([O-])[O-] |
| **Molecular weight or molecular weight range** | 127.8 g/mol |
| **Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)** | Not applicable |
| **Description of the manufacturing process and identity of the source (for UVCB substances only)** | Not applicable |
| **Degree of purity (%) (if relevant for the entry in Annex VI)** | Not relevant |

* no definite structural formula is available for describing the complexity of the structure of these substances, including metastable structures, hydrated and hydroxylated forms

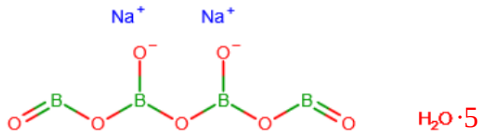
### 1.1.4 Annex VI Index No. 005-011-01-1

**Table 6: Substance identity and information related to molecular and structural formula of disodium tetraborate decahydrate (CAS No: 1330-43-3; 1303-96-4)**

| | |
|---|---|
| **Name(s) in the IUPAC nomenclature or other international chemical name(s)** | Disodium tetraborate decahydrate |
| **Other names (usual name, trade name, abbreviation)** | Borax<br>Borax 10 mol<br>Borax 10-Hydrate<br>borax decahydrate<br>DECAHYDRATE BORAX |
| **ISO common name (if available and appropriate)** | Not available |
| **EC number (if available and appropriate)** | 215-540-4 |
| **EC name (if available and appropriate)** | Disodium tetraborate decahydrate |
| **CAS number (if available)** | 1303-96-4 |
| **Other identity code (if available)** | Not available |
| **Molecular formula** | Na2B4O7·10H2O |
| **Structural formula** |  |
| **SMILES notation (if available)** | [Na+].[Na+].[O-]B1OB2OB([O-])OB(O1)O2.O.O.O.O.O.O.O.O.O.O |
| **Molecular weight or molecular weight range** | 381.38 g/mol |
| **Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)** | Not applicable |
| **Description of the manufacturing process and identity of the source (for UVCB substances only)** | Not applicable |
| **Degree of purity (%) (if relevant for the entry in Annex VI)** | Not relevant |

### 1.1.5 Annex VI Index No. 005-011-02-9

**Table 7: Substance identity and information related to molecular and structural formula of disodium tetraborate pentahydrate (CAS No: 1330-43-3; 12179-04-3)**

| | |
|---|---|
| **Name(s) in the IUPAC nomenclature or other international chemical name(s)** | Disodium tetraborate pentahydrate |
| **Other names (usual name, trade name, abbreviation)** | Borax<br>Borax 5 mol<br>borax pentahydrate<br>Etibor-68<br>Neobor<br>V-BOR Refined Pentahydrate Borax |
| **ISO common name (if available and appropriate)** | Not available |
| **EC number (if available and appropriate)** | 215-540-4 |
| **EC name (if available and appropriate)** | Disodium tetraborate pentahydrate |
| **CAS number (if available)** | 12179-04-3 |
| **Other identity code (if available)** | Not available |
| **Molecular formula** | Na2B4O7·5H2O |
| **Structural formula** |  |
| **SMILES notation (if available)** | B(=O)OB([O-])OB([O-])OB=O.O.O.O.O.O.[Na+].[Na+] |
| **Molecular weight or molecular weight range** | 291.35 g/mol |
| **Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)** | Not applicable |
| **Description of the manufacturing process and identity of the source (for UVCB substances only)** | Not applicable |
| **Degree of purity (%) (if relevant for the entry in Annex VI)** | Not relevant |

## 1.2 Composition of the substances

The constituents of the borates included in the present CLH-proposal are given below (Tables 8-14). There are no impurities or additives that affect the classification of the substances.

### 1.2.1 Annex VI Index No. 005-007-00-2

**Table 8: Constituents (non-confidential information) of boric acid (CAS No: 10043-35-3; 11113-50-1)**

| Constituent (Name and numerical identifier) | Concentration range (% w/w minimum and maximum in multi-constituent substances) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) |
|---|---|---|---|
| Boric acid | ≥ 80% - ≤ 100% | Repr. 1B, H360FD | Repr. 1B, H360FD<br>Repr. 1A, H360<br>STOT SE 1, H370<br>STOT RE 1, H372<br>Skin Irrit. 2, H315<br>STOT SE 3, H335 |

### 1.2.2 Annex VI Index No. 005-008-00-8

**Table 9: Constituents (non-confidential information) of diboron trioxide (CAS No: 1303-86-2)**

| Constituent (Name and numerical identifier) | Concentration range (% w/w minimum and maximum in multi-constituent substances) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) |
|---|---|---|---|
| Diboron trioxide | ≥ 80% - ≤ 100% | Repr. 1B, H360FD | Repr. 1B, H360FD<br>Acute Tox. 4, H302<br>Repr. 1A, H360<br>STOT RE 1, H372<br>Eye Irrit. 2, H319<br>STOT SE 3, H336 |

### 1.2.3 Annex VI Index No. 005-011-00-4

**Table 10: Constituents (non-confidential information) of disodium tetraborate heptaoxide, hydrate (CAS No: 12267-73-1)**

| Constituent (Name and numerical identifier) | Concentration range (% w/w minimum and maximum in multi-constituent substances) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) |
|---|---|---|---|
| Disodium tetraborate heptaoxide, hydrate | ≥ 80% - ≤ 100% | Repr. 1B, H360FD | Repr. 1B, H360DF<br>Eye Irrit. 2, H319<br>Repr. 1B, H360 |

**Table 11: Constituents (non-confidential information) of disodium tetraborate, anhydrous (CAS No: 1330-43-4)**

| Constituent (Name and numerical identifier) | Concentration range (% w/w minimum and maximum in multi-constituent substances) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) |
|---|---|---|---|
| Disodium tetraborate, | ≥ 80% - ≤ 100% | Repr. 1B, H360FD | Repr. 1B, H360DF |

| Constituent (Name and numerical identifier) | Concentration range (% w/w minimum and maximum in multi-constituent substances) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) |
|---|---|---|---|
| anhydrous | | | Eye Irrit. 2, H319<br>Repr. 2, H360<br>Repr. 1A, H360<br>Acute Tox. 4, H302<br>Eye Dam. 1, H318<br>Repr. 1B, H360 |

**Table 12: Constituents (non-confidential information) of orthoboric acid, sodium salt (CAS No: 13840-56-7)**

| Constituent (Name and numerical identifier) | Concentration range (% w/w minimum and maximum in multi-constituent substances) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) |
|---|---|---|---|
| Orthoboric acid, sodium salt | ≥ 80% - ≤ 100% | Repr. 1B, H360FD | Repr. 1B, H360DF<br>Repr. 1B, H360 |

### 1.2.4 Annex VI Index No. 005-011-01-1

**Table 13: Constituents (non-confidential information) of disodium tetraborate decahydrate (CAS No: 1303-96-4)**

| Constituent (Name and numerical identifier) | Concentration range (% w/w minimum and maximum in multi-constituent substances) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) |
|---|---|---|---|
| Disodium tetraborate decahydrate | ≥ 80% - ≤ 100% | Repr. 1B, H360FD | Repr. 1B, H360DF<br>Eye Irrit. 2, H319<br>Repr. 2, H360<br>Repr. 1A, H360<br>Acute Tox. 4, H302<br>Eye Dam. 1, H318<br>Repr. 1B, H360<br>Aquatic Chronic 3, H412<br>STOT SE 3, H335 |

### 1.2.5 Annex VI Index No. 005-011-02-9

**Table 14: Constituents (non-confidential information) of disodium tetraborate pentahydrate (CAS No: 12179-04-3)**

| Constituent (Name and numerical identifier) | Concentration range (% w/w minimum and maximum in multi-constituent substances) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) |
|---|---|---|---|
| Disodium tetraborate pentahydrate | ≥ 80% - ≤ 100% | Repr. 1B, H360FD | Repr. 1B, H360DF<br>Eye Irrit. 2, H319<br>Repr. 2, H360<br>Repr. 1A, H360<br>Acute Tox. 4, H302<br>Eye Dam. 1, H318<br>Repr. 1B, H360 |

# 2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

## 2.1 Proposed harmonised classification and labelling according to the CLP criteria

### 2.1.1 Annex VI Index No. 005-007-00-2

**Table 15: Boric acid**

| | Index No | International Chemical Identification | EC No | CAS No | Classification | | Labelling | | | Specific Conc. Limits, M-factors | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard Class and Category Code(s) | Hazard statement Code(s) | Pictogram, Signal Word Code(s) | Hazard statement Code(s) | Suppl. Hazard statement Code(s) | | |
| Current Annex VI entry | 005-007-00-2 | boric acid [1]<br>boric acid [2] | 233-139-2 [1]<br>234-343-4 [2] | 10043-35-3 [1]<br>11113-50-1 [2] | Repr. 1B | H360FD | GHS08<br>Dgr | H360FD | | Repr. 1B;<br>H360FD: C ≥ 5,5% | |
| Dossier submitters proposal | 005-007-00-2 | boric acid [1]<br>boric acid [2] | 233-139-2 [1]<br>234-343-4 [2] | 10043-35-3 [1]<br>11113-50-1 [2] | **Retain:**<br>Repr. 1B | **Retain:**<br>H360FD | **Retain:**<br>GHS08<br>Dgr | **Retain:**<br>H360FD | | **Remove:**<br>Repr. 1B;<br>H360FD: C ≥ 5,5% | |
| Resulting Annex VI entry if agreed by RAC and COM | 005-007-00-2 | boric acid [1]<br>boric acid [2] | 233-139-2 [1]<br>234-343-4 [2] | 10043-35-3 [1]<br>11113-50-1 [2] | Repr. 1B | H360FD | GHS08<br>Dgr | H360FD | | * | |

***The generic concentration limit of 0,3% will apply**

### 2.1.2 Annex VI Index No. 005-008-00-8

**Table 16: Diboron trioxide**

| | Index No | International Chemical Identification | EC No | CAS No | Classification | | Labelling | | | Specific Conc. Limits, M-factors | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard Class and Category Code(s) | Hazard statement Code(s) | Pictogram, Signal Word Code(s) | Hazard statement Code(s) | Suppl. Hazard statement Code(s) | | |
| Current Annex VI entry | 005-008-00-8 | diboron trioxide | 215-125-8 | 1303-86-2 | Repr. 1B | H360FD | GHS08 Dgr | H360FD | | Repr. 1B; H360FD: ≥ 3,1% | |
| Dossier submitters proposal | 005-008-00-8 | diboron trioxide | 215-125-8 | 1303-86-2 | **Retain:** Repr. 1B | **Retain:** H360FD | **Retain:** GHS08 Dgr | **Retain:** H360FD | | **Remove:** Repr. 1B; H360FD: ≥ 3,1% | |
| Resulting Annex VI entry if agreed by RAC and COM | 005-008-00-8 | diboron trioxide | 215-125-8 | 1303-86-2 | Repr. 1B | H360FD | GHS08 Dgr | H360FD | | * | |

***The generic concentration limit of 0,3% will apply**

### 2.1.3 Annex VI Index No. 005-011-00-4

**Table 17: Tetraboron disodium heptaoxide, hydrate; disodium tetraborate, anhydrous; orthoboric acid, sodium salt**

| | Index No | International Chemical Identification | EC No | CAS No | Classification | | Labelling | | | Specific Conc. Limits, M-factors | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard Class and Category Code(s) | Hazard statement Code(s) | Pictogram, Signal Word Code(s) | Hazard statement Code(s) | Suppl. Hazard statement Code(s) | | |
| Current Annex VI entry | 005-011-00-4 | tetraboron disodium heptaoxide, hydrate [1]<br>disodium tetraborate, anhydrous [2]<br>orthoboric acid, sodium salt [3] | 235-541-3 [1]<br>215-540-4 [2]<br>237-560-2 [3] | 12267-73-1 [1]<br>1330-43-4 [2]<br>13840-56-7 [3] | Repr. 1B | H360FD | GHS08<br>Dgr | H360FD | | Repr. 1B;<br>H360FD: ≥ 4,5% | |
| Dossier submitters proposal | 005-011-00-4 | tetraboron disodium heptaoxide, hydrate [1]<br>disodium tetraborate, anhydrous [2]<br>orthoboric acid, sodium salt [3] | 235-541-3 [1]<br>215-540-4 [2]<br>237-560-2 [3] | 12267-73-1 [1]<br>1330-43-4 [2]<br>13840-56-7 [3] | **Retain:**<br>Repr. 1B | **Retain:**<br>H360FD | **Retain:**<br>GHS08<br>Dgr | **Retain:**<br>H360FD | | **Remove:**<br>Repr. 1B;<br>H360FD: ≥ 4,5% | |
| Resulting Annex VI entry if agreed by RAC and COM | 005-011-00-4 | tetraboron disodium heptaoxide, hydrate [1]<br>disodium tetraborate, anhydrous [2]<br>orthoboric acid, sodium salt [3] | 235-541-3 [1]<br>215-540-4 [2]<br>237-560-2 [3] | 12267-73-1 [1]<br>1330-43-4 [2]<br>13840-56-7 [3] | Repr. 1B | H360FD | GHS08<br>Dgr | H360FD | | * | |

***The generic concentration limit of 0,3% will apply**

### 2.1.4 Annex VI Index No. 005-011-01-1

Table 18: Disodium tetraborate decahydrate

| | Index No | International Chemical Identification | EC No | CAS No | Classification | | Labelling | | | Specific Conc. Limits, M-factors | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard Class and Category Code(s) | Hazard statement Code(s) | Pictogram, Signal Word Code(s) | Hazard statement Code(s) | Suppl. Hazard statement Code(s) | | |
| Current Annex VI entry | 005-011-01-1 | disodium tetraborate decahydrate | 215-540-4 | 1303-96-4 | Repr. 1B | H360FD | GHS08 Dgr | H360FD | | Repr. 1B; H360FD: ≥ 8,5% | |
| Dossier submitters proposal | 005-011-01-1 | disodium tetraborate decahydrate | 215-540-4 | 1303-96-4 | **Retain:** Repr. 1B | **Retain:** H360FD | **Retain:** GHS08 Dgr | **Retain:** H360FD | | **Remove:** Repr. 1B; H360FD: ≥ 8,5% | |
| Resulting Annex VI entry if agreed by RAC and COM | 005-011-01-1 | disodium tetraborate decahydrate | 215-540-4 | 1303-96-4 | Repr. 1B | H360FD | GHS08 Dgr | H360FD | | * | |

*The generic concentration limit of 0,3% will apply

### 2.1.5 Annex VI Index No. 005-011-02-9

**Table 19: Disodium tetraborate pentahydrate**

| | Index No | International Chemical Identification | EC No | CAS No | Classification | | Labelling | | | Specific Conc. Limits, M-factors | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard Class and Category Code(s) | Hazard statement Code(s) | Pictogram, Signal Word Code(s) | Hazard statement Code(s) | Suppl. Hazard statement Code(s) | | |
| Current Annex VI entry | 005-011-02-9 | disodium tetraborate pentahydrate | 215-540-4 | 12179-04-3 | Repr. 1B | H360FD | GHS08 Dgr | H360FD | | Repr. 1B; H360FD: ≥ 6,5% | |
| Dossier submitters proposal | 005-011-02-9 | disodium tetraborate pentahydrate | 215-540-4 | 12179-04-3 | **Retain:** Repr. 1B | **Retain:** H360FD | **Retain:** GHS08 Dgr | **Retain:** H360FD | | **Remove:** Repr. 1B; H360FD: ≥ 6,5% | |
| Resulting Annex VI entry if agreed by RAC and COM | 005-011-02-9 | disodium tetraborate pentahydrate | 215-540-4 | 12179-04-3 | Repr. 1B | H360FD | GHS08 Dgr | H360FD | | * | |

*The generic concentration limit of 0,3% will apply

**Table 20: Reason for not proposing harmonised classification and status under public consultation – applies for all substances covered by the proposal.**

| Hazard class | Reason for no classification | Within the scope of public consultation |
|---|---|---|
| **Explosives** | Hazard class not assessed in this dossier | No |
| **Flammable gases (including chemically unstable gases)** | Hazard class not assessed in this dossier | No |
| **Oxidising gases** | Hazard class not assessed in this dossier | No |
| **Gases under pressure** | Hazard class not assessed in this dossier | No |
| **Flammable liquids** | Hazard class not assessed in this dossier | No |
| **Flammable solids** | Hazard class not assessed in this dossier | No |
| **Self-reactive substances** | Hazard class not assessed in this dossier | No |
| **Pyrophoric liquids** | Hazard class not assessed in this dossier | No |
| **Pyrophoric solids** | Hazard class not assessed in this dossier | No |
| **Self-heating substances** | Hazard class not assessed in this dossier | No |
| **Substances which in contact with water emit flammable gases** | Hazard class not assessed in this dossier | No |
| **Oxidising liquids** | Hazard class not assessed in this dossier | No |
| **Oxidising solids** | Hazard class not assessed in this dossier | No |
| **Organic peroxides** | Hazard class not assessed in this dossier | No |
| **Corrosive to metals** | Hazard class not assessed in this dossier | No |
| **Acute toxicity via oral route** | Hazard class not assessed in this dossier | No |
| **Acute toxicity via dermal route** | Hazard class not assessed in this dossier | No |
| **Acute toxicity via inhalation route** | Hazard class not assessed in this dossier | No |
| **Skin corrosion/irritation** | Hazard class not assessed in this dossier | No |
| **Serious eye damage/eye irritation** | Hazard class not assessed in this dossier | No |
| **Respiratory sensitisation** | Hazard class not assessed in this dossier | No |
| **Skin sensitisation** | Hazard class not assessed in this dossier | No |
| **Germ cell mutagenicity** | Hazard class not assessed in this dossier | No |
| **Carcinogenicity** | Hazard class not assessed in this dossier | No |
| **Reproductive toxicity** | Existing classification as Repr. 1B (H360FD) retained. Existing SCLs removed and replaced with GCLs. | Yes |
| **Specific target organ toxicity-single exposure** | Hazard class not assessed in this dossier | No |
| **Specific target organ toxicity-repeated exposure** | Hazard class not assessed in this dossier | No |
| **Aspiration hazard** | Hazard class not assessed in this dossier | No |
| **Hazardous to the aquatic environment** | Hazard class not assessed in this dossier | No |
| **Hazardous to the ozone layer** | Hazard class not assessed in this dossier | No |

## 3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The borates covered by the present CLH-proposal have harmonised classifications as Repr. 1B, H360DF, with various specific concentration limits (SCL). The SCLs were set based on an approach proposed by BAuA (1998) in which the molecular weight of the different borates was used to recalculate the contribution of their boron contents to the overall hazard. Existing SCLs for the borates were derived from the overall NOAEL for embryotoxic/teratogenic effects of 9.6 mg B/kg bw/day, based on a reduction in mean fetal body weight/litter and an increased incidence in short rib XIII at 76 mg/kg bw/day (13.3 mg B/kg bw/day).

The RAC concluded in March 2014 on the classification of the borates disodium octaborate, anhydrous[7] and disodium octaborate tetrahydrate[8] (EC No. 234-541-0, Index No. 005-020-00-3), using new recommendations on how to determine the concentration limits for reproductive toxicity (first included in version 4.0 of in the CLP Guidance, November 2013). According to the guidance, the SCL should be based on the most sensitive reproductive effect. For borates, it was found to be the increased incidence of short rib XIII in a developmental toxicity study in rats. The fetal incidence of this malformation was 1.2 and 1.5% at the lowest observed adverse effect level, LOAEL (13.3 mg B/kg bw/day) and the highest dose (25 mg B/kg bw/day) respectively. As the incidences were low, it was not possible to derive an ED10 (the dose that corresponds to a 10% increase in incidence compared to controls). Hence, the LOAEL was used instead. Correcting for the percentage of boron (w/w), the LOAEL of 13.3 mg B/kg bw/day corresponds to a LOAEL of 51.5 mg/kg bw/day disodium octaborate, anhydrous and 63.3 mg/kg bw/day disodium octaborate tetrahydrate. Both substances were found to belong to the medium potency group (4 mg/kg bw/day < ED10 (LOAEL) < 400 mg/kg bw/day). For medium potency substances, the GCL applies. As disodium octaborate, anhydrous and disodium octaborate tetrahydrate are classified in category 1B, the GCL is 0.3% w/w.

A proposal for a revised harmonised classification of boric acid submitted in September 2013 did not include a revision of the SCL and the concentration limit was therefore not addressed in detail by the RAC. However, in the opinion for boric acid[9] the RAC notes that the SCL of 5.5% was derived by using the "German method" and that the GCL of 0.3% would apply for boric acid if the CLP guidance available at the time (version 4.0 - November 2013) had been used.

| **RAC general comment** |
| --- |
| The proposal submitted by Sweden and subject to a public consultation (from 10/12/2018 until 22/02/2019) concerns several borates with existing entries in Annex VI of the Regulation (EC) No 1272/2008 (CLP Regulation). As shown in the Table below, these borates are currently harmonised as toxic to reproduction for both developmental and fertility effects, i.e. Repr. 1B (H360FD). They also have various specific concentration limits (SCLs) which were set based on the developmental effects of the boron moiety (B) using an approach proposed by the German Federal Institute for Occupational Safety and Health (BAuA, 1998). |

[7] https://www.echa.europa.eu/documents/10162/7d740d8c-5cd5-872b-5da2-e549983a9ff9

[8] https://www.echa.europa.eu/documents/10162/658b802c-1ca3-663e-4bd4-437369d715de

[9] https://www.echa.europa.eu/documents/10162/4db9bc68-844e-c557-8914-ab491743d471

***Table**: Borates covered by this RAC opinion*

| Entry in CLP (Index number) | Chemical name(s) | CAS | EC | Existing specific concentration limit (SCL) (% w/w) | Proposed generic concentration limit (GCL) (% w/w) |
|---|---|---|---|---|---|
| 005-007-00-2 | boric acid | 10043-35-3 11113-50-1 | 233-139-2 234-343-4 | 5,5 | 0,3 |
| 005-008-00-8 | diboron trioxide | 1303-86-2 | 215-125-8 | 3,1 | 0,3 |
| 005-011-00-4 | disodium tetraborate, anhydrous; boric acid, disodium salt | 1330-43-4 | 215-540-4 | 4,5 | 0,3 |
| | tetraboron disodium heptaoxide, hydrate | 12267-73-1 | 235-541-3 | 4,5 | 0,3 |
| | orthoboric acid, sodium salt | 13840-56-7 | 237-560-2 | 4,5 | 0,3 |
| 005-011-01-1 | disodium tetraborate decahydrate; borax decahydrate | 1303-96-4 | 215-540-4 | 8,5 | 0,3 |
| 005-011-02-9 | disodium tetraborate pentahydrate; borax pentahydrate | 12179-04-3 | 215-540-4 | 6,5 | 0,3 |

RAC concluded in March 2014 on the classification of two disodium octaborates (EC 234-541-0 and 234-541-0) as Repr. 1B (H360FD) with a GCL of 0.3% w/w (Commission Regulation (EU) 2016/1179 of 19 July 2016). A proposal for a revised harmonised classification of boric acid submitted in September 2013 did not include a suggestion to revise the SCL and it was therefore not addressed by RAC. However, in the opinion for boric acid RAC noted that a GCL of 0.3% would apply if the concentration limit had been addressed. Table 3.7.2 of Annex I to the CLP Regulation contains generic concentration limits (GCLs) above which classification for reproductive toxicity is required for mixtures. The GCL of 0.3% (w/w) applies to reproductive toxicants in Category 1A and 1B.

Hence, the objective of the CLH proposal was to harmonise the GCL value for the seven borates to 0.3% w/w. The reason given by the dossier submitter (DS) for combining the borates in one CLH report is that the data and argumentation are the same for all the substances.

## 4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Justification that action is needed at Community level: Change in existing entry due to new evaluation of existing data.

Since the borates covered by the present proposal were subject to harmonised classification, new recommendations on how to derive concentration limits for reproductive toxicity has been agreed upon. Revising the SCL for the borates will ensure that all borates are assessed similarly and according to the new guidance. It will result in a level playing field in between the borates as well as in relation to other classified substances.

## 5 IDENTIFIED USES

Boron is a widely occurring element found mainly in minerals in sediments and sedimentary rock. It is found in the environment primarily combined with oxygen in borates, and never as a free element. Boron appears to be a micronutrient in animals and humans (Nielsen 2002; Pizzorno 2015), and the World Health Organization has classified boron as being "probably essential" for humans.

Borates are versatile substances used as both industrial chemicals and biocides. According to the REACH registration dossiers, borates are manufactured and used in several industries in Europe, including the glass, ceramics, detergents and insulation fiberglass industries and are used to produce other borate compounds. Boric acid and sodium tetraborates are also used in a range of consumer products including cosmetic and personal care products. Boric acid, diboron trioxide, disodium tetraborate decahydrate, disodium tetraborate pentahydrate and disodium tetraborate, anhydrous have been evaluated as active substances under the biocide product regulation (BPR), and were all approved in 2011 for use in wood preservatives.

Boric acid has recently been evaluated and approved for use in additives in plastic food contact materials (EFSA, 2018). Boric acid is also used as an antimicrobial preservative and as a buffering agent to control the pH. Additionally, it can have the function as tonicity-adjusting agent (EMA, 2017).

## 6 DATA SOURCES

Experimental data and information on the borates included in the present CLH-report originates from the publically disseminated REACH Registration Dossiers (ECHA 2018a;b;c) and Assessment Reports under the Biocide Product Regulation (BPR) (ECHA, 2011a;b;c;d;e). Two of the borates covered by the proposal (tetraboron disodium heptaoxide, hydrate and orthoboric acid, sodium salt) have not been registered under REACH nor have they been evaluated under BPR, and therefore lack such data. Relevant studies available in the scientific literature have also been included.

## 7 PHYSICOCHEMICAL PROPERTIES

The information on physicochemical properties originates from the publically disseminated REACH Registration Dossiers. The values are taken from the key study or, in the absence of a key study the study with the highest reliability score. Physicochemical properties are available for five of the seven substances included in the proposal (Tables 21-25). Tetraboron disodium heptaoxide, hydrate (CAS No: 12267-73-1) and orthoboric acid sodium salt (CAS No: 13840-56-7) covered by Annex VI Index No. 005-011-00-4 are not registered within REACH nor have been evaluated under BPR, and therefore lack data. Similar to the Annex XV dossier for disodium tetraborates (ECHA, 2010a), the physicochemical properties for tetraboron disodium heptaoxide, hydrate are considered herein to be described by the physicochemical properties for the pentahydrate and the decahydrate forms of disodium tetraborate.

### 7.1.1 Annex VI Index No. 005-007-00-2

**Table 21: Summary of physicochemical properties for boric acid (CAS No: 10043-35-3; 11113-50-1)**

| Property | Value | Reference [1] | Comment (e.g. measured or estimated) |
|---|---|---|---|
| **Physical state at 20°C and 101,3 kPa** | Solid | Study report 2003 | Observed |
| **Melting/freezing point** | > 1 000 °C | Study report 2003 | Measured |
| **Boiling point** | Data waived | - | - |
| **Relative density** | 1.49 | Study report 2003 | Measured |
| **Vapour pressure** | 0 Pa | Study report 1998 | Measured |
| **Surface tension** | Data waived | - | - |
| **Water solubility** | 49.2 g/L at pH 3.7 and 20 °C | Study report 2003 | Measured |
| **Partition coefficient n-octanol/water** | -1.09 at 22 °C | Study report 2003 | Measured |
| **Flash point** | Data waived | - | - |
| **Flammability** | No ignition on contact with air | Study report 2010 | Observed |
| **Explosive properties** | Data waived | - | - |
| **Self-ignition temperature** | No ignition on contact with air | Study report 2010 | Observed |
| **Oxidising properties** | Data waived | - | - |
| **Granulometry** | 74.395 µm | Study report 2010 | Measured |
| **Stability in organic solvents and identity of relevant degradation products** | Data waived | - | - |
| **Dissociation constant** | 8.94 at 20 °C | Study report 2010 | Measured |
| **Viscosity** | Data waived | - | - |

[1] As cited in the publically disseminated REACH registration dossier

### 7.1.2 Annex VI Index No. 005-008-00-8

**Table 22: Summary of physicochemical properties for diboron trioxide (CAS No: 1303-86-2)**

| Property | Value | Reference[1] | Comment (e.g. measured or estimated) |
|---|---|---|---|
| **Physical state at 20°C and 101,3 kPa** | Solid | Study report 2010 | Observed |
| **Melting/freezing point** | > 633 K | Study report 2003 | Measured |
| **Boiling point** | Not determined | - | - |
| **Relative density** | 1 838 kg/m³ at 21.5 °C | Study report 2003 | Measured |
| **Vapour pressure** | Data waived | - | - |
| **Surface tension** | Data waived | - | - |
| **Water solubility** | 22 g/L at pH 3.7 and 20 | Secondary literature | Not specified |

| Property | Value | Reference[1] | Comment (e.g. measured or estimated) |
|---|---|---|---|
| | °C | source | |
| **Partition coefficient n-octanol/water** | Data waived | - | - |
| **Flash point** | Data waived | - | - |
| **Flammability** | No ignition on contact with air | Study report 2010 | Observed |
| **Explosive properties** | Data waived | - | - |
| **Self-ignition temperature** | No ignition on contact with air | Study report 2010 | Observed |
| **Oxidising properties** | Data waived | Study report 2010 | - |
| **Granulometry** | 262.074 µm | Study report 2010 | Measured |
| **Stability in organic solvents and identity of relevant degradation products** | Data waived | - | - |
| **Dissociation constant** | 8.94 at 20 °C | Study report 2010 | Read across from boric acid |
| **Viscosity** | 61 GPa at 260 ºC;<br>3.9 kPa at 500 ºC | Secondary literature source | Not specified |

[1] As cited in the publically disseminated REACH registration dossier

### 7.1.3 Annex VI Index No. 005-011-00-4

**Table 23: Summary of physicochemical properties for disodium tetraborate, anhydrous (CAS No: 1330-43-4)**

| Property | Value | Reference[1] | Comment (e.g. measured or estimated) |
|---|---|---|---|
| **Physical state at 20°C and 101,3 kPa** | Solid | Study report 2003 | Observed |
| **Melting/freezing point** | > 1 000 °C | Study report 2003 | Measured |
| **Boiling point** | 1 575 °C | Secondary literature source | Not specified |
| **Relative density** | 2.35 at 26 ºC | Study report 2005 | Measured |
| **Vapour pressure** | 0.213 kPa at 20 °C | Study report 1998 | Measured |
| **Surface tension** | 71.0 ± 0.4 mN/m at 23 °C and a concentration of 0.3 g/L | Other company data, 1963 | Measured |
| **Water solubility** | 49.74 g/L at pH 3.7 and 20 °C | Study report 2003 | Measured |
| **Partition coefficient n-octanol/water** | -1.53 at 22 °C | Study report 2003 | Measured |
| **Flash point** | Data waived | - | - |
| **Flammability** | No ignition on contact with air | Study report 2010 | Observed |
| **Explosive properties** | Data waived | - | - |
| **Self-ignition temperature** | No ignition on contact | Study report 2010 | Observed |

| Property | Value | Reference[1] | Comment (e.g. measured or estimated) |
|---|---|---|---|
| | with air | | |
| **Oxidising properties** | Data waived | Study report 2010 | - |
| **Granulometry** | 29.131 µm | Study report 2010 | Measured |
| **Stability in organic solvents and identity of relevant degradation products** | Data waived | - | - |
| **Dissociation constant** | 9 at 25 °C | Study report 2010 | Measured |
| **Viscosity** | Data waived | - | - |

[1] As cited in the publically disseminated REACH registration dossier

### 7.1.4 Annex VI Index No. 005-011-01-1

**Table 24: Summary of physicochemical properties for disodium tetraborate decahydrate (CAS No: 1303-96-4)**

| Property | Value | Reference[1] | Comment (e.g. measured or estimated) |
|---|---|---|---|
| **Physical state at 20°C and 101,3 kPa** | Solid | Study report 2003 | Observed |
| **Melting/freezing point** | > 1 000 °C | Study report 2003 | Measured |
| **Boiling point** | 1 575 °C | Secondary literature source | Not specified |
| **Relative density** | 1.72 at 23 ºC | Study report 2005 | Measured |
| **Vapour pressure** | 0.213 kPa at 20 °C | Study report 1998 | Measured |
| **Surface tension** | 71.0 ± 0.4 mN/m at 23 °C and a concentration of 0.3 g/L | Other company data, 1963 | Measured |
| **Water solubility** | 49.74 g/L at pH 3.7 and 20 °C | Study report 2003 | Measured |
| **Partition coefficient n-octanol/water** | -1.53 at 22 °C | Study report 2003 | Measured |
| **Flash point** | Data waived | - | - |
| **Flammability** | No ignition on contact with air | Study report 2010 | Observed |
| **Explosive properties** | Data waived | - | - |
| **Self-ignition temperature** | No ignition on contact with air | Study report 2010 | Observed |
| **Oxidising properties** | Data waived | Study report 2010 | - |
| **Granulometry** | 88 µm | Study report 2010 | Measured |
| **Stability in organic solvents and identity of relevant degradation products** | Data waived | - | - |
| **Dissociation constant** | 9 at 25 °C | Study report 2010 | Measured |
| **Viscosity** | Data waived | - | - |

[1] As cited in the publically disseminated REACH registration dossier

### 7.1.5 Annex VI Index No. 005-011-02-9

**Table 25: Summary of physicochemical properties for disodium tetrabotrate pentahydrate (CAS No: 12179-04-3)**

| Property | Value | Reference[1] | Comment (e.g. measured or estimated) |
|---|---|---|---|
| **Physical state at 20°C and 101,3 kPa** | Solid | Study report 2003 | Observed |
| **Melting/freezing point** | > 1 000 °C | Study report 2003 | Measured |
| **Boiling point** | 1 575 °C | Secondary literature source | Not specified |
| **Relative density** | 2.35 at 26 ºC (disodium tetraborate, anhydrous)<br>1.72 at 23 ºC (disodium tetraborate decahydrate) | Study report 2005 | Measured |
| **Vapour pressure** | 0.213 kPa at 20 °C | Study report 1998 | Measured |
| **Surface tension** | 71.0 ± 0.4 mN/m at 23 °C and a concentration of 0.3 g/L | Other company data, 1963 | Measured |
| **Water solubility** | 49.74 g/L at pH 3.7 and 20 °C | Study report 2003 | Measured |
| **Partition coefficient n-octanol/water** | -1.53 at 22 °C | Study report 2003 | Measured |
| **Flash point** | Data waived | - | - |
| **Flammability** | No ignition on contact with air | Study report 2010 | Observed |
| **Explosive properties** | Data waived | - | - |
| **Self-ignition temperature** | No ignition on contact with air | Study report 2010 | Observed |
| **Oxidising properties** | Data waived | Study report 2010 | - |
| **Granulometry** | 95.71 µm | Study report 2010 | Measured |
| **Stability in organic solvents and identity of relevant degradation products** | Data waived | - | - |
| **Dissociation constant** | 9 at 25 °C | Study report 2010 | Measured |
| **Viscosity** | Data waived | - | - |

[1] As cited in the publically disseminated REACH registration dossier

## 8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this dossier.

## 9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

When exposed via the oral or inhalational route borates are easily taken up (up to 100%) into the blood stream and distributed throughout the tissues and organs of the body. By dermal exposure, an uptake of 0.5% over intact skin is considered as a maximum uptake. Boric acid is not metabolized

in the body but is excreted as such mainly via the urine, with an elimination half-life of less than 24 hours in humans.

In aqueous solutions at physiological and acidic pH, low concentrations of simple borates such as boric acid $B(OH)_3$, diboron trioxide ($B_2O_3$), tetraboron disodium heptaoxide, hydrate ($Na_2B_4O_7 \cdot H_2O$) disodium tetraborate, anhydrous ($Na_2B_4O_7$), orthoboric acid sodium salt ($Na_3BO_3$), disodium tetraborate decahydrate ($Na_2B_4O_7 \cdot 10H_2O$) and disodium tetraborate pentahydrate ($Na_2B_4O_7 \cdot 5H_2O$) will predominantly exist as undissociated boric acid. Above pH 10 the metaborate anion $B(OH)_4$ becomes the main species in solution. The toxicokinetics and toxicological effects of systemic boric acid, diboron trioxide, tetraboron disodium heptaoxide hydrate, disodium tetraborate anhydrous, orthoboric acid sodium salt, disodium tetraborate decahydrate and disodium tetraborate pentahydrate will therefore be expected to be similar on a boron equivalents basis.

As stated in the CLH-reports of disodium octaborate, anhydrate and disodium octaborate tetrahydrate (2013), read-across from boric acid to other borates and between borates has long been accepted in a regulatory context. Experts from the CL Working Group, the TC-C&L and the ATP Committee agreed that borates have similar properties and therefore that read-across between substances can be applied (boric acid, diboron trioxide, disodium tetraborate anhydrous, disodium tetraborate decahydrate and disodium tetraborate) and was indeed applied when setting the existing SCLs. Moreover, in a report on boron, drawn up in 1998 as part of the International Programme on Chemical Safety established jointly by the World Health Organisation, the International Labour Organisation and the United Nations Environment Programme, the experts stated that the chemical and toxicological properties of boric acid, disodium tetraborate pentahydrate, disodium tetraborate decahydrate, and other borates are expected to be similar on a mol boron/litre equivalent basis when dissolved in water or biological fluids at the same pH and low concentration. They add that diboron trioxide will exhibit properties identical to those of boric acid, as it is an anhydride that will hydrolyse to give boric acid. The RAC opinion on new scientific evidence on the use of boric acid and borates in photographic applications by consumers (ECHA, 2010b) also used read-across between the different borates as the DNEL was expressed as mg B/kg bw/day. Judgment of the European Court of Justice on borates concludes that read-across may indeed be used for the assessment of borates (Case C-15/10: Judgment of the Court (Fourth Chamber) of 21 July 2011 - Etimine SA v Secretary of State for Work and Pensions)[10].

Read-across between borates is also used by the registrants to fulfil the data requirements in the REACH registrations of borates included in the present proposal (see Table I and II, Annex I).

### 9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

It is well established that borates have similar toxicokinetics and toxicological effects and that low concentrations of simple borates will mainly exist as undissociated boric acid in aqueous solutions at physiological and acidic pH. The existing SCLs for boric acid, diboron trioxide and the sodium borates were indeed derived on a boron-equivalent basis and it can therefore be assumed that a similar read-across may be used in the derivation of new concentration limits for the substances.

[10] http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?isOldUri=true&uri=CELEX:62010CJ0015

# 10 EVALUATION OF HEALTH HAZARDS

## 10.1 Acute toxicity

Not evaluated in this dossier.

## 10.2 Skin corrosion/irritation

Not evaluated in this dossier.

## 10.3 Serious eye damage/eye irritation

Not evaluated in this dossier.

## 10.4 Respiratory sensitisation

Not evaluated in this dossier.

## 10.5 Skin sensitisation

Not evaluated in this dossier.

## 10.6 Germ cell mutagenicity

Not evaluated in this dossier.

## 10.7 Carcinogenicity

Not evaluated in this dossier.

## 10.8 Reproductive toxicity

All relevant scientific data related to the reproductive toxicity of boron published before March 2014 has been thoroughly reviewed by the RAC in the discussions forming the opinions on harmonised classifications of boric acid (2014), disodium octaborate anhydrate (2014) and disodium octaborate tetrahydrate (2014).

This CLH-report proposes no change to the existing harmonised classifications; however, a withdrawal of the specific concentration limits is suggested. Therefore, only the reproductive toxicity studies that were previously pointed out as key studies for harmonised classification and derivation of concentration limits for borates by the RAC (RAC opinions on boric acid, disodium octaborate, anhydrous and disodium octaborate tetrahydrate, 2014) and relevant studies published thereafter are given and discussed below.

For completeness, an overview of all studies on reproductive toxicity that are included in the publically disseminated REACH Registration Dossiers[11] and/or in the Assessment Reports under BPR are given in Annex I, Table I (animal data) and Table II (human data).

[11] Accessed 2018-10-15

### 10.8.1 Adverse effects on sexual function and fertility

To our knowledge, no new animal studies on effects of boron on sexual function and fertility has been published since 2014. The studies given in Table 26 were appointed key studies by the RAC in their 2014 opinions on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate. One human study on the effects of boron on male fertility has been published since March 2014. It is given in Table 27.

**Table 26: Summary table of key animal studies on adverse effects on sexual function and fertility**

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td>2-year feeding study<br>Rat<br>Sprauge-Dawley<br>M/F<br>35(M)+35(F) per dose<br>70(M)+70(F) controls</td><td>Boric acid, 0; 670 (117); 2000 (350); 6690 (1170) ppm boric acid equivalent to 0, 33 (5.9), 100 (17.5), 334 (58.5) mg boric acid (B)/kg bw /day.</td><td>Testes atrophy at 24 months:<br><table><tr><td>Dose (B) mg/kg bw/day</td><td>0 (0)</td><td>33 (5.9)</td><td>100 (17.5)</td><td>334 (58.5)</td></tr><tr><td>N of animals</td><td>3/10</td><td>1/10</td><td>4/10</td><td>10/10</td></tr></table><br>NOAEL is 2000 ppm equivalent to 100 (17.5) boric acid (B)/kg bw/day.<br>LOAEL is 6690 ppm, equivalent to 334 (58.5) mg boric acid (B)/kg bw/day</td><td>Study report, 1966<br>Study report, 1967<br>Weir and Fisher, 1972<br>Weir, 1996a[1]</td></tr>
<tr><td>2-year feeding study<br>Rat<br>Sprauge-Dawley<br>M/F<br>35(M)+35(F) per dose<br>70(M)+70(F) controls</td><td>Disodium tetraborate decahydrate, 0, 1030, 3080, 10300 ppm equivalent to 0, 52 (5.9), 155 (17.5), 516 (58.5) mg disodium tetraborate decahydrate (B)/kg bw/day.</td><td>Testes atrophy at 24 months:<br><table><tr><td>Dose (B) mg/kg bw/day</td><td>0 (0)</td><td>52 (5.9)</td><td>155 (17.5)</td><td>516 (58.5)</td></tr><tr><td>N of animals</td><td>3/10</td><td>1/10</td><td>4/10</td><td>10/10</td></tr></table><br>NOAEL is 3080 ppm, equivalent to 155 (17.5) mg disodium tetraborate decahydrate (B)/kg bw/day.<br>LOAEL is 10300 ppm, equivalent to 516 (58.5) mg disodium tetraborate decahydrate (B)/kg bw/day.</td><td>Study report, 1966<br>Study report, 1967<br>Weir and Fisher, 1972<br>Weir, 1996b[1]</td></tr>
</table>

[1] As cited in the RAC opinions on disodium octaborate anhydrate and disodium octaborate tetrahydrate, 2014

**Table 27: Summary table of human information on effects on sexual function and fertility, published since March, 2014**

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| Publication | Boron, occupational and environmental exposure | Low exposure group: DBE = 15.07 mg B/day, (74.03 ng B/g blood)<br>Medium exposure group: DBE = 19.85 mg B/day, (126.6 ng B/g blood)<br>High exposure group: DBE = 26.84 mg B/day, (269.2 ng B/g blood)<br>Extreme exposure group: DBE = 47.17 mg B/day, (570.6 ng B/g blood, 571 ppb) | The study did not observe statistical significant differences in sperm quality parameters (concentration, morphology, motility) or reproductive hormone levels (LSH, FH and testosterone) between exposure groups. | Duydu *et al*., 2018a |

### 10.8.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

#### 10.8.2.1 Animal information

The animal data on effects on fertility of the borates included in the present proposal has previously been assessed by the RAC (RAC opinion on boric acid; disodium octaborate anhydrate and disodium octaborate tetrahydrate, 2014). The RAC concluded that studies of reproductive toxicity and repeated dose toxicity studies in mice, rats and dogs clearly indicate that boron impairs fertility through an effect on the testes. The effects observed in the different species are similar in nature. Based on data from the 2-year feeding study with boric acid in rats, the NOAEL for fertility is therefore 100 mg/kg bw/day, equal to 17.5 mg B/kg bw/day. The LOAEL is 334 mg/kg bw/day, equal to 58.5 mg B/kg bw/day. This conclusion is supported by the similar study with disodium tetraborate decahydrate. There were no indications that the impaired fertility is secondary to other toxic effects.

#### 10.8.2.2 Human information

The human data published until March 2014 on the potential effects of boron exposure on fertility is discussed in the RAC opinions on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate. The data consists of epidemiological studies of males exposed to boron via the environment and/or their occupation. RAC concluded that the human studies showed no clear evidence of adverse effects on male fertility by boron. The boron exposures in the human studies were well below the LOAELs for fertility reported from studies in mice and rats. The RAC pointed out that the epidemiological studies had several limitations in study design, and therefore should be regarded as additional information.

Recently, Duydu *et al*. (2018a) published a study investigating the effects of boron on semen parameters and reproductive hormone levels (FSH, LH and testosterone) in environmentally and occupationally exposed workers in Turkey (Bandirma and Bigadic regions). The workers (n =122) where divided into three exposure groups based on their mean daily boron exposure (DBE). In the

highest exposure group (n=98) the DBE was 47.17 mg B/day, corresponding to 570.6 ng B/g blood (571 ppb, with highest individual value 1100 ppb). No difference related to semen parameters, FSH, LH and testosterone levels was detected between the exposure groups. For comparison, animal studies has revealed that boric acid treatment results in increased serum FSH and LH levels and decreased serum testosterone levels (Ku *et al*., 1993; Fail *et al*., 1998). The LOAELs in the animal studies correspond to serum boron concentrations of 10 000 to 17 000 ppb (Ku *et al*., 1993).

The available human data collectively shows no effects on fertility parameters, semen parameters, FSH, LH or testosterone levels at boron exposure levels that were well below the LOAELs from corresponding animal studies. Since the available human data does not contradict the animal data, there is no evidence that the effects observed in animals are not relevant to humans.

### 10.8.3 Comparison with the CLP criteria

The borates covered by the present proposal have harmonised classifications as Repr. 1B, H360DF. No change to the classifications is proposed.

Concentration limits:

According to the current CLP guidance (v.5 July 2017), concentration limits for adverse effects on sexual function and fertility should be based on the lowest ED10. The RAC has previously concluded that the most sensitive effect on sexual function and fertility is testicular atrophy in a toxicity study in rats with boric acid (RAC opinions on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate, 2014). There is no reason to reconsider this conclusion based on the human information published since 2014. The incidence of testicular atrophy at 24 months was 10%, 40% and 100% at doses corresponding to 5.9, 17.5 and 58.5 mg/kg bw/day boron. The incidence in control animals was 30% (Study report, 1966a). The same incidences were observed with disodium tetraborate decahydrate (Study report, 1966b). Hence, the ED10 corresponds to 17.5 mg B/kg bw/day (100 mg boric acid/kg bw/day). According to section 3.7.2.6.3 of the CLP Guidance, a substance with a 4 mg/kg bw/day < ED10 < 400 mg/kg bw/day belongs to the medium potency group. None of the modifying factors related to type or severity of effect, data availability, dose-response relationship, mode/mechanism of action, toxicokinetics or bioaccumulation applies for boric acid. Since boric acid has a harmonised classification for reproductive toxicity in category 1B (H360FD), the GCL of 0.3% would apply (Table 3.14 of the CLP guidance). Concentration limits were derived in a similar way for diboron trioxide and the sodium borates by correcting for the percentage of boron (calculations are available in Table 30). All borates included in the present proposal fall within the range of the medium potency group for effects on fertility, which means that the GCL of 0.3% should apply. Similar to boric acid, the modifying factors described above does not apply for the borates.

### 10.8.4 Adverse effects on development

To our knowledge, no new animal studies on the effects of boron on development has been published since March 2014. The studies given in Table 28 were appointed key studies by the RAC in the 2014 opinions on harmonised classifications of boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate. Two epidemiological studies regarding developmental effects by boron exposure has been published since 2014. These are given in Table 29.

**Table 28: Summary table of key animal studies on adverse effects on development**

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td>Prenatal developmental toxicity study<br>OECD TG 414<br>Rat<br>Sprague-Dawley<br>F<br>28-32 per dose<br>GD 0-20</td><td>Boric acid<br>Doses: 0, 250, 500, 750,1000, 2000 ppm), equivalent to 19 (3.3), 36 (6.3), 55(9.6), 76 (13.3) and 143 (25) mg boric acid (mg B)/kg bw/day</td><td>Dams: no toxicity. NOAEL is 2000 ppm, equivalent to 25 mg B/kg bw/day.<br>Fetuses: at 750 ppm boric acid, corresponding to 13.3 mg B/kg bw/day: reduction in the mean fetal bodyweight per litter; short 13th rib; wavy rib.
<table>
<tr><th>Dose (mg boron/kg bw/day)</th><th>Mean fetal bw/litter, gd 20 (% of control weight)</th><th>Short 13th rib, gd 20 (%, fetuses/ litter)</th><th>Wavy rib, gd 20 (%, fetuses/ litter)</th></tr>
<tr><td>0</td><td>100</td><td>0.7</td><td>0</td></tr>
<tr><td>3.3</td><td>99</td><td>0.6</td><td>0.3</td></tr>
<tr><td>6.3</td><td>98</td><td>0.6</td><td>0</td></tr>
<tr><td>9.6</td><td>97</td><td>0.7</td><td>0.8</td></tr>
<tr><td>13.3</td><td>96*</td><td>1.2*</td><td>2.1*</td></tr>
<tr><td>25.0</td><td>88*</td><td>1.5*</td><td>9.9*</td></tr>
</table>
* $p < 0.05$, pair-wise comparison to concurrent control group.<br>NOAEL is 750 ppm, equivalent to 9.6 mg B/kg bw/day.<br>LOAEL is 1000 ppm, equivalent to 13.3 mg B/kg bw/day.</td><td>Study report, 1994<br>Price, 1996[1]</td></tr>
</table>

[1] As cited in the RAC opinions on disodium octaborate anhydrate and disodium octaborate tetrahydrate, 2014

**Table 29: Summary table of human information on effects on development, published since March, 2014**

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| Publication | Boron, environmental exposure | Prospective study.<br>Mother:child cohort in Northen Argentina.<br>n: 194.<br>1-3 samples of serum, whole blood and urine was taken during pregnancy.<br>Infant weight , length and head circumference was measured at birth. | Serum B > 80 µg/l were found to be inversely associated with birth length (B-0.69 cm, 95% CI:-1.4, p=0.043 per 100 µg/L serum B).<br>No statistical significant associations between boron exposure and birth weight or head circumference were found. | Igra *et al.*, 2016 |
| Publication | Boron, | Retrospective study | No boron-mediated differences | Duydu *et al.*, 2018b |

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | environmental exposure | Females residing in Marmara, Turkey.<br>n: 190<br>Pregnancy outcomes (sex ratio, preterm birth, birth weights, congenital anomalies, abortions, miscarriage, stillbirth, early neonatal death, neonatal death and infant death) determined based on questionnaire.<br>Boron blood levels at time of pregnancy were estimated from levels at time of study. | on pregnancy outcomes was detected between exposure groups (low exposure n=143; medium exposure n=29 and high exposure n=27)<br>Estimated blood boron levels ranged from 151.81 to 957.66 (mean 274.58) ng/g in the high exposure group. | |

### 10.8.5 Short summary and overall relevance of the provided information on adverse effects on development

#### 10.8.5.1 Animal information

The existing animal data for effects on development of the borates included in the present proposal has previously been assessed by the RAC (RAC opinions on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate, 2014). The conclusion of the RAC was that developmental toxicity (malformations) was clearly observed in studies in rats and rabbits, the rat being the most sensitive species, with an overall NOAEL of 9.6 mg B/kg bw/day. The LOAEL corresponds to 13.3 mg B/kg bw/day. Malformations consisted primarily of anomalies of the eyes, the central nervous system, the cardiovascular system, and the axial skeleton (Price *et al*., 1996). The most common malformations were enlargement of lateral ventricles in the brain and agenesis or shortening of rib XIII. There were no indications that the developmental effects were secondary to other toxic effects. In addition, the RAC stated that the teratogenicity was possibly caused by an altered hox gene expression, caused by inhibition of histone deacetylases, a mechanism that is likely to be relevant also for humans.

#### 10.8.5.2 Human information

Epidemiological studies on possible adverse pregnancy outcomes in female workers, or females environmentally exposed to boron via food or drinking water were not available in 2014, and such data was therefore not discussed in the 2014 RAC opinions on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate.

In 2016, an epidemiological study investigating boron-mediated developmental effects in pregnant women from exposure via drinking water was published (Igra *et al*., 2016). The study was performed in a mother-child cohort in northern Argentina (n = 194). 1–3 samples of serum, whole blood and urine were collected per woman during pregnancy and analysed for boron. The samples were also analysed for lithium, cesium and arsenic, which was also present in the drinking water. Infant weight, length and head circumference were measured at birth. The serum boron

concentrations during pregnancy was 0.73–605 µg/L (median 133 µg/L). The study found that serum boron concentrations above 80 µg/L were inversely associated with birth length (0.69 cm shorter, p=0.043), per 100 µg/L increase in serum boron). The study authors report that the impact of boron was stronger when the exposure was restricted to the third trimester, when the serum boron concentrations were the highest (0.73–447 µg/L). An increase in serum boron of 100 µg/L in the third trimester corresponded to 0.9 cm shorter and 120 g lighter new-borns (p = 0.001 and 0.021, respectively).

The information contained in the publication suggests that the women's serum boron levels are in the same range as boron levels in whole blood. A serum concentration of 80 µg B/L (above which effects on birth size were detected) would then correspond to around 75 ng B/g blood, assuming a blood density of 1060 kg/m$^3$. This concentration is below the level of 1270 ng B/g blood that corresponds to the NOAEL for developmental effects in rats (Price *et al*., 1997).

The study has a high participation rate (88%) and a prospective design but a small sample size and a lack of samples in both early and late pregnancy for all the participating women. Although the authors adjusted for potential confounding by lithium exposure in the model, they state that they cannot rule out that the observed diminished birth length is a result of combined exposure to both boron and lithium. Lithium was found to be associated with decreased birth length but not birth weight in a previous study by the same authors (Harari *et al*., 2015).

Recently, a retrospective epidemiological study on the effect of boron on human development was published (Duydu *et al*., 2018b). The study investigates pregnancy outcomes in 199 females (giving birth to 326 children; 162 girls and 164 boys) residing in boron-rich areas in Turkey (Bandirma and Bigadic) and thus being environmentally exposed to the substance. Pregnancy outcomes (including items sex ratio, preterm birth, birth weights, congenital anomalies, abortions, miscarriage, stillbirth, early neonatal death, neonatal death and infant death) were determined based on a questionnaire survey. The daily boron exposure at the time of pregnancy was estimated from boron levels in food and water at the time of the study using the "double plate method" or by blood samples, by assuming that the environmental exposure had been chronic and constant over time. Individual blood boron levels were used to classify females into three exposure groups (low, medium, and high). There was no effects from boron exposure on pregnancy outcomes, including birth weight, in any group.

The blood boron concentrations of the participating women in the highest exposure group (mean 274.6 ng B/g blood, highest value 957.7 ng B/g blood) are clearly below those corresponding to the NOAEL for developmental effects in rats, i.e. 9.6 mg B/kg bw/day, corresponding to 1270 ng B/g blood (Price *et al*., 1997).

The human information on developmental effects should be seen as additional information. The prospective study detected a dose dependent influence on birth size at boron exposure levels that were below the NOAEL for developmental effects in animal studies. However, it is possible that the results were influenced by co-exposure to lithium. The retrospective study reports no adverse effects on development at exposure levels that were well below the NOAELs for developmental effects in animal studies. There are some methodological limitations, mainly associated with the retrospective design and the small sample size. Overall, the available human data does not contradict the animal data and gives no evidence that the effects observed in animals are not relevant to humans.

### 10.8.6 Comparison with the CLP criteria

The borates covered by the present proposal have harmonised classifications as Repr. 1B, H360DF. No change to the classifications is proposed.

Concentration limits

According to the current CLP guidance (v.5 July 2017), concentration limits for adverse effects on development should be based on the lowest ED10. The RAC has previously concluded that the most sensitive effect on development by borates is the increased incidence of short rib XIII, considered a malformation (RAC opinions on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate, 2014). The human information which has been published since 2014 gives no reason to challenge this conclusion. The fetal incidence of the short XIII malformation was 1.2 and 1.5% at the LOAEL (13.3 [76] mg B [boric acid]/kg bw/day) and the highest dose (25 [143] mg B [boric acid]/kg bw/day), respectively. As the incidences are low, it is not possible to derive an ED10. In this instance, the LOAEL should be used for setting the SCL according to the guidance. Boric acid belongs to the medium potency groups (4 mg/kg bw/day < ED10 (LOAEL) < 400 mg/kg bw/day). None of the modifying factors related to type or severity of effect, data availability, dose-response relationship, mode/mechanism of action, toxicokinetics or bioaccumulation applies. As boric acid has a harmonised classification for reproductive toxicity in category 1B (H360FD) according to the CLP guidance, the GCL of 0.3% would apply (Table 3.14 of the CLP guidance). Concentration limits were derived for diboron trioxide and the sodium borates from the same LOAEL and by correcting for the percentage of boron (calculations are available in Table 30). All the borates included in the present classification proposal fall within the range of the medium potency group for adverse effects on development, which means that the GCL of 0.3% should apply. Similar to boric acid, the modifying factors described above does not apply for the borates.

Table 30: Derivation of ED10 values and concentration limits for borate compounds based on boron contents

| **Substance** | **Formula** | **EC** | **CAS** | **Molecular weight (g/mol)** | **Conversion factor for equivalent dose of boron**[1] | **ED10 for fertility corrected for boron-content** (mg/kg bw/day) | **LOAEL for development corrected for boron-content** (mg/kg bw/day) | **Proposed generic concentration limit (GCL, % w/w), fertility** | **Proposed generic concentration limit (GCL, % w/w), development** |
|---|---|---|---|---|---|---|---|---|---|
| Boric acid | $H_3BO_3$ | 233-139-2; 234-343-4 | 10043-35-3; 11113-50-1 | 61.83 | 0.17 | 17.5/0.17 = 103 | 13.3/0.17 = 78 | 0.3 | 0.3 |
| Diboron trioxide | $B_2O_3$ | 215-125-8 | 1303-86-2 | 69.62 | 0.31 | 17.5/0.31 = 56 | 13.3/0.31 = 43 | 0.3 | 0.3 |
| Tetraboron disodium heptaoxide, hydrate | $Na_2B_4O_7 \cdot H_2O$ | 215-540-4 | 12267-73-1 | 219.24 | 0.20 | 17.5/0.20 = 88 | 13.3/0.20 = 67 | 0.3 | 0.3 |
| Disodium tetraborate anhydrous | $Na_2B_4O_7$ | 235-541-3 | 1330-43-4 | 201.22 | 0.21 | 17.5/0.21 = 83 | 13.3/0.21 = 63 | 0.3 | 0.3 |
| Orthoboric acid, sodium salt | $Na_3BO_3$ | 237-560-2 | 13840-56-7 | 127.80 | 0.08 | 17.5/0.08 = 219 | 13.3/0.08 = 166 | 0.3 | 0.3 |
| Disodium tetraborate decahydrate | $Na_2B_4O_7 \cdot 10H_2O$ | 215-540-4 | 1303-96-4 | 381.38 | 0.11 | 17.5/0.11 = 159 | 13.3/0.11 = 121 | 0.3 | 0.3 |
| Disodium tetraborate pentahydrate | $Na_2B_4O_7 \cdot 5H_2O$ | 215-540-4 | 12179-04-3 | 291.35 | 0.15 | 17.5/0.15 = 117 | 13.3/0.15 = 89 | 0.3 | 0.3 |

[1] Molecular weight of boron equals 10.8 g/mol

### 10.8.7 Adverse effects on or via lactation

In the absence of relevant data, there are no indications that boron exposure through lactation has adverse effects. It should however be noted that numerous studies have shown that borates are absorbed from the gastrointestinal tract, as indicated by increased levels of boron in the blood, tissues or urine or by systemic toxic effects in exposed individuals or laboratory animals. In addition, boron compounds have been found in human breast milk (BfR, 2005), with reported (background) concentrations of approximately 4 µg B/L (Hunt *et al*., 2005, as reported in WHO, 2009) and in an experiment where 1–13 g of boric acid was given to lactating women 10–285 mg/l was found in milk (Moseman, 1994). The dossier submitter proposes no classification for adverse effects on or via lactation due to lack of data.

### 10.8.8 Conclusion on classification and labelling for reproductive toxicity

The borates covered by the present proposal have harmonised classifications as Repr. 1B, H360FD. Withdrawal of the specific concentration limits is warranted and therefore the GCL:s of 0.3% applies for both developmental effects and effects on sexual function and fertility.

## RAC evaluation of reproductive toxicity

### Summary of the Dossier Submitter's proposal

The dossier submitter provided summaries of the available reproductive studies in animals with borates and identified the key studies for determination of the dose corresponding to a 10% increase in an adverse effect, relative to the control response ($ED_{10}$ value) for effects on sexual function and fertility and for effects on development. $ED_{10}$ and LOAEL values were derived for the seven borates using the conversion factor for equivalent dose of boron as the effects observed for the tested borates can be extrapolated to the non-tested borates as all the borates will convert into un-dissociated boric acid at physiological conditions. An $ED_{10}$ of 17.5 mg/kg bw/day boron equivalent (B) for effects on sexual function and fertility and a LOAEL of 13.3 mg/kg bw/day boron equivalent for effects on development were derived using the method described in the CLP guidance (Guidance on the application of the CLP criteria, v.5 July 2017) and in line with the previous assessment by RAC of the two octaborates (RAC, 2014). In addition, summaries of the available epidemiological studies were provided. It was concluded that the absence of observed effects in humans does not contradict the effects observed in animals because the human exposure levels were below the NOAEL in animals.

The $ED_{10}$ for effects on sexual function and fertility for each of the seven borates (Table below) were between 4 and 400 mg/kg bw/day (medium potency group). The LOAEL for effects on development for each of the seven borates (Table below) were also between 4 and 400 mg/kg bw/day (medium potency group). In addition, none of the modifying factors were applicable according to the DS. Therefore, the GCL would be applicable and the SCL should be removed for the seven borates.

***Table**: Derivation of $ED_{10}$ values and concentration limits for borate compounds based on boron contents*

[1] Molecular weight of boron equals 10.8 g/mol

| **Substance** | **Formula** | **EC** | **CAS** | **Molecular weight (g/mol)** | **Conversion factor for equivalent dose of boron[1]** | **$ED_{10}$ for fertility corrected for boron-content** (mg/kg bw/day) | **LOAEL for development corrected for boron-content** (mg/kg bw/day) | **Propos generic concen limit (C w/w), fertility** |
|---|---|---|---|---|---|---|---|---|
| Boric acid | $H_3BO_3$ | 233-139-2; 234-343-4 | 10043-35-3; 11113-50-1 | 61.83 | 0.17 | 17.5/0.17 = 103 | 13.3/0.17 = 78 | 0.3 |
| Diboron trioxide | $B_2O_3$ | 215-125-8 | 1303-86-2 | 69.62 | 0.31 | 17.5/0.31 = 56 | 13.3/0.31 = 43 | 0.3 |
| Tetraboron disodium heptaoxide, hydrate | $Na_2B_4O_7 \bullet H_2O$ | 215-540-4 | 12267-73-1 | 219.24 | 0.20 | 17.5/0.20 = 88 | 13.3/0.20 = 67 | 0.3 |
| Disodium tetraborate anhydrous | $Na_2B_4O_7$ | 235-541-3 | 1330-43-4 | 201.22 | 0.21 | 17.5/0.21 = 83 | 13.3/0.21 = 63 | 0.3 |
| Orthoboric acid, sodium salt | $Na_3BO_3$ | 237-560-2 | 13840-56-7 | 127.80 | 0.08 | 17.5/0.08 = 219 | 13.3/0.08 = 166 | 0.3 |
| Disodium tetraborate decahydrate | $Na_2B_4O_7 \bullet 10H_2O$ | 215-540-4 | 1303-96-4 | 381.38 | 0.11 | 17.5/0.11 = 159 | 13.3/0.11 = 121 | 0.3 |
| Disodium tetraborate pentahydrate | $Na_2B_4O_7 \bullet 5H_2O$ | 215-540-4 | 12179-04-3 | 291.35 | 0.15 | 17.5/0.15 = 117 | 13.3/0.15 = 89 | 0.3 |

## Comments received during public consultation

Comments were received from Member States Competent Authorities (MSCA), industry or trade associations, companies or downstream users, individuals and academic institutions. Several MSCA agreed to the proposed removal of the SCLs for the seven borates. However, the other commenters did not agree with the proposed removal and brought forward a number

of arguments challenging the justification provided by the DS. These comments can be grouped into the following main arguments:

- The absence of an observed increase in effects on reproduction in the epidemiological studies supports a very low potency hazard for boron substances (modifying factor);
- A GCL of 0.3% or 3% based on boron content should be applied and would be in line with other European legislation;
- Comments regarding the methodology for deriving the SCL;
- The effects used to derive the $ED_{10}$/LOAEL for developmental effects were considered variations and not malformations and would therefore not be used for the derivation of the $ED_{10}$/LOAEL;
- Alternative $ED_{10}$ values should be applied which are close to the border for low potency and therefore, applying the low potency group should be considered;
- The strong impact of the removal of the SCLs on the borates supply chain;
- It is not justified that a reduction of the concentration limit in mixtures will improve safety and therefore the proposed change is unnecessary.

Most of these arguments will be taken into account in the RAC assessment and in the comparison with the classification criteria. The exceptions are made with the arguments of the impact of the proposed change on the borates supply chain and the relevance of the proposed changes for risk assessment. It should be noted that (the) socio-economic impact/analysis is not part of the CLP criteria used for the assessment of the classifications and the related SCL or GCL.

In addition, specific comments were provided on the summary of the study by Igra *et al*., 2016. In this prospective epidemiology study, a decrease in birth length was determined for the offspring of mothers with a serum boron concentration above 80 µg/L. The DS considered the results as additional information that does not contradict the animal data. The industry provided comments concerning the co-exposure to other substances, the effect of altitude on birth parameters and other limitations. This study and these comments were not assessed as the interpretation of the results of this study does not affect the derivation of the GCL or SCL.

## Assessment and comparison with the classification criteria

### *Method for deriving potency classes for substances inducing reproductive effects*

Industry (European Borates Association, EBA) questioned the approach as included in the CLP guidance. It was stated that the method used to differentiate substances into potency classes is questionable because it takes into account only the dose level at which effects on reproduction are observed but not the difference in severity of the reproductive effects between substances. Therefore, a case by case assessment would be necessary. RAC agrees that for certain effects, such as the difference in adversity between a reduction in sperm counts and a reduction in the number of offspring, this difference could be taken into account for potency setting as it is likely that the $ED_{10}$ for both effects for the same substance could be different. For this reason, a minimal level of severity is already required according to the guidance. Furthermore, the severity of the effects should be taken into account as a modifying factor (CLP guidance paragraph 3.7.2.6.5.1).

Additionally, it was suggested by industry to take the difference between animal studies and epidemiological studies, including human relevance as a modifying factor, into consideration (Annex I to comments received from EBA). RAC agrees that effects observed in animals that

have shown not to be relevant for humans should not be taken into account. However, absolute or quantitative differences between animals and humans should already be taken into account within the modifying factor 'Mode or mechanism of action' (CLP guidance 3.7.2.6.5.4).

Overall, RAC considers the current approach as described in the CLP guidance, using three broad classes, reasonable for assigning substances to a potency classes and associated SCLs or GCLs.

***Derivation of the $ED_{10}$ values for effects on sexual function and fertility and development***

No new reproductive studies in animals were available for the evaluation of the seven borates. Therefore, the same data as previously used by RAC for the disodium octaborates were used to derive the $ED_{10}$ (or LOAEL) value(s).

Reproductive toxicity and repeated dose toxicity studies in mice, rats and dogs clearly indicate that borates impair fertility through atrophy and seminiferous tubule degeneration in the testes. The effects observed in the different species are similar in nature. Based on the data from the 2-year feeding study on boric acid in rats (Weir, 1996a), the overall NOAEL for fertility is 100 mg/kg bw/day, equivalent to 17.5 mg /kg bw/day of boron. This conclusion on the testicular effects and the overall NOAEL is also supported by the study conducted with disodium tetraborate decahydrate (Weir, 1996b). As the incidence of the animals with testis atrophy was increased by 10% at the NOAEL, this value is also the $ED_{10}$ (100 mg/kg bw/day, equivalent to 17.5 mg /kg bw/day of boron) for this effect (see Table below).

***Table**. Incidence of testis atrophy after chronic exposure to boric acid (Study report, 1966)*

| Dose (B) mg/kg bw/day | 0 (0) | 33 (5.9) | 100 (17.5) | 334 (58.5) |
|---|---|---|---|---|
| No of animals | 3/10 | 1/10 | 4/10 | 10/10 |

For effects on development, the overall NOAEL for embryotoxic/teratogenic effects was 9.6 mg /kg bw/day boron equivalent, based on a reduction in mean foetal body weight/litter and an increased incidence in short rib XIII malformation at 76 mg/kg bw/day (13.3 mg /kg bw/day boron equivalent) (Price *et al*., 1996). The foetal incidence of short rib XIII malformation was 1.2 % and 1.5% at the LOAEL (13.3 mg /kg bw/day boron equivalent) and the highest dose tested (25 mg /kg bw/day boron equivalent) respectively (Price *et al*., 1996). As the incidences are low, it is not possible to derive an $ED_{10}$. In line with the guidance, in such cases the LOAEL of 13.3 mg/kg bw/day boron equivalent should be used for setting the SCL. This value is in accordance with the previous RAC assessment for disodium octaborates (RAC, 2014).

In the public comments it was stated that the effects used to ascertain the LOAEL for developmental effects, namely reduced foetal body weight, increased incidence of short rib XIII, wavy rib and decreased incidence of extra rib on lumbar I, should be considered as variations. Therefore, these effects should not be taken into account for deriving the potency group and the SCL/GCL. According to RAC and in line with the previous RAC opinion on the disodium octaborates the effects on the ribs should be considered malformations as there are several related effects on the ribs which were not fully reversible. A low level agreement (grey zone, value 38.5) was reached on the classification of short rib as a malformation or variation upon assessment and discussion by a large group of teratologists (Solecki *et al*, 2001). In

addition, a strong increase in foetuses with cardiovascular defects per litter (72% vs 3% in controls) was observed in the developmental study in rabbits (Price *et al*, 1996) at 25 mg B/kg bw/day. The $ED_{10}$ for this effect is estimated at approximately 150 mg/kg bw/day for boric acid and 26 mg/kg bw/day for boron. This results in an $ED_{10}$ value for all borates within the medium potency group.

Also, for effects on sexual function and fertility, it was suggested to use the LOAEL instead of the $ED_{10}$. In line with the guidance, RAC is of the opinion that an $ED_{10}$ is a better descriptor of the potency than a LOAEL and whenever possible this should be used. Furthermore, it is noted that the LOAEL would still be within the medium potency range. It was also argued to use the $ED_{10}$ values for effects on sexual function and fertility (123.5 mg/kg bw/day) and for effects on development (195 mg/kg bw/day) for boric acid as derived by Muller *et al*. (2012). RAC does not agree with the proposed suggestion as for effects on development an LOAEL approach should be applied. The $ED_{10}$ value for effects on fertility differ only to a very limited extent and was based on another study. The reason for this difference cannot be determined by RAC. Therefore, no changes are applicable. Further, it is noted that both suggested alternative $ED_{10}$ values are still within the range for medium potency.

In an analysis of the distribution of the $ED_{10}$ values for boric acid for effects on sexual function and fertility (123.5 mg/kg bw/day) and for effects on development (195 mg/kg bw/day) compared to the distribution of $ED_{10}$ values from Muller *et al*. (2012), it is stated that $ED_{10}$ values are close to the border for low potency (Annex I of the EBA comments). The same comment stated that only 13% (development) and 22% (fertility) of the substances are within the medium group have a higher $ED_{10}$ value (between the $ED_{10}$ for boric acid and the border of 400 mg/kg bw/day). Since RAC does not agree with the use of an $ED_{10}$ value for effects on development, this issue on the $ED_{10}$ is not considered relevant. For effects on fertility RAC applies a marginally lower $ED_{10}$ value. Therefore, RAC does not agree that the data show that the $ED_{10}$ for boric acid is close to the border for low potency.

Overall, RAC sees no justification to deviate from the previous assessment of the $ED_{10}$/LOAEL for borates. Even if a higher LOAEL or $ED_{10}$ would be applicable for developmental effects, the $ED_{10}$ value for effects on sexual function and fertility would still result in a medium potency class and be determinative for the overall GCL or SCL for effects on reproduction. Based on the values for boron derived above, the comparable values for the individual boron compounds were calculated (see Table above). This results in a medium potency group for all seven borates.

***Derivation of the potency group taking into account the modifying factors***

Type and severity of the effect

The type of effects observed in reproductive toxicity studies following exposure to borates and used to determine the $ED_{10}$ included malformations were considered as severe. The same applies to the increase in testis atrophy. Therefore, this does not change the potency group.

Data availability

The available data for the borates was considered adequate compared to the REACH requirements and does not justify adaptation of the potency group.

Dose-response relationship

Borates showed a normal dose-response relationship for effects on sexual function and fertility and no adaptation of the potency group was considered necessary. For effects on development a LOAEL is used to derive the potency group and the incidence of effects at the LOAEL is only 0.5% above the control value (0.7% in controls and 1.2% at 13.3 mg /kg bw/day boron equivalents). Calculation of an $ED_{10}$ value is not possible as this would require extrapolation beyond the tested dose levels. However, the $ED_{10}$ value would be much higher than the LOAEL and potentially resulting in an $ED_{10}$ value corresponding to a lower potency group. However, according to the guidance, in such situations the higher potency group based on the LOAEL should be used.

Mode or mechanism of action

No conclusive information was available on the mode or mechanism of action of borates for the induction of malformations or effects on sexual function. Several epidemiological studies are available showing no increase in effects on sexual function or fertility or on developmental effects at mean boron blood levels considerably below the blood levels estimated for the NOAEL for observed effects in rats. Therefore, this comparison does not demonstrate an absolute or quantitative difference between humans and animals and modification of the potency group is not justified.

Toxicokinetics

There were no data available that indicate that borate toxicokinetics from animals would not be relevant for humans and no adaption to the potency group is needed.

Bio-accumulation of substance

Borates are not considered to be bio-accumulating substances from the data available.

***Conclusion on modifying factors and potency group***

No modifying factors were identified that would affect the potency group. Therefore, RAC concludes that the final potency group for the seven borates is medium potency.

***Derivation of a GCL or SCL***

Several commenters suggested assigning a GCL or SCL based on the boron content as only borates mixtures containing the same percentage of boron are equipotent. This is supported by the use of a boron based approach also in other EU legislation and opinions of EU scientific committees. RAC notes that Annex VI of CLP contains the option to apply Note 1 to a substance stating "*The concentration stated or, in the absence of such concentrations, the generic concentrations set out in this Regulation are the percentages by weight of the metallic element calculated with reference to the total weight of the mixture*". This Note is applied to several metal containing compounds classified as Repr. 1B and/or Carc. 1B including cobalt dichloride, cadmium sulphide and lead compounds. In addition, for chromates Note 3 is available stating "*The concentration stated is the percentage by weight of chromate ions dissolved in water calculated with reference to the total weight of the mixture*". This Note is applicable to potassium chromate. Since these Notes only apply to metals and metal compounds, RAC is of the opinion that it does not apply to boron. The GCL would be applicable to all seven borates as they all fall into the medium potency group and the differences in

potency between these borates based on the amount of boric acid that can be formed is only small (see table above). In view of that, RAC agrees with the proposal of the DS in setting a GCL of 0.3% for all seven borates, which is also in line with the previous conclusion of RAC on the two disodium octaborates in 2014.

Regarding the medium potency group for reproductive toxicity, determined according to the CLP Guidance, no modifying factors were identified that could have an impact. Therefore, in agreement with the DS's proposal, the final potency group for the seven borates is concluded by RAC as being medium potency (boundaries: 4 mg/kg bw/day < $ED_{10}$ value < 400 mg/kg bw/day) (Table 3.13 and Section 3.7.2.6.8.5 of the CLP Guidance).

**RAC agrees with the DS that the SCLs of the seven borates should be removed from the existing entries in CLP** as the current SCLs are not in line with the approach according to the CLP guidance. RAC agrees with DS that in line with the CLP guidance on the medium potency group, **a GCL of 0.3% applies**, which is in accordance with the previous evaluation of RAC (RAC 2014).

***Conclusion***

All relevant scientific data related to the reproductive toxicity of boron has previously been assessed by RAC. The available (recent) human data collectively show no effects on fertility and sexual function. However, there is no evidence that the effects observed in animals are not relevant to humans (RAC, 2014).

## Supplemental information - In depth analyses by RAC

The following section is given as supplemental information, since it was discussed by RAC as an alternative option to the RAC opinion. This option implies that the current CLP guidance is not fully followed and that the guidance needs to be adapted, which is beyond the remit of RAC. However, it could be argued that based on the application of Notes 1 and 3 for several metal compounds and chromates in Annex VI of CLP, which are also not mentioned in the guidance, that defining GCL or SCLs based on the toxic moiety is an overarching principle. Moreover, this implies that the concentration limits previously set by RAC for the two octaborates (RAC, 2014) need to be changed accordingly. Therefore, this option is mainly provided to illustrate the issue and provide actual figures to show the impact.

Several commenters suggested assigning a GCL or SCL based on the boron content since only borates mixtures containing the same percentage of boron are equipotent. This is supported by the use of a boron-based approach also in other EU legislation and opinions of EU scientific committees. RAC notes that Annex VI of CLP contains the option to apply Note 1 to a substance as "*The concentration stated or, in the absence of such concentrations, the generic concentrations set out in this Regulation are the percentages by weight of the metallic element calculated with reference to the total weight of the mixture*". This Note is applied to several metal containing compounds classified as Repr. 1B and/or Carc. 1B including cobalt dichloride, cadmium sulphide and lead compounds. In addition, for chromates Note 3 is available stating "*The concentration stated is the percentage by weight of chromate ions dissolved in water calculated with reference to the total weight of the mixture*". This Note is applicable to potassium chromate.

Note 1 is applied for several substances in Annex VI including substances classified as toxic to

reproduction. This Note is used to inform that the classification of a mixture should be based on the weight percentage of the metallic element in a mixture compared to the GCL or SCL and not on the percentage by weight of the compound containing the metal. This Note is used because the toxic effects of metals are often caused by the ion of the metal and classification is often based on read-across. By determining the classification of the mixture based on the percentage by weight of the metal element, all mixtures containing a compound with that metal are classified when comparable effects can be expected. For chromates however, the chrome ion is not the toxic moiety but the chromate itself. This indicates that application of this principle is applicable to the toxic moiety and not to the element itself.
This concept would also be relevant for borates as most borates dissociate into boric acid and classification of most borates is based on read-across. Note 1 cannot be applied to the borates because boron is not a metal. For that reason, the current SCLs were applied so that each borate had an SCL equipotent to the boron content. However, a Note similar to Note 1 or Note 3 could be introduced in the CLP legislation specifically for boron containing compounds.

The toxicity of borates is not induced by boron but by boric acid. In addition, boron is generally found in nature bound to oxygen and is never found as the free element (Cotton *et al*. 1999). According to ATSDR, "*In aqueous solution, boron is normally present as boric acid and the monovalent ion, $B(OH)_4$-, with the dominant form of inorganic boron in natural aqueous systems as undissociated boric acid*" (Choi and Chen, 1979). Therefore, a GCL is proposed for all borates (see the RAC opinion). By applying a new Note, it would be required to base the GCL on the formation of 0.3% boric acid from the available boron in the borates. This is also in line with the use of Note 3 for chromate. Classification based on a GCL for the formation of boric acid would result in actual (minimum) concentration limits for the boron compounds in mixtures resulting in classification in the range of 0.16 to 0.66% (Table below).

***Table**: Calculation of the borate concentration in a mixture without classification as Repro 1B for a GCL based on the formation of 0.3% boric acid from the available borates*

| **Substance** | **Formula** | **EC** | **Molecular weight (g/mol)** | **Conversion factor for equivalent dose of boron** | **Minimum Borate concentration (%) in a mixture requiring classification** |
|---|---|---|---|---|---|
| Boric acid | $H_3BO_3$ | 233-139-2; 234-343-4 | 61.83 | 0.17 | 0.3 |
| Diboron trioxide | $B_2O_3$ | 215-125-8 | 69.62 | 0.31 | 0.16 |
| Tetraboron disodium heptaoxide, hydrate | $Na_2B_4O_7 \bullet H_2O$ | 215-540-4 | 219.24 | 0.20 | 0.26 |
| Disodium tetraborate anhydrous | $Na_2B_4O_7$ | 235-541-3 | 201.22 | 0.21 | 0.25 |
| Orthoboric acid, sodium salt | $Na_3BO_3$ | 237-560-2 | 127.80 | 0.08 | 0.66 |

| | | | | | |
|---|---|---|---|---|---|
| Disodium tetraborate decahydrate | $Na_2B_4O_7•10H_2O$ | 215-540-4 | 381.38 | 0.11 | 0.48 |
| Disodium tetraborate pentahydrate | $Na_2B_4O_7•5H_2O$ | 215-540-4 | 291.35 | 0.15 | 0.35 |

### 10.9 Specific target organ toxicity-single exposure

Not evaluated in this dossier.

### 10.10 Specific target organ toxicity-repeated exposure

Not evaluated in this dossier.

### 10.11 Aspiration hazard

Not evaluated in this dossier.

## 11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this dossier.

## 12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this dossier.

## 13 ADDITIONAL LABELLING

Not relevant.

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# 15 ANNEXES

## 15.1 Annex I

Table I: Overview of experimental animal studies for boric acid; diboron trioxide; disodium tetraborate, anhydrous; disodium tetraborate decahydrate and disodium tetraborate pentahydrate on reproductive toxicity available in the publically disseminated REACH Registration Dossiers or in the Assessment Reports under BPR. Tetraboron disodium heptaoxide, hydrate and orthoboric acid, sodium salt are not registered nor evaluated as active substances under the biocide regulation and therefore lack data.

| **Test substance** | **Type of study** | **Species/ Strain/ Breed** | **NOAEL** | **Reliability score** | **Reference[1]** | **In the registration dossier /CAR of substance (CAS)** |
|---|---|---|---|---|---|---|
| *Fertility/sexual function* | | | | | | |
| Boric acid | Three generation reproductive toxicity | Sprague-Dawley rat | 17.5 mg B/kg bw/day | 2 | Study report, 1966; Weir and Fisher, 1972 Weir, 1966 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Sodium tetraborate decahydrate | Three generation reproductive toxicity | Sprague-Dawley rat | 17.5 mg B/kg bw/day | 2 | Study report, 1966; Weir and Fisher, 1972 Weir, 1966 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Two generation reproductive toxicity | Swiss CD-1 mice | 27 mg B/kg bw/day (LOAEL) | 2 | Fail *et al*., 1998; 1991 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Fertility, other | Rat, strain not specified | 35 mg B/kg bw/day | 3 | Caujolle *et al*., 1962 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Fertility, other | Wistar rat | 8.75 mg B/kg bw/day | 2 | Yoshizaki *et al*., 1999 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2) |

| Test substance | Type of study | Species/ Strain/ Breed | NOAEL | Reliability score | Reference[1] | In the registration dossier /CAR of substance (CAS) |
|---|---|---|---|---|---|---|
| | | | | | | • Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Sodium tetraborate decahydrate | Fertility, other | Sprague-Dawley rat | 50 mg B/kg bw | 2 | Lee *et al.*, 1978 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Fertility, other | CD-1 rat | 21 mg B/kg bw/day | 3 | Harris *et al.*, 1992 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Fertility, other | In vitro, rat | - | 2 | Study report, 2013 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2) |
| *Development* | | | | | | |
| Boric acid | BMD – study development | In silico | 10.3 mg B/kg bw/day ($BMDL_{0.5}$) | 2 | Allen *et al.*, 1996 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Prenatal development toxicity study, OECD 414 | Sprague-Dawley rat | 9.6 mg B/kg bw/day | 1 | Study report, 1994<br>Price CJ *et al.*, 1994 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |

| Test substance | Type of study | Species/ Strain/ Breed | NOAEL | Reliability score | Reference[1] | In the registration dossier /CAR of substance (CAS) |
|---|---|---|---|---|---|---|
| Boric acid | Prenatal development toxicity study, OECD 414 | New Zealand White rabbit | 21.8 mg B/kg bw/day | 1 | Publication, 1991 Price CJ *et al*., 1991 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Developmental toxicity | Sprague-Dawley rat | 0.1% boric acid (LOAEL) | 2 | Publication, 1990 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Developmental toxicity | Swiss albino CD-1 mice | 43 mg B/kg bw/day | 2 | Publication, 1989; Heindel *et al*., 1992 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Developmental toxicity | Sprague-Dawley rat | 250 mg boric acid/kg bw/day | 4 | Harrouk *et al*., 2005 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Developmental toxicity – MoA study | CD-1 mice | - | 2 | Di Renzo *et al*., 2007 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Developmental toxicity – | Sprague-Dawley rat | - | 2 | Wéry *et al*., 2003 | • Boric acid (10043-35-3, 11113-50-1) |

| Test substance | Type of study | Species/ Strain/ Breed | NOAEL | Reliability score | Reference[1] | In the registration dossier /CAR of substance (CAS) |
|---|---|---|---|---|---|---|
| | MoA study | | | | | • Diboron trioxide (1303-86-2) |
| Boric acid | Developmental toxicity | Sprague-Dawley rat (embryos) | - | 2 | Narotsky *et al.*, 2004 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2) |
| Boric acid | Developmental toxicity | Frog | - | 2 | Fort *et al.*,1998; 1999a; 1999b; 2000; 2002 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2) |
| Boric acid | Developmental toxicity | Sprague-Dawley rat; CD-1 mice | - | 2 | Lanoue *et al.*, 1998; 1999 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2) |
| Boric acid | Developmental toxicity | Trout; Zebrafish | - | 2 | Eckhert, 1998; Eckhert and Rowe, 1999; Rowe *et al.*, 1998 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2) |
| Boric acid | Developmental toxicity, in vitro | Embryonic stem cells, fibroblasts | - | 1 | Study report, 2013 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2) |
| *Repeated dose toxicity studies reporting effects on fertility parameters* | | | | | | |
| Boric acid | 2-years feeding study | Sprague-Dawley rat | 17.5 mg B/kg bw/day | 2 | Study report, 1966; Study report 1967; Weir and Fisher, 1972 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Sodium tetraborate decahydrate | 2-years feeding study | Sprague-Dawley rat | 17.5 mg B/kg bw/day | 2 | Study report, 1966; Study report 1967; Weir and Fisher, 1972 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Chronic toxicity, oral | Beagle dog | 41 mg B/kg bw/day (LOAEL) | 3 | Study report 1967; Weir and Fisher, 1972 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate |

| Test substance | Type of study | Species/ Strain/ Breed | NOAEL | Reliability score | Reference[1] | In the registration dossier /CAR of substance (CAS) |
|---|---|---|---|---|---|---|
| | | | | | | pentahydrate (12179-04-3) |
| Boric acid | Short-term repeated dose toxicity: oral | Fisher 344 rats | 61 mg B/kg bw/day (LOAEL) | 2 | Treinen and Chapin, 1991 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Short-term repeated dose toxicity: oral | Rat | 140 mg B/kg bw/day (LOAEL) | 3 | Bouissou and Castagnol, 1965 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Short-term repeated dose toxicity: oral | Long-Evans rat | 47.4 mg B/kg bw/day (LOAEL) | 3 | Seal and Weeth, 1980 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Short-term repeated dose toxicity: oral | Sprague-Dawley rat | 100 mg boric acid/kg bw/day (LOAEL) | 2 | Kocatürk *et al*. 2005 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Short-term repeated dose toxicity: oral | B6C3F1 mouse | 142 mg B/kg bw/day (LOAEL) | 2 | Publication, 1987 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Disodium | Short-term | Long- | 47.4 mg | 3 | Seal and | • Boric acid (10043-35-3, |

| Test substance | Type of study | Species/ Strain/ Breed | NOAEL | Reliability score | Reference[1] | In the registration dossier /CAR of substance (CAS) |
|---|---|---|---|---|---|---|
| tetraborate decahydrate | repeated dose toxicity: oral | Evans rat | B/kg bw/day (LOAEL) | | Weeth, 1980 | 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Sub-chronic toxicity: oral | Fisher 344 rat | 26 mg B/kg bw/day | 2 | Ku *et al*. 1993 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Sub-chronic toxicity: oral | Sprague-Dawley rat | 26 mg B/kg bw/day | 2 | Study report, 1962; Weir and Fisher, 1972 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Sub-chronic toxicity: oral | Beagle dog | 4.4 mg B/kg bw/day | 3 | Study report, 1963; Weir and Fisher, 1972 Paynter, 1963 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Boric acid | Sub-chronic toxicity: oral | Rat | 0.3 mg B/L | 3 | Krasovskii *et al*. 1976 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |

[1] As cited in the publically disseminated REACH registration dossiers and/or biocide assessment reports

Table II: Overview of human epidemiology studies for boric acid; diboron trioxide; disodium tetraborate, anhydrous; disodium tetraborate decahydrate and disodium tetraborate pentahydrate with endpoint toxicity to reproduction/fertility, which are included in the publically disseminated REACH Registration Dossiers or in the Assessment Reports under BPR. Tetraboron disodium heptaoxide, hydrate and orthoboric acid, sodium salt are not registered nor evaluated as active substances under the biocide regulation and therefore lack data.

| **Type of study** | **Reference[1]** | **In the registration dossier / CAR of substance (CAS)** |
|---|---|---|
| Worker reproductive toxicity study | Duydu *et al*., 2011 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Worker reproductive toxcity study | Scialli *et al*., 2010 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Worker reproductive toxcity study | Robbins *et al*., 2010 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Cohort study (retrospective) | Study report, 1992<br>Whorton *et al*., 1994a;b | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Cohort study (retrospective) | Sayli *et al*., 1998 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Epidemiology study | Sayli, 1998 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Epidemiology study | Sayli, 2001 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Epidemiology study | Sayli *et al*., 2004 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Epidemiology study | Sayli, 2003 | • Boric acid (10043-35-3, 11113-50-1) |

| Type of study | Reference[1] | In the registration dossier / CAR of substance (CAS) |
|---|---|---|
| | | • Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Epidemiology study | Col *et al*., 2000 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Epidemiology study | Yazbeck *et al*., 2005 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Occupational exposure study | Robbins *et al*., 2008 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Epidemiology study | Chang *et al*., 2006 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Retrospective case control study | Acs *et al*. 2006 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |
| Retrospective cohort study | Tuccar *et al*., 1998 | • Boric acid (10043-35-3, 11113-50-1)<br>• Diboron trioxide (1303-86-2)<br>• Disodium tetraborate, anhydrous (1330-43-4)<br>• Disodium tetraborate decahydrate (1303-96-4)<br>• Disodium tetraborate pentahydrate (12179-04-3) |

[1] As cited in the publically disseminated REACH registration dossiers and/or biocide assessment reports