European Union Risk Assessment Report

DISODIUM TETRABORATE, ANHYDROUS
BORIC ACID
BORIC ACID, CRUDE NATURAL (1)

CAS No: 1330-43-4	EINECS No: 215-540-4
CAS No: 11113-50-1	EINECS No: 234-343-4
CAS No: 10043-35-3	EINECS No: 233-139-2

RISK ASSESSMENT

GENERAL NOTE

The Risk Assessment has not been achieved.

This report contains different documents:

- **Physical and Chemical properties**
October 2007 (pages 47)

- **Environment**
October 2007 (pages 151)

- **Environment - References**
October 2007 (pages 19)

- **Human Health**
November 2007 (pages 57)

- **Human Health – Industry version**
October 2007 (pages 57)

- **Human Health – References**
October 2007 (pages 9)

DRAFT – 19 October 2007

SUBSTANCE EVALUATION REPORT

Substance Name:	**Boric Acid**	**Disodium Tetraborate, anhydrous**
EC Number:	**233-139-2**	**215-540-4**
CAS Number:	**10043-35-3**	**1330-43-4,**

Rapporteur Member State : Austria

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CONCLUSION OF THE SUBSTANCE EVALUATION

Substance Name:

EC Number:

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Registration dossiers numbers:

Conclusion of the substance evaluation:

INFORMATION ON HAZARD AND RISKS

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

Boric acid (H_3BO_3), anhydrous borax ($Na_2B_4O_7$) and its hydrated forms, borax pentahydrate ($Na_2B_4O_7.5H_2O$) and borax decahydrate ($Na_2B_4O_7.10H_2O$) are commercially available substances used in the production of numerous products. Boric acid (orthoboric acid) exists in nature as the mineral sassolite. It is a white crystalline material; its solubility in water increases rapidly with temperature and is a weak acid. Borax decahydrate (disodium tetraborate decahydrate) exists in nature as the mineral tincal. Borax is readily soluble in water and the pH of a borax solution increases slightly with increasing concentration and drops slightly with increasing temperature.

1.1 Name and other identifiers of the substance

Chemical Name:	Boric acid	Disodium tetraborate anhydrous Disodium tetraborate pentahydrate Disodium tetraborate decahydrate
EC Name:	233-139-2	215-540-4[1]
CAS Number:	10043-35-3	Disodium tetraborate anhydrous: 1330-43-4 Disodium tetraborate pentahydrate: 12179-04-03 Disodium tetraborate decahydrate: 1303-96-4
IUPAC Name:	ortho-boric acid; boric acid	Disodium tetraborate anhydrous Disodium tetraborate pentahydrate Disodium tetraborate decahydrate
Synonyms	ortho boric acid; boracic acid	**Disodium tetraborate anhydrous:** Anhydrous borax, sodium tetraborate, boron sodium oxide ($B_4Na_2O_7$); boron sodium oxide ($H_2B_4O_7$); boric acid ($H_2B_4O_7$), disodium salt **Disodium tetraborate pentahydrate:** Borax 5-mol, sodium borate ($Na_2B_4O_5(OH)_4$) trihydrate; sodium tetraborate pentahydrate; boron sodium oxide ($B_4Na_2O_7$), pentahydrate, boric acid ($H_2B_4O_7$), disodium salt, pentahydrate **Disodium tetraborate decahydrate:** Borax; sodium tetraborate dechydrate; borax decahydrate; sodium biborate decahydrate; sodium pyroborate decahydrate; boron sodium oxide ($B_4Na_2O_7$), decahydrate; boric acid ($H_2B_4O_7$), disodium salt decahydrate
Trade names:	Optibor	**Disodium tetraborate anhydrous:** Borax glass; Dehybor; Pyrobor; Etibor 68 **Disodium tetraborate pentahydrate:** Neobor; V-bor; Etibor 48 **Disodium tetraborate decahydrate:** Boricin; Borascu; Inkabor; Deca

The CAS numbers and EC numbers indicated in the table above are those used by the European Borates Association (EBA) members. There is another entry for boric acid (CAS# 11113-50-1, EC# 234-343-4)[2] which is described as "crude natural, containing not more than 85% of H_3BO_3, calculated on a dry weight basis". This boric acid is not supplied by the EBA members and is a Low Production Volume substance[3]. Therefore, this risk assessment only considers the boric acid EC# 233-139-2, CAS# 10043-35-3.

[1] The hydrated forms are listed in EINECS (European Inventory of Existing Commercial Chemical Substance) under the anhydrous form of sodium tetraborate. There is an industry agreement to use the anhydrous EINECS entry.

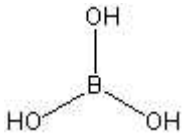
[2] Commission Regulation (EC) No 2364/2000 concerning the fourth list of priority substances as foreseen under Council Regulation No 793/93.

[3] ECB ESIS: European chemical Substances Information System, Version 5.00

All hydrated forms of disodium tetraborates are all listed under one EC number (EC#215-540-4) for that of the anhydrous form in the European Inventory of Existing Commercial Chemical Substances (EINECS). However some hydrated salts were listed, but there is an industry agreement to use the anhydrous EINECS entry[4]. Each of the hydrated states (pentahydrate and decahydrate) have separate CAS numbers to provide a unique identifier for each. Disodium tetraborate pentahydrate is identified by EBA members with CAS# 12179-04-3, although this substance is also listed under CAS# 12267-73-1 and 12045-88-4. Disodium tetraborate decahydrate is indentified by EBA members by 1303-96-4, although the substance is also listed under CAS# 13840-56-7.

1.2 Composition of the substance

For each constituent/ impurity/ additive, fill in the following table (which should be repeated in case of more than one constituent). The information is particularly important for the main constituent(s) and for the constituents (or impurity) which influence the outcome of the dossier.

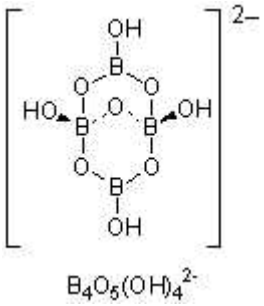
Chemical Name:	Boric Acid
EC Number:	233-139-2
CAS Number:	10043-35-3
IUPAC Name:	ortho-boric acid, boric acid
Molecular Formula:	H_3BO_3 other frequently used formulas are: $B(OH)_3$ or $B_2O_3.3H_2O$
Structural Formula:	
Molecular Weight:	61.8
Typical concentration (% w/w):	≥100%
Concentration range (% w/w):	99.9 – 100.34 The purity being ≥ 100% is due to the variation of crystal water in boric acid. Since boric acid consists of diboron-trioxide and water ($H_3BO_3 \leftrightarrow 1/2B_2O_3 + 3/2H_2O$), even a slight decrease in the structural water content will yield to a higher diboron-trioxide content which will increase the purity

Chemical Name:	Disodium tetraborate anhydrous
EC Number:	215-540-4

[4] ***Extract from:*** *Manual of Decisions for Implementation of The Sixth and Seventh Amendments to Directive 67/548/EEC on Dangerous Substances (Directives 79/831/EEC And 92/32/EEC). Last modified: 23 January 2002*

2.3. Criteria for reporting Substances for EINECS

14. Hydrates of a substance or hydrated ions, formed by association of a substance with water should not be reported. The anhydrous form can be reported and will, by implication, represent all hydrated forms. The products of discrete chemical reactions in which water is a reactant, i.e. a metal hydroxide formed by the reaction of a metal oxide and water can be reported.

CAS Number:	Disodium tetraborate anhydrous: 1330-43-4 Disodium tetraborate pentahydrate: 12179-04-03 Disodium tetraborate decahydrate: 1303-96-4
IUPAC Name:	Disodium tetraborate anhydrous Disodium tetraborate pentahydrate Disodium tetraborate decahydrate
Molecular Formula:	$Na_2B_4O_7$ $Na_2B_4O_7 \bullet 5H_2O$ $Na_2B_4O_7 \bullet 10H_2O$
Structural Formula:	 $B_4O_5(OH)_4^{2-}$
Molecular Weight:	Disodium tetraborate anhydrous: 201.22 Disodium tetraborate pentahydrate: 291.35 Disodium tetraborate decahydrate: 381.37
Typical concentration (% w/w):	>100% for all three hydrates
Concentration range (% w/w):	Disodium tetraborate anhydrous: 99.0 – 101.9% Disodium tetraborate pentahydrate: 101.6 – 103.1% Disodium tetraborate decahydrate: 101.0 – 104.6% The purity being ≥ 100% is due to the variation of crystal water in boric acid. Since boric acid consists of diboron-trioxide and water ($H_3BO_3 \leftrightarrow 1/2B_2O_3 + 3/2H_2O$), even a slight decrease in the structural water content will yield to a higher diboron-trioxide content which will increase the purity.

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	White, crystalline, odourless solid	
VII, 7.2	Melting/freezing point	3.2	No melting point detected in the range 25-1000°C.	If heated above 100°C water is lost and boric acid converts initially to metaboric acid (HBO_2) and on further heating forms boric oxide (B_2O_3). Cordia JA (2003)
VII, 7.3	Boiling point	3.3	not required	Melting point of boric oxide is >300°C.
VII, 7.4	Relative density	3.4 density	$D^{23}_4 = 1.489 \pm 0.006$	Cordia JA (2003)
VII, 7.5	Vapour pressure	3.6	not required	Melting point of boric oxide is >300°C.
VII, 7.6	Surface tension	3.10	not applicable	Surface tension is not expected for inorganic substances.
VII, 7.7	Water solubility	3.8	49.20 ± 0.35 g/l at 20 ± 0.5°C	Cordia JA (2003)
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	not required	Inorganic substance
VII, 7.9	Flash point	3.11	not required	Inorganic substance
VII, 7.10	Flammability	3.13	non-flammable	Rowe SM & Merritt M (2003)
VII, 7.11	Explosive properties	3.14	not explosive	Rowe SM & Merritt M (2003)
VII, 7.12	Self-ignition temperature			
VII, 7.13	Oxidising properties	3.15	No oxidising properties	
VII, 7.14	Granulometry	3.5	D_{50} = 50 – 250 μm	Commercial boric acid products exist as granules or finer powders.
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	not required	Inorganic substance
XI, 7.16	Dissociation constant	3.21	Boric acid is a Lewis acid (hydroxide ion acceptor) rather than a Brønsted acid (proton	At low boron concentrations (B ≤ 0.025 M) the following equilibrium is found $B(OH)_3 + 2H_2O \leftrightarrow [B(OH)_4]^- + H_3O^+$

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
			donator). For this purpose the formula for boric acid is best written as $B(OH)_3$. pKa = 9.0 at 25°C for boric acid in dilute solutions only (B ≤ 0.025 M). At higher boron concentrations, polynuclear complexes are formed and several dissociation/formation constants apply.	pKa = 9.0 at 25 °C In dilute aqueous solutions (B ≤ 0.025 M) boric acid exists as undissociated boric acid $B(OH)_3$ at pH < 7, at pH > 11 the metaborate ion $[B(OH)_4]^-$ becomes the main species in solution. At in-between values (pH 7-11) both species are present. At higher boron concentrations (B > 0.025 M) an equilibrium is formed between $B(OH)_3$, polynuclear complexes of $B_3O_3(OH)_4^-$, $B_4O_5(OH)_4^{2-}$, $B_3O_3(OH)_5^{2-}$, $B_5O_6(OH)_4^-$ and $B(OH)_4^-$. In short: $B(OH)_3 \leftrightarrow$ polynuclear anions $\leftrightarrow B(OH)_4^-$. In acid solution at pH<5, boron is mainly present at $B(OH)_3$ and in alkaline solution at pH>12.5, boron is mainly present as $B(OH)_4^-$. At inbetween values (pH 5-12) polynuclear anions are found as well as $B(OH)_3$ and $B(OH)_4^-$. The dissociation constant depends upon temperature, ionic strength and presence of group I metal ions (Na, K, Cs). In the presence of metal ions (e.g. Na, Mg, Ca) ion-pair complexes are formed, which further reduce the undissociated boric acid concentration: $M^{n+} + B(OH)_4^- \leftrightarrow MB(OH)_4^{(n-1)+}$ These ion pair complexes are expected to be present in solutions of disodium tetraborate, disodium octaborate and buffered solutions of boric acid and boric oxide. Ingri N (1963)

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
XI, 7.17,	Viscosity	3.22	Not relevant	Solid substance
	Reactivity towards container material	3.18	Suitable container materials: Paper, Cardboard, Plastic (Polypropylene, High density polyethylene) Unsuitable container materials: Base metals	
	Thermal stability	3.19	Boric acid is stable up to approximately 75°C.	It dehydrates on further heating to form metaboric acid and then boric oxide: $B(OH)_3 = HBO_2 + H_2O$ (Temperature range 120 to 180°C) $HBO_2 = 0.5\ B_2O_3 + H_2O$ (Temperature range 180 to ~400°C). Boric oxide and metaboric acid will convert to boric acid on contact with water or on exposure to moist air. Rapid heating to ~250°C may cause boric acid to melt. During heating, a small quantity of boric acid can evaporate with the evolved water vapour. This will be visible as white fumes of condensed boric acid as the gas cools.

Table 1: Summary of physico- chemical properties for boric acid

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	White, crystalline, odourless solid	
VII, 7.2	Melting/freezing point	3.2	737°C	Cordia JA (2003)b
VII, 7.3	Boiling point	3.3	not required	Melting point is >300°C.
VII, 7.4	Relative density	3.4 density	$D^{23}_4 = 2.354 \pm 0.007$	Spruit WET (2005)
VII, 7.5	Vapour pressure	3.6	not required	Melting point is >300°C.
VII, 7.6	Surface tension	3.10	not applicable	Surface tension is not expected for inorganic substances.
VII, 7.7	Water solubility	3.8	27.0 ± 2.7 g/l at 20 ± 0.5°C Derived from studies with the pentahydrate and decahydrate	The water solubility for disodium tetraborate anhydrous as such cannot be determined because disodium tetraborate anhydrous is converted into boric acid/borate upon dissolution in water: $Na_2B_4O_7 + 7\ H_2O = 2\ NaB(OH)_4 + 2\ B(OH)_3$. The water solubility found will be the water solubility for boric acid in the presence of sodium ions. The water solubility for disodium tetraborate anhydrous is equal to an equivalent amount of disodium tetraborate pentahydrate or disodium tetraborate decahydrate. Cordia JA (2003)b and c
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	not required	Inorganic substance
VII, 7.9	Flash point	3.11	not required	Inorganic substance
VII, 7.10	Flammability	3.13	non-flammable	
VII, 7.11	Explosive properties	3.14	not explosive	The molecular structure of disodium tetraborate anhydrous does not indicate the presence of reactive or instable groups in the molecule. The molecular structure does not indicate that disodium tetraborate anhydrous will explode under the conditions of the test as described in Test Guideline A.14 of EC Directive 92/69/EEC.

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
VII, 7.12	Self-ignition temperature			
VII, 7.13	Oxidising properties	3.15	No oxidising properties	
VII, 7.14	Granulometry	3.5	D_{50} = 50 – 250 μm	Commercial boric acid products exist as granules or finer powders.
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	not required	Inorganic substance
XI, 7.16	Dissociation constant	3.21	Boric acid is a Lewis acid (hydroxide ion acceptor) rather than a Brønsted acid (proton donator). For this purpose the formula for boric acid is best written as $B(OH)_3$. pKa = 9.0 at 25 °C for boric acid in dilute solutions only (B ≤ 0.025 M). At higher boron concentrations, polynuclear complexes are formed and several dissociation/formation constants apply.	The dissociation constant for disodium tetraborate anhydrous as such cannot be determined because disodium tetraborate anhydrous is converted into boric acid/borate upon dissolution in water: $Na_2B_4O_7 + 7\ H_2O = 2\ NaB(OH)_4 + 2\ B(OH)_3$. The dissociation constant found will be the dissociation constant for boric acid in the presence of sodium ions. At low boron concentrations (B ≤ 0.025 M) the following equilibrium is found: $B(OH)_3 + 2H_2O \leftrightarrow B(OH)_4^- + H_3O^+$ with pKa = 9.0 at 25 °C In dilute aqueous solutions (B ≤ 0.025 M) boric acid exists as undissociated boric acid $B(OH)_3$ at pH < 7, at pH > 11 the metaborate ion $B(OH)_4^-$ becomes the main species in solution. At inbetween values (pH 7-11) both species are present. At higher boron concentrations (B > 0.025 M) an equilibrium is formed between $B(OH)_3$, polynuclear complexes of $B_3O_3(OH)_4^-$, $B_4O_5(OH)_4^{2-}$, $B_3O_3(OH)_5^{2-}$, $B_5O_6(OH)_4^-$ and $B(OH)_4^-$. In short: $B(OH)_3 \leftrightarrow$ polynuclear anions $\leftrightarrow B(OH)_4^-$. In acid solution at pH<5, boron is mainly present at $B(OH)_3$ and in alkaline solution at pH>12.5, boron is mainly present as $B(OH)_4^-$. At inbetween values (pH 5-12) polynuclear anions

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
				are found as well as $B(OH)_3$ and $B(OH)_4^-$. The dissociation constant depends upon temperature, ionic strength and presence of group I metal ions (Na, K, Cs). In the presence of metal ions (e.g. Na, Mg, Ca) ion-pair complexes are formed, which further reduce the undissociated boric acid concentration: $M^{n+} + B(OH)_4^- \leftrightarrow MB(OH)_4^{(n-1)+}$ These ion pair complexes are expected to be present in solutions of disodium tetraborate, disodium octaborate and buffered solutions of boric acid and boric oxide. Ingri N (1963)
XI, 7.17,	Viscosity	3.22	Not relevant	Solid substance
	Reactivity towards container material	3.18	Suitable container materials: Paper, Cardboard, Plastic (Polypropylene, High density polyethylene) Unsuitable container materials: Base metals	
	Thermal stability	3.19	Disodium tetraborate anhydrous is stable up to 524/527 °C. At this temperature a phase transition occurs. A melting point is found at 737°C.	Cordia JA (2003)b

Table 2: Summary of physico- chemical properties for disodium tetraborate anhydrous

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	White, crystalline, odourless solid	
VII, 7.2	Melting/freezing point	3.2	No melting point can be defined because of decomposition of the active substance.	When disodium tetraborate pentahydrate is heated, it gradually loses water of crystallisation, forming disodium tetraborate anhydrous, $Na_2B_4O_7$. An endothermal peak is observed at 131 °C, due to the loss of water. Due to a phase transition an exothermal peak is observed at 524/527°C. The crystal form of $Na_2B_4O_7$ melts at 737°C. Cordia JA (2003)b
VII, 7.3	Boiling point	3.3	not required	Melting point of disodium tetraborate anhydrous is >300°C.
VII, 7.4	Relative density	3.4 density	$D^{23}_4 = 1.860 \pm 0.008$	Cordia JA (2003)b
VII, 7.5	Vapour pressure	3.6	not required	Melting point of disodium tetraborate anhydrous is >300°C.
VII, 7.6	Surface tension	3.10	not applicable	Surface tension is not expected for inorganic substances.
VII, 7.7	Water solubility	3.8	40.06 ± 2.70 g/l at 20 ± 0.5°C	Cordia JA (2003)b
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	not required	Inorganic substance
VII, 7.9	Flash point	3.11	not required	Inorganic substance
VII, 7.10	Flammability	3.13	non-flammable	
VII, 7.11	Explosive properties	3.14	not explosive	The molecular structure of disodium tetraborate pentahydrate does not indicate the presence of reactive or instable groups in the molecule. The molecular structure does not indicate that disodium tetraborate anhydrous will explode under the conditions of the test as described in Test Guideline A.14 of EC Directive 92/69/EEC.
VII, 7.12	Self-ignition temperature			

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
VII, 7.13	Oxidising properties	3.15	No oxidising properties	
VII, 7.14	Granulometry	3.5	D_{50} = 50 – 250 µm	Commercial boric acid products exist as granules or finer powders.
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	not required	Inorganic substance
XI, 7.16	Dissociation constant	3.21	Boric acid is a Lewis acid (hydroxide ion acceptor) rather than a Brønsted acid (proton donator). For this purpose the formula for boric acid is best written as $B(OH)_3$. pKa = 9.0 at 25 °C for boric acid in dilute solutions only (B ≤ 0.025 M). At higher boron concentrations, polynuclear complexes are formed and several dissociation/formation constants apply.	The dissociation constant for disodium tetraborate pentahydrate as such cannot be determined because disodium tetraborate pentahydrate is converted into boric acid/borate upon dissolution in water: $Na_2B_4O_7.5H_2O + 2\ H_2O = 2\ NaB(OH)_4 + 2\ B(OH)_3$. The dissociation constant found will be the dissociation constant for boric acid in the presence of sodium ions. At low boron concentrations (B ≤ 0.025 M) the following equilibrium is found: $B(OH)_3 + 2H_2O \leftrightarrow B(OH)_4^- + H_3O^+$ with pKa = 9.0 at 25 °C In dilute aqueous solutions (B ≤ 0.025 M) boric acid exists as undissociated boric acid $B(OH)_3$ at pH < 7, at pH > 11 the metaborate ion $B(OH)_4^-$ becomes the main species in solution. At inbetween values (pH 7-11) both species are present. At higher boron concentrations (B > 0.025 M) an equilibrium is formed between $B(OH)_3$, polynuclear complexes of $B_3O_3(OH)_4^-$, $B_4O_5(OH)_4^{2-}$, $B_3O_3(OH)_5^{2-}$, $B_5O_6(OH)_4^-$ and $B(OH)_4^-$. In short: $B(OH)_3 \leftrightarrow$ polynuclear anions $\leftrightarrow B(OH)_4^-$. In acid solution at pH<5, boron is mainly present at $B(OH)_3$ and in alkaline solution at pH>12.5, boron is mainly present as $B(OH)_4^-$. At inbetween values (pH 5-12) polynuclear anions are found as well as $B(OH)_3$ and $B(OH)_4^-$. The dissociation constant depends upon temperature, ionic strength and presence of group I metal ions (Na, K, Cs). In the presence of metal ions (e.g. Na, Mg, Ca) ion-pair complexes are formed, which further reduce the undissociated boric acid concentration: $M^{n+} + B(OH)_4^- \leftrightarrow MB(OH)_4^{(n-1)+}$ These ion pair complexes are expected to be present in solutions of disodium tetraborate,

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
				disodium octaborate and buffered solutions of boric acid and boric oxide. Ingri N (1963)
XI, 7.17,	Viscosity	3.22	Not relevant	Solid substance
	Reactivity towards container material	3.18	Suitable container materials: Paper, Cardboard, Plastic (Polypropylene, High density polyethylene) Unsuitable container materials: Base metals	
	Thermal stability	3.19	Disodium tetraborate pentahydrate is stable up to 131°C.	At this temperature water of crystallisation is lost to form disodium tetraborate anhydrous. Cordia JA (2003)b

Table 3: Summary of physico- chemical properties for disodium tetraborate pentahydrate

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	White, crystalline, odourless solid	
VII, 7.2	Melting/freezing point	3.2	No melting point detected below 1000°C.	Cordia JA (2003)c
VII, 7.3	Boiling point	3.3	not required	Melting point of disodium tetraborate anhydrous is >300°C.
VII, 7.4	Relative density	3.4 density	$D^{23}_4 = 1.74 \pm 0.01$	Cordia JA (2003)c
VII, 7.5	Vapour pressure	3.6	not required	Melting point of disodium tetraborate anhydrous is >300°C.
VII, 7.6	Surface tension	3.10	not applicable	Surface tension is not expected for inorganic substances.
VII, 7.7	Water solubility	3.8	49.74 ± 3.63 g/l at 20 ± 0.5°C	Cordia JA (2003)c
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	not required	Inorganic substance
VII, 7.9	Flash point	3.11	not required	Inorganic substance
VII, 7.10	Flammability	3.13	non-flammable	
VII, 7.11	Explosive properties	3.14	not explosive	The molecular structure of disodium tetraborate pentahydrate does not indicate the presence of reactive or instable groups in the molecule. The molecular structure does not indicate that disodium tetraborate anhydrous will explode under the conditions of the test as described in Test Guideline A.14 of EC Directive 92/69/EEC.
VII, 7.12	Self-ignition temperature			
VII, 7.13	Oxidising properties	3.15	No oxidising properties	
VII, 7.14	Granulometry	3.5	$D_{50} = 50 – 250$ µm	Commercial boric acid products exist as granules or finer powders.
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	not required	Inorganic substance

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
XI, 7.16	Dissociation constant	3.21	Boric acid is a Lewis acid (hydroxide ion acceptor) rather than a Brønsted acid (proton donator). For this purpose the formula for boric acid is best written as $B(OH)_3$. pKa = 9.0 at 25 °C for boric acid in dilute solutions only (B ≤ 0.025 M). At higher boron concentrations, polynuclear complexes are formed and several dissociation/formation constants apply.	The dissociation constant for disodium tetraborate decahydrate as such cannot be determined because disodium tetraborate decahydrate is converted into boric acid/borate upon dissolution in water: $Na_2B_4O_7.10H_2O = 2\ NaB(OH)_4 + 2\ B(OH)_3 + 3H_2O$. The dissociation constant found will be the dissociation constant for boric acid in the presence of sodium ions. At low boron concentrations (B ≤ 0.025 M) the following equilibrium is found: $B(OH)_3 + 2H_2O \leftrightarrow B(OH)_4^- + H_3O^+$ with pKa = 9.0 at 25 °C In dilute aqueous solutions (B ≤ 0.025 M) boric acid exists as undissociated boric acid $B(OH)_3$ at pH < 7, at pH > 11 the metaborate ion $B(OH)_4^-$ becomes the main species in solution. At inbetween values (pH 7-11) both species are present. At higher boron concentrations (B > 0.025 M) an equilibrium is formed between $B(OH)_3$, polynuclear complexes of $B_3O_3(OH)_4^-$, $B_4O_5(OH)_4^{2-}$, $B_3O_3(OH)_5^{2-}$, $B_5O_6(OH)_4^-$ and $B(OH)_4^-$. In short: $B(OH)_3 \leftrightarrow$ polynuclear anions $\leftrightarrow B(OH)_4^-$. In acid solution at pH<5, boron is mainly present at $B(OH)_3$ and in alkaline solution at pH>12.5, boron is mainly present as $B(OH)_4^-$. At inbetween values (pH 5-12) polynuclear anions are found as well as $B(OH)_3$ and $B(OH)_4^-$. The dissociation constant depends upon temperature, ionic strength and presence of group I metal ions (Na, K, Cs). In the presence of metal ions (e.g. Na, Mg, Ca) ion-pair complexes are formed, which further reduce the undissociated boric acid concentration: $M^{n+} + B(OH)_4^- \leftrightarrow MB(OH)_4^{(n-1)+}$ These ion pair complexes are expected to be present in solutions of disodium tetraborate, disodium octaborate and buffered solutions of boric acid and boric oxide. Ingri N (1963)
XI, 7.17,	Viscosity	3.22	Not relevant	Solid substance
	Reactivity towards container material	3.18	Suitable container materials: Paper, Cardboard, Plastic (Polypropylene, High	

REACH ref Annex, §	Property	IUCLID section	Value	Comment / Reference
			density polyethylene) Unsuitable container materials: Base metals	
	Thermal stability	3.19	Disodium tetraborate decahydrate is stable up to 47/48°C when water of crystallization is lost to form disodium tetraborate pentahydrate.	Cordia JA (2003)c

Table 4: Summary of physico- chemical properties for disodium tetraborate decahydrate

For comparative purposes, exposures to borates are often expressed in terms of boron (B) equivalents based on the fraction of boron in the source substance on a molecular weight basis. Conversion factors are given in Table 5 below. The B equivalents used are a generic designation rather than a designation of the element boron. As noted previously, only the boric acid and borate ion are present at environmentally and physiologically relevant concentrations, so presentation of concentrations as boron equivalents is appropriate.

		Conversion factor for equivalent dose of B
Boric acid	H_3BO_3	0.1748
Disodium tetraborate anhydrous	$Na_2B_4O_7$	0.2149
Disodium tetraborate pentahydrate	$Na_2B_4O_7 \bullet 5H_2O$	0.1484
Disodium tetraborate decahydrate	$Na_2B_4O_7 \bullet 10H_2O$	0.1134

Table 5: Conversion factors to boron equivalents

2 MANUFACTURE AND USES

2.1 Manufacture

The majority of boric acid is manufactured by reacting inorganic borate minerals with sulphuric acid in an aqueous solution. Sodium borate minerals are the principle source in the US and calcium borates are the principle source in Turkey. Borax pentahydrate and decahydrate are manufactured by dissolving the sodium borate minerals in hot liquor and recrystallising. The anhydrous form is then produced from its hydrated forms. There are no European primary manufacturers of boric acid or the disodium tetraborates.

2.2 Identified uses

Borates are used in several important industries in Europe – including the glass, ceramics, detergents, wood treatment and insulation fiberglass industries. Borates are particularly versatile, have a multitude of different properties and are used in a variety of different products and processes. There are more than 140 different types of end-use applications, ranging from use in diverse articles and products such as adhesives, brake fluids, cosmetics, hygienic powders, fabrics, matches, ink, motor oil, waxes, starch, paper, plaster, fire retardants, wood preservatives, photographic solutions *etc*. Boric acid and other borates are also used in a range of consumer products including cosmetic and personal care products and also in detergents. Moreover, borates are essential for all plants – their use as fertilizers increases crop yields (including grapes, potatoes, sugar beets, alfalfa and olives) and quality.

Borates may not constitute a large proportion of a particular product but often they are an indispensable component. In many cases there may not be an appropriate substitute for them, either in terms of performance or cost. The various different functions of borates is summarized below:

The major uses of borates in Europe are for insulation and textile fibreglass (34%), frit and glazes for ceramics (23%), cleaning and bleaching (12%) and borosilicate glass (7%), (CEH, 2003), with smaller markets in metal and alloy manufacture, agriculture, flame retardants and biocides.

An anthropogenic source of boron in the environment that is not associated with any boric acid or borate product is that associated with coal combustion products, such as fly ash and bottom ash. These materials may be land-applied or land-filled and contain relatively high boron concentrations (several thousand mg/kg, Schwab et al. 1991).

2.2.1 Detergents and Cleaners

Many different forms of borates are used to produce laundry detergents, household or industrial cleaners and personal care products. In these applications, borates' unique properties serve to enhance stain removal and bleaching, stabilize enzymes, provide alkaline buffering, soften water and boost surfactant performance.

Because borates act as a biostat, they also serve to control bacteria and fungi in personal care products. The vast majority of clothes worn in the world are still washed by hand. New trials on laundry soap bars demonstrate that borates significantly improve the cleaning action, and reduce levels of dirt re-deposition, leading to brighter, cleaner clothes.

Product Uses	Boric Acid	Anhydrous borax	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Soaps			X Powder hand soap	
Liquid/Laundry Detergents			X	X Stabilizes Enzymes
Bleach				X Sodium Perborate Precursor
Cleaning Products				X
Additive (e.g. hand cleaners, polishes waxes, and industrial cleaning compounds)			X	X

2.2.2 Personal Care Products

Borates work in many personal care products such as cosmetic creams, skin lotions, hair shampoos, dyes and gels, eye drops, bath salts, and denture cleaners. Boric acid and borax are added to some liquid fabric detergents up to 2% concentration to stabilise the protease and other enzymes in the formulation. Boric acid and disodium tetraborate decahydrate are also used at concentrations of 5% in cosmetics in the US and in talc in Europe; up to 3% in other cosmetics in Europe; and up to 0.5% in oral hygiene products in Europe and elsewhere (Beyer et al., 1983; EC, 2000). Historically in Europe, borates were used to manufacture sodium perborate for the detergent market. This application has virtually disappeared, however.

Products	Boric Acid	Anhydrous borax	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Cosmetics	X		X Lotions, creams & ointments	
Toiletries	X		X	
Pharmaceuticals	X		X	

2.2.3 Glass and Glass Fibers

Fiberglass:

Borates are an important ingredient in both insulation fiberglass - which represents the largest single use of borates worldwide - and textile fiberglass, used in everything from circuit boards to surfboards. In both products, borates act as a powerful flux and lower glass batch melting temperatures.

They also control the relationship between temperature, viscosity and surface tension to create optimal glass fiberization. The end result is strong fibers that are biosoluble, and resistant to water and chemical attack. Insulation fiberglass works by trapping air within its mesh of fibers to prevent heat loss. Borates in the glass fibers also absorb more infrared radiation, adding to their insulation performance.

Glass:

Borosilicate glass is the foundation for all heat-resistant glass applications and the myriad products they make possible - from halogen lightbulbs and Pyrex® cookware to cathode-ray tubes and liquid crystal displays.

Borosilicate refers to glass which contains from five to 30 percent boric oxide. Borates impart many valuable properties to borosilicate glass, from their ability to lower melt temperatures and inhibit devitrification in the glassmaking process, to their ability to increase mechanical strength, as well as resistance to thermal shock, chemicals and water in the final product.

Products	Boric Acid	Anhydrous borax	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Insulation & Textile Fiber Glass	X			X
Borosilicate Glass	X			X
Refractories			X Used as stabilizer & bonding agent that gives intermediate-temperature glassy bond. Frequently volatilizes from system.	

2.2.4 Ceramics

Borates have been an essential ingredient in ceramic glazes for centuries, and are gaining acceptance as an equally essential ingredient in ceramic tile bodies where they allow manufacturers to use a wider range of clays, heighten productivity and decrease energy usage.

Glazes and enamels are the thin, glassy coatings fused onto ceramics and metals in tiles, tableware, bone china, porcelain, pots and pans, and household appliances. Borates are used to initiate glass

formation and reduce glass viscosity, helping to form a smooth surface; and to reduce thermal expansion, facilitating a good fit between the glaze or enamel and the item it covers. Borates in glazes and enamels also increase the refractive index, or luster; enhance durability and resistance to chemicals; and help dissolve coloring agents.

Products	Boric Acid	Anhydrous borax	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Glaze & Enamel	X			X
Frits	X			

2.2.5 Metallurgy

Borates are used in the production of steel and non-ferrous metals, alloys, rare earth magnets, amorphous metals, welding fluxes and plating compounds.

Products	Boric Acid	Anhydrous borax	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Steel & non-ferrous metal production (Flux agent)	X Prevents oxidation of metal surfaces		X	X
Precious metal recovery				
Welding, brazing & soldering fluxes	X			
Amorphous metals				
Plating	X			

2.2.6 Industrial Fluids

Borates are well established and widely used in the manufacturing of industrial fluids such as antifreezes, lubricants, brake fluids, metalworking fluids, water treatment chemicals and fuel additives.

Products	Boric Acid	Anhydrous borax	Borax Decahydrate	Borax Pentahydrate

			(10 mol)	(5 mol)
Metal working fluids	X			X
Anti-freeze (engine coolant)				
Lubricants			X Also used in dry powdered lubricants	X Also used in dry powdered lubricants
Brake fluids				
Water treatment chemicals	X		X	X
Fuel additives	X			

2.2.7 Adhesives

Starch is a natural polymeric product and is found in almost every plant. Today, the principal sources of most commercial starches are maize, potato, tapioca and wheat. Adhesives derived from starch can be significantly improved by borate additives to achieve increased viscosity, quicker tack, and better fluid properties.

Products	Boric Acid	Anhydrous borax	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Starch Adhesive Formulation (corrugated Paper & Paperboard)	X		X	X
Casein and dextrin based adhesive	X		X	X

2.2.8 Flame Retardant

Cellulose, the basis of wood, cotton, and most other plant-derived raw materials, is in widespread industrial use but is inherently flammable in many of its forms – paper being a typical example. The use of borates in cellulose materials imparts flame retardancy, enabling them to meet stringent safety standards and regulations.

Products	Boric Acid	Anhydrous borax	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Wood products	X			
Cellulose Insulation	X		X	X
Cotton batting in mattresses/futons	X			
Fabrics	X			
Paper	X			

2.2.9 Biocides

Borate treatment for wood is used as a long-lasting protection against wood destroying organisms. There are several types of borate wood preservatives used to treat solid wood, engineered wood composites and other interior building products like studs, plywood, joists and rafters.

Products	Boric Acid	Anhydrous borax	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Wood preservative	X			
Non-professional remedial products	X			
Professional remedial products	X			

2.2.10 Agriculture

Boron is an essential micronutrient for plants, vital to their growth and development. Without sufficient boron, plant fertilization, seeding and fruiting are not possible.

On every continent of the world, crop yields and food quality are diminished due to insufficient boron concentrations in the soil. These deficiencies can be corrected with borate fertilizers, produced to meet farmers' varied needs and application methods. In areas of acute deficiency, borates can increase crop yields by 30 to 40 percent. Boron applications have been document for 132 crops in over 80 countries (Shorrocks, 1997)

Products	Boric Acid	Anhydrous borax	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Fertilizer	X		X	X

2.3 Uses advised against

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

This should include the classification (including specific concentration limits) listed in Annex I of Directive 67/548/EEC (including the Index Number)

Boric acid and disodium tetraborate anhydrous, pentahydrate and decahydrate are currently unclassified according to Directive 67/548/EEC. These substances have been proposed for classification as part of the 30th Adaptation to Technical Progress (ATP) of Directive 67/548/EEC.

Boric acid – Repr. Cat 2; R60-61 with specific concentration limit of ≥ 5.5%
Disodium tetraborate anhydrous – Repr. Cat 2, R60-61, specific concentration limit of ≥ 4.5%
Disodium tetraborate pentahydrate – Repr. Cat 2, R60-61, specific concentration limit of ≥ 6.5%
Disodium tetraborate decahydrate – Repr. Cat 2, R60-61, specific concentration limit of ≥ 8.5%
The adoption of the 30th ATP is on hold pending a response by the Commission to the World Trade Organisation's Technical Barriers to Trade committee.[5]

3.2 Self classification(s)

This should include the classification, the labelling and the specific concentrations limits. The reason and justification for no classification should be reported here.

It should be stated whether the classification is made according to Directive 67/548/EEC criteria or according to GHS criteria.

[5] Joint Research Centre Follow-up I of the meeting of the Technical Committee on Classification and Labelling in Arona, 26-28 September 2007, Ispra 8th October 2007.

4 ENVIRONMENTAL FATE PROPERTIES

4.1 Degradation

4.1.1 Stability

Corresponds to IUCLID 4.1

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

4.1.2.2 Screening tests

4.1.2.3 Simulation tests

4.1.3 Summary and discussion of persistence

4.2 Environmental distribution

4.2.1 Adsorption/desorption

Corresponds to IUCLID 4.4.1

4.2.2 Volatilisation

Corresponds to IUCLID 4.4.2

4.2.3 Distribution modelling

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

4.3.1.2 Measured bioaccumulation data

4.3.2 Terrestrial bioaccumulation

4.3.3 Summary and discussion of bioaccumulation

4.4 Secondary poisoning

Assessment of the potential for secondary poisoning

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

5.2.2 Acute toxicity: inhalation

5.2.3 Acute toxicity: dermal

5.2.4 Acute toxicity: other routes

5.2.5 Summary and discussion of acute toxicity

C&L including weight-of-evidence considerations.

5.3 Irritation

5.3.1 Skin

5.3.2 Eye

5.3.3 Respiratory tract

5.3.4 Summary and discussion of irritation

C&L including weight-of-evidence considerations.

5.4 Corrosivity

5.5 Sensitisation

5.5.1 Skin

5.5.2 Respiratory system

5.5.3 Summary and discussion of sensitisation

C&L including weight-of-evidence considerations.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

5.6.2 Repeated dose toxicity: inhalation

5.6.3 Repeated dose toxicity: dermal

5.6.4 Other relevant information

5.6.5 Summary and discussion of repeated dose toxicity:

C&L, dose-response estimation including weight-of-evidence considerations.

5.7 Mutagenicity

5.7.1 In vitro data

5.7.2 In vivo data

5.7.3 Human data

5.7.4 Other relevant information

5.7.5 Summary and discussion of mutagenicity

C&L, dose-response estimation including weight-of-evidence considerations.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

5.8.2 Carcinogenicity: inhalation

5.8.3 Carcinogenicity: dermal

5.8.4 Carcinogenicity: human data

5.8.5 Other relevant information

5.8.6 Summary and discussion of carcinogenicity

C&L, dose-response estimation including weight-of-evidence considerations.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

5.9.2 Developmental toxicity

5.9.3 Human data

5.9.4 Other relevant information

5.9.5 Summary and discussion of reproductive toxicity

C&L, dose-response estimation including weight-of-evidence considerations.

5.10 Other effects

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

5.11.1 Overview of typical dose descriptors for all endpoints

5.11.2 Correction of dose descriptors if needed (for example route-to-route extrapolation)

5.11.3 Application of assessment factors

5.11.4 Selection/ identification of the critical DNEL(s)/ the leading health effect

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

Including C&L

6.2 Flammability

Including C&L

6.3 Oxidising potential

Including C&L

7 ENVIRONMENTAL HAZARD ASSESSMENT

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Short-term toxicity to fish

Long-term toxicity to fish

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Long-term toxicity to aquatic invertebrates

7.1.1.3 Algae and aquatic plants

7.1.1.4 Sediment organisms

7.1.1.5 Other aquatic organisms

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

7.1.2.1 PNEC water

7.1.2.2 PNEC sediment

7.2 Terrestrial compartment

7.2.1 Toxicity test results

7.2.1.1 Toxicity to soil macro organisms

7.2.1.2 Toxicity to terrestrial plants

7.2.1.3 Toxicity to soil micro-organisms

7.2.1.4 Toxicity to other terrestrial organisms

Toxicity to birds

Toxicity to other above ground organisms

7.2.2 Calculation of Predicted No Effect Concentration (PNEC_soil)

7.3 Atmospheric compartment

7.4 Microbiological activity in sewage treatment systems

7.4.1 Toxicity to aquatic micro-organisms

7.4.2 PNEC for sewage treatment plant

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

7.6 Conclusion on the environmental classification and labelling

8 PBT AND VPVB ASSESSMENT

8.1 Comparison with criteria from annex XIII

8.2 Assessment of substances of an equivalent level of concern

8.3 Emission characterisation

8.4 Conclusion of PBT and vPvB assessment

9 EXPOSURE ASSESSMENT

9.1 General discussion on releases and exposure

9.1.1 Summary of the existing legal requirements

9.1.2 Summary of the effectiveness of the implemented risk management measures

9.2 Manufacturing

9.2.1 Occupational exposure

9.2.2 Environmental release

9.3 "Use 1"

For each use include such a sub-chapter. Subsequently, if there is another "Use 2" this will lead to sub-chapter 9.4 "Use 1" including 9.4.1 Human exposure, 9.4.1.1 Occupational exposure, 7.4.1.2 Consumer exposure and 9.4.2 Environmental release. The other sub-chapters will then be renumbered.

9.3.1 Human exposure

9.3.1.1 Occupational exposure

9.3.1.2 Consumer exposure

9.3.2 Environmental release

9.4 Other sources (for example natural sources)

9.4.1 Human exposure

9.4.1.1 Occupational exposure

9.4.1.2 Consumer exposure

9.4.2 Environmental release

9.5 Environmental exposure assessment

9.5.1 Summary of emissions

9.5.2 Predicted environmental concentrations

9.5.2.1 Regional concentrations

Atmosphere

Aquatic compartment

Sediment

Soil compartment

9.5.2.2 Local concentrations

Atmosphere

Aquatic compartment

Sediment

Soil compartment

9.5.2.3 Exposure concentrations of man via the environment

9.5.3 Measured levels

Atmosphere

Aquatic compartment

Sediment

Soil compartment

Secondary poisoning

9.5.4 Selected environmental concentrations of risk characterisation

Atmosphere

Aquatic compartment

Sediment

Soil compartment

Secondary poisoning

9.6 Combined human exposure assessment

10 RISK CHARACTERISATION

10.1 Human health

10.1.1 Workers

10.1.2 Consumers

10.1.3 Indirect exposure of humans via the environment

10.1.4 Combined exposures

10.2 Environment

10.2.1 Aquatic compartment (including sediment and sewage treatment plant and secondary poisoning)

10.2.2 Terrestrial compartment (including secondary poisoning)

10.2.3 Atmospheric compartment

10.2.4 Microbiological activity in sewage treatment systems

OTHER INFORMATION

It is suggested to include here information on any consultation which took place during the development of the dossier. This could indicate who was consulted and by what means, what comments (if any) were received and how these were dealt with. The data sources (e.g registration dossiers, other published sources) used for the dossier could also be indicated here.

REFERENCES

[click to insert references classed alphabetically by author. For details on referencing, see explanatory note]

ANNEX

[click here to insert text, or delete heading as appropriate]

Figure 1 vbvnbv

Example 1 hff

Hgkhjfkg

DRAFT of 19 October 2007

SUBSTANCE EVALUATION REPORT

Substance Name:	**Boric Acid**	**Borax decahydrate**
EC Number:	**233-139-2**	**215-540-4**
CAS Number:	**10043-35-3**	**1303-96-4**

Rapporteur Member State : **Austria**

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FIGURES

EXAMPLES

CONCLUSION OF THE SUBSTANCE EVALUATION

Substance Name:

EC Number:

CAS number:

Registration dossiers numbers:

Conclusion of the substance evaluation:

INFORMATION ON HAZARD AND RISKS

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

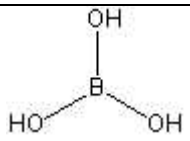
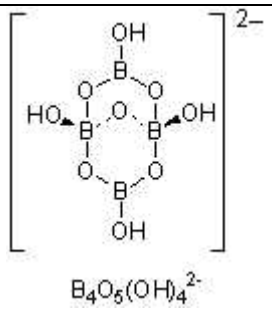
1.1 Name and other identifiers of the substance

Boric acid (H_3BO_3), borax ($Na_2B_4O_7.10H_2O$) and borax pentahydrate (($Na_2B_4O_7.5H_2O$) are commercial products used in production of numerous products. Boric acid (Orthoboric acid) exists in nature as the mineral sassolite. It is a white crystalline material; its solubility in water increases rapidly with temperature and is a weak acid. Borax decahydrate (disodium tetraborate decahydrate) exists in nature as the mineral tincal. Borax is readily soluble in water and the pH of a borax solution increases slightly with increasing concentration and drops slightly with increasing temperature. Substance identification is contained in Table 1.

Table 1: Substance Identification

	Boric Acid	**Borax**
CAS No	10043-35-3	1303-96-4
EINECS No	233-139-2	215-540-4[1]
IUPAC Name	ortho-boric acid: boric acid	Disodium tetraborate decahydrate
Synonyms	ortho boric acid, boracic acid and boric acid	Borax; Sodium tetraborate dechydrate; Borax decahydrate; sodium biborate decahydrate; sodium pyroborate decahydrate; Boron sodium oxide (B4Na2O7), decahydrate; Boric acid (H2B4O7), disodium salt decahydrate
Molecular Formula	H_3BO_3	$Na_2B_4O_7 \bullet 10H_2O$

[1] Listed in EINECS (European Inventory of Existing Commercial Chemical Substance) under the anhydrous form of sodium tetraborate.

Structural Formula		
Molecular Weight	61.83	381.37

Chemical Name:

EC Name:

CAS Number:

IUPAC Name:

1.2 Composition of the substance

For each constituent/ impurity/ additive, fill in the following table (which should be repeated in case of more than one constituent). The information is particularly important for the main constituent(s) and for the constituents (or impurity) which influence the outcome of the dossier.

MOLECULAR DESCRIPTION/MACRO-MOLECULAR DESCRIPTION (PHYSICAL STATE/PARTICLE SIZE)

Boric acid crystallises as white waxy plates (triclinic system). At the molecular level, boric acid consists of triangular $B(OH)_3$ molecules as depicted in the structural formula diagram above. In the solid state these molecules assemble into planar sheets held together by hydrogen bonding. The stacking pattern of these molecular layers is completely disordered, indicating that rather weak van der Waals forces are operating. The layers are 3.18A apart. This arrangement accounts for the slippery feel of boric acid, and the cleavage planes observed in boric acid crystals. The acidic behaviour is due to the molecule being a base acceptor, rather than a proton donor. Commercial boric acid products exist as granules or finer powders and are stable under normal conditions. Particle sizes in commercial products tend to be in the range of d_{50} = 50µm - 250µm.

Borax decahydrate is a white, free-flowing crystalline material, in the monoclinic system. In the crystal, the polyborate ion has the structure depicted in the structural formula above. The sodium ions exist in two crystallographically unique positions, each being octahedrally coordinated by water molecules. These octahedra share edges to form chains that cross-link the polyborate ions to form parallel sheets. A network of hydrogen bonds integrates these sheets. There are eight moles of the water of crystallisation, and two moles of water exist as hydroxyl groups. Commercial borax decahydrate products exist as crystalline granular or powder materials; particle sizes typically no greater than 2000µm, with a d_{50} = 50µm - 250µm.

Boric acid, borax decahydrate, and related borates are moderately soluble in water (see Table 2 below). The chemical species present in solution depend on concentration and pH. At concentrations below 0.025 M, essentially only mononuclear species $B(OH)_3$ and $B(OH)_4^-$ are present[2] (Cotton and Wilkinson, 1988). The relative proportion of $B(OH)_3$ and $B(OH)_4^-$ is controlled by pH, reflecting the pK_a of 9.2. Polyborate structures, such as in borax decahydrate, depolymerise rapidly in solution. Therefore, at physiologically relevant concentrations, only the boric acid and borate ion are present (Power and Woods, 1997). In dilute aqueous solutions and physiological conditions the predominant species present is undissociated boric acid (de Vette et al. 2001).

1.3 PHYSICO-CHEMICAL DATA

Table 2: Physico-chemical data for boric acid

Boric acid **CAS NO 10043-35-3**		
	Results/remarks	**Ref.**
Macro-molecular description	White crystalline solid	
Molecular Weight	61.83	
Melting and Boiling Points	Not applicable. If heated above above 100 °C it looses water and is converted to metaboric acid and, on further heating, it is converted to boric oxide.	Mellor 1980
Vapour Pressure	9.9×10^{-6} Pa @ 25 °C	Tremain, 1998
Octanol-water Partition Coefficient (Log Pow)	-1.09 @ 22 ± 1 °C	Cordia, 2003a
Water Solubility	49.20 g/l @ 20± 0.5 °C	Cordia, 2003°
K_{oc} - soil	62 to 438	deVette et al. 2000
K_{oc} - sediment	68 to 120	Hanstveit et al. 2001
Density D 23/4	1.489	Cordia, 2003a
Viscosity	Not relevant	
pH-Value	4.05 @ 20 °C at a concentration of 32.969 g/l	Cordia, 2003°
pK_a	9.15 @ 20 °C	Dawber and Matusin, 1982
Oxidation	No oxidising properties	

Table 3: Physico-chemical data for borax

[2] A 0.025 M solution of boric acid is equivalent to about 1500 mg-Boric acid/L, or about 270 mg-B/L.

Borax **CAS NO 1303-96-4 EINECs No 214-540-4**		
	Results/remarks	**Ref.**
Macro-molecular description	White crystalline solid	
Molecular Weight	381.37	
Melting Point and boiling Point	Not applicable. Dehydrates on heating above 50 ^{o}C to pentahydrate and then to anhydrous borax. Anhydrous borax melts at 742 ^{o}C.	Mellor 1980
Vapour Pressure	Negligible @ 20^{o}C	Based on data for boric acid
Octanol-water Partition Coefficient (Log Pow)	-1.53 @ 22 ± 1 ^{o}C	Cordia, 2003b
Water Solubility	49.74 ± 3.63 @ 20 ± 0.5 ^{o}C	Cordia, 2003b
K_{oc}	See boric acid	
Density D23/4	1.742	Cordia, 2003b
Viscosity	Not relevant	
pH-Value	9.32 at concentration of 40.004 g/l	Cordia, 2003b
pK_a		
Oxidation	No oxidising properties	

For comparative purposes, exposures to borates are often expressed in terms of boron (B) equivalents based on the fraction of boron in the source substance on a molecular weight basis. Conversion factors are given in Table 4 below. The B equivalents used are a generic designation rather than a designation of the element boron. As noted previously, only the boric acid and borate ion are present at environmentally and physiologically relevant concentrations, so presentation of concentrations as boron equivalents is appropriate.

Table 4: Conversion factors to Boron Equivalents

		Conversion factor for Equivalent dose of B
Boric acid	H_3BO_3	0.1748
Disodium tetraborate decahydrate	$Na_2B_4O_7 \bullet 10H_2O$	0.1134
Disodium tetraborate pentahydrate	$Na_2B_4O_7 \bullet 5H_2O$	0.1484

Chemical Name:

EC Number:

CAS Number:

IUPAC Name:

Molecular Formula:

Structural Formula:

Molecular Weight:

Typical concentration (% w/w):

Concentration range (% w/w):

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1		
VII, 7.2	Melting/freezing point	3.2		
VII, 7.3	Boiling point	3.3		
VII, 7.4	Relative density	3.4 density		
VII, 7.5	Vapour pressure	3.6		
VII, 7.6	Surface tension	3.10		
VII, 7.7	Water solubility	3.8		
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	-1.09	Cordia, 2003a
VII, 7.9	Flash point	3.11		
VII, 7.10	Flammability	3.13		
VII, 7.11	Explosive properties	3.14		
VII, 7.12	Self-ignition temperature			
VII, 7.13	Oxidising properties	3.15		
VII, 7.14	Granulometry	3.5		
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17		
XI, 7.16	Dissociation constant	3.21		
XI, 7.17,	Viscosity	3.22		
	Auto flammability	3.12		
	Reactivity towards container material	3.18		
	Thermal stability	3.19		
	[enter other property or delete row]			

Table 1: Summary of physico- chemical properties

2 MANUFACTURE AND USES

2.1 Manufacture

The majority of boric acid is manufactured by reacting inorganic borate minerals with sulphuric acid in an aqueous solution. Sodium borates are the principle source in the US and calcium borates are the principle source in Turkey. Borax decahydrate is manufactured by dissolving the sodium borate mineral in hot liquor and recrystalizing. There are no European primary manufacturers of boric acid or borax.

2.2 Identified uses[3]

Borates are used in several important industries in Europe – including the glass, ceramics, detergents, wood treatment and insulation fiberglass industries. Borates are particularly versatile, have a multitude of different properties and are used in a variety of different products and processes. There are more than 140 different types of end-use applications, ranging from use in diverse articles and products such as adhesives, brake fluids, cosmetics, hygienic powders, fabrics, matches, ink, motor oil, waxes, starch, paper, plaster, fire retardants, wood preservatives, photographic solutions *etc*. Boric acid and other borates are also used in a range of consumer products including cosmetic and personal care products and also in detergents. Moreover, borates are essential for all plants – their use as fertilizers increases crop yields (including grapes, potatoes, sugar beets, alfalfa and olives) and quality.

Borates may not constitute a large proportion of a particular product but often they are an indispensable component. In many cases there may not be an appropriate substitute for them, either in terms of performance or cost. The various different functions of borates is summarized below:

The major uses of borates in Europe are for insulation and textile fibreglass (34%), frit and glazes for ceramics (23%), cleaning and bleaching (12%) and borosilicate glass (7%), (CEH, 2003), with smaller markets in metal and alloy manufacture, agriculture, flame retardants and biocides.

An anthropogenic source of boron in the environment that is not associated with any boric acid or borate product is that associated with coal combustion products, such as fly ash and bottom ash. These materials may be land-applied or land-filled and contain relatively high boron concentrations (several thousand mg/kg, Schwab et al. 1991).

2.2.1 Detergents and Cleaners

Many different forms of borates are used to produce laundry detergents, household or industrial cleaners and personal care products. In these applications, borates' unique properties serve to enhance stain removal and bleaching, stabilize enzymes, provide alkaline buffering, soften water and boost surfactant performance.

- [3] Austria comment: *Page 2: "Industrial inputs → Tonnage levels* are needed (uses)."
  Page 3: "**Concerning added boron concentration.** For each identified use (uses are missing in the draft) a PEC concentration has to be calculated. An added site-specific and use specific risk approach needs to be conducted; but this is missing."

  Response: Agree, information to be included; tonnage levels based on EBA values to be included as basis for quantitative exposure estimations for applications.

Because borates act as a biostat, they also serve to control bacteria and fungi in personal care products. The vast majority of clothes worn in the world are still washed by hand. New trials on laundry soap bars demonstrate that borates significantly improve the cleaning action, and reduce levels of dirt re-deposition, leading to brighter, cleaner clothes.

Product Uses	Boric Acid	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Soaps		X Powder hand soap	
Liquid/Laundry Detergents		X	X Stabilizes Enzymes
Bleach			X Sodium Perborate Precursor
Cleaning Products			X
Additive (e.g. hand cleaners, polishes waxes, and industrial cleaning compounds)		X	X

2.2.2 Personal Care Products

Borates work in many personal care products such as cosmetic creams, skin lotions, hair shampoos, dyes and gels, eye drops, bath salts, and denture cleaners. Boric acid and borax are added to some liquid fabric detergents up to 2% concentration to stabilise the protease and other enzymes in the formulation. Boric acid and disodium tetraborate decahydrate are also used at concentrations of 5% in cosmetics in the US and in talc in Europe; up to 3% in other cosmetics in Europe; and up to 0.5% in oral hygiene products in Europe and elsewhere (Beyer et al., 1983; EC, 2000). Historically in Europe, borates were used to manufacture sodium perborate for the detergent market. This application has virtually disappeared, however.

Products	Boric Acid	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Cosmetics	X	X Lotions, creams & ointments	
Toiletries	X	X	
Pharmaceuticals	X	X	

2.2.3 Glass and Glass Fibers

Fiberglass:

Borates are an important ingredient in both insulation fiberglass - which represents the largest single use of borates worldwide - and textile fiberglass, used in everything from circuit boards to surfboards. In both products, borates act as a powerful flux and lower glass batch melting temperatures.

They also control the relationship between temperature, viscosity and surface tension to create optimal glass fiberization. The end result is strong fibers that are biosoluble, and resistant to water and chemical attack. Insulation fiberglass works by trapping air within its mesh of fibers to prevent heat loss. Borates in the glass fibers also absorb more infrared radiation, adding to their insulation performance.

Glass:

Borosilicate glass is the foundation for all heat-resistant glass applications and the myriad products they make possible - from halogen lightbulbs and Pyrex® cookware to cathode-ray tubes and liquid crystal displays.

Borosilicate refers to glass which contains from five to 30 percent boric oxide. Borates impart many valuable properties to borosilicate glass, from their ability to lower melt temperatures and inhibit devitrification in the glassmaking process, to their ability to increase mechanical strength, as well as resistance to thermal shock, chemicals and water in the final product.

Products	Boric Acid	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Insulation & Textile Fiber Glass	X		X
Borosilicate Glass	X		X
Refractories		X Used as stabilizer & bonding agent that gives intermediate-temperature glassy bond. Frequently volatilizes from system.	

2.2.4 Ceramics

Borates have been an essential ingredient in ceramic glazes for centuries, and are gaining acceptance as an equally essential ingredient in ceramic tile bodies where they allow manufacturers to use a wider range of clays, heighten productivity and decrease energy usage.

Glazes and enamels are the thin, glassy coatings fused onto ceramics and metals in tiles, tableware, bone china, porcelain, pots and pans, and household appliances. Borates are used to initiate glass

formation and reduce glass viscosity, helping to form a smooth surface; and to reduce thermal expansion, facilitating a good fit between the glaze or enamel and the item it covers. Borates in glazes and enamels also increase the refractive index, or luster; enhance durability and resistance to chemicals; and help dissolve coloring agents.

Products	Boric Acid	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Glaze & Enamel	X		X
Frits	X		

2.2.5 Metallurgy

Borates are used in the production of steel and non-ferrous metals, alloys, rare earth magnets, amorphous metals, welding fluxes and plating compounds.

Products	Boric Acid	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Steel & non-ferrous metal production (Flux agent)	X Prevents oxidation of metal surfaces	X	X
Precious metal recovery			
Welding, brazing & soldering fluxes	X		
Amorphous metals			
Plating	X		

2.2.6 Industrial Fluids

Borates are well established and widely used in the manufacturing of industrial fluids such as antifreezes, lubricants, brake fluids, metalworking fluids, water treatment chemicals and fuel additives.

Products	Boric Acid	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)

Metal working fluids	X		X
Anti-freeze (engine coolant)			
Lubricants		X Also used in dry powdered lubricants	X Also used in dry powdered lubricants
Brake fluids			
Water treatment chemicals	X	X	X
Fuel additives	X		

2.2.7 Adhesives

Starch is a natural polymeric product and is found in almost every plant. Today, the principal sources of most commercial starches are maize, potato, tapioca and wheat. Adhesives derived from starch can be significantly improved by borate additives to achieve increased viscosity, quicker tack, and better fluid properties.

Products	Boric Acid	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Starch Adhesive Formulation (corrugated Paper & Paperboard)	X	X	X
Casein and dextrin based adhesive	X	X	X

2.2.8 Flame Retardant

Cellulose, the basis of wood, cotton, and most other plant-derived raw materials, is in widespread industrial use but is inherently flammable in many of its forms – paper being a typical example. The use of borates in cellulose materials imparts flame retardancy, enabling them to meet stringent safety standards and regulations.

Products	Boric Acid	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)

Wood products	X		
Cellulose Insulation	X	X	X
Cotton batting in mattresses/futons	X		
Fabrics	X		
Paper	X		

2.2.9 Biocides

Borate treatment for wood is used as a long-lasting protection against wood destroying organisms. There are several types of borate wood preservatives used to treat solid wood, engineered wood composites and other interior building products like studs, plywood, joists and rafters.

Products	Boric Acid	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)
Wood preservative	X		
Non-professional remedial products	X		
Professional remedial products	X		

2.2.10 Agriculture

Boron is an essential micronutrient for plants, vital to their growth and development. Without sufficient boron, plant fertilization, seeding and fruiting are not possible.

On every continent of the world, crop yields and food quality are diminished due to insufficient boron concentrations in the soil. These deficiencies can be corrected with borate fertilizers, produced to meet farmers' varied needs and application methods. In areas of acute deficiency, borates can increase crop yields by 30 to 40 percent. Boron applications have been document for 132 crops in over 80 countries (Shorrocks, 1997)

Products	Boric Acid	Borax Decahydrate (10 mol)	Borax Pentahydrate (5 mol)

Fertilizer	X	X	X

2.3 Uses advised against

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

This should include the classification (including specific concentration limits) listed in Annex I of Directive 67/548/EEC (including the Index Number)

3.2 Self classification(s)

This should include the classification, the labelling and the specific concentrations limits. The reason and justification for no classification should be reported here.

It should be stated whether the classification is made according to Directive 67/548/EEC criteria or according to GHS criteria.

4 ENVIRONMENTAL FATE PROPERTIES

Boron is ubiquitous and widely distributed in the environment in rocks, soil and water and is released into the environment primarily by weathering of rock and soil, volatilisation of sea water, and anthropogenic activity. It is estimated that 2 x 10^9 kg/year of boron is released into the environment through natural events (Park and Schlesinger, 2002). Boron mining for all uses is estimated to be about 3 to 4 x 10^8 kg/yr (Argust, 1998). The amount of boron mined is about equal to the amount generated by volcanoes to the atmosphere. Exposure to boric acid and borax from European applications must consequently be evaluated against background concentrations and natural flows.

Most anthropogenic boron in Europe originates from mines in Turkey and California. Ratios of the boron isotopes ^{11}B and ^{10}B provide a tool to distinguish locally-derived boron from anthropogenic boron, although this has not been widely done (Vengosh et al 1994, Chatelet and Gaillardet, 2005). ^{11}B separates preferentially into dissolved boron (ie boric acid), whereas ^{10}B is preferentially incorporated into solid phase (Vengosh et al 1994). The boron-11 isotope enrichment value (identified as $\delta^{11}B$) ranges from about 39‰in seawater, to about 0‰ in average continentual crust, to -0.9 to +10.2‰ in sodium borate minerals from Turkey and California (Vengosh et al 1994). The ratio has been used to identify anthropogenic boron fractions in surface waters (Chatelet and Gaillardet, 2005) and groundwaters (Vengosh et al. 1994, Kloppmann et al, 2005).

4.1 Degradation.

4.1.1 Stability

Boric acid, borax decahydrate, and inorganic borates (for example, boric acid, boric oxide, sodium metaborates, tetraborates and octaborates) are moderately soluble in water (see Section 1.3). The chemical species present in solution depend on concentration and pH.

At concentrations below 0.025 M ($B \leq 0.025$ M; 270 mg-B/L), essentially only mononuclear species $B(OH)_3$ and $B(OH)_4^-$ are present (Cotton and Wilkinson, 1988). The relative proportion of $B(OH)_3$ and $B(OH)_4^-$ is controlled by pH:

$B(OH)_3 + 2H_2O \leftrightarrow [B(OH)_4]^- + H_3O^+$ $\qquad pK_a = 9.0$ at 25 °C

In dilute aqueous solutions (<0.025 M), boric acid remains un-dissociated at pH < 7, whereas at pH > 11 the metaborate ion $[B(OH)_4]^-$ becomes the main species in solution. At pH values between 7 and 11, both species are present.

The dissolution to un-dissociated boric acid by all the borates was confirmed in the study by De Vette et al., 2001, who identified and compared the dissociation products of sodium borates (disodium tetraborate decahydrate and disodium octaborate tetrahydrate) and boric acid in dilute aqueous solutions. The data showed through Raman spectra that the predominant species present was un-dissociated boric acid.

At higher boron concentrations (B > 0.025 M) an equilibrium is formed between $B(OH)_3$, polynuclear complexes of $B_3O_3(OH)_4^-$, $B_4O_5(OH)_4^{2-}$, $B_3O_3(OH)_5^{2-}$, $B_5O_6(OH)_4^-$ and $B(OH)_4^-$. In short: $B(OH)_3 \leftrightarrow$ polynuclear anions $\leftrightarrow B(OH)_4^-$. In acid solution at pH < 5, boron is mainly present as $B(OH)_3$ and in alkaline solution at pH > 12.5, boron is mainly present as $B(OH)_4^-$. At pH values (pH 5-12) polynuclear anions are found as well as $B(OH)_3$ and $B(OH)_4^-$. Polyborate structures, such as in borax decahydrate, depolymerise rapidly in solution.

Therefore, at physiologically relevant concentrations, only the boric acid and borate ion are present (Power and Woods, 1997). In dilute aqueous solutions and physiological conditions the predominant species present is undissociated boric acid (de Vette et al. 2001). Consequently, consideration of boric acid addresses the relevant environmental stability properties for borates.

Hydrolysis

Boric acid is an inorganic compound and does not have any chemical bonds prone to hydrolysis. Hydrolysis is therefore not a relevant degradation pathway under environmentally relevant conditions.

Photolysis in water

Boric acid is an inorganic compound without any light absorption characteristics in dilute solutions. It is therefore unlikely that the concentration of boric acid in water is influenced by light. Boric acid is therefore considered to be resistant to photochemical degradation. Biodegradation

Boric acid is an inorganic substance and therefore biodegradation is not a relevant pathway

4.1.1.1 Biodegradation estimation

Not relevant

4.1.1.2 Screening tests

Not relevant

4.1.1.3 Simulation tests

Not relevant

4.1.2 Summary and discussion of persistence

Boric acid is a persistent molecule, not subject to hydrolysis, photodegradation or biodegradation. Other borates yield boric acid upon dissolution in water (or borate anion in higher pH conditions). Over 200 minerals contain boron, mostly present as the sodium or calcium borate salt.

4.2 Environmental distribution

The environmental distribution of boric acid is dominated by its water solubility. Sorption to some types of soils and sediments can be locally significant, but sorption of boric acid should probably be regarded as a reversible situation, i.e., the substance is not tightly nor permanently bound. Borates entering the aquatic environment will form undissociated boric acid (H_3BO_3) and the borate anion. Their solubility defines that borates will be diluted and dispersed throughout the aquatic environment ultimately reaching the sea.

Because borates are found in plants, human and animal wastes will introduce borates from foods into wastewater. Combined with dissolution from local geological sources, ambient concentrations of boron will vary regionally, independent of uses of boron in processes and products.

4.2.1 Adsorption/desorption

Boron adsorption on soils and soil minerals has been described using various modelling approaches, including the empirical Freundlich and Langmuir adsorption isotherms (Elrashidi and O'Connor, 1982), a phenomenological model for clay surfaces (Keren and Gast 1981) and constant capacitance models of surface complexation (Goldberg et al. 2000). Empirical models may only apply to the specific conditions of an experimental measurement, which generates the interest in other, more mechanistic models to quantitatively estimate boron adsorption.

In general, boron should be considered mobile in soil, according to the classification scheme of ASTM (2001). There is some evidence that water-soluble borates have a slight tendency for adsorption to soil, sediment particles and sewage sludge, depending e.g. on pH, organic matter content and the number of active adsorption sites (Butterwick et al., 1989). Significant adsorption, however, was only detected at alkaline pH levels of up to 9.5 when boron is mainly present as the borate ion (WHO, 1998; Blume et al., 1980).

Greatest adsorption was found in soils with high amounts of fine particles particularly with iron and aluminium compounds on the surface (Sprague, 1972). Depending on soil properties the adsorption of boron was mostly found to be reversible and the compound was easily leached. Boric acid**,** the predominant borate species present at acidic pH levels, was found to be mobile in soil and sediment. At relevant environmental pH values of ≤ 7 no significant adsorption of boron compounds in soil and the aquatic compartments are to be expected (EPA, 1975; Koehnlein, 1972.) Goldberg et al. (2000) reviewed boron binding and characterized boron adsorption as being maximal around pH 9 and exhibiting a parabolic shape around that maximum. Soil factors that affect boron availability in soils are pH, soil texture (eg., clay content and composition), soil moisture and temperature (Goldberg, 1993).

A number of published studies attempted to determine sorption coefficients using the Freundlich model. From the Freundlich equation, $C_{soil} = K_F \times C_{solution}^{(1/n)}$, it follows that the K_F is equal to a partition coefficient K_P (defined as $C_{soil}/C_{solution}$) when 1/n is 1 and sorption is linear. For the majority of soils this is not the case. Values for 1/n usually are between 0.7 and 1.0 (Allen and Walker, 1987).

The OECD Sorption/desorption Guideline 106 (OECD, 2000) notes that distribution coefficient (Kd) values below 0.3 $cm^3\ g^{-1}$ cannot be estimated accurately from a decrease in concentration in the aqueous phase even when the soil/solution ratio of volumes is 1:1. The Guideline also notes that low values of 1/n (where n is the regression constant from the Freundlich adsorption equation) mean that the sorption is nonlinear.

In many of the published studies, the observed sorption is low or the regression constant is below the 0.7 value. Use of these two criteria (1/n > 0.7 and Kf * soil/solution ratio > 0.3) may be used to define the limits of acceptable test results, i.e., those within the limits of accuracy of the Guideline method. However, strict use of the criteria to screen data will result in a classic example of left-censored data: all smaller values are systematically excluded. This could lead to a biased overestimate of the true partition coefficient.

In studies conducted using the draft OECD 106 Guideline, sorption of boric acid was measured in four soil types (DeVette et al., 2000). The results of the study indicate that adsorption of boric acid to soils is generally low. The amount of adsorbed boron was determined from the difference in boron concentrations in solution before and after shaking. In case of little sorption, the differences

in concentrations were so small that any analytical inaccuracy leads to large differences between replicates and/or negative sorption, as was the case in this study.

Additional literature data are summarized in the Table 4-1 below. In all studies, the adsorption was determined from the decrease in concentrations in the water phase, as in the above study. According to OECD 106, sorption coefficients can only be determined accurately in this case when the product of the adsorption coefficient and the soil:solution ratio is > 0.3 (OECD, 2000). A second criterion, that $0.7 < 1/n < 1.1$, may be used to identify studies with a reasonably linear regression. Those data values meeting both criteria are indicated in bold-face print in the Table 4-1below.

Table 4-1 Sorption of boron to soils. Data in bold meet validity criterion of OECD 106.

Soil type[a]	pH	OC	Clay	CEC	Soil :solution ratio	Concentration range[d]	K_F	1/n	Reference
		[%]	[%]	[mmol/kg]	[g :mL]	[mg B/L]	[L/kg]		
Sandy loam	7.7	0.9	15	10.7	1 :10	1-50	0.87	0.659	deVette et al. 2000
Low humic sand	7.4	0.4	2	2.0	1 :10	1-50	3.946	0.685	
Loam	7.8	0.9	26	13.4	1 :10	1-50	1.93	0.802	
Humic sand	5.5	1.4	3	9.8	1 :10	1-50	0.749	0.542	
silt loam	6.02[b]	1.00	25.0	162	1:1	0 – 100	1.93	0.644	Elrashidi and O'Connor, 1982
sandy loam	6.02[b]	0.45	10.0	55	1:1	0 – 100	0.409	0.666	
loamy sand	7.03[b]	0.17	3.4	16	1:1	0 – 100	0.087	0.935	
Sand	8.00[b]	0.02	5.0	62	1:1	0 – 100	0.125	0.947	
Sand	7.89[b]	0.04	7.7	81	1:1	0 – 100	0.421	1.19	
Sand	7.82[b]	0.04	5.6	78	1:1	0 – 100	0.162	0.843	
Clay	7.57[b]	0.97	57.0	352	1:1	0 – 100	3.99	0.572	
clay loam	7.54[b]	1.10	27.3	185	1:1	0 – 100	3.33	0.623	
sandy loam	7.62[b]	0.57	14.5	141	1:1	0 – 100	2.53	0.618	
sandy loam	7.42[b]	0.43	13.7	140	1:1	0 – 100	2.16	0.645	
Clay	4.8[c]	1.54	54.7	302	1:10	0.01 – 100	1.49	0.363	Buchter et al., 1989
sandy loam	8.5[c]	0.44	10.7	147	1:10	0.01 – 100	0.851	0.787	
loamy sand	5.7[c]	0.61	8.3	20	1:10	0.01 – 100	None	-	
loamy sand	5.9[c]	6.62	0.9	225	1:10	0.01 – 100	**8.41**	**0.891**	
sandy loam	3.9[c]	11.6	17.6	269	1:10	0.01 – 100	None	-	
clay loam	6.0[c]	1.67	28.2	110	1:10	0.01 – 100	1.39	0.518	
loamy sand	6.9[c]	0.21	2.8	41	1:10	0.01 – 100	None	-	
Silt	6.6[c]	0.83	6.2	86	1:10	0.01 – 100	None	-	
Sand	4.3[c]	1.98	3.8	27	1:10	0.01 – 100	None	-	
Loam	7.6[c]	4.39	23.9	481	1:10	0.01 – 100	1.60	0.641	
loamy sand	5.3[c]	0.67	2.8	20	1:10	0.01 – 100	None	-	
sandy loam[e]	7.8	1.56	14.5		1:1	5 – 200	**4.21**	**0.735**	Singh, 1971
sandy loam[f]	7.8	1.56	14.5		1:1	5 – 200	**4.80**	**0.731**	
loam[e]	7.8	0.195	27.6		1:1	5 – 200	**1.63**	**0.924**	
loam[f]	7.8	0.195	27.6		1:1	5 – 200	**1.85**	**0.955**	
loamy sand[e]	8.2	0.154	8.5		1:1	5 – 200	**0.571**	**0.903**	
loamy sand[f]	8.2	0.154	8.5		1:1	5 – 200	**1.44**	**0.921**	

Soil type[a]	pH	OC [%]	Clay [%]	CEC [mmol/kg]	Soil :solution ratio [g :mL]	Concentration range[d] [mg B/L]	K_F [L/kg]	1/n	Reference
Sand	6.27	0.13	4	7.9	1:1	2 - 100	0.218	0.701	Datta and Bhadoria, 1999[g]
sandy loam	6.04	0.21	16	18.0	1:1	2 – 100	0.229	0.756	
loamy sand	5.90	0.17	12	36.4	1:1	2 – 100	0.212	0.760	
clay loam	5.80	0.70	36	93.5	1:1	2 – 100	2.826	0.570	
Loam	5.14	0.73	24	63.9	1:1	2 – 100	1.538	0.594	
Loam	4.99	0.78	20	97.6	1:1	2 – 100	1.610	0.597	
Loam	6.38	0.32	20	52.7	1:1	2 – 100	1.509	0.589	
silt loam	5.51	0.57	24	95.6	1:1	2 – 100	1.799	0.620	
clay loam	6.26	0.37	36	32.2	1:1	2 – 100	1.359	0.579	
Loam	6.11	0.27	24	82.2	1:1	2 – 100	2.564	0.546	
Loam	6.03	0.53	20	114	1:1	2 – 100	1.359	0.653	
sandy loam	5.50	0.28	16	42.5	1:1	2 – 100	0.460	0.657	
sandy loam	5.68	0.43	8	32.0	1:1	2 – 100	0.780	0.613	
sandy loam	5.54	0.22	20	37.4	1:1	2 – 100	**0.400**	**0.726**	
sandy loam	5.63	0.32	12	34.9	1:1	2 – 100	0.686	0.588	
sandy loam	5.42	0.30	20	50.6	1:1	2 – 100	0.576	0.658	
sandy loam	5.13	0.30	12	93.7	1:1	2 – 100	**0.439**	**0.734**	
sandy loam	6.06	0.29	20	56.4	1:1	2 – 100	1.940	0.615	
sandy clay loam	5.97	0.53	24	107	1:1	2 – 100	1.138	0.675	
clay loam	5.86	0.48	40	144	1:1	2 – 100	3.005	0.585	
Clay	5.80	0.49	44	199	1:1	2 – 100	2.891	0.621	
sandy clay loam	5.30	0.53	32	87.8	1:1	2 - 100	1.581	0.620	
Clay	5.68	0.54	44	176	1:1	2 – 100	3.283	0.539	
clay loam	5.90	0.69	40	156	1:1	2 – 100	2.810	0.602	
clay loam	5.50	0.56	36	115	1:1	2 – 100	2.949	0.569	

a: USDA classification;
b: 1:1 soil/0.01 M $CaCl_2$;
c: 1:1 soil/water;
d: number of concentrations not reported in Elrashidi and O'Connor (1982), but > 5 according to figures; 10 concentrations used in Buchter et al. (1989), 6 in Singh (1971) and 8 in Datta and Bhadoria (1999);
e: 22 °C; f: 24 °C; g: article gives ranges of K_F and 1/n, raw data provided by author; None: no sorption observed

In the study of Elrashidi and O'Connor (1982), K_F was significantly correlated with clay and organic carbon content (OC) , Cation Exchange Capacity (CEC), specific surface area and conductivity of the equilibrium solution when applying simple regression. Applying multiple regression, a significant contribution of OC, specific surface area and Fe_2O_3 content of the soil was found. Buchter et al. (1989) found significant simple correlation coefficients for OC, amorphous Fe_2O_3 and Al_2O_3. Datta and Bhadoria (1999) identified Fe_2O_3, clay and OC-content, pH and CEC as significant factors for boron retention by soils. According to Goldberg (1997), the main boron adsorbing surfaces in soil are aluminium and iron oxides, magnesium hydroxides, clay minerals and calcium carbonate.

Xu and Peak (2007) investigated boric acid adsorption on pure am-$Al(OH)_3$ and 5% (w/w) humic acid. They concluded that both humic acid coating on the aluminum hydroxide, and presence of

atmospheric dissolved carbon dioxide decreased boric acid adsorption on the aluminum hydroxide. The batch adsorption studies showed peak adsorption at pH 9.2 (the pKa of boric acid), as in other studies. At low boron concentrations (0.38 mmol-boric acid/L), only minor differences in adsorption were noted for pure aluminum hydroxide vs. the humic acid-coated aluminum hydroxide. At higher boron concentrations (1.51 mmol-boric acid/L), adsorption on pure aluminum hydroxide was about twice that on the humic-acid-coated aluminum hydroxide. The presences of carbon dioxide also descreased boric acid adsorption vs. adsorption under a pure nitrogen atmosphere, althought the magnitude of this change varied from negligible to about 30%.

From the 9 values that meet the validity criterion, an average K_F of 2.6 L/kg with 1/n of 0.83 is obtained. Note however that the standard deviation of this value is 2.7. Because the standard deviation is as large as the mean, the precision of this value cannot be regarded as very good: there is a significant probability that a K_F of 0.0 might be the true value.

Note that the highest K_F value (8.41) was taken from a data set (Buchter et al. 1989) where 6 of the 11 test results showed no sorption. In fact, the accepted value was more than 5 times the next largest K_F estimate. This suggests this value might be considered an extreme (outlier). Removal of this possible outlier results in a average K_F of 1.9 L/kg (standard deviation of 1.7). However, this means that only the data from the oldest study (Singh 1971) has been retained.

Given the limited number of soil types and limited data used to estimate a partition coefficient, the confidence in the K_F estimate should not be too high. As noted initially, the Freundlich model is empirical and does not provide a means to evaluate the influence of pH, soil texture, soil moisture, temperature or other components regarded has having significant influence on the bioavailability of boron in soil.

4.2.2 Volatilisation

The vapour pressure for boric acid is extremely low so volatilization is expected to be minimal. The exception is over the oceans, where evaporation of aerosols leads to small but measured quantities of boric acid vapour in the marine atmosphere. The solubility of such materials means that they

4.2.3 Distribution modelling

4.3 Bioaccumulation

The WHO (1998) review of boron noted that highly water soluble materials are unlikely to bioaccumulate to any significant degree and that borate species are all present essentially as undissociated and highly soluble boric acid at neutral pH. The available data indicate that both experimental data and field observations support the interpretation that borates are not significantly bioaccumulated

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

For inorganic chemicals, estimates of bioaccumulation potential are not reliably predicted by octanol/water partitioning data. Although boric acid has a low measured Pow value (log Pow = -1.09, Cordia, 2003a), the result should not be considered an appropriate model system.

4.3.1.2 Measured bioaccumulation data

Laboratory data in oysters and salmon demonstrate low Bioconcentration Factors (BCF) for boron, although the tests pre-date current protocols. Thompson et al. (1976) reported BCF values of 0.7 to 1.4 L/kg for Pacific oysters (*Crassostrea gigas*) and showed that boron levels in tissue of sockeye salmon (*Oncorhynchus nerka*) were not significantly different from test water concentrations. Tissue concentrations in the oyster returned to background in 25 days. Hamilton and Wiedmeyer (1990) reported BCF < 0.1 in Chinook salmon fed boron-supplemented diets for 60 to 90 days.

Suloway et al. (1983) reported a bioconcentration factor of 0.3 L/kg for fathead minnow (*Pimephales promelas*) and green sunfish (*Lepomis cyanella*), when exposed to components of coal fly ash extract containing boron at concentrations ranging from 1.23 to 91.7 mg/L.

Saiki et al. (1993) measured boron levels in aquatic food chains in the Lower San Joaquin River (California, United States) and its tributaries. They observed the highest concentrations of boron in detritus and filamentous algae, and lower concentrations in invertebrates and fish. Saiki et al did not calculate accumulation factors and many of their analytical values were below their detection limits. Using only measurements above detection limits, the average BCF for filamentous algae was 137 L/kg (standard deviation of 224). Bioaccumulation factors (BAF) for plankton and invertebrates were less than 20 L/kg; BAF for fish were < 5 L/kg. (Since these are field data, the body concentrations reflect uptake via both food and from water; BCF values theoretically reflect uptake from water only.) If measurements below detection limits are taken to be equal to the detection limit value, the estimated values are: algae-BCF ca.190 L/kg, plankton and invertebrates-BAF <20 L/kg, and fish-BAF ca. 8 L/kg.

4.3.2 Terrestrial bioaccumulation

Regarding bioconcentration into terrestrial plants, boron is known to be a critical element and is incorporated into cell wall structure. Consequently, some bioconcentration is expected as a result of active transport. As reviewed by WHO (1998), Eaton measured leaf concentrations of plants grown in sand culture beds supplied with liquid nutrient solutions. He found leaf concentrations indicating BCF of 12 to 361 L/kg when the solution contained 5 mg-B/L, and BCF of 84-155 L/kg in 25 mg-B/L solution (Eaton, 1944). Boron concentrations were generally lower in roots, stems, and fruits..

Riley et al. (1994) derived BCF's for whole plants of 38 - 49 kg_{soil}/kg_{plant} on a dry weight basis.

The phytotoxicity of boron limits potential for excessive accumulations beyond “normal” plant tissue concentrations. Oertli and Kohl (1961) noted that necrotic or chlorotic tissues contained only a few times the boron content of green tissues. For example, green carrot tissues contained 470 to 960 mg/kg boron, while necrotic tissue contained 2000 mg/kg – suggesting that even with excess supplies of external boron, accumulations in plant tisse would be only 2 to 5 times “normal” tissue concentrations. Healthy bean tissue contained 630 to 680 mg/kg boron, whereas necrotic tissue contained 1960-2510 mg/kg, s 3.3 to 4-fold ratio. Thus any potential for bioaccumulation by plants is offset by their intolerance of high tissue concentrations of boron. This contrasts with bioaccumulative substances that have no apparent deletrious effects on plants so there is no limiting factor.

Mallard ducks have been studied as representative of terrestrial non-predatory organisms that consume plant food. Pendleton et al. (1995) monitored body tissue levels after 48 days on diets with 1600 mg-B/kg for up to 48 days. They reported a BCF < 0.1 and noted that liver and blood residues were eliminated within 1 day on a “clean diet.” Stanley et al. (1996) also reported BCF $\leq$ 0.1 in mallard egg and livers after feeding boron-added diets.

Data also exist for herbivorous mammals that confirm rapid elimination of boron. Assuming first order kinetics for elimination, the half-life was estimated to be approximately one hour for mice and less than 12 hours for rats (Farr and Konikowski 1963; Ku et al. 1991, 1993). In rabbits, 50 to 66% of an orally administered dose of boric acid was excreted in the urine in the first 24 hours after dosing (Draize and Kelley, 1959). In cows, Owen (1944) observed essentially quantitative recoveries of boron in the urine and feces of animals fed daily rations fortified with borax

4.3.3 Summary and discussion of bioaccumulation

For both aquatic and terrestrial food chains, bioaccumulation is not significant. Boron is incorporated into plant cell walls, so some accumulation vs. the environment may be anticipated, i.e., active transport. Data from both lab and field observations indicate that body burdens of boron decrease at higher trophic levels.

4.4 Secondary poisoning

Because boron is incorporated into plant cell walls, a diet rich in plant material is correspondingly high in boron, compared to diets rich in meat or fish. However, measured BCF in plants, as derived from Riley et al. (1994) range from 38 to 49 kg_{soil}/kg_{plant}, well below BCF values used to establish significant bioconcentration (BCF 3000 to 5000). Data from animals and humans indicates that boron is quickly removed via feces and urine, so body concentrations do not continually increase. Consequently, the potential for secondary poisoning is not significant.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

5.2.2 Acute toxicity: inhalation

5.2.3 Acute toxicity: dermal

5.2.4 Acute toxicity: other routes

5.2.5 Summary and discussion of acute toxicity

C&L including weight-of-evidence considerations.

5.3 Irritation

5.3.1 Skin

5.3.2 Eye

5.3.3 Respiratory tract

5.3.4 Summary and discussion of irritation

C&L including weight-of-evidence considerations.

5.4 Corrosivity

5.5 Sensitisation

5.5.1 Skin

5.5.2 Respiratory system

5.5.3 Summary and discussion of sensitisation

C&L including weight-of-evidence considerations.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

5.6.2 Repeated dose toxicity: inhalation

5.6.3 Repeated dose toxicity: dermal

5.6.4 Other relevant information

5.6.5 Summary and discussion of repeated dose toxicity:

C&L, dose-response estimation including weight-of-evidence considerations.

5.7 Mutagenicity

5.7.1 In vitro data

5.7.2 In vivo data

5.7.3 Human data

5.7.4 Other relevant information

5.7.5 Summary and discussion of mutagenicity

C&L, dose-response estimation including weight-of-evidence considerations.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

5.8.2 Carcinogenicity: inhalation

5.8.3 Carcinogenicity: dermal

5.8.4 Carcinogenicity: human data

5.8.5 Other relevant information

5.8.6 Summary and discussion of carcinogenicity

C&L, dose-response estimation including weight-of-evidence considerations.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

5.9.2 Developmental toxicity

5.9.3 Human data

5.9.4 Other relevant information

5.9.5 Summary and discussion of reproductive toxicity

C&L, dose-response estimation including weight-of-evidence considerations.

5.10 Other effects

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

5.11.1 Overview of typical dose descriptors for all endpoints

5.11.2 Correction of dose descriptors if needed (for example route-to-route extrapolation)

5.11.3 Application of assessment factors

5.11.4 Selection/ identification of the critical DNEL(s)/ the leading health effect

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

Including C&L

6.2 Flammability

Including C&L

6.3 Oxidising potential

Including C&L

7 ENVIRONMENTAL HAZARD ASSESSMENT

Boron is a naturally occurring element that is essential to a variety of organisms. In plants, it is necessary for a variety of metabolic processes (e.g. nitrogen metabolism, nucleic acid metabolism and membrane integrity and stability) and has been known to be an essential micronutrient for terrestrial plants for several decades (Butterwick et al., 1989, Eisler, 2000). Shorrocks (1997) documented the use of boron applications for 132 crops in over 80 countries, demonstrating the widespread nature of agricultural use of boron.

Evidence exists that it is essential for nitrogen fixation in some species of algae (Smyth and Dugger, 1981), fungi and bacteria (Saiki et al., 1993, Fernandez et al., 1984), some diatoms and algae and macrophytes (Eisler, 2000). Required levels may vary, especially among plants, such that essential levels for one species may be toxic to another (Eisler, 1990).

A beneficial effect to fish at low concentrations was shown for carp and rohu (Raymond and Butterwick, 1992). Work with rainbow trout and zebrafish has shown that embryo-larval development was adversely affected in waters deficient in boron (Rowe et al., 1998, Eckhert, 1998). Fort et al. (1998) reported that abnormal development in frog embryos (*Xenopus laevis)* was observed when larval stages were exposed to 0.003 mg-B/L or less. Boron does not appear to be essential for all species, however.

The concentration-response curve for boron is likely to be U-shaped for many species, with adverse effects observed at very high and very low concentrations, while no adverse effects are observed at the intermediate concentrations (Lowengart, 2001). Figure 7-1 illustrates such a pattern for plants (Gupta et al., 1985) although the response has been normalized to 100%, making the curve an inverted-U shape.

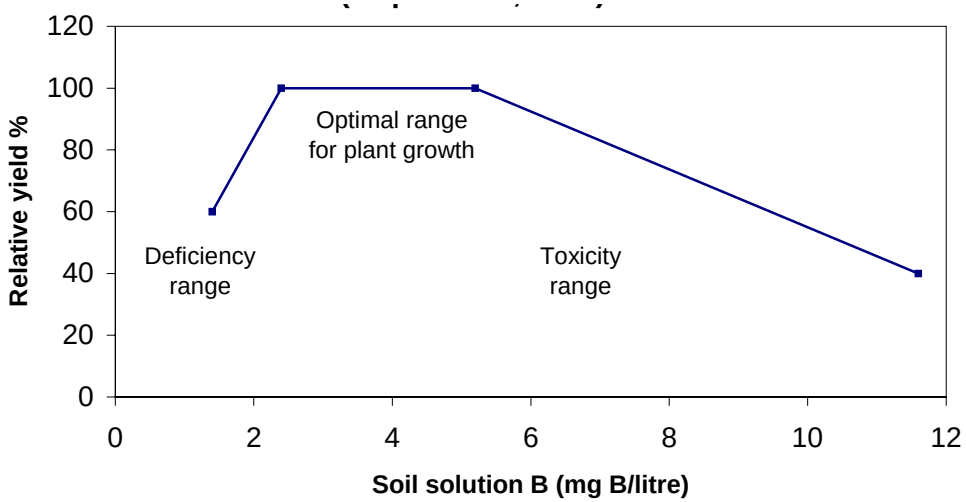


Figure 7-1. U-Shaped Toxicity Pattern: Plant yield as influenced by soil boron concentrations (Gupta et al., 1985)

Plant and animal species vary in the concentrations associated with deficiency and toxicity. Monocotyledons (e.g., corn and grasses) require about one-quarter as much boron as dicotyledons (e.g., tomatoes, carrots, clovers, beets) (Butterwick et al., 1989). The mobility of boron within the plant may help explain the observed deficiency and toxicity patterns. Boron is more mobile in plants that produce the simple sugars known as polyols (e.g., sorbitol and mannitol) than in species that do not produce polyols. In polyol-producing species, boron is translocated from one part of the plant to another and so may reach the meristem and affect growth. In the absence of polyols, boron is relatively immobile within the plant (Brown et al., 2002). A polyol-producing plant may be both more tolerant of boron deficiency and more sensitive to higher boron concentrations because of the mobility of boron within the plant. This is important in agricultural applications of boron, which may be applied as a soil treatment or as foliar spray.

Agricultural application of boron depends on the plant and cultivar, as well as the local soil. Recommended application rates range from 0.5 to 7.6 kg-B/ha (Borax, 2002), but typically are in the range of 1 to 2 kg-B/ha (Shorrocks, 1997). If one assumes typical soil densities of 1700 kg/cubic meter and a mixing depth of 20 cm (default values used in the EUSES model), an application rate of 1 to 2 kg-B/ha results in an estimated soil concentration of 0.3 to 0.6 mg-B/kg-soil. Mortvedt et al. (1992) estimated soil concentrations of 0.16 to 2.0 mg-B/kg-soil for several crops with application rates of 0.45 to 5.7 kg/ha. The intentional application of borates to achieve such soil concentrations should be acknowledged in the risk assessment process.

Work with rainbow trout and zebrafish has demonstrated boron deficiencies: embryo-larval development was adversely affected in waters with very low boron concentrations. Rowe et al. (1998) concluded that embryonic growth of rainbow trout was reduced below 0.1 mg-B/L and that zygote development was affected in zebrafish at concentrations below 0.002 mg-B/L. At these low concentrations, fish demonstrate increased mortality and reduced development – they are in the deficiency zone, equivalent to the left-hand part of the curve in Fig. 7-1. Zebrafish development was normal at 0.5 mg-B/L. Trout as well showed optimal conditions – equivalent to the "optimal range" zone in Fig. 7-1. Finally, toxic effects were observed for both trout and zebrafish at higher boron concentrations – equivalent to the "toxicity range" show for plants in

Fig. 7-1. These data demonstrate that extremely low boron concentrations can cause adverse effects through boron deficiency, i.e., the left-hand part of the curve in Fig. 7-1.

Boron is a constitutent of many culture media and dilution waters used in aquatic toxicity tests. For example, the algal growth media used in the OECD 201 test typically contains 0.185 mg/L of boric acid (0.03 mg-B/L). Boron is also present in the M4 and M7 media used in OECD 202 for Daphnia. M4 contains ca. 2.9 mg/L boric acid or 0.51 mg-B/L, while M7 contains 0.71 mg/L boric acid, or 0.12 mg-B/L.

In addition to boron deliberately being added to test media, it may also be present as a natural constituent of water, sediment and soils used in toxicity testing. The presence of boron,either natural or added in the controls of the various ecotoxicity tests needs to be carefully considered in interpreting the data. At present, few details of the boron content of the control waters, soils and sediments may be available, making it difficult to determine the significance of the results.

Effects on environmental organisms

A variety of borates are in use, so for simplicity, the effects of borates can be expressed as boron equivalents, e.g,, as mg-B/L or mg-B/kg. [4] Boric acid is the form that exists at most environmental concentrations and under most environmentally and physiologically relevant conditions. Studies on the ecotoxicity of boron have been performed with various compounds, such as boric acid (H_3BO_3), anhydrous sodium tetraborate ($Na_2B_4O_7$), and hydrated sodium tetraborates ($Na_2B_4O_7.xH_2O$). For the purpose of this evaluation, all endpoints are converted to concentrations of elemental boron (B) using the relative molar mass.

An extremely large number of studies exist on the ecotoxicity of boron, including laboratory and field tests. Many studies pre-date current standard ecotoxicity test protocols and other relevant data come from studies that are not carried out in accordance with traditional toxicity test designs. As a result, concerns about data quality must be addressed so that a balanced evaluation can be made that acknowledges all relevant data, but places more emphasis on better quality data.

Evaluations of study reliability were made for the studies discussed in this section following the Klimisch et al. (1997) codes. These evaluations follow the TGD guidelines regarding reliability and relevancy. The studies most closely following standard protocols were rated "*Reliable without restriction*" with the descriptive qualifiers: Guideline study, or Comparable to guideline study.

High quality studies that did not strictly follow standard protocols were rated "*Reliable with restriction*" with the descriptive qualifiers: Well-done study and report that meets basic scientific principles, or Peer-reviewed technical publication or Comparable to guideline study with acceptable restrictions.

[4] To convert boron equivalents to boric acid concentrations, divide the boron equivalent by 17.5%. This reflects the ratio of the molar mass of boron, 10.811 g/mol to the molar mass of boric acid (H_3BO_3), 61.833 g/mol. For example, 1.75 mg-B/L is equivalent to 10. mg-boric acid/L.

Studies with significant deviations from current scientific or protocol practices were rated "*Not reliable*" with the descriptive qualifiers: Method not validated, or Documentation insufficient for assessment or Does not meet important criteria of current standard methods, or Methods deficient in critical aspects, or Test system unsuited for standard method.

Some reported test results could not be evaluated because of limited information and were rated "*Not assignable*" with the descriptive qualifiers: Insufficient documentation to permit review or Secondary literature citing some other primary source or Only reports an endpoint value or summary statement.

A number of review articles have been published which may be compilations of endpoints. Examples include the US EPA Acquire database, WHO (1998), and Raymond & Butterwick (1982). Some reviews do include a re-analysis of data (e.g., Dyer, 2001), so can contribute to evaluation of data and derivation of PNECs.

7.1 Aquatic Compartment (including sediment)

7.1.1 Toxicity test results

Available test results are summarized in Tables 7-1 (Fish), Table 7-2 (Aquatic Invertebrates), Table 7-3 (Algae and Aquatic Plants), Table 7-4 (Sediment organisms) and Table 7-5 (Other Aquatic Organisms). Compilations of the numerous literature values have been published by Eisler (1990, 2000), Raymond and Butterwick (1992), ECETOC (1997), WHO (1998), Van de Plassche (1999), and Dyer (2001).

7.1.1.1 Fish

Short-term toxicity to fish.

The most reliable tests of acute effects on fish (4 day duration) show mortality effects (LC50) in the range of 125 to 600 mg-B/L (Table 7-1). These include salmonids (Oncorhynchus kisutch, O. tshawtscha) and several endangered species (Gila elegans, Ptychocheilus lucia, Xyrauchen texanus, and Catostomas latipinnis). Juveniles and fry appear to be the most sensitive fish life-stage (Hamilton, 1995; Hamilton and Buhl, 1990).

A few studies reported endpoints in the 5 to 15 mg-B/L range, but these were judged not reliable, or did not have sufficient information to permit data quality review. For example, Turnbull et al. (1954) reported a 24-hour TLm to bluegill of 4.6 mg-B/L in response to the test substance sodium tetraborate decahydrate. However, they also reported a 24-hour TLm of 2389 mg-B/L in response to the test substance boron trifluoride. Their procedure used relatively large fish (ca. 5 g, 7 cm). No information was provided on replication, intervals between test concentrations, or similar operational details. Guhl (1992a) reported 96-hour LC50 for zebrafish of 14.2 mg-B/L, but cited an unpublished study from Henkel KGaA. Terhaar et al. (1976) reported median lethal times for boric acid of 10 hours, exposed to 1750 mg-B/L which

was extrapolated to an acute toxicity estimate of 17.5 to 175 mg-B/L. These studies cannot be adequately reviewed or compared to standard protocols, thus they cannot be judged reliable.

Long-term toxicity to fish

Longer exposures to boron have been tested, giving chronic, or sub-chronic study results (Table 7-1). A 34 day study following OECD 210 methods using *Brachydanio rerio* showed a NOEC values for mortality, growth and conditionof 5.6 mg-B/L (Hooftmann et al 2000a). This is the single fish study fully compliant with standard guidelines. Another study of *Brachydanio reiro* eggs and embryos showed no toxic effects at exposures less than 10 mmol B/L (Rowe et al., 1998).

Several studies in Table 7-1 were conducted by Birge and Black (1977) for embryo-larval stages of rainbow trout, goldfish, largemouth bass and channel catfish and are reported as 7 to 9 day embryo-larval stage (ELS) tests. In their 1977 report to their funding agency, Birge and Black reported low level effects to trout (an EC1) at 0.001 mg-B/L, with embryonic mortality and teratogenesis as the endpoints in their 28 day study. This value was an extrapolation from observed data to an unmeasured concentration and was not corrected for control responses. This value was not consistent when the work was repeated. In subsequent work, Black et al. (1993) reported consistent LOEC values at 0.1 mg-B/L for trout in reconstituted water. However, when using waters containing 0.23 to 0.75 mg-B/L, effects were seen only at 1.0 mg-added B/L and higher. A longer (87 day) test showed no effects at concentrations up to 18 mg-B/L. Black et al. also collected data on boron concentrations in streams with wild populations of rainbow trout and where trout hatcheries are in operation. They found that wild trout populations survived in streams with 0.01 to 13.1 mg-B/L. They concluded that a concentration of 0.75 to 1.0 mg-B/L appeared to be a “reasonable environmentally acceptable limit” for aquatic systems

Other reviews pointed out limitations of the 1977 trout values. Guhl (1992) pointed out that the control responses were reported by Birge and Black to be about 12% mortality, but the other data were not adjusted to recognize this baseline. Consequently, reporting a 4-6% response as a significant effect is problematic. Guhl pointed out that the later OECD guidelines permit 30% control mortality, suggesting that smaller responses cannot be relied upon, given the practical limitations of the test. Other studies of field populations showed rainbow trout hatcheries operating in UK and Germany with local waters containing up to 0.272 mg-B/L without evident difficulties (Unilever, 1994).

Additional information came with demonstration that boron is essential for rainbow trout, zebrafish, and frogs (Eckhert, 1998, Rowe et al., 1998, Fort et al., 1998). The essentiality threshold for rainbow trout appears to be at about 0.1 mg-B/L so tests run with lower concentrations may lead to boron deficiencies.

Because of this and other limitations, the Birge and Black trout studies were rated "Not reliable" and not used in derivation of a PNEC.[6] .

Dyer (2001) obtained the original data from the Birge and Black (1977) studies, as well as later data on trout and largemouth bass from Birge and Black (1981) and Birge et al. (1984). Dyer recalculated LC10 values for Oncorhynchus mykiss (trout), Carassius auratus (goldfish), Ictalurus punctatus (channel catfish) and Micropterus salmoides (largemouth bass), shown in Table 7-1. The data for the catfish, goldfish and bass were not as extreme, so have not generated as much controversy and follow-on research. Because the LC10 endpoint is consistent with current practice, the recalculated values were regarded as "reliable with restriction."

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Several daphnid values are reported, including several studies of high quality. Acute values (24-48 hour EC_{50}) range from 73 to 226 mg-B/L for *Daphnia magna* (Table 7-2). Data for other daphnids are reported but are of low reliability, also reported acute values in the 100-180 mg-B/L range for *Ceriodaphnia dubia* and *Simocephalus vetulus.*

Maier and Knight (1981) reported that water hardness had no effect on the acute toxicity to the midge *Chironomus decorus*, with a 48-hour EC50 of 1376 mg-B/L.

Long-term toxicity to aquatic invertebrates

Hooftman et al (2000a) report a NOEC for growth and reproduction of 10 mg-B/L in the only study that fully complied with standard guidelines (Table 7-2). Other values (14 to 21 day tests) for *Daphnia magna* growth and reproduction range from 6 to 27 mg-B/L.

Maier and Knight (1981) report a chronic NOEC for *Chironomus decorus* of 10 mg-B/L in a 4-day test of the 4th instar stage.

Older studies report NOEC values for emergence of mosquito species range from 4.4 to 18 mg-B/L (Fay, 1959), although these studies are probably too old to be used in derivation of a PNEC or SSD.

7.1.1.3 Algae and aquatic plants

Algal and aquatic plant studies (Table 7-3) suggest less toxicity than to fish or daphnids: An OECD 201 study of *Selenastrum capricornutum* (Hanstveit and Oldersma 2000) reported a

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[6] The European Union member states have reviewed other data on fish early-life-stage tests and decided not to use data from Birge's test method if other fish data are available. See, for example, page 40 of http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/DRAFT/R307_0403_env.pdf

and page 29 of http://chimie.ineris.fr/fr/lespdf/metodexpchron/naphtalene.pdf. These and other sources note that the results from Birge's studies are consistently an order of magnitude below studies from other researchers with no clear explanation for the discrepancies.

NOEC concentration of 17.5 mg-B/L.. Davis et al. (2002) reported a NOEC value of 6.1 mg-B/L for the duckweed *Spirodella polyrhiza*. They reported endogenous boron level of 0.9 mg-B/L from the various nutrient meda used.

Other studies reported NOEC values for *Chlorella pyrenoidosa* (10 mg-B/L), *Scenedesmus subspicatus* (24 mg-B/L), *Anacystis nidulans* (50 mg-B/L) and *Lemna minor* (60 mg-B/L), as summarized in Table 7-2.

Studies of the reed *Phragmites australis* reported no effects in long term tests (4 months to 2 years) ranging from 0.7 to 4 mg-B/L (Guhl 1992a, Bergman et al. 1995, Guhl 2000). Although these studies can be considered reliable, the lack of an exposure showing adverse effects (ie a LOEC) precludes their results from being described as NOEC values. Guhl (1992a) uses the term "concentration without effect" to describe the endpoint where no effect was observed at the highest (or only) concentration tested.

7.1.1.4 Sediment organisms

Limited data on sediment organisms is shown in Table 7-4. Short term studies of the aquatic tubificid worm showed no mortality at 85 to 1313 mg-B/L (Mann, 1973). Studies of the midge *Chironomous decorus* showed a 2-day EC50 of 1376 mg-B/L (Maier & Knight, 1991). As noted above, a NOEC of 10 mg-B/L was reported for C. decorus (Maier & Knight) but the study system did not include any sediment.

The single guideline study using spiked sediments showed a NOEC for growth and emergence of 180 mg-B/L for the midge *Chironomous riparius* in a 28 day test (Hooftman et al. 2000b)..

7.1.1.5 Other aquatic organisms

Additional aquatic species.

Values from several amphibians, protozoans and other aquatic species are shown in Table 7-5. Studies of the frog Rana pipiens and the toad Bufo fowleri were considered reliable with restriction with NOEC values of 7.5 and 41 mg-B/L, respectively. Studies of development of the salamanders *Ambystoma jeffersonian and Ambystoma maculatum* and the frog *Rana* sylvatica showed effects at the lowest exposure tested (LOEC 49.5 mg-B/L).

Several protozoan studies are considered reliable with restriction due to limited information about the tests and results. However, values for *Paramecium caudatum, Opercularia bimarginata, Uronema pardaczi,* and *Enterosiphon sulcatum* are summarized in Table 7-5 with chronic endpoints ranging from 10 to 30 mg-B/L. The accepted NOEC for the bacteria *Pseudomonas putida* is 7.6 mg-B/L (Guhl 1992a).

Multi-species studies

A number of biocenosis (multispecies) studies have been carried out (Guhl, 1992a, 2000). A summary of these studies is detailed in Table 7-5. In a laboratory microcosm test using abundance and presences of prokaryotes and micro-eucaryotes of six trophic stages, the NOEC for borate was found to be 2.5 mg-B/L and LOEC of 5 mg-B/L.A laboratory river model, consisting of sequence of several vessels fed a mixture of treated wastewater and drinking

water was monitored for biotic indices of the prokaryotes and micro-eucaryotes. No adverse effect was found at 1 mg-B/L so the the threshold for effect is greater than 1 mg-B/L. Studies of outdoor ponds with up to 29 species over two years showed no significant difference when treated with 0.7 mg-B/L. Field studies in outdoor ponds over two vegetation periods showed no toxic effects of borate at concentrations between 0.16 and 1.52 mg-B/L.

Field Studies

Awareness of the early trout studies led to studies of wild trout population data and these reviews suggest that boron is not very toxic to wild trout where boron occurs naturally. Loewengart (2001) pointed out that nearly half of streams in California (USA) with viable populations of wild trout have boron concentrations equal to or above 0.1 mg-B/L. One stream (Little Warm Springs Creek, California) had a boron concentration of 13 mg/L.

The Firehole River (Wyoming, USA) has a world-renowned trout fishery, even though it has elevated boron concentrations. The river receives geothermal input from geysers and hot springs, so has warm waters as well as elevated boron with variations over space and time in the water system. Studies of trout reproduction in the Firehole River system reported that trout delayed spawing until winter, presumably to reduce stress from high summer temperatures, but in doing so, reproduce successfully in stream areas where boron is highest, ranging from 0.4 to 1.2 mg-B/L (Meyer et al. 1998). Of note here is that the boron concentration encountered by the trout is variable, both seasonally and spatially. While the trout population may be considered to be adapted, it has not adapted to a single background concentration, but rather to a range of values.

Barros (2005) investigated rainbow trout condition and reproduction in the Rio de los Patos and Rio Agua Caliente in Argentina. This population was introduced into this river system in 1969 and has maintained itself since then. This study demonstrated that rainbow trout reproduces and maintains abundant populations in the range of 1.0 to 17.0 mg-B/L and 16.9 to 27.1 mg-B/L in the two rivers, respectively. Boron concentrations vary in this system, so mobile individuals may encounter varied exposures. Nesting sites (redds) were limited by the presence of suitable substrate, not by boron concentration.

Similar results are reported by Guhl (1992a) for other trout species in German surface waters and hatcheries, with trout populations in waters of 0.8 to 1.2 mg-B/L (Schilling lake in upper Bavaria) as well as in waters of 0.1 mg-B/L (Taubergiessen area in southern Baden) and in hatcheries with 0.01 to 0.08 mg-B/L (Albaum and Lohmar facilities). These studies provide an additional line of evidence regarding environmentally acceptable boron concentrations.

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Aquatic studies have been used to create species sensitivity distributions (SSD). SSD incorporate all available information into a summary statistic by calculating a designated percentile of the distribution, such as the 5th percentile. Such values indicate a concentration that is predicted to protect 95% of all species (included those not tested) (Versteeg at al., 1999).

According to the TGD-Part II, p.103 (ECB, 2003), statistical extrapolation by means of the Species Sensitivity Distribution-method (SSD) can be used when enough data are available. Since chronic NOEC's are available for more than 15 species from nine taxa, including pisces, crustacea, insecta, algae and macrophyta, the SSD-method can be applied.

Dyer et al. (2001) calculated the Acute 5th percentile concentration for aquatic species. Using the procedure of Aldenberg and Slob (1993), the acute 5th percentile SSD concentration is 43 mg-B/L. Using a similar procedure of Stephan et al. (1985) produces a similar acute value, 46 mg-B/L.

Dyer (2001) applied a weight-of-evidence approach to the available aquatic chronic data, including the 1977 Birge and Black study. Using several published methods to calculate the species sensitivity distribution (SSD), the estimated chronic 5th percentile ranged from 1.3 to 3.4 mg-B/L, based on a log-logistic model. Consequently the chronic aquatic $PNEC_{0.05}$ was determined to be at least 1.3 mg-B/L. Using the recalculated endpoints from Birge and Black, Dyer calculated the chronic 5th percentile concentration for aquatic species to be 3.45 mg-B/L. Dyer (2001) based the Chronic 5th percentile concentration on species mean acute values if multiple tests were available. The data used by Dyer (2001) are shown in Table 7-12..

The Netherlands (2006) calculated a SSD based on selected chronic aquatic toxicity data using the software ETX 2.0 (Van Vlaardingen et al. 2004), and reported the HC_5 was 3.2 mg-B/L (90% CI 1.8 to 4.8 mg-B/L). The data used are also indicated on Table 7-12.

Using the current evaluation of reliable chronic aquatic data and the ETX 2.0 software, an HC_5 value of 3.84 mg-B/L (90% CI 2.2 to 5.6 mg-B/L). As shown in Table 7-12, this evaluation used many of the same values, but also included several algal studies.

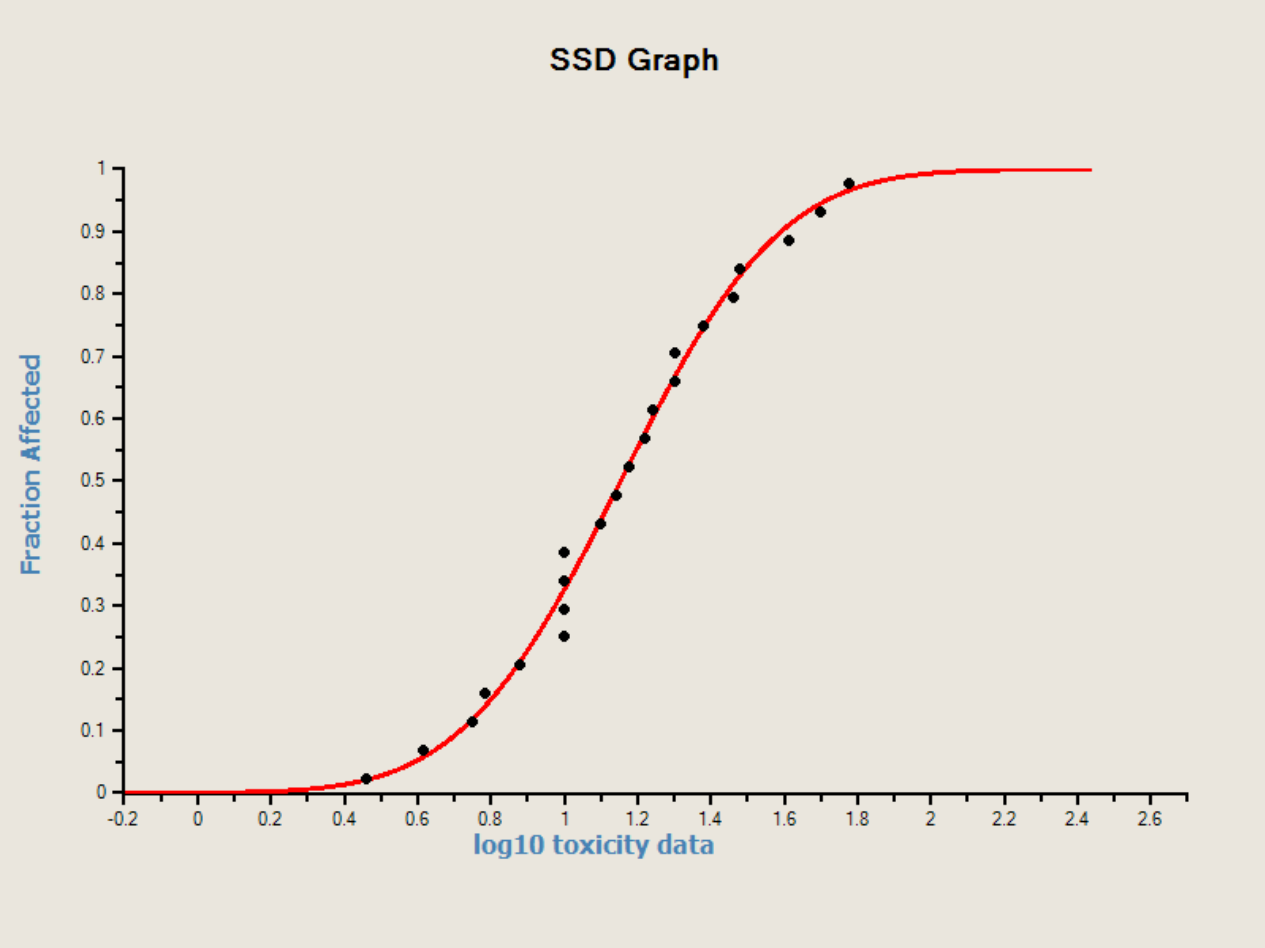
In cases where there were several studies of the same species judged to be reliable, a species geometric mean value was calculated. For data such as for *Ictalurus punctatus, Bufo fowleri* and *Oncorhynchus mykiss*, all studies were done in the same laboratory, so the species mean procedure is appropriate.

For the *Ambystoma* and *Rana sylvatica* data, the reported values were actually LOEC rather than NOEC values, so they were incorrectly included in Dyer (2001).

The Netherlands (2006) data selection included several values taken from Van der Plassche et al. (1999) that could not be verified from original studies because the cited reference was a review article (Raymond and Butterwick 1992) that provided ranges of endpoints distinct from the number shown in the Netherlands review. The endpoint for the fathead minnow (*Pimephales promelas*), for example, cited the Van der Plasseche et al. review, listing the Raymond and Butterwick article as the source. That reference cited an unpublished Procter and Gamble company study, so the information cannot be evaluated.

Figure 7-2. Chronic Aquatic Toxicity: Species Sensitivity Distribution

SSD curve from data in Table 7-12 (software: ETX 2.0, Van Vlaardingen et al. 2004)



The use of Birge and Black (1977) data for trout has been discouraged if other data are available. To investigate how this would affect the SSD, the trout NOEC value was removed from the data set and the ETX software run again. The resulting HC_5 was 4.29 mg-B/L (90% CI 2.5 to 6.2 mg-B/L).

Based on the data evaluated as reliable, the recommended HC_5 is 3.8 mg-B/L.

Endpoints based on guideline chronic studies are: *Brachydanio rerio*- 5.6 mg-B/L, *Selenastrum capricornutum* – 17.5 mg-B/L, and *Daphnia magna* – 10 mg-B/L.

Marine environment The PNEC for the marine environment should be based on the available marine toxicity data with the corresponding assessment factor. When insufficient marine toxicity data are available, an HC_5, resulting from freshwater data can also be used. However, the TGD does not mention which assessment factor(s) should be applied to the freshwater HC_5 for extrapolation to the marine environment.

Only limited data for the marine environment are available. Table 7-1 notes values for fish: 96h LC_{50} values of 74 mg B/L for *Limanda limanda* and 40 and 113 mg B/L for *Oncorhynchus kisutch* (< 1-y old). Data for the eel are not judged suitable for use.

Data for sea urchin (*Anthocidaris crassipina)* reproduction (Table 7-5) reported a NOEC of 79 mg-B/L.

Antia and Change (1975) provide a large set of data for marine green algae, bluegreen algae and diatoms (Table 7-2). Test durations varied with algal type and intrinsic growth rate, ranging from 10 to 40 days. NOEC values were 5 mg/L (1 alga), 10 mg-B/L (10 algae), 50 mg-B/L (4 algae) and 100 mg-B/L (2 algae). The most sensitive alga was *Emiliania huxleyi*, while the least sensitive were *Agmenellum quadruplicatum* and *Anacystis marina*. The endogenous boron level was reported to be 3.65 mg-B/L, reflecting the natural seawater diluent used.

It has to be noted that oceans have a natural level of boron of about 5 mg/L (Raymond and Butterwick, 1992). Because the natural level of boron in seawater exceeds the natural levels in most freshwater, it would seem that marine organisms would be less sensitive to boron than freshwater organisms. Further, organisms in estuarine areas, where salinity varies between fresh- and salt-water conditions, would naturally experience background concentrations from <1 to ca. 5 mg-B/L. Consequently, a PNEC derived using normal TGD approaches would therefore likely to fall within the margin of error of boron measurements and natural fluctuations.

The TGD (Table 25) proposes that for saltwater, using the lowest long-term NOEC from three freshwater or waltwater species (normally algae and/or crustaceans and/or fish) representing three trophic levels, an application factor of 100 be applied.

The Netherlands (2006) suggested a $PNEC_{added,\ marine}$ of 0.02 mg-B/L. This was derived by using the lowest freshwater NOEC with an application factor of 100. The lowest NOEC in their selected data was for trout (Table 7-12), although the exact source of the value presented (2 mg-B/L) is unclear.[8]

The TGD in a footnote to this proposal goes further to suggest that the AF may be reduced to a minimum of 10 where short-term tests for additional species representing marine taxonomic groups (for example echinoderms or mollusks) have been carried out and indicate that there are not the most sensitive group, and it has been determined with a high probability that long-term NOECs generated for these species would not be lower than tha already obtained.

The study on sea urchin spawning and development (Kobayashi, 1971) represents the potential effects on a sensitive life-stage of this echinoderm. The measured NOEC, 79 mg-B/L strongly suggests that this taxa is not more sensitive than either fish, algae, or freshwater invertebrates.

[8] The Netherlands (2006) identifies van der Plassche et al (1999) as the source of the value, with a reference to Raymond and Butterwick (1992). However that reference simply presents a number of NOEC values from the Birge and Black (1977) studies, none of which is "2".

Further, the preliminary Technical Reference Document RIP 3.2-1B (WP3) suggests that a lower AF may be considered for substances with a non-specific mode of action. Specific mechanisms for borate action appear to be borate anion interaction with polyols of biological importance. The most likely target compounds of borate, within the cell, are the pyridine nucleotides such as NAD and NADP (Lloyd, 1993). Hunt (1998) suggested a number of roles in reversible inhibition of enzymes through reaction with a nitrogen group or with one to four hydroxyl groups. The widespread distribution of borate, including in marine waters suggests that organisms a number of biochemical roles. Identification of transporter molecules provides evidence of organism ability to actively regulate borate levels (Takano et al. 2002, Park et al, 2004, 2005). These provide evidence that borates have a range of interactions and controls, not an irreversible and uncontrolled cellular or biochemical impact.

Based on these lines of evidence, an AF of 10 is proposed for derivation of a $PNEC_{added,marine}$ in combination with the lowest freshwater NOEC from guideline chronic studies, ie. the *Brachydanio rerio* NOEC of 5.6 mg-B/L. The resulting value would be: 0.56 mg-B/L (added).

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7.1.2.1 PNEC water

To address residual uncertainty, an assessment factor is applied to the toxicity test results, or other endpoints. For a calculated HC_5, an assessment factor of between 5 and 1 is to be applied. For field or multispecies data, a similar factor may be justified.

The following points have to be considered when determining the size of the assessment factor:
- the overall quality of the database and endpoints covered, e.g. if all the data are generated from “true” chronic studies (covering all sensitive life stages).
- the diversity and representativity of the taxonomic groups covered by the database and the extent to which differences in the life forms, feeding strategies and trophic levels of the organisms are represented.
- knowledge on presumed mode of action of the chemical (covering also long-term exposure).
- statistical uncertainties around the 5^{th} percentile estimate, e.g. reflected in the goodness of fit or the size of the confidence interval around the 5^{th} percentile, and consideration of different levels of confidence (e.g. by a comparison between the 5% of the SSD (50%) with the 5% of the SSD (95%).
- comparisons between field and mesocosm studies, where available, and the 5^{th} percentile and mesocosm/field studies to evaluate the laboratory to field extrapolation.

The data incorporated into the chronic SSD evaluation, combined with the multispecies data and the field studies address most of the points to be considered:
- Over 35 NOECs for 22 species divided over nine taxa were available to calculate the SSD. This includes fish early life-stage data and full life-cycle studies for daphnids and algae. These are considered the sensitive life stages.
- Additional embryo-larval studies have been conducted for fish and amphibians that demonstrate the potential for deficiency symptoms in these aquatic species.
- Studies on the biocidal mode of action in sensitive insect species have been published.

- The statistical properties of the SSD estimates of the 5th percentile show a reasonably good fit as calculated by the ETX 2.0 software. The output stated that the data fit a log-normal distribution at all significance levels.
- Only one NOEC fell below the HC_5 value – the largemouth bass species mean.value of 2.89 mg-B/L. Two studies were incorporated into that mean, and only one of those was itself below the HC_5.
- Multispecies studies under laboratory conditions found no-effect concentrations of 1 to >4 mg-B/L. Outdoor studies reported no effects from 0.7 to 1.52 mg-B/L. Because there were no higher exposures tested, these are not, strictly speaking, NOEC, so selecting the lowest of these is not valid. Rather, the higher values suggest that no effects occur up to that value.
- Studies of trout populations indicated successful survival and reproduction in waters ranging from 1.2 to 17 mg-B/L and higher. Notably, these concentrations are variable, so the success of this sensitive species represents a more generalized situation than simple development of a locally tolerant population.
- Investigations of other fish and aquatic organisms in the field (as noted by Dyer, 2001) indicate absence of adverse effects at ambient boron concentrations approaching the 5th percentile SSD (HC_5) value, supporting a reduced application factor.

Based on the abundance of data, the goodness of fit to an SSD model, and the demonstrated viability of ecosystems near or even exceeding the calculated HC_5 value, an application factor of 2 would result in PNEC that field and multispecies data suggest would be protective and well within the concentrations encountered in the natural environment. Using an application factor of 2 with an HC_5 value of 3.8 mg-B/L would result in a PNEC-water of 1.9 mg-B/L.

The TGD recommends comparing PNEC values derived by different calculations. Three alternatives are calculated below.

1. The combination of HC_5 = 3.8 and AF = 2 would result in $PNEC_{added,aquatic}$ of 1.9 mg-B/L.

2. The default (maximum recommended) AF for use with a SSD is 5. A combination of this with the HC_5 = 3.8 and AF = 5 would result in $PNEC_{added,aquatic}$ of 0.77 mg-B/L.

3. Use of the lowest NOEC (*Brachydanio rerio*, 5.6 mg-B/L) with the AF=10 would result in $PNEC_{added,aquatic}$ of 0.56 mg-B/L.

4. If the trout data from Birge and Black are eliminated from the procedure, then HC_5 = 4.3 and AF = 5 would result in $PNEC_{added,aquatic}$ of 0.89 mg-B/L.

5. The Netherlands (2006) proposed a HC_5 = 3.2 and AF = 5 which resulted in a proposed $PNEC_{added,aquatic}$ of 0.64 mg-B/L for exposures related to wood-treatment (i.e, situations within the scope of the Biocidal Products Directive).

The Netherlands acknowledged that the data set met the TGD criteria regarding the diversity and representivity of the data set. Since that review, additional plant and protozoan data have been incorporated into the analysis.

One of the TGD criteria addresses the overall quality of the dataset and endpoints covered. The quality of the Birge and Black data has been of concern, but the concern has been that results from that group are too conservative and tend to overstate risk. The endpoints have included the full life cycle for algae and daphnids, and critical life stages for fish and insects. Thus the criteria should be considered to be met.

A third criteria is knowledge of the mode of action of the chemical. Specific mechanisms for borate action appear to be borate anion interaction with polyols of biological importance. The most likely target compounds of borate, within the cell, are the pyridine nucleotides such as NAD and NADP (Lloyd, 1993). Hunt (1998) suggested a number of roles in reversible inhibition of enzymes through reaction with a nitrogen group or with one to four hydroxyl groups. The widespread distribution of borate, including in marine waters suggests that organisms a number of biochemical roles. Identification of transporter molecules provides evidence of organism ability to actively regulate borate levels (Takano et al. 2002, Park et al, 2004, 2005). Evidence from frog studies indicates that boron deficiencies interfere with Xenopus organogenesis, slow metamorphosis and increase abnormal development. Studies in Brachydanio showed that embryonic development was arrested by boron depletion, but could be resumed when boron became available (Rowe et al. 1988). While knowledge of the mode of action is not complete, many roles and interactions are known. This criteria should be considered to be met, at least partially.

A fourth criteria is to compare the HC_5 with field and mesocosm studies. Guhl (1992a, 2000) described outdoor pond studies were no effects were observed at 0.7 to 1.52 mg-B/L. The CWE of 1.52 mg-B/L is almost consistent with the $PNEC_{added,aquatic}$ derived from HC_5 = 3.8 and AF = 2, and certainly corroborates the adequacy of all the other PNEC values. The CWE from this study would support an AF=2.5, using the HC_5 = 3.8. This critiera should be considered to be met, at least in part.

The final criterion is the statistical uncertainties around the 5th percentile (HC5) as reflected in the goodness of fit or the size of the confidence interval around the HC5. Inspection of the SSD (Fig. 7-2), as well as the statistical tests in ETX confirm that the dataset fits the curve very well, particularly at the lower extreme.

The statistics of the SSD also show that choice of the $PNEC_{added,aquatic}$ will have minimal effect on the expected levels of ecological protection: all values are highly protective. The "fraction affected" (FA) can be calculated using the ETX 2.0 program by using the $PNEC_{added,aquatic}$ values as exposure estimates (Van Vlaardingen et al. 2004). Comparing various $PNEC_{added,aquatic}$ values noted above with the fraction not affected ($1\text{-}FA_{median}$) shows that the lower values provide minimal additional protection:

Scenario	$PNEC_{added,aquatic}$ (mg-B/L)	Fraction of Species protected
Recommended Selection: HC_5 = 3.8 with AF=2	1.9	$\geq$ 99.4%
Default AF: HC_5 = 3.8 with AF=5	0.77	$\geq$ 99.99%

Deterministic approach	0.56	≥ 99.99%
Excluding trout data, default AF: HC_5 = 4.3 with AF=5	0.89	≥ 99.97%
The Netherlands BPD proposal: HC_5 = 3.2 with AF=5	0.64	≥ 99.99%
Using multispecies data: HC_5 = 3.8 with AF=2.5	1.52	≥ 99.77%
Using European drinking water standard for boron	1	≥ 99.96%

All the $PNEC_{added,aquatic}$ values would be expected to protective of over 99% of aquatic species. As the above table shows, if the criterion value is below 1 mg-B/L, any expected increase in species protection is less than 0.1%. Evidence from ecological studies suggests that such levels of fluctuations would be within the usual range of species dynamics. The level of statistical uncertainty associated with an AF=2 is very low.

Based on comparison of alternative $PNEC_{added,aquatic}$ values, an AF of 2 would be consistent with all the TGD criteria for derivation of an AF. This would result in a $PNEC_{added,aquatic}$ of 1.9 mg-B/L.

7.1.2.2 PNEC sediment

The TGD notes that substances potentially capable of depositing on or sorbing to sediments to a significant extent have to be assessed for toxicity to sediment-dwelling organisms (p. 111). The TGD further clarifies that substances with a Koc < 500-1000 L/kg or log Kow ≥ 3 may be considered triggers for significant sorption. While the Koc and Kow parameters do not readily apply to inorganics and metals, the low partitioning factor for boric acid (Kp = 2.6 L/kg) suggests that boric acid and borates are not likely to be significantly sorbed and the need for assessment of toxicity to sediment-dwelling organisms is small.

Data for sediment dwelling organisms is limited with only a single chronic study available (Table 7-4) which reported a 28-day NOEC of 180 mg-B/kg-dry weight for the midge *Chironomous riparious.* Use of an application factor of 100 with this single chronic study would result in a PNEC-sediment of 1.8 mg-B/kg-dry wt.

Other data on sediment-dwelling organisms included data on another midge (Chironomus decorus) and on tubificid annelids. The midge studies were done in sediment-free test systems, so the results cannot be applied. The tubificid worm data is also expressed as mg-B/L, so the results cannot be applied

Application of the equilibrium partitioning approach of the TGD could be done by assuming that the $PNEC_{added,aquatic}$ is appropriate and that the partitioning data for soil applies to sediment as well. The Kp for soil was estimated as 2.6 L/kg, although the variability of the estimate was

very large (standard deviation 2.7). Using Formulas 24 and 70 of TGD-Part-II would result in an estimated PNEC-sediment of 2.6 mg B/kg-dry wt, based on the $PNEC_{added,aquatic}$ above.

The recommended $PNEC_{added,sediment}$ is 2.6 mg-B/kg-dry wt because it is based on a more complete data set than the deterministic approach based on a single insect test.

7.2 Terrestrial compartment

Boron is naturally present in soil at average levels of between 10-20 ppm although there are geographical areas that are much higher (ECETOC, 1997). It is only the water soluble boron content of the soil that is available to the plant (Goldberg, 1993). Boron availability to plants is strongly associated with the soil soluble boron, usually measured as the hot-water-soluble fraction. This usually ranges from 0.4% to 4.7% of total boron. Availability is also affected by soil composition and pH (Eisler, 2000).

Effects of boron on terrestrial organisms have been studied extensively for plants, particularly in connection with boron deficiencies. Studies on soil microbes are limited, but suggest that bacteria and fungi are not particularly sensitive to boron. Studies on invertebrates include those to demonstrate efficacy of high boron concentrations as pesticides, some on non-target species, and one OECD 207 test on earthworm.

Boron has been recognized as essential for higher plants, but is phytotoxic when in excess. Boron deficiency is more widespread than that of any other micronutrient (Gupta et al. 1985). Toxic levels generally do not occur on agricultural lands unless boron has been added in excessive quantities, such as with fertilizer minerals, irrigation water, sewage sludge or coal ash. Symptoms of boron toxicity are similar across species and consist of a marginal and tip chlorosis which is quickly followed by a necrosis. Most research on plants has been associated with agricultural applications and crop yield. Such studies are usually longer term than specified by OECD or similar guidelines.

Because boron is a necessary plant micronutrient, it is intentionally added in some instances where required by crop plants and limited in the natural soil. This may be in the form of formulated fertilizers broadcast to agricultural soils or sprays applied directly to the plant or vicinity of the plants. In these instances, it is appropriate to use a PNEC for agricultural soil that protects the agricultural uses of the soil, rather than a PNEC derived to protect non-agricultural or non-industrial soil. This is consistent with TGD distinctions in developing PEC for agricultural, natural/grassland, and industrial soil (TGD, Section 2.3.8.5).

A PNEC for agricultural soil should be derived based on toxicity, but also with consideration of the risk of deficiency. For natural soils, the presumption is that locally-adapted species will not be adversely affected by boron deficiency, so only boron toxicity is relevant for deriving a PNEC.

7.2.1 Toxicity test results

Terrestrial studies have mostly involved plants, reflecting the widespread boron deficiencies observed in certain agricultural regions. As detailed below, studies of terrestrial invertebrates suggest that plant toxicity is the more sensitive endpoint. As noted above, agricultural application rates of 1-2 kg-B/ha translate to soil concentration additions of 0.3 to 0.6 mg-B/kg..

7.2.1.1 Toxicity to soil macro organisms

Terrestrial invertebrate chronic values were approximately 10 times lower than acute values, as shown in Table 7-7. Data from repeated testing of earthworms (*Lumbricus terrestris, Eisenia andrei and E. fetida)* was conducted by Stantec (2004) and Stantec/AEC (2003) in connection with developing a method for testing contaminated soils. The 14-day acute LC50 for survival was for *Lumbricus terrestris, Eisenia andrei* and *E. fetida* were 473, 609 and 693 mg-B/kg-dry soil, respectively, Tests of chronic response of *E. andrei* in 56 to 63 day tests resulted in NOEC value of 54 mg-B/kg dry soil (determined as the geometric mean of 4 tests). Tests of the collembolan *Folsomia candida* found NOEC values (based on reproduction) of 14 and 21 mg-B/kg dry soil, giving a geometric mean value of 17 mg-B/kg dry soil (EPFL, 2003). Tests of the collembolan *Onychiurus folsom* found NOEC values (based on reproduction) of 22 and 44 mg-B/kg dry soil, giving a geometric mean value of 31 mg-B/kg dry soil (ESG, 2003). A 14-d study per the OECD guideline for *Eisenia Andrei* reported a NOEC value of >175 mg-B/kg-dry soil (Henzen, 2000). These data, summarized in Table 7-7, represent 5 species including 3 earthworms and 2 collembolans. The most sensitive species of the group was found to be the collembolan (springtail) *Onychiurus folsomi.*

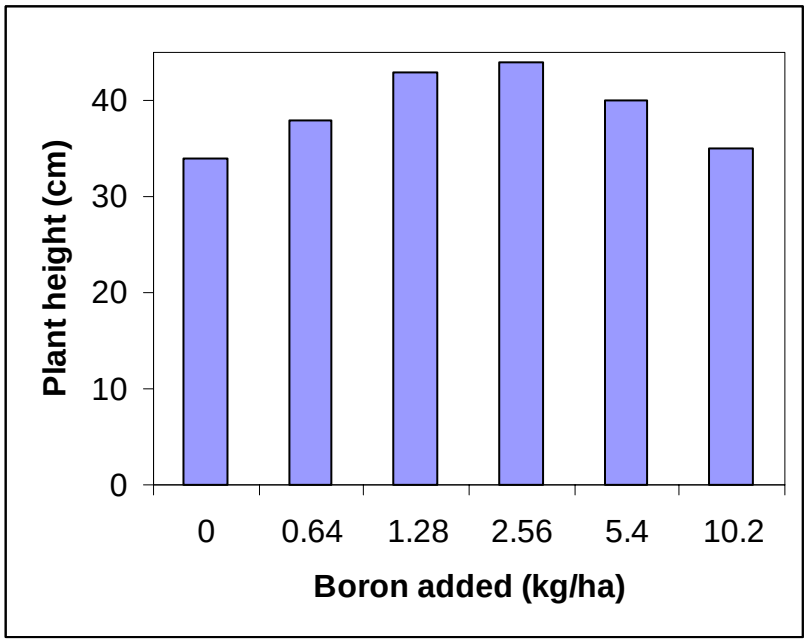
7.2.1.2 Toxicity to terrestrial plants

Boron is an essential micronutrient for all plants and borates are added to agricultural land in amounts determined by the needs of the crop. However, boron is phytotoxic at higher concentrations.

An illustration of a deficiency-toxicity pattern is shown in Fig. 7-3. Shuxiang et al. (2002) measured oil rape (*Brassica oleracea* cv "Zhongyou 119") growth in B-deficient soil from southeast China. Plant height showed optimal growth at 1.28-2.56 kg-B/ha addition. Biomass was significantly increased at the 2.56 kg-B/ha addition relative to other treatments. Symptoms of boron toxicity (scorching of older leaf margins) were seen at the highest addition level.

Figure 7-3. Boron deficiency and toxicity in oil rape (*Brassica oleracea)*

Plant height at harvest in pot experiments using a B-deficient soil (after Shuxiang et al., 2002).



The band between essentiality and toxicity is typically narrow (e.g., less than 10-fold). Symptoms of boron toxicity are similar in most plants and consist of chlorosis of the tips and margins of older leaves (Shorrocks, 1997). Leaves normally contain 40-100 mg B/kg dry weight, rising to 250 mg B/kg dry weight when soils approach toxic levels. A level of between 700-1000 mg/B/kg will occur in cases of extreme toxicity (Nable et al, 1997). However, most studies of plants focus on yield which is the endpoint of agricultural interest. This may be considered a chronic, sub-lethal endpoint.

Table 7-8 summarizes a number of plant studies. Many of these are publications from the technical published literature. Of particular relevant are those for the species *Brassica oleracea, Helianus annus, Hordeum vulgare, Medicago sativa,* and *Sorghum vulgare* as these appear to be among the more sensitive species.

Riley et al (1994) evaluated several endpoints in barley (*Hordeum vulgare* L.vc. Stirling), including harvest index, leaf necrosis, and plant growth form. Riley et al. noted that foliar injury symptoms characteristic of B toxicity can be markedly expressed without reductions in the growth or grain yield of barley plants. They indeed found that yield, measured as harvest index, was not affected by boron soil additions of up to 4 mg-B/kg. Boron concentrations did increase, more markedly in shoots than roots. Concentrations in grain were very low relative to straw (2-4 mg-B/kg-grain) except at the highest soil exposure (8 mg-B/kg-soil). At maturity, the percentage of leaf covered in dark necrotic spots and lesions generally increased with increasing B. The number of tillers produced was not altered markedly, but the percentage of tillers that lodged did increase. This change was notable at the 2 mg-B/kg-soil level. Thus the NOEC obtained from this study was 1 mg-B/kg-soil, based on percentage of lodged tillers. Riley et al. noted that the cultivar Stirling barley appears the most susceptible to B toxicity .

Aitken and McCallum (1988) evaluated toxicity of boron in soil porewater to sunflower (*Helianthus annuus*) over 14 days, reporting a toxicity threshold of 1.9 to 2.4 mg-B/L,

depending on which model was fitted to the data. The measured endpoint was dry weight of above-ground biomass. However, toxicity was not observed in all soil types tested. Plants were transplanted to soils with boric acid, so germination was not evaluated and plants were actually more than 14 days beyond germination. Thus while the duration of the study may appear short, the study may be considered longer than typical acute studies.

Gupta and Cutcliffe (1984) measured responses of the bean *Phaseolus vulgars* and the cabbage *Brassica olearacae* following field applications of 0, 2.2, 4.4 and 8.8 kg-B/ha. Assuming typically soil densities, this is equivalent to additions of 1.5, 2.9 and 5.9 mg-B/kg-soil. Gupta and Cutcliffe found toxicity at 2.9 mg-B/kg-soil for the bean, but no adverse effects on cabbage yield at all application rates. The resulting NOEC values are: bean NOEC 1.5 mg-B/kg-soil, and cabbage 2.9 mg-B/kg-soil.

Van de Plassche et al. (1999) report plant toxicity results for alfalfa (*Medicago sativa*) and sorghum (*Sorghum vulgare sudanense)* citing the previous review by Crommentuijn et al.(1995). That review cites (without any comments about the details of the original studies or their reliability) studies on alfalfa by Gestring and Soltanpour (1987) with a geometric mean NOEC of 11 mg-B/kg-soil. Similarly, the work of Adriano et al (1988) on sorghum is cited with a geometric mean chronic NOEC of 5 mg-B/kg-soil. These values were incorporated into the assessment by the Netherlands (2006) without elaboration.

A number of entries in Table 7-8 are from unpublished reports by Aquaterra Environmental so some discussion of these results is appropriate. These studies were in support of a newly published test method for contaminated soils proposed by Environment Canada (2005) for measuring emergence and growth of terrestrial plants. The method recommends use of boric acid as a reference toxicant. The short term study results (7- and 10-day EC50s for shoot length) for the 12 plant species tested ranged from 79 mg-B/kg-soil (dry wt) for carrot (*Daucus carota*) to 281 mg-B/kg-soil (dry wt) for alfalfa (*Medicago sativa*). In an interlaboratory study, 6 laboratories tested cucumber (*Cucumis sativus* var. Marketmore 76) and found the mean 7-day EC50 for shoot length was 121 mg-B/kg-soil (dry wt)

The Aquaterra study used a reference soil described as a fine loam with a relatively high organic content (11.6 to 12.2%); boron content was only reported graphically, appearing to range from zero to 20-30 mg-B/kg-dw. The regression line describing the nominal vs. measured boron concentrations suggested that control soil (nominally zero boron) really had virtually no boron (X-intercept = -5.28). The artificial soil included sphagnum moss, but was measured to have a lower organic content (3-5%) than the reference soil. Boron content of the artificial soil appeared graphically to be higher (X-intercept = 20.3). Boron analysis was by nitric acid digestion, allowing no determination of the bioavailable fraction; presumably virtually all the added boric acid was available within the timeframe of the testing.

The tests reported by Aquaterra are short term (5 to 9 days) with endpoints being seedling emergence, shoot which is a short-term response of a critical life-stage, so evaluation as “no-effect-concentration” may be considered appropriate. Some indications of hormesis (stimulation at low exposures) do occur, even though the lowest boron addition was extremely high (addition of 28 mg-B/kg-dry soil).

Another large number of species results are by Eaton (1944), testing 50 species in outdoor sand solution. Eaton tested 6 exposure levels, from trace boron amounts (0.3 to 0.4 mg-B/L-nutrient solution) and recorded plant weight at maturity, measured boron concentrations in plant tissues, and noted symptoms of toxicity and deficiency. Deficiency was determined symptomatically in the trace solution, but also by less than maximal weight. Eaton's results have been used by Sprague (1972) and Eisler (2000) as the basis of tolerance groupings. Table 7-11 shows such a grouping.

Butterwick et al (1989) observed that the range of concentrations within which boron is essential to some plants overlaps the range where it is toxic to other species. Sprague noted that over 70% of the plants tested by Eaton did best with more than a trace of boron, and 46% did best with more than 1 mg-B/L. The ratio of concentration where toxicity symptoms was observed to the concentration where deficiency was measured (toxicity/deficiency) indicates a relatively narrow range of tolerance: for 49% of the cases, the ratio was 2 or less. In 39% of the cases, the ratio indicated that symptoms of toxicity were evident at or below concentrations where plant growth was optimal.

Based on the soil solution test results, Eisler (2000) suggested that 1 mg-B/L be considered a likely guideline for protection of sensitive plant species. Eisler (2000) and Gupta (1985) suggested that concentrations of 5 to 10 mg-B/L are consistently associated with toxic effects.

No SSD or similar statistical distribution appears in the literature.

Applying the equilibrium partitioning approach to a soil solution or soil pore-water criterion of 1 mg-B/L, a value based on dry soil can be developed. Using the average K_P of 2.6 L/kg, the soil-water partition coefficient $K_{soil\text{-}water}$ is calculated as 4.16 m^3/m^3, assuming that boron does not partition into air (see TGD-Part II, p. 47, formula 24). With this $K_{soil\text{-}water}$, a pore water concentration of 1 mg B/L is equivalent to a soil concentration of 2.4 mg B/kg dwt soil (see TGD-Part II, p. 85, formula 67). Based on Eaton's data, about 46% of plants would exhibit less-than-optimal growth (ie, deficiency) at soil solution levels below 1 mg-B/L. Consequently, selecting such a low criterion would set the total risk (probability of toxicity plus probability of deficiency) at nearly half of the species studied.

Consideration of total risk.

A significant issue for a risk assessment is the treatment of the entire range of plant species. Because the range of deficiency to toxicity for boron is relatively narrow among plants, and the requirement for boron varies, a threshold set to prevent toxicity to sensitive plants could simultaneously mean that another group of plants will suffer advers deficiency effects. As noted by Sprague (1972) and others, a threshold of 1 mg-B/L soil solution would result in amost half of plants suffering deficiency. Risk estimations that consider only sensitive species could result in setting PNEC-soil that put significant percentages of plants at risk of deficiency.

If the targeted risk management goal is to protect the majority of species, eg. 95% or more, then the default conceptual model of exposure/response is not correct. The default conceptual model only considers preventing adverse effects (toxicity) by evaluating what fraction of species would be protected by exposures less than the PNEC. The default model, or S-shaped curve, includes a presumption that less exposure is always better. For an essential nutrient, the correct conceptual model includes evaluation of what fraction of species would be adversely affects by

deficiencies at exposures less than the PNEC. The actual risk is the combination of probability of adverse effects from toxicity plus the probability of adverse effects from deficiency.

A parallel situation for human nutrition was considered by a joint FAO/WHO workshop (2006) which noted that use of standard safety or application factors could result in recommendations leading to less-than-adequate levels of nutrients or related substances. The workshop noted that situations where the beneficial levels of intake overlap the level associated with toxicity risk would be problematic. A strategy recommended by IPCS (2002) to define the upper (toxic) and lower (deficiency) boundaries in the risk assessment was to select lower and upper boundaries that include 2.5% probability of adverse effects, i.e., the range was set to be protective of 95% of the population based on total risk.

In derivation of PNEC $_{\text{added, terrestrial}}$ application factors are used, ranging from a (theoretical) minimum of 1, up to 1000, based on the nature and type of data. The narrow range between toxicity and deficiency in plants, as shown by data indicating the concentration range between toxicity symptoms and deficiency symptoms is less than 5 (53% of cases) and often less than 2 (49% of cases), suggests a scientific reason why smaller AF might be suitable, particularly if subtle endpoints are used.

Wongmo et al (2004) illustrated the narrow band between toxicity threshold and deficiency. He tested several cultivars of barely, including the Stirling strain used by Riley et al (1994), which demonstrated a low NOEC of 1 mg-B/kg-soil. In Wongmo's tests, boron was added at 1.1 kg/ha (equivalent to 0.75 mg-B/kg-soil) to a soil withmeasured boron levels of 0.15 mg-B/kg. Addition of boron increased yields of the Stirling cultivar significantly, demonstrating that extrapolating much below the NOEC from the Riley et al. study would not be protective, but harmful. This strengthens the case that a PNEC for agricultural soil might neeed separate development than for natural/grassland soils.

7.2.1.3 Toxicity to soil micro-organisms

Bowen and Gauch (1966) evaluated fungi and found toxic effects at 50 to 4000 mg-B/kg using solid culture media. They reported a strong inhibition in micromycetes at concentrations above 1000 mg-B/kg. Several reported NOEC values include: *Aspergillus niger* (black mould), 1200 mg-B/L; *Neurospora crassa* (bread mould), 100 mg-B/L; *Penicillium chrysogenum,* 1000 mg B/L; and *Saccharomyces cerevisia* (yeast), 5 mg-B/L. Because these values were based on concentrations in nutrient solution, they cannot be readily translated to PNEC values for dry soil.

Crommentuijn *et al* (1995) summarized reports on the effect of boron on a range of microbial processes including nitrification and dehydrogenase, arylsulfatase and urease enzyme activity. A range of soil types were tested with organic matter and clay contents ranging from 2.27 to 9.27% and 17 to 45% respectively. No differences in effects were observed between the different soils. Interpretation of the effect data is difficult because of poor concentration-response relationships. However, the studies do indicate that nitrification was more sensitive than dehyrodgenase and arylsulfatase activity and of similar sensitivity to urease activity. The lowest effect concentration was reported as an EC_{11} of 5.4 mg/kg boron (dry weight) for urease

activity, although other tests from the same authors reported endpoints 10-fold greater. The NOEC's and EC_{50} in this report were established by applying factors to the test concentrations, depending on the observed effect percentage, as part of the Dutch procedure for setting general environmental quality criteria. The NOEC's and EC_{50} should therefore not be used as such for the present assessment.

Studies of soil processes include: Inhibition of dehydrogenase activity: 24-h EC_{50} = 152 (for unenriched soil) and 363 mg B/kg dry soil (for enriched soil) (Rogers and Li, 1985; study with $Na_2B_4O_7.10H_2O$), and Nitrogen mineralisation: 20-days EC_{10} = 54 mg B/kg dwt soil (Liang and Tabatabai, 1977; study with $Na_2B_4O_7$). These also were cited by Crommentuijn et al (1995), which in turn was cited in the assessment by the Netherlands (2006).

Boron compounds historically have been used against bacteria in the form of antiseptics and as preservatives in cosmetics and food. Some species of fungi exhibit effects of boron toxicity, resulting in the aborted growth of hyphae, perithecia and ascospores (Bowen & Gauch, 1966). The use of borates as preservatives in foods has been largely discontinued.

Borates are extensively used in biodeterioration control and wood preservation. These applications are regulated as pesticides for control of wood rotting fungi and wood-boring beetles and termites. Application rates up to about 1.2% (w/w) are required to be effective.

Although test results for the fungi *Penicilium* and yeast *Saccharomyces* are reported in Table 7-9, they were reported in mg-B/L, so are not readily translated to soil. Consequently, the critical studies are for dehydrogenase in soil and nitrification in soil.

7.2.1.4 Toxicity to other terrestrial organisms

Toxicity to birds

Study summaries of toxicity to birds are shown in Table 7-10. Body weight of bobwhite quail fed 3160 ppm boric acid (9.5 mg-B/kg) in their diet was reduced to 78% of control average in a standardized 8 day test (Beavers, 1984). Mortality was not affected, even at the highest dose of 5620 ppm boric acid. Adult mallard ducks fed up to 1000 mg-B/kg-diet (fresh weight basis) for 21 days were not affected, although duckling weight gain was reduced when fed 30 and 300 mg-B/kg-diet (Smith and Anders, 1989). Boron fed to mallards at 450 ppm boron (wet weight) for 90 days or more showed no effects other than male liver weight/body weight increased (from 0.020 to 0.022) relative to controls (although the ratio was 0.020 in the 900 ppm boron group) (Stanley et al., 1996). Ducklings of pairs fed the 450 ppm diet showed increased duckling survival between 7 and 14 days relative to control. Both adults and ducklings were affected by the 900 ppm boron diet.

These data may be used to determine the risks for secondary poisoning. However, as previously established, bioaccumulation and biomagnification are not likely to play a significant role for borates.

Toxicity to other above ground organisms

Values for toxicity to honeybee are reported in Table 7-10, but cannot be considered reliable.

Data for terrestrial mammals is available, including rodents, rabbits, dogs, sheep and cattle. Derivation of a PNEC for soil would require evaluating the amount of soil incidentally ingested. Factors such as these are available (e.g. US EPA Wildlife Exposure Factors Handbook); however the likely results would not show NOEC or EC10 values below those for plants.

7.2.2 Calculation of Predicted No Effect Concentration (PNEC_soil)

Based on data from soil macro-organisms, soil micro-organisms and terrestrial plants, the PNEC-soil will reflect boron toxicity to plants. Mean chronic values for annelids and collembolans range from 14 to 54 mg-B/kg-soil, while micro-organism endpoints exceed 50 mg-B/L. Plant data suggest toxicity effects down to 1 mg-B/kg-soil.

If the most sensitive plant endpoint (1 mg-B/kg-soil) is used as the critical NOEC for soil, then use of a default application factor of 10 results in a criterion of 0.1 mg-B/kg-dry soil.

Appropriateness of default approach

Microfertilization Practice: Agricultural practice applies boron to soil at rates varying with crop, but generally in the range of 0.5 to 7.6 kg-B/ha. This corresponds to a soil concentration of 0.15 to 2.3 mg-B/kg. Mortvedt et al. (1992) reported application rates resulting in 0.16 to 2.0 mg-B/kg. Van de Plassche et al. (1999) used a smaller soil density (1400 kg/m^3) but obtained approximately the same results. Other recommended fertilisation rates for boron-poor soil are 1 to 1.5 kg B/ha (Van Dijk, 2003; BC, 1991).

The default approach would result in concluding that current agricultural practices present unacceptable risks to plants. This conclusion is clearly at odds with the widespread recognition and history of beneficial effects of boron microfertilization.

Irrigation Practice: Studies in which crops were irrigated with boron containing waste water, report no effects on crop growth or yield at boron concentrations up to 2 mg B/L (Raymond and Butterwick, 1992). Guidelines for boron content in irrigation water give maximum levels of 0.5 - 1.0 mg B/L for sensitive crops, depending on the amount of irrigation needed. These guidelines are based on concerns that, in arid environments, boron will accumulate in surface soils from continuous evaporation. When precipitation patterns result in net outflux of ground- or surface-water, such accumulation has not been observed. Consequently, these guidelines are of regional importance.

Probability of Risk of deficiency: Using the average K_P of 2.6 L/kg, the soil-water partition coefficient $K_{soil\text{-}water}$ is calculated as 4.16 m^3/m^3, assuming that boron does not partition into air (see TGD-Part II, p. 47, formula 24). With this $K_{soil\text{-}water}$, a NOEC of 1 mg B/kg dwt soil is equivalent to a pore water concentration of 0.41 mg B/L (see TGD-Part II, p. 85, formula 67). This is below the toxicity level for sensitive plants as defined in Table 4.2.3-2, indicating that the NOEC of 1 mg B/kg dwt soil is relatively low. Based on Eaton's data,, about 46% of plants would exhibit less-than-optimal growth (ie, deficiency) at soil solution levels below 1 mg-B/L. Consequently, selecting such a low criterion would set the total risk (probability of toxicity plus probability of deficiency) at nearly half of the species studied.

If one started with a soil solution level of 1 mg-B/L, as suggested by several authors as protective for most plants, then using the equilibrium partitioning approach would lead to a soil level of 2.4 mg-B/kg dw soil.

Relation to background concentrations: It should be noted that the background concentrations of boron can be as high as 200 mg B/kg, with usual levels of 45-124 mg/kg dwt. A $PNEC_{soil}$ that is < 1/10 of the natural background will be hard to detect, and this will have implications for field studies and monitoring programs. Consequently, criteria much less than 4.5 to 12 mg/kg dwt would pose practical problems and appear at odds with the naturally occurring variations.

Other plant data contradicts a conclusion of significant difference: while a NOEC for the monocot barley (*Hordeum vulgare*) was reported to be 1 mg-B/kg-soil, The NOEC for the barley based on yield was 4 mg-B/kg-soil.

The NOEC based on yield for beans (*Phaseolus vulgaris*) was reported to be 1.5 mg-B/kg-soil.

No published SSD reports are available that use a screened set of terrestrial ecotoxicity data. Given the number of results generally available, it would seem likely that such a distribution would be informative and useful. However, the review of plant data done by Eisler (2000) and others provides an approximation of a SSD approach. Their recommendation was that 1 mg-B/L be seen as a suitable criterion to protect most sensitive plants. As noted above, this is equivalent to a criterion of 2.4 mg-B/kg-dry soil.

Selection of a Critical value.

Selection of the lowest plant NOEC would lead to a criterion of 1 mg-B/kg-dry soil based on Riley et al (1994) study of *Hordeum vulgare.* However, this endpoint is based on plant appearance and may not reflect more ecologically and socially relevant endpoints (plant structure and biomass or yield). From the same study, plant structure (root/shoot ratio) had a NOEC of 2 mg/kg dry soil, and yield had a NOEC of 4 mg/kg-dry soil. A later study with the same strain of barley indicated no toxicity but rather improved biomass and yield at 0.75 mg-B/kg-soil addition (Wongmo et al. 2004).

The next lowest NOEC was 1.5 mg-B/kg dry soil based on the Gupta and Cutcliffe (1984) field study with *Phaseolus vulgaris.*

A NOEC of 1.0 mg-B/kg dry soil is recommended because it is based on a suitable study, and it is consistent with published reviews from soil solution data in combination with an equilibrium partitioning approach.

Selection of an Application Factor.

Given the nature of the data set which includes long-term field studies (e.g. entire growing seasons) plus laboratory studies, the history of use of boron in agricultural applications to benefit plant growth, the evidence of deficiency at low exposures, ample justification exists for the selection of an application factor less than 10.

First, tolerance of higher plants for high concentrations in soils has been demonstrated for several metals where metal-tolerant populations have developed in environments with increased metals, whereas in uncontaminated areas non-tolerant populationsof the same species are present. The cultivar of barley used to determine the critical NOEC has been recognized as one of the more sensitive varieties being used.

In addition, the PNEC $_{added, terrestrial}$ is regarded as a concentration that can be added to the background without inducing toxic adverse effects on the terrestrial ecosystem. However, background concentratons of boron can be as high as 200 mg-B/kg with usual levels of 45-124 mg/kg dw. A PNEC $_{added, terrestrial}$ that is < $1/10^{th}$ of the natural background will be hard to detect and this will have implications for field studies and monitoring programs.

Plants are likely the most sensitive species; NOECs for earthworms, springtails and microorganisms are about a factor of 10 higher.Calculations of the HC_5 values for seedling emergence data from Aquaterra by the Netherlands (2006) indicate that the EC20 is 4 mg-B/kg dry soil for monocotyledons, and 16 mg-B/kg-dry soil for dicotyledons. Although the EC20 is not a NOEC, the data do suggest that the low NOEC of 1 mg-B/kg dry soil is protective for the majority of plant species.

The endpoint in the barley NOEC of 1 mg-B/kg dry soil was for the number of tillers lodged. Other endpoints for root/shoot ratio and relative grain yield in that study were 2 and 4 mg-B/kg dry soil, are more in line with other available data and can be considered as more relevant to long-term population effects.

The use of boron as a micronutrient fertilizer is widespread and effective in improving crop yields. Because of the narrow range between toxicity and deficiency, a smaller AF for agricultural soil would be justified. Agricultural practice applies boron to soil at rates varying with crop, but generally at rates which correspond to a added soil concentrations of 0.15 to 2.3 mg-B/kg.

Given these factors, it is considered justified to use an AF of 5 (instead of 10) with the NOEC of 1, and set the PNEC $_{added, terrestrial}$ to 0.2 mg-B/kg dry soil. For agricultural soil, a smaller AF would be appropriate to reflect the necessities of current practice; an AF of 1 would conform to current fertilization practices.

Therefore two PNEC $_{added, terrestrial}$ values are established:

A PNEC $_{added, terrestrial}$ of 0.2 mg-B/kg dry soil for natural/grassland soils, and

A PNEC $_{added, terrestrial}$ of 1. mg-B/kg dry soil for agricultural soils where fertilization with boron is practiced.

7.3 Atmospheric compartment

Boron is released into the atmosphere from natural sources and by human activities. The relative contribution is unknown. According to some authors, coal-fired power plants are a major source (Cox et al., 1978; Gladney et al., 1978, both cited by Eisler, 1990). Other studies indicate that degassing of sea-salt particles and volcanic boron emissions represent almost all atmospheric boron sources and that anthropogenic sources such as coal burning and agricultural

fires contribute to a minor extent (Rose et al., 2000, and citations therein). Atmospheric boron may be taken up by plants, most probably via boron enriched rain. Some evidence exists of phytotoxic effects due to direct deposition of boron via cooling tower drift from geothermal steam (Eisler, 1990). It is, however, not possible to express toxic thresholds on the basis of atmospheric concentrations.

7.4 Microbiological activity in sewage treatment systems

7.4.1 Toxicity to aquatic micro-organisms

Effects of boric acid on micro-organisms are summarized in Table 7-6. Using the standardized OECD 209 method, Hanstvelt and Schoonmade (2001) reported 24% inhibition at 175 mg-B/L, and an EC10 can be calculated from their data as 58 mg-B/L. A NOEC was reported by the study authors of 17.5 mg-B/L, but was not determined via any statistical means. In actuality, there was 4% inhibition at this exposure, so it is an EC4, thus more stringent than intended by the OECD 209 protocol. An EC10 value was calculated by linear regression from the data which showed a good fit ($R^2 = 0.863$) with a value of 58.0 mg-B/L. This study complies with GLP practice, is rated as highly reliable in quality, and is consistent with earlier tests of activated sludge. This is the preferred test for derivation of the PNEC-stp.

Gerike et al. (1976), using an earlier version of the OECD activated sludge method reported LOEC and NOEC of 120 and 20 mg-B/L, respectively. Guhl (1992, 2000) reported activated sludge LOEC and NOEC of 50 and 20 mg-B/L, respectively.

Guhl (1992, 2000) reported on ciliate growth inhibition to Entosiphon sulcatum, Opercularia bimarginata, and Paramecium caudatum, with NOEC values of 15, 10, and 20 mg-B/L, respectively. Bringmann and Kuehn (1980b) reported a toxicity threshold (EC5) to the ciliate *Uronema pardaczi* of 23 mg-B/L.

Other reports include tests of the microbe, *Pseudomonas putida*, with NOEC values ranging from 7.6 to 1040 mg-B/L However, these study reports are of varying reliability as noted in Table 7-6 and it appears that the high value (1040) is incorrect. The geometric mean value of the Henkel studies is 50.8 mg-B/L (EC10 values of 340 and 7.6 mg-B/L)

7.4.2 PNEC for sewage treatment plant

The TGD provides for several alternative approaches to derivation of the $PNEC_{STP}$.

1. Using the EC10 of the Respiration inhibition test (OECD 209, Hanstvelt and Schoonmade, 2000) with an application factor (AF) of 10 results in a value of 5.8 mg-B/L .

2. Using the putative NOEC value from the same study (Hanstvelt and Schoonmade, 2000) with an AF of 10 results in a $PNEC_{STP}$ of 1.8 mg B/L. This value was recommended by the Netherlands (2006). However, Guhl (1992a, 2000) observes that

average STP boron content has been measured as over 2 mg-B/L, and as high as 3 mg-B/L. This suggests that this value is not consistent with actual STP operations.

3. Using the NOEC reported by Gerike et al. of 20 mg-B/L with an AF of 10 results in a $PNEC_{STP}$ of 2 mg-B/L. As noted, actual operations suggest this value is not consistent with satisfactory performance in STP.

4. Using the ciliate growth inhibition data, a lower AF is indicated by the TGD.Using the lowest of the three ciliate values (NOEC = 10 mg-B/L for Opercularia bimarginata) with an application factor of 1 would result in a $PNEC_{STP}$ of 10 mg-B/L.

5. Using the lowest *Pseudomonas putida* data point (EC10 of 7.6 mg-B/L, Guhl 1992a) with an application factor of 1 (per Table 17 in TGD), would result in a $PNEC_{STP}$ of 7.6 mg-B/L. Using a geometric mean of the NOEC or EC10 values of three tests (291, 7.6, 340) with AF of 1 gives a $PNEC_{STP}$ of 91 mg-B/L

The data on sewage treatment plants appears consistent, specifically that no effects are seen at boron exposures of 8 to 20 mg-B/L. The TGD notes that in some cases the $PNEC_{STP}$ varies because different application factors are applied per Table 4-6 and in such cases expert judgment should be used to determine which effect value should be used. In the present case, the application factor applied to activated sludge drives the $PNEC_{STP}$ from that calculation significantly below the $PNEC_{STP}$ calculated from ciliate inhibition tests. Pseudomonas inhibiton. This disproportionate result suggests that the appropriate $PNEC_{STP}$ would emphasize the data rather than choice of application factor. Thus use of the mose sensitive data point (from the Pseudomonas putida data set) would recommend a $PNEC_{STP}$ of 7.6 mg-B/L.

Based on evidence that operating STP plants experience average boron concentrations above the values derived by approaches 2 and 3 above, these values are not considered realistic. Using the TGD approach with the EC10 from the respiration inhibition test results in a $PNEC_{STP}$ of 5.8 mg-B/L. This is consistent with values derived from ciliate protozoan studies and *P. putida* studies.

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

Because borates are not considered bioaccumulative, no separate procedure is necessary to address secondary poisoning. Data on dietary intake studies with birds showed acute LD50 values exceeding studies levels of 527 to 2100 mg-B/kg-food. (TO BE DEVELOPED Further).

7.6 Conclusion on the environmental classification and labelling

No environmental classification or labelling is required, based on a complete data set of required elements. The lowest acute 96-hour LC50 for fish is 408 mg-B/L, the lowest 48-hour EC50 for *Daphnia magna* is 133 mg-B/L and the lowest EC50 for algae is equivalent to 44.5 mg-B/L. Expressed as boric acid or as sodium tetraborate, all values exceed 100 mg/L.

Table 7-1. Fish Toxicity Data

Species	Endpoint Type	Test Duration (days)	Test Conditions	Tested Substance	Endpoint	Value	Reliability Statement	Limitations	Reference	Comments
Anguilla anguilla (eel)	LC100	1	Salt water (12 to 25 ppt)	Disodium tetraborate	1311 to >1748	mg-B/L	Review only, no data		WHO 1998	
Anguilla anguilla (eel)	LC100	1	Salt water (12 to 25 ppt)	Sodium borate	99.2	mg-B/L	Review only, no data		WHO 1998	
Brachydanio rerio (Danio rerio Zebrafish)	LC50	4	Fresh water	Boric acid	14	mg-B/L	Review only, no data	*Only reports end-point. Value is cited from an unpublished study using ISO 7346/II method*	Guhl, 1992	Unpublished data from HENKEL KGaA
***Brachydanio rerio (Danio rerio* Zebrafish)**	**NOEC**	**34**	**Fresh water, 210 mg/L hardness**	**Boric acid**	**5.6**	**mg-B/L**	**Reliable without restriction**	***Guideline study***	**Hooftman et al 2000**	**Usable for PNEC-chronic and SSD derivation**
***Brachydanio rerio (Danio rerio* Zebrafish)**	**NOEC**	**180**	**Fresh water, varied hardness**	**Boric acid**	**13**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed study, non-standard method, in conjunction with boron-depleted fish***	**Rowe et al 1998**	**Usable for PNEC-chronic and SSD derivation**
Brachydanio rerio (Danio rerio Zebrafish)	LOEC	34	Fresh water, 210 mg/L hardness	Boric acid	18	mg-B/L	Reliable without restriction	*Guideline study*	Hooftman et al 2000	
Brachydanio rerio (Danio rerio Zebrafish)	Deficiency threshold (LOEC)	180	Fresh water, varied hardness	Boric acid	0.0002	mg-B/L	Reliable with restriction	*Peer-reviewed study, non-standard method to evaluate boron-depleted fish*	Rowe et al 1998	Endpoint is deficiency, so not relevant to derivation of PNEC or SSD

***Carassius auratus* (Goldfish)**	**LC10**	**7**	**Fresh water, 50 mg/L hardness**	**Borax**	**20**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
***Carassius auratus* (Goldfish)**	**LC10**	**7**	**Fresh water, 200 mg/L hardness**	**Borax**	**16**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
***Carassius auratus* (Goldfish)**	**LC10**	**7**	**Fresh water, 50 mg/L hardness**	**Boric acid**	**16**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
***Carassius auratus* (Goldfish)**	**LC10**	**7**	**Fresh water, 200 mg/L hardness**	**Boric acid**	**16**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
Carassius auratus (Goldfish)	LC01	7	Fresh water, 50 mg/L hardness, synthetic reconstituted water	Borax	1.4	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint not considered reliable.
Carassius auratus (Goldfish)	LC01	7	Fresh water, 200 mg/L hardness, synthetic reconstituted water	Borax	0.9	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint not considered reliable.

Carassius auratus (Goldfish)	LC01	7	Fresh water, 50 mg/L hardness, synthetic reconstituted water	Boric acid	0.6	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint not considered reliable.
Carassius auratus (Goldfish)	LC01	7	Fresh water, 200 mg/L hardness, synthetic reconstituted water	Boric acid	0.2	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint not considered reliable.
Carassius auratus (Goldfish)	LC10 (embryo-larval)	7	Fresh water, 200 mg/L hardness	Boric acid	15	mg-B/L	Review only, no data		Raymond & Butterwick, 1992	Cited in V.d. Plassche et al 1989. Appears to be Dyer's recalculation of Birge & Black (1977)
***Catostomas latipinnis* (Flannelmouth sucker)**	**LC50**	**4**	**Fresh water, 144 mg/L hardness**	**Boric acid**	**125**	**mg-B/L**	**Reliable with restriction**	***Non-standard species, raw data not reported.***	**Hamilton and Buhl 1997**	**Usable for PNEC-acute derivation**
*Gambusia affinis (*mosquitofish)	LC50 of adult females	4	Fresh water, farm ponds with high turbidity	Borax	408	mg-B/L	Not reliable	*Non-standard method, used adult fish, highly turbid water*	Wallen et al 1957	
*Gambusia affinis (*mosquitofish)	LC50 of adult females	4	Fresh water, farm ponds with high turbidity	Boric acid	980	mg-B/L	Not reliable	*Non-standard method, used adult fish, highly turbid water*	Wallen et al 1957	
*Gambusia affinis (*mosquitofish)	LC50 of adult females	4	Fresh water	Borax	408	mg-B/L	Review only, no data		Raymond & Butterwick, 1992	Value cited from Wallen et al. 1957.

Gambusia affinis (mosquitofish)	LC50 of adult females	4	Fresh water	Boric acid	978	mg-B/L	Review only, no data		Raymond & Butterwick, 1992	Value cited from Wallen et al. 1957.
***Gila elegans* (Bony tail)**	**LC50 of swimup fry**	**4**	**Fresh water, 196 mg/L hardness**	**Boric acid**	**280**	**mg-B/L**	**Reliable with restriction**	***Non-standard species, raw data not reported.***	**Hamilton, 1995**	**Usable for PNEC-acute derivation**
***Ictalurus punctatus* (Channel catfish)**	**LC10**	**9**	**Fresh water, 50 mg/L hardness**	**Borax**	**33**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
***Ictalurus punctatus* (Channel catfish)**	**LC10**	**9**	**Fresh water, 200 mg/L hardness**	**Borax**	**16**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
***Ictalurus punctatus* (Channel catfish)**	**LC10**	**9**	**Fresh water, 50 mg/L hardness**	**Boric acid**	**5**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
Ictalurus punctatus (Channel catfish)	LC01	9	Fresh water, 50 mg/L hardness, synthetic reconstituted water	Borax	5.5	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint not considered reliable.

Ictalurus punctatus (Channel catfish)	LC01	9	Fresh water, 200 mg/L hardness, synthetic reconstituted water	Borax	1.7	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint not considered reliable.
Ictalurus punctatus (Channel catfish)	LC01	9	Fresh water, 50 mg/L hardness, synthetic reconstituted water	Boric acid	0.5	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint not considered reliable.
Ictalurus punctatus (Channel catfish)	LC01	9	Fresh water, 200 mg/L hardness, synthetic reconstituted water	Boric acid	0.2	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint not considered reliable.
Ictalurus punctatus (Channel catfish)	LC10 (embryo-larval)	9	Fresh water, 50 mg/L hardness	Boric acid	5	mg-B/L	Review only, no data	*Cites Birge & Black 1977*	Raymond & Butterwick, 1992	Cited in V.d. Plassche et al 1989
Kuhlia sandvicensis (aholehole fish)						mg-B/L	Not assignable	*Document not reviewed*	Hiatt et al 1953	*Document not reviewed*
Lepomis macrochirus (bluegill sunfish)	TLm	4	Fresh water, 80-110 mg/L hardness	Boron trifluoride + NaOH	5	mg-B/L	Not reliable	*Non-standard method, raw data not reported, author suggests high alkalinity a factor*	Turnbull et al 1954	
Lepomis macrochirus (bluegill sunfish)	LC50	1	freshwater	Disodium tetraborate	4.6	mg-B/L	Review only, no data	*Cites Turnbull 1954 study*	Raymond & Butterwick, 1992	

Limanda limanda **(Dab)**	**LC50**	**4**	**Sea water**	**Na metaborate**	**74**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed study***	**Taylor et al 1985**	**Usable for PNEC-acute derivation**
Micropterus salmoides **(Largemouth bass)**	**NOEC**	**11**	**Fresh water**	**Borax**	**1.39**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication. Duration of early-life stage test shorter than current method***	**Black et al 1993**	**Usable in PNEC-chronic and SSD derivation**
Micropterus salmoides **(Largemouth bass)**	**LC10**	**11**	**Fresh water, 200 mg/L hardness**	**Borax**	**6**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black (1981) using current approaches. Usable for SSD derivation**
Oncorhynchus kisutch **(Coho salmon)**	**LC50**	**4**	**Fresh water, 211 mg/L hardness**	**Boric acid**	**447**	**mg-B/L**	**Reliable with restriction**	***Non-standard species, raw data not reported.***	**Hamilton and Buhl 1990**	**Usable for PNEC-acute derivation**
Oncorhynchus kisutch **(Coho salmon)**	**LC50**	**4**	**Brackish water, 333 mg/L hardness**	**Boric acid**	**600**	**mg-B/L**	**Reliable with restriction**	***Non-standard species, raw data not reported, brackish water.***	**Hamilton and Buhl 1990**	**Usable for PNEC-acute derivation**
Oncorhynchus kisutch (Coho salmon)	LC50	4	Salt water (28 ppt)	Borax	40	mg-B/L	Review only, no data	*Cites Thompson et al.1976*	Raymond & Butterwick, 1992	
Oncorhynchus kisutch (Coho salmon)	LC50	11.8	Salt water	Borax	113	mg-B/L	Review only, no data	*Cites Thompson et al.1976*	Raymond & Butterwick, 1992	
Oncorhynchus mykiss **(rainbow trout)**	**NOEC**	**32 - 87**	**Fresh water**	**Boric acid**	**1**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed publication. Test duration shorter than current method. Used variety of dilution waters and trout stock. Value is author's recommendation based on their data***	**Black et al. 1993**	**Authors recommended value is based on multiple tests in their lab. Calculation of species mean not feasible because of dosing pattern. Usable for PNEC-chronic or SSD derivation.**

Oncorhynchus mykiss **(rainbow trout)**	**LC10**	**28**	**Fresh water, 50 mg/L hardness, synthetic reconstituted water**	**Borax**	**8**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
Oncorhynchus mykiss **(rainbow trout)**	**LC10**	**28**	**Fresh water, 50 mg/L hardness, synthetic reconstituted water**	**Borax**	**15**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
Oncorhynchus mykiss **(rainbow trout)**	**LC10**	**28**	**Fresh water, 200 mg/L hardness**	**Borax**	**30**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
Oncorhynchus mykiss **(rainbow trout)**	**LC10**	**28**	**Fresh water, 50 mg/L hardness, synthetic reconstituted water**	**Boric acid**	**2**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**
Oncorhynchus mykiss **(rainbow trout)**	**LC10**	**28**	**Fresh water, 188 mg/L hardness**	**Boric acid**	**0.7**	**mg-B/L**	**Reliable with restriction**	***Calculated LC10 from original data, per probit method, peer-reviewed study. Test duration shorter than current method.***	**Dyer, 2001**	**Recalculated endpoint using original data from Birge & Black, 1977 using current approaches. Usable for SSD derivation**

Oncorhynchus mykiss (rainbow trout)	NOEC (mortality)	87	Fresh water, well-water	Boric acid	2.1, 18	mg-B/L	Reliable with restrictions	*Peer-reviewed publication. Doses widely spaced (10x). High exposure initiated with 20-day old embryos*	Black et al 1993	Although NOEC 2.1 mg-B/L is probably usable for derivation of PNEC-chronic and SSD, authors' recommend using lower value based on other tests in this publication.
Oncorhynchus mykiss (rainbow trout)	Deficiency threshold (NOEC)	>14	Fresh water, varied hardness	Boric acid	0.5	mg-B/L	Reliable with restriction	*Peer-reviewed study, non-standard method*	Rowe et al 1998	Endpoint is deficiency, so not relevant to derivation of PNEC or SSD
Oncorhynchus mykiss (rainbow trout)	Deficiency threshold (LOEC)	>14	Fresh water, varied hardness	Boric acid	0.1	mg-B/L	Reliable with restriction	*Peer-reviewed study, non-standard method*	Rowe et al 1998	Endpoint is deficiency, so not relevant to derivation of PNEC or SSD
Oncorhynchus mykiss (rainbow trout)	LOEC	>14	Fresh water, varied hardness	Boric acid	11	mg-B/L	Reliable with restriction	*Peer-reviewed study, non-standard method*	Rowe et al 1998	
Oncorhynchus mykiss (rainbow trout)	LC01	28	Fresh water, 50 mg/L hardness, synthetic reconstituted water	Borax	0.07	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Value in range of boron deficiency. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint within range of boron deficiency in trout, so effect may not reflect toxicity from excess. Endpoint within range of control variability, not considered reliable.
Oncorhynchus mykiss (rainbow trout)	LC01	28	Fresh water, 200 mg/L hardness, synthetic reconstituted water	Borax	0.07	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Value in range of boron deficiency. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint within range of boron deficiency in trout, so effect may not reflect toxicity from excess. Endpoint within range of control variability, not considered reliable.

Oncorhynchus mykiss (rainbow trout)	LC01	28	Fresh water, 50 mg/L hardness, synthetic reconstituted water	Boric acid	0.1	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Value in range of boron deficiency. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint within range of boron deficiency in trout, so effect may not reflect toxicity from excess. Endpoint within range of control variability, not considered reliable.
Oncorhynchus mykiss (rainbow trout)	LC01	28	Fresh water, 200 mg/L hardness, synthetic reconstituted water	Boric acid	0.001	mg-B/L	Not reliable	*Used non-standard endpoint extrapolated beyond data. Value in range of boron deficiency. Test duration shorter than current method.*	Birge & Black, 1977	Endpoint within range of boron deficiency in trout, so effect may not reflect toxicity from excess. Endpoint within range of control variability, not considered reliable.
Oncorhynchus mykiss (rainbow trout)	NOEC (mortality)	32	Fresh water, reconsti-tuted and field-collected waters	Boric acid	0.1	mg-B/L	Reliable with restrictions	*Peer-reviewed publication. Value in range of boron deficiency. Test duration shorter than current method. Doses widely spaced (10x)*	Black et al 1993	Endpoint within range of boron deficiency in trout, so effect may not reflect toxicity from excess. Teratogenesis reported at or below the NOEC-mortality exposures
Oncorhynchus mykiss (rainbow trout)	NOEC (embyro-larval survival)	28-32			2	mg-B/L	Review only, no data		Raymond & Butterwick, 1992	Cited in V.d. Plassche et al 1989
***Oncorhynchus tshawtscha* (Chinook salmon)**	**LC50**	**4**	**Fresh water, 211 mg/L hardness**	**Boric acid**	**600**	**mg-B/L**	**Reliable with restriction**	***Non-standard species, raw data not reported.***	**Hamilton and Buhl 1990**	**Usable for PNEC-acute derivation**
***Oncorhynchus tshawtscha* (Chinook salmon)**	**LC50**	**4**	**Brackish water, 333 mg/L hardness**	**Boric acid**	**725**	**mg-B/L**	**Reliable with restriction**	***Non-standard species, raw data not reported, brackish water.***	**Hamilton and Buhl 1990**	**Usable for PNEC-acute derivation**
Pimephales promelas (fathead minnow)	LT50	>4 3.3	Fresh water	Boric acid	17.5 175	mg-B/L	Not reliable	*Non-standard method, raw data not reported, non-standard endpoint reported*	Terhaar et al 1972	

Pimephales promelas (fathead minnow)	NOEC (egg and fry growth)	30			14	mg-B/L	Review only, no data	Review cites endpoint only, citing an unpublished Procter & Gamble 1979 study. Accepted as reliable by Netherlands (2006)	Raymond & Butterwick, 1992	Cited in V.d. Plassche et al 1989
Pimephales promelas (fathead minnow)	NOEC-mortality	60	Fresh water	Boric acid	24	mg-B/L	Review only, no data	Review cites endpoint only, citing an unpublished Procter & Gamble 1979 study. Accepted as reliable by Netherlands (2006)	Raymond & Butterwick, 1992	Cited in V.d. Plassche et al 1989
Poecilia reticulata (guppy)	NOEC	1	Fresh water	Boric acid	875	mg-B/L	Not reliable	*Non-standard method, raw data not reported*	Mann 1973	
***Ptychocheilus lucius* (Colarado squawfish)**	**LC50 of swimup fry**	**4**	**Fresh water, 196 mg/L hardness**	**Boric acid**	**279**	**mg-B/L**	**Reliable with restriction**	***Non-standard species, raw data not reported.***	**Hamilton, 1995**	**Usable for PNEC-acute derivation**
Rasbora heteromorpha (harlequinfish)						mg-B/L	Not assignable	*Document not reviewed*	Tooby et al 1975	
***Xyrauchen texanus* (razorback sucker)**	**LC50 of swimup fry**	**4**	**Fresh water, 196 mg/L hardness**	**Boric acid**	**233**	**mg-B/L**	**Reliable with restriction**	***Non-standard species, raw data not reported.***	**Hamilton, 1995**	**Usable for PNEC-acute derivation**

Note: Studies evaluated as “Reliable without restriction” or “Reliable with restriction” and usable for derivation of a PNEC are indicated in bold.

Table 7-2 Aquatic Invertebrate Toxicity Data										
Species	**Endpoint Type**	**Test Duration (days)**	**Test Conditions**	**Tested Substance**	**Endpoint**	**Value**	**Reliability Statement**	**Limitations**	**Reference**	**Comments**
Aedes aegypti larvae (mosquito)	NOEC, LOEC (emergence)	newly hatched larvae through emer-gence	Fresh water	Boric acid	18, 44	mg-B/L	Reliable with restriction	*Peer-reviewed technical publication that meets basic scientific principles. Exposure period not expressed in days. Data presented as % contol*	Fay, 1959	Publication pre-dates current protocols. Data not useful for PNEC or SSD derivation.
Anopheles quadrimaculatus larvae (mosquito)	NOEC / LOEC (emergence)	newly hatched larvae through emer-gence	Fresh water	Boric acid	4.4 / 8.8	mg-B/L	Reliable with restriction	*Peer-reviewed technical publication that meets basic scientific principles. Exposure period not expressed in days. Data presented as % contol*	Fay, 1959	Publication pre-dates current protocols. Data not useful for PNEC or SSD derivation.
Ceriodaphnia cf pulchella (daphnid)	EC50	1	Fresh water 250 mg/L hardness	Boric acid	101	mg-B/L	Not reliable	*Peer-reviewed technical publication. Test duration (1 day) was less than guideline study (2 to 4 days). Non-standard species tested.*	Hickey 1989	
Ceriodaphnia dubia (daphnid)	EC50	1	Fresh water 250 mg/L hardness	Boric acid	181	mg-B/L	Not reliable	*Peer-reviewed technical publication. Test duration (1 day) was less than guideline study (2 to 4 days).*	Hickey 1989	
***Ceriodaphnia dubia* (daphnid)**	**NOEC (growth, repro-duction)**	**14**	**Fresh water 250 mg/L hardness**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Comparable to guideline study with acceptable restrictions. Peer-reviewed technical publication. Well-done study and report that meets basic scientific principles***	**Hickey 1989**	**Usable for PNEC or SSD derivation**

***Ceriodaphnia dubia* (daphnid)**	**LOEC (growth, repro-duction)**	**14**	**Fresh water 250 mg/L hardness**	**Boric acid**	**18**	**mg-B/L**	**Reliable with restriction**	***Comparable to guideline study with acceptable restrictions. Peer-reviewed technical publication. Well-done study and report that meets basic scientific principles***	**Hickey 1989**	**Usable for PNEC or SSD derivation**
***Chironomus decorus* (midge)**	**EC50**	**2**	**Fresh water, 10 to 170 mg/L hardness**	**Boric acid**	**1376 (hard-ness had no effect)**	**mg-B/L**	**Reliable with restriction**	***Comparable to Guideline study. Pre-dates OECD Guideline***	**Maier and Knight, 1991**	**Usable for PNEC-acute derivation for watger.**
***Chironomus decorus* (midge)**	**NOEC**	**4**	**Fresh water, 10 to 170 mg/L hardness**	**Boric acid**	**10 (hard-ness had no effect)**	**mg-B/L**	**Reliable with restriction**	***Duration shorter than current guidelines and Aquatic exposure only (no sediment)***	**Maier and Knight, 1991**	**Usable for PNEC-chronic and SSD derivation.**
Culex quinquefasciatus larvae (mosquito)	NOEC, LOEC (emergence)	newly hatched larvae through emer-gence	Fresh water	Boric acid	18, 44	mg-B/L	Reliable with restriction	*Peer-reviewed technical publication that meets basic scientific principles. Exposure period not expressed in days. Data presented as % contol*	Fay, 1959	Publication pre-dates current protocols. Data not useful for PNEC or SSD derivation.
Daphnia carinata (daphnid)	EC50	1	Fresh water 250 mg/L hardness	Boric acid	268	mg-B/L	Not reliable	*Peer-reviewed technical publication. Test duration (1 day) was less than guideline study (2 to 4 days). Non-standard species tested.*	Hickey 1989	
***Daphnia magna* (daphnid)**	**EC50**	**2**	**Fresh water, 170 mg/L hardness**	**Boric acid**	**133**	**mg-B/L**	**Reliable without restriction**	***Comparable to Guideline study. Pre-dates OECD Guideline***	**Gersich, 1984**	**Usable for PNEC-acute derivation**
***Daphnia magna* (daphnid)**	**EC50**	**2**	**Fresh water, 160 mg/L hardness**	**Boric acid**	**226**	**mg-B/L**	**Reliable without restriction**	***Comparable to Guideline study. Pre-dates OECD Guideline***	**Lewis and Valentine, 1981**	**Usable for PNEC-acute derivation**

***Daphnia magna* (daphnid)**	**EC50**	**2**	**Fresh water, 10 to 170 mg/L hardness**	**Sodium tetraborate deca-hydrate**	**141 (hard-ness had no effect)**	**mg-B/L**	**Reliable without restriction**	***Comparable to Guideline study. Pre-dates OECD Guideline***	**Maier and Knight, 1991**	**Usable for PNEC-acute derivation**
***Daphnia magna* (daphnid)**	**LC50**	**1**	**Fresh water 272 mg/L hardness**	**Borax**	**73**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication. Units unclear; presumed to be reported as borate ion (27.8% B)***	**Bringman and Kühn, 1977a**	**Used in van de Plassche 1999. Usable for PNEC-acute derivation**
Daphnia magna (daphnid)	EC50	1	Fresh water 250 mg/L hardness	Boric acid	320	mg-B/L	Not reliable	*Peer-reviewed technical publication. Test duration (1 day) was less than guideline study (2 to 4 days).*	Hickey 1989	
***Daphnia magna* (daphnid)**	**NOEC (growth, repro-duction)**	**14**	**Fresh water, 170 mg/L hardness**	**Boric acid**	**13.8, 14.3 (2 tests)**	**mg-B/L**	**Reliable without restriction**	***Comparable to guideline study with acceptable restrictions. Peer-reviewed technical publication. Study meets guidelines except that temperature was elevated to 24°C to accelerate growth and test duration was shorter (14 days) than current methods.***	**Gersich and Milazzo, 1990**	**Usable for PNEC or SSD derivation**
***Daphnia magna* (daphnid)**	**NOEC (growth, repro-duction)**	**21**	**Fresh water, 170 mg/L hardness**	**Boric acid**	**6.4**	**mg-B/L**	**Reliable without restriction**	***Comparable to Guideline study. Pre-dates OECD Guideline***	**Gersich, 1984**	**Usable for PNEC or SSD derivation**
***Daphnia magna* (daphnid)**	**NOEC (growth, repro-duction)**	**21**	**Fresh water 210 mg/L hardness**	**Boric acid**	**10**	**mg-B/L**	**Reliable without restriction**	***Guideline study***	**Hooftman et al 2000a**	**Usable for PNEC or SSD derivation**
***Daphnia magna* (daphnid)**	**NOEC (repro-duction)**	**21**	**Fresh water, 160 mg/L hardness**	**Boric acid**	**6**	**mg-B/L**	**Reliable without restriction**	***Comparable to Guideline study. Pre-dates OECD Guideline***	**Lewis and Valentine, 1981**	**Usable for PNEC or SSD derivation**

***Daphnia magna* (daphnid)**	**NOEC (growth)**	**21**	**Fresh water, 160 mg/L hardness**	**Boric acid**	**27**	**mg-B/L**	**Reliable without restriction**	***Comparable to Guideline study. Pre-dates OECD Guideline***	**Lewis and Valentine, 1981**	**Usable for PNEC or SSD derivation**
Daphnia magna (daphnid)	NOEC (growth, repro-duction)	21	Fresh water, 170 mg/L hardness	Boric acid	6.4	mg-B/L	Reliable without restriction	*Comparable to guideline study with acceptable restrictions. Peer-reviewed technical publication. Well-done study and report that meets basic scientific principles*	Gersich et al., 1985	Appears to use data from Gersich (1984).
Daphnia magna (daphnid)	LOEC (growth, repro-duction)	21	Fresh water 210 mg/L hardness	Boric acid	18	mg-B/L	Reliable without restriction	*Guideline study*	Hooftman et al 2000a	
Daphnia magna (daphnid)	LC50	21	Fresh water, 160 mg/L hardness	Boric acid	53.2	mg-B/L	Reliable without restriction	*Comparable to Guideline study. Pre-dates OECD Guideline*	Lewis and Valentine, 1981	
***Daphnia magna* (daphnid)**	**NOEC (mean of 4 tests)**	**14 to 21**	**Fresh waters**	**Boric acid**	**9**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication. Report meets basic scientific principles***	**Dyer 2001**	**Usable for SSD derivation. Uses data from Gersich 1984, Lewis and Valentine 1993, Guhl 1992, and Hickey 1989**
***Daphnia magna* (daphnid)**	**NOEC (growth, repro-duction)**	**14**	**Fresh water 250 mg/L hardness**	**Boric acid**	**18**	**mg-B/L**	**Reliable with restriction**	***Comparable to guideline study with acceptable restrictions. Peer-reviewed technical publication. Well-done study and report that meets basic scientific principles***	**Hickey 1989**	**Usable for PNEC or SSD derivation**
Daphnia magna (daphnid)	LOEC (growth, repro-duction)	14	Fresh water 250 mg/L hardness	Boric acid	32	mg-B/L	Reliable with restriction	*Comparable to guideline study with acceptable restrictions. Peer-reviewed technical publication. Well-done study and report that meets basic scientific principles*	Hickey 1989	

Daphnia magna (daphnid)	NOEC (growth, repro-duction)	21	Fresh water	Boric acid	10	Mg-B/L	Reliable with restriction	*Only reports end-point. Value is cited from an unpublished study using OECD 202 p.2 method*	Guhl, 1992a	Data from HENKEL KGaA. Not usable for PNEC or SSD derivation
Simocephalus vetulus (daphnid)	EC50	1	Fresh water 250 mg/L hardness	Boric acid	123	mg-B/L	Not reliable	*Peer-reviewed technical publication. Test duration (1 day) was less than guideline study (2 to 4 days). Non-standard species tested.*	Hickey 1989	

Note: Studies evaluated as "Reliable without restriction" or "Reliable with restriction" and usable for derivation of a PNEC are indicated in bold.

Table 7-3. Algae and aquatic plant toxicity data										
Species	**Endpoint Type**	**Test Duration (days)**	**Test Conditions**	**Tested Substance**	**Endpoint**	**Value**	**Reliability Statement**	**Limitations**	**Reference**	**Comments**
Agmenellum quadruplicatum	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**100**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Amphidinium carteri	**NOEC (growth rate)**	**27**	**Sea water media**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Anabaena PCC7119	LOEC-growth	4	Freshwater	Boric acid	50	mg-B/L	Reliable with restriction	*Concentrations not measured; raw data not reported*	Mateo, Martinez, Bonilla, Fernandex-Valeinte & Maeso 1987	Nitrate reductase activity decreased at high boron.
Anacystis marina	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**100**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Anacystis nidulans	**NOEC-growth**	**4**	**Freshwater**	**Boric acid**	**50**	**mg-B/L**	**Reliable with restriction**	***Concentrations not measured; raw data not reported***	**Martinez, Mateo, Bonilla & Fernandez-Valiente 1986**	**Usable for PNEC or SSD derivation**

Anacystis nidulans	LOEC-growth	4	Freshwater	Boric acid	75	mg-B/L	Reliable with restriction	*Concentrations not measured; raw data not reported*	Martinez, Mateo, Bonilla & Fernandez-Valiente 1986	
Anacystis nidulans	LOEC-growth	4	Freshwater	Boric acid	100	mg-B/L	Reliable with restriction	*Concentrations not measured; raw data not reported*	Mateo, Martinez, Bonilla, Fernandez-Valiente & Maeso 1987	Nitrate reductase activity decreased at high boron.
Bellerochea polymorpha (diatom)	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**50**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Chlorella pyrenoidosa	**NOEC-growth**	**4**	**Freshwater**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Concentrations not measured; raw data not reported***	**Fernandez, Sanchez, Bonilla, Mateo & Ortega, 1984**	**Usable for PNEC or SSD derivation**
Chlorella pyrenoidosa	LOEC-growth	4	Freshwater	Boric acid	50	mg-B/L	Reliable with restriction	*Concentrations not measured; raw data not reported*	Maeso, Fernandez-Valiente, Bonilla & Mateo 1985	
Chlorella pyrenoidosa	NOEC-growth	14	Freshwater	Boric acid	0.4	mg-B/L	Not reliable	*Non-standard endpoint; conc not measured; raw data not reported; method not consistent with standard methods*	Wong & Wong, 1990	Cited in Sheedy et al. (1991)
Chlorella pyrenoidosa	LOEC-growth	14	Freshwater	Boric acid	0.8	mg-B/L	Not reliable	*Non-standard endpoint; conc not measured; raw data not reported; method not consistent with standard methods*	Wong & Wong, 1990	Cited in Sheedy et al. (1991)

Chlorella sp.	NOEC – field study		Freshwater		>250	mg-B/L	Not assignable	*Study not reviewed*	Webber, Kemp & Rice 1977	Cited in ECETOC (1997)
Chlorella vulgaris	LOEC-growth	90-120	Freshwater	Disodium tetraborate	2.2	mg-B/L	Not assignable	*Study not reviewed*	Den Dooren de Jong 1965	Cited in US EPA AQUIRE database
Chlorella vulgaris	NOEC-growth	90-120	Freshwater	Disodium tetraborate	1.1	mg-B/L	Not assignable	*Study not reviewed*	Den Dooren de Jong 1965	Cited in US EPA AQUIRE database
Chroomonas salina	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Cyclotella cryptica (diatom)	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Dunaliella tertiolecta	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**50**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Emiliania huxleyi	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**5**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Isochrysis galbana	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Lemna minor	**NOEC-growth**	**7**	**Freshwater**		**60**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles***	**Wang, 1986**	**Usable for PNEC or SSD derivation**
Lemna minor	LOEC-growth	7	Freshwater		>60	mg-B/L	Reliable with restriction	*Peer-reviewed technical publication that meets basic scientific principles*	Wang, 1986	

Microcystis aeruginosa	**Tox Threshold-growth (EC3)**	**8**	**Freshwater**	**Disodium tetraborate**	**20**	**mg-B/L**	**Reliable with restriction**	***No data reported; non-standard endpoint; exposure estimates ignore background sources; conc not measured. Accepted by Netherlands (2006).***	**Bringmann & Kuhn 1978a**	**Endpoint reported as 73 mg/L; assumed to be borate ion concentration. Usable for SSD derivation..**
Monallantus salina	LOEC (growth rate)	50	Sea water media	Boric acid	10	mg-B/L	Reliable with restriction	*Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density*	Antia & Chang 1975	Endogenous B= 3.65 mg-B/L.
Monochrysis lutheri	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Myriophyllum spicatum	EC50 (root weight)	32	Freshwater	Borate	40.3	mg-B/L	Review only, no data		Raymond & Butterwick, 1992	
Myriophyllum spicatum	EC50 (root weight)	32	Freshwater	Borate	40.3	mg-B/L	Review only, no data		Raymond & Butterwick, 1992	
Myriophyllum spicatum	EC50 (root weight)	32	Freshwater	Borate	40.3	mg-B/L	Review only, no data		Raymond & Butterwick, 1992	
Nannochloris oculata	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Phaeodactylum tricornutum (diatom)	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC-chronic or SSD derivation**
Phragmites australis (reed)	**NOEC-growth**	**4 months**	**Freshwater, pot culture**	**Boric acid**	**>4**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles***	**Bergman et al. 1995**	**Usable in corroboration of PNEC value, determination of application factor.**

Phragmites australis (reed) in field study	**NOEC**	**2 years**	**Fresh water**	**Boric acid**	**1.52**	**mg-B/L**	**Reliable with restriction**	**Peer-reviewed technical publication. Data not shown; endpoints from plants occuring at sites with varied boron polllution include leaf and structure damage**	**Guhl 1992a, HENKEL 1991**	**Usable in corroboration of PNEC value, determination of application factor.**
Phragmites australis (reed) in outdoor experimental ponds	**NOEC**	**2 years**	**Fresh water**	**Boric acid**	**≥ 0.7**	**mg-B/L**	**Reliable with restriction**	**Peer-reviewed technical publication. Data not shown; endpoints included plant growth and structure over 2 growing seasons**	**Guhl 1992a, Henkel, 1991**	**Usable in corroboration of PNEC value, determination of application factor.**
Porphyridium cruentum	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**50**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Rhodomonas lens	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Scenedesmus quadricauda	Tox Threshold-growth	8	Freshwater	Disodium tetraborate	0.12	mg-B/L	Not reliable	*No data reported; non-standard endpoint; exposure estimates ignore background sources; conc not measured*	Bringmann & Kuhn 1977b	Value recalculated from reported value, assuming test substance was anhydrous sodium tetraborate (22.49% boron), as stated by authors. Endpoint more stringent than currently accepted EC10.
Scenedesmus quadricauda	Tox Threshold-growth	8	Freshwater	Disodium tetraborate	0.1	mg-B/L	Not reliable	*No data reported; non-standard endpoint; exposure estimates ignore background sources; conc not measured*	Bringmann & Kuhn 1978a	Value originally reported in Bringmann & Kuhn 1977b

Scenedesmus quadricauda	Tox Threshold-growth	7	Freshwater	Disodium tetraborate	0.041	mg-B/L	Not reliable	*Value cited in AQUIRE (0.041) is not found in reference. See limitations of related papers*	Bringmann & Kuhn 1980a	Cited in US EPA AQUIRE database. Value originally reported in Bringmann & Kuhn 1977b.
Scenedesmus subspicatus	**EC10 (Cell multiplication inhibition)**		**Freshwater**	**Borax**	**24**	**mg-B/L**	**Reliable with restriction**	***Only reports end-point. Value is cited from an unpublished study using DIN38412 T.9 method. Accepted as reliable by Netherlands (2006)***	**Guhl 1992a, HENKEL, 1991**	**Cited in ECETOC (1997). Data from HENKEL KGaA. Usable in SSD derivation**
Scenedesmus subspicatus	EC10		Freshwater	Boric acid	24	mg-B/L	Not assignable	*Study not reviewed. Unpublished study*	Kopf & Wilk 1995	Cited in ECETOC (1997) Probably HENKEL 1991 study.
Selenastrum capricornutum	**ECb10**	**3**	**Freshwater**	**Boric acid**	**24.5**	**mg-B/L**	**Reliable without restriction**	***Guideline study. Growth calculated as biomass per OECD 201***	**Hanstveit & Oldersma 2000**	**Usable for PNEC or SSD derivation**
Selenastrum capricornutum	**ECr10**	**3**	**Freshwater**	**Boric acid**	**35**	**mg-B/L**	**Reliable without restriction**	***Guideline study. Growth calculated as growth rate per OECD 201***	**Hanstveit & Oldersma 2000**	**Usable for PNEC or SSD derivation**
Selenastrum capricornutum	**No Effect Concentration (calc)**	**3**	**Freshwater**	**Boric acid**	**27**	**mg-B/L**	**Reliable without restriction**	***Guideline study. Best estimate of no-effect concentration calc. as per OECD 201***	**Hanstveit & Oldersma 2000**	**Usable for PNEC or SSD derivation**
Selenastrum capricornutum	**NOEC-growth**	**3**	**Freshwater**	**Boric acid**	**17.5**	**mg-B/L**	**Reliable without restriction**	***Guideline study. Observed NOEC.***	**Hanstveit & Oldersma 2000**	**Usable for PNEC or SSD derivation**
Selenastrum capricornutum	**EC50 - growth / EC50-biomass**	**3**	**Freshwater**	**Boric acid**	**52.5 / 40**	**mg-B/L**	**Reliable without restriction**	***Guideline study***	**Hanstveit & Oldersma 2000**	**Usable for PNEC or SSD derivation**
Selenastrum capricornutum	EC50 - growth	4	Freshwater	Disodium tetraborate	3.3	mg-B/L	Not assignable	*Study not reviewed*	Hickey, Blaise & Costan 1991	Cited in US EPA AQUIRE database

Skeletonema costatum (diatom)	**NOEC (growth rate)**	**40**	**Sea water media**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Spirodella polyrhiza	**NOEC (growth rate)**	**10**	**Fresh water**	**Boric acid**	**6.1**	**mg-B/L**	**Reliable without restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as incresed fronds/day***	**Davis et al. 2002**	**Endogenous B = 0.9 mg/L. Usable for PNEC or SSD derivation**
Spirodella polyrhiza (duckweed)	LOEC (growth as total frond numbers)	10	Fresh water	Boric acid	3.6	mg-B/L	Reliable without restriction	*Peer-reviewed technical publication that meets basic scientific principles. Growth measured as total fronds produced in 10 days*	Davis et al. 2002	Endogenous B = 0.9 mg/L. Total frond production reduced at next higher exposure (3.6 mg-B/L) so no NOEC for total frond number can be derived.
Tetraselmis maculata	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**
Thalassiosira fluviatilis (diatom)	**NOEC (growth rate)**	**10**	**Sea water media**	**Boric acid**	**50**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Growth measured as optical density***	**Antia & Chang 1975**	**Endogenous B= 3.65 mg-B/L. Usable for PNEC or SSD derivation**

Note: Studies evaluated as “Reliable without restriction” or “Reliable with restriction” and usable for derivation of a PNEC are indicated in bold.

Table 7-4. Sediment Toxicity data										
Species	**Endpoint Type**	**Test Duration (days)**	**Test Conditions**	**Tested Substance**	**Endpoint**	**Value**	**Reliability Statement**	**Limitations**	**Reference**	**Comments**
Chironomus decorus (midge)	EC50	2	Fresh water, 10 to 170 mg/L hardness	Boric acid	1376 (hard-ness had no effect)	mg-B/L	Reliable with restriction	*Comparable to Guideline study. Pre-dates OECD Guideline*	Maier and Knight, 1991	Usable for PNEC-acute derivation for watger. Not relevant to sediment because water-only exposure.
Chironomus decorus (midge)	NOEC	4	Fresh water, 10 to 170 mg/L hardness	Boric acid	10 (hard-ness had no effect)	mg-B/L	Reliable with restriction	*Duration shorter than current guidelines. Aquatic exposure only (no sediment)*	Maier and Knight, 1991	Usable for PNEC-chronic derivation for water. Not relevant to sediment because water-only exposure
***Chironomus riparius* (midge)**	**NOEC (growth, emergence) using spiked sediments**	**28**	**Fresh water 210 mg/L hardness**	**Boric acid**	**180**	**mg-B/kg-dry sediment**	**Reliable without restriction**	***Guideline study***	**Hooftman et al 2000b**	**Usable for PNEC or SSD derivation**
Tubificid (aquatic worm)	NOEC (mortality)	1	Fresh water	Boric acid	1313	mg-B/L	Not reliable	*Non-standard species, data not presented*	Mann, 1973	
Tubificid (aquatic worm)	NOEC (mortality)	1	Fresh water	Borax	85	mg-B/L	Not reliable	*Non-standard species, data not presented*	Mann, 1973	

Note: Studies evaluated as “Reliable without restriction” or “Reliable with restriction” and usable for derivation of a PNEC are indicated in bold.

Table 7-5. Other Aquatic Toxicity data

Species	Endpoint Type	Test Duration (days)	Test Conditions	Tested Substance	Endpoint	Value	Reliability Statement	Limitations	Reference	Comments
Ambystoma jeffersonian (salamander)	LOEC - larval deformities	23	Freshwater		49.5	mg-B/L	Reliable with restriction	*Peer-reviewed technical publication that meets basic scientific principles*	Laposata and Dunson, 1998	
Ambystoma maculatum (salamander)	LOEC - larval deformities	23	Freshwater		49.5	mg-B/L	Reliable with restriction	*Peer-reviewed technical publication that meets basic scientific principles*	Laposata and Dunson, 1998	
***Anthocidaris crassipina* (sea urchin)**	**NOEC (develop-ment)**	**0.5**	**Sea water**	**Boric acid**	**79**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication. Well-done study and report that meets basic scientific principles. Pre-dates standardized methods***	**Kobayashi, 1971**	**Usable for PNEC or SSD derivation**
***Bufo fowleri* (toad)**	**LC10-mortality, larval development**	**7.5**	**Freshwater**		**41**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles***	**Dyer, 2001**	**Mean of 2 tests, usable for SSD derivation**
Bufo fowleri (toad)	NOEC (embryo-larval)	7			30	mg-B/L	Review only, no data		Raymond & Butterwick, 1992	Cited in V.d. Plassche et al 1989
Chilomonas paramecium (protozoan)	Toxic threshold	2	Fresh water	Borax	10.6	mg-B/L	Not assignable	*Insufficient information to evaluate test. (See comments)*	Bringman and Kuhn, 1980	Species is not mentioned in text, althought several reviews state test results and cite this publication.
Entosiphon sulcatum (protozoan)	Toxicity threshold	3	Fresh water		0.28	mg-B/L	Not reliable	*Peer-reviewed technical publication. No data presented. Method not in current use. Uses killed bacteria as food*	Bringmann 1978	

*Entosiphon sulcatum ** (protozoan)*	EC5	3	Fresh water		0.28, 0.3	mg-B/L	Not reliable	*Only reports end-point. Value is cited from another publication*	Guhl 1992a	Data appear to be cited from Bringmann 1978., but citation is to Schoberl and Huber 1988 and Bringmann & Kuhn 1980.
Entosiphon sulcatum (protozoan)	Toxicity threshold	3	Fresh water (culture medium)	Borax	0.28	mg-B/L	Not reliable	*Peer-reviewed technical publication. Method not in current use. Non-standard endpoint. Data previously published (Bringmann 1978*	Bringman and Kühn, 1980	
Entosiphon sulcatum (protozoan)	**NOEC**	**3**	**Fresh water (culture medium)**	**Boric acid**	**15**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication. Data not presented. Compared feeding live food (bacteria) with dead food, noting significant decrease in growth if not fed live bacteria. LOEC 22 mg-B/L***	**Guhl 2000**	**Author points out that this species is commonly found in wastewater treatment plants, with an annual average of 2.12 mg-B/L, suggesting that this species. Usable for PNEC-chronic or SSD derivation. Usable for PNEC-stp derivation.**
Entosiphon sulcatum (protozoan)	NOEC	3	Fresh waters		15	mg-B/L	Review only, no data	*Peer-reviewed technical publication. Report meets basic scientific principles*	Dyer 2001	Cites Guhl 1992b. Guhl 2000 provides study details.
Entosiphon sulcatum (protozoan)	NOEC		Fresh water		15	mg-B/L	Not assignable	*No publication available*	Guhl 1992b	
Microcosm (multispecies)	NOEC	28	Freshwater		2.5	mg-B/L	Review only, no data	*Insufficient information to evaluate test. Only reports an endpoint value or summary*	Guhl 1992a	Cited in ECETOC (1997)
Microcosm (multispecies)	LOEC	28	Freshwater		5	mg-B/L	Review only, no data	*Insufficient information to evaluate test. Only reports an endpoint value or summary*	Guhl 1992a	Cited in ECETOC (1997). Described in HENKEL (1991)
Model river system (multispecies)	Concentration without effect	42	Freshwater		1	mg-B/L	Review only, no data	*Insufficient information to evaluate test. Only reports an endpoint value or summary*	Guhl 1992a	Cited in ECETOC (1997) Described in HENKEL (1991)

Multi-species (Biocenosis)	NOEC (Biotic indices)	28	Fresh water		2.5	mg-B/L	Not reliable	Method from Guhl 1987; unpublished study. Endpoint not specified beyond "biotic indices"	Guhl 1991	Endpoint is biotic indices; usable for corroboration but not specified in document
Multi-species (Biocenosis)	NOEC	28	Fresh water		2.5	mg-B/L	Review only, no data	Only endpoint value reported; cites another publication.	Guhl 1992a	Cites Guhl 1991.
Multi-species (Biocenosis) Protozoan community based on activated sludge	**NOEC**	**42**	**Freshwater**		**20**	**mg-B/L**	**Reliable with restriction**	***Multi-species test so non-standard method. Data not reported. NOECs for protozoan populations, ecological indices, sludge dry weight and O2 consumption evaluated.***	**Guhl 2000**	**Usable in corroboration of PNEC value, determination of application factor.**
Multi-species (Biocenosis) Protozoan community based on activated sludge	**LOEC**	**42**	**Freshwater**		**50**	**mg-B/L**	**Reliable with restriction**	***Multi-species test so non-standard method. Data not reported***	**Guhl 2000**	**LOEC based on changes in 2 species (of 10 spp monitored). Usable in corroboration of PNEC value, determination of application factor.**
Multi-species (Field study)	Concentration without effect	150	Freshwater		0.16, 1.52	mg-B/L	Review only, no data	*Insufficient information to evaluate test. Only reports an endpoint value or summary*	Guhl 1992a	Cited in ECETOC (1997). Adequate information for review is provided in Guhl 2000 (see Phragmites entry)
Multi-species (Outdoor ponds)	Concentration without effect	2 years	Freshwater		0.7	mg-B/L	Not reliable	*Non-standard method (multi-species). Discussion only of measurements on Phragmites*	Guhl 1992a	Cited in ECETOC (1997). See entry for Phragmites.
Opercularia bimarginata (protozoan)	**NOEC**	**3**	**Fresh water**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles.. Raw data not presented***	**Guhl 2000**	**Value is that used by Dyer (2001). Usable for PNEC or SSD derivation.**
Opercularia bimarginata (protozoan)	NOEC		Fresh water		10	mg-B/L	Not assignable	*Document not reviewed*	Guhl 1992b	Used by Dyer (2001)

***Paramecium caudatum* (protozoan)**	**NOEC, LOEC**	**3**	**Fresh water**	**Boric acid**	**20, 25**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed publication that meets basic scientific principles. Raw data not reported.***	**Guhl 2000**	**Value was cited by Dyer (2001) although referenced Guhl 1992b. Usable for PNEC-chronic or SSD derivation**
Paramecium caudatum (protozoan)	NOEC	3	Fresh water	Boric acid	18	mg-B/L	Not assignable	*Document not reviewed*	Ambartsumyan, MS, 1965	
Paramecium caudatum (protozoan)	Toxicity threshold	3	Fresh water		<70	mg-B/L	Not assignable	*Insufficient information to evaluate test. (See comments)*	Bringman and Kühn, 1980	Species is not mentioned in text, althought several reviews state test results and cite this publication.
Pseudomonas putida (microbe)	Toxicity threshold	0.67	Fresh water (culture medium)	Disodium tetraborate	223	mg-B/L	Not reliable	*No data reported; non-standard endpoint; exposure estimates ignore background sources; conc not measured*	Bringman and Kühn, 1977b	Endpoint reported as 1040 mg/L of test substance (21.49%B). Some cite value as borate ion (28%B) with endpoint 291 mg-B/L. Value also reported in Bringmann & Kuhn 1980a
Pseudomonas putida (microbe)	NOEC	0.67	Fresh waters	Boric acid	59	mg-B/L	Not reliable	*Peer-reviewed technical publication. Values used include over-estimates of response (eg, EC3).*	Dyer 2001	Geometric mean of Bringmann & Kuhn (1977b) and Guhl (1992a). However, uses incorrect value from Bringmann & Kuhn.
Pseudomonas putida (microbe)	NOEC (growth)	3	Fresh water		291	mg-B/L	Review only, no data	*Insufficient information to evaluate test. Secondary literature citing some other primary source. Only reports an endpoint value or summary*	Guhl 1992a	Cites Bringmann und Kuhn (1980) Water Res 14: 231. Cited in ECETOC (1997). Data from Bringmann & Kuhn 1977b, but assuming borate ion, not sodium tetraborate.
Pseudomonas putida (microbe)	NOEC (growth)	3	Fresh water		291, 290 (2 tests)	mg-B/L	Review only, no data	*Only endpoint value reported; cites another publication.*	Guhl 1992	Cites Schoberl & Huber 1988, and Bringmann & Kuhn 1980. Cited in ECETOC 1997
***Pseudomonas putida* (microbe)**	**EC10**	**3**	**Fresh water**		**7.6**	**mg-B/L**	**Reliable with restriction**	***Only reports end-point. Value is cited from an unpublished study using DIN38412 T.8 method. Accepted as reliable by***	**Guhl 1992a**	**Cited in ECETOC (1997). Data from HENKEL KGaA. Usable for SSD derivation.**

								Netherlands (2006)		
Pseudomonas putida (microbe)	NOEC		Fresh water		291	mg-B/L	Review only, no data	*Only endpoint value reported without citation of source*	Schöbel and Huber, 1988	Test result is taken from Bringman & Kuhn (1977). Reported endpoint assumes value of 1040 mg/L was borate ion (28% B).
Pseudomonas putida (microbe)	EC0	0.67	Fresh water		3.4	mg-B/L	Review only, no data	*Only reports end-point. Value is cited from an unpublished study using DIN38412 T.8 method*	Guhl 1992a	Cited in ECETOC (1997). Data from HENKEL KGaA.
Rana pipiens (frog)	**LC10**	**7.5**	**Freshwater**		**29**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles***	**Dyer, 2001**	**Mean of 4 tests. Usable for PNEC-chronic or SSD derivation**
Rana pipiens (frog)	NOEC (embryo-larval)	7	Fresh water, 200 mg/L hardness	Disodium tetraborate	15	mg-B/L	Review only, no data	*Cite Birge and Black 1977*	Raymond & Butterwick, 1992	Cited in V.d. Plassche et al 1989
Rana sylvatica (frog)	LOEC (larval deformities)	23	Freshwater		49.5	mg-B/L	Reliable with restriction	*Peer-reviewed technical publication that meets basic scientific principles*	Laposata and Dunson, 1998	
Uronema pardaczi	**EC5**	**0.83**	**Freshwater**	**Disodium tetraborate**	**23**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication. Only endpoint (Toxicity Threshold) is reported, set at 5% reduction in population growth. EC5 more stringent than currently accepted EC10, may be within normal variability.***	**Bringmann & Kuhn, 1980b**	**Value recalculated assuming test substance was Na2B4O7 (21.49% B) as stated by authors. Cited by Guhl 2000. Usable for PNEC and SSD derivation.**

Note: Studies evaluated as "Reliable without restriction" or "Reliable with restriction" and usable for derivation of a PNEC are indicated in bold.

Table 7-6.Sewage and Sewage organism data

Species	Endpoint Type	Test Duration (days)	Test Conditions	Tested Substance	Endpoint	Value	Reliability Statement	Limitations	Reference	Comments
Activated sludge	EC10 (Inhibition of respiration)	3 hour	Sewage treatment plant	Boric acid	58	mg-B/L	Reliable without restriction	*Guideline study (OECD 209)*	Hanstvelt and Schoonmade, 2000	Preferred for PNEC-stp derivation. EC10 value calculated from original data
Activated sludge	EC20 (Inhibition of respiration)	3 hour	Sewage treatment plant	Boric acid	112	mg-B/L	Reliable without restriction	*Guideline study (OECD 209)*	Hanstvelt and Schoonmade, 2000	
Activated sludge	EC50 (Inhibition of respiration)	3 hour	Sewage treatment plant	Boric acid	>175	mg-B/L	Reliable without restriction	*Guideline study (OECD 209)*	Hanstvelt and Schoonmade, 2000	Usable for PNEC-stp derivation
Activated sludge	NOEC (treatment plant performance)	3 hr	OECD (1971)		20	mg-B/L	Reliable with restriction	*Peer-reviewed technical publication. Method based on OECD method for COD. Acclimation period included in standard method*	Gerike et al 1976	Cited in Guhl 1992a, 2000. Usable for PNEC-stp derivation
Entosiphon sulcatum (protozoan)	NOEC (growth inhibition test)	3	Fresh water (culture medium)	Boric acid	15	mg-B/L	Reliable with restriction	*Peer-reviewed technical publication. Data not presented. Compared feeding live food (bacteria) with dead food, noting significant decrease in growth if not fed live bacteria.*	Guhl 2000	Author points out that this species is commonly found in wastewater treatment plants, with an annual average of 2.12 mg-B/L, suggesting that this species. Usable for PNEC-chronic or SSD derivation. Usable for PNEC-stp derivation.

								LOEC 22 mg-B/L		
Opercularia bimarginata (protozoan)	**NOEC (growth inhibitin test)**	**3**	**Fresh water**	**Boric acid**	**10**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication that meets basic scientific principles. Raw data not presented***	**Guhl 2000**	**Value is that used by Dyer (2001). Usable for PNEC or SSD derivation.**
***Paramecium caudatum* (protozoan)**	**NOEC, LOEC (growth inhibitin test)**	**3**	**Fresh water**	**Boric acid**	**20, 25**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed publication that meets basic scientific principles. Raw data not reported.***	**Guhl 2000**	**Value was cited by Dyer (2001) although referenced Guhl 1992b. Usable for PNEC-chronic or SSD derivation**
Photobacterium phosphorum (Microtox)	EC20 (inhibiton of lumines-cence)		Saltwater		18	mg-B/L	Reliable with restriction	*Data from unpublished study using DIN 38412 Part 34 method. Raw data not provided.*	HENKEL KGaA, 1991	Endpoint not relevant to freshwater sewage treatment plant
Pseudomonas putida (microbe)	Toxicity threshold (Growth inhibition test)	0.67	Fresh water (culture medium)	Disodium tetraborate	233	mg-B/L	Not reliable	*No data reported; non-standard endpoint; exposure estimates ignore background sources; conc not measured*	Bringman and Kühn, 1977b	Endpoint reported as 1040 mg/L of test substance (21.49%B). Some cite value as borate ion (28%B) with endpoint 291 mg-B/L. Value also reported in Bringmann & Kuhn 1980a
Pseudomonas putida (microbe)	NOEC (growth inhibition test)	0.67	Fresh waters	Boric acid	59	mg-B/L	Not reliable	*Peer-reviewed technical publication. Values used include over-estimates of response (eg, EC3).*	Dyer 2001	Geometric mean of Bringmann & Kuhn (1977b) and Guhl (1992a). However, uses incorrect value from Bringmann & Kuhn.

Pseudomonas putida (microbe)	NOEC (growth inhibition test)	3	Fresh water		291	mg-B/L	Review only, no data	*Secondary literature citing some other primary source. Only endpoint value reported.*	Guhl 1992	Cites Bringmann und Kuhn (1980) Water Res 14: 231. Cited in ECETOC (1997).
Pseudomonas putida (microbe)	EC10 (Growth inhibition test)	0.67	Fresh water		7.6	mg-B/L	Review only, no data	*Only reports end-point. Value is cited from an unpublished study using DIN38412 T.8 method*	Guhl 1992a	Cited in ECETOC (1997). Data from HENKEL KGaA
Pseudomonas putida (microbe)	EC0 (Growth inhibition test)	0.67	Fresh water		3.4	mg-B/L	Review only, no data	*Only reports end-point. Value is cited from an unpublished study using DIN38412 T.8 method*	Guhl 1992a	Cited in ECETOC (1997). Data from HENKEL KGaA.
Pseudomonas putida (microbe)	EC10 (Growth inhibition test)	0.67	Fresh water		340	mg-B/L	Reliable with restrictions	*Data from unpublished study using DIN 38412 Part 27 method. Raw data not provided.*	HENKEL KGaA, 1991	
Pseudomonas putida (microbe)	EC10 (Growth inhibition test)	0.67	Fresh water		7.6	mg-B/L	Review only, no data	*Only reports end-point. Value is cited from an unpublished study using DIN38412 T.8 method*	HENKEL KGaA, 1991	Cited in Guhl, 1992a and ECETOC (1997)
Pseudomonas putida (microbe)	NOEC (Growth inhibition test)		Fresh water		291	mg-B/L	Review only, no data	*Only endpoint value reported without citation of source*	Schöbel and Huber, 1988	Test result is taken from Bringman & Kuhn (1977). Reported endpoint assumes value of 1040 mg/L was borate ion (28% B).
Uronema pardaczi	**EC5 (growth inhibition test)**	**0.83**	**Freshwater**	**Disodium tetraborate**	**23**	**mg-B/L**	**Reliable with restriction**	***Peer-reviewed technical publication. Only endpoint (Toxicity Threshold) is reported, set at 5% reduction in population growth. EC5 more***	**Bringmann & Kuhn, 1980b**	**Value recalculated assuming test substance was Na2B4O7 (21.49% B) as stated by authors. Cited by Guhl 2000. Usable for PNEC and SSD derivation.**

			stringent than currently accepted EC10, may be within normal variability.	

Note: Studies evaluated as “Reliable without restriction” or “Reliable with restriction” and usable for derivation of a PNEC are indicated in bold.

Table 7-7

Terrestrial Soil Macro-organisms Toxicity Data

Species	Endpoint Type	Test Duration (days)	Test Conditions	Tested Substance	Endpoint	Value	Reliability Statement	Limitations	Reference	Comments
Eisenia andrei (earthworm)	LC50	14	Reference and artificial soil	Boric acid	609	mg-B/kg-dry soil	Reliable with restriction	*Tested to develop new guideline, comparability with accepted methods not established. Data not presented.*	Stantec/AEC 2003, Stantec 2004	Cited by Netherlands, 2006. Geometric means of 8 tests
Eisenia andrei (earthworm)	NOEC All endpoints	56 to 63	Artificial soil	Boric acid	54	mg-B/kg-dry soil	Reliable with restriction	*Tested to develop new guideline, comparability with accepted methods not established. Data not presented.*	Stantec/AEC 2003, Stantec 2004	Cited by Netherlands, 2006. Geometric means of 4 tests
Eisenia fetida (earthworm)	LC50 Adult survival	14		Boric acid	693	mg-B/kg-dry soil	Reliable with restriction	*Tested to develop new guideline, comparability with accepted methods not established. Data not presented.*	Stantec/AEC 2003, Stantec 2004	Cited by Netherlands, 2006. Geometric means of 4 tests
Eisenia fetida (earthworm)	NOEC	14		Boric acid	>175	mg-B/kg-dry soil	Reliable without restriction	Guideline study	Henzen 2000	
Folsomia candida (collembolan)	NOEC	28	Reference and artificial soil	Boric acid	17	mg-B/kg-dry soil	Reliable with restriction	*Comparable to guideline study with acceptable restrictions. Only reports an endpoint value, Data not presented.*	EPFL, 2003	Cited by Netherlands, 2006. Geometric means of 2 tests

Lumbricus terrestris (earthworm)	LC50	14	Reference and artificial soil	Boric acid	473	mg-B/kg-dry soil	Reliable with restriction	*Tested to develop new guideline, comparability with accepted methods not established. Data not presented.*	Stantec/AEC 2003, Stantec 2004	Cited by Netherlands, 2006. Geometric means of 2 tests
Onychiurus folsomi (collembolan)	NOEC	35	Reference soil	Boric acid	**31**	mg-B/kg-dry soil	Reliable with restriction	*Tested to develop new guideline, comparability with accepted methods not established. Data not presented.*	ESG International 2003	Cited by Netherlands, 2006. Geometric means of 2 tests

Table 7-8 Terrestrial Plant Toxicity Data

Species	Endpoint Type	Test Duration (days)	Test Conditions	Tested Substance	Endpoint	Value	Reliability Statement	Limitations	Reference	Comments
Acer macrophyllum Pursh (Big-leaf Maple)	Threshold (yield reduction)			Not specified	0.5 to 0.9	ppm Extractable boron	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Glaubig and Bingham 1985	
Agropyion riparium (Streambank wheatgrass)	NOAEC (Shoot wet weight)	7	Clay-loam soil	Boric acid	28	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Agropyion riparium (Streambank wheatgrass)	NOAEC (Shoot length)	7	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
***Agropyion riparium* (Streambank wheatgrass)**	**EC20 (Seedling emergence)**	**7**	**Clay-loam soil**	**Boric acid**	**14**	**mg-B/kg dry soil**	**Reliable with restriction**	***Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.***	**Aquaterra Environmental 1998**	Geometric mean of this study and similar in artificial soil is 4 mg-B/kg dry soil
Agropyron dasystachyum (Northern wheatgrass)	NOAEC (Shoot wet weight)	7	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Agropyron dasystachyum (Northern wheatgrass)	EC20 (Seedling emergence)	7	Artificial soil	Boric acid	94	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Agropyron dasystachyum (Northern wheatgrass)	EC20 (Seedling emergence)	7	Clay-loam soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
***Agropyron riparium* (Streambank**	**EC20 (Seedling emergence**	**7**	**Artificial soil**	**Boric acid**	**1**	**mg-B/kg dry soil**	**Reliable with restriction**	***Study meets basic scientific principles but not a peer-reviewed technical***	**Aquaterra Environmental 1998**	**Note: Data suggest hormetic pattern.**

wheatgrass)	**)**							***publication. Not all data shown.***		
Agropyron smithii (Western wheatgrass)	EC20 (Seedling emergence)	7	Artificial soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Agropyron smithii (Western wheatgrass)	EC20 (Seedling emergence)	7	Clay-loam soil	Boric acid	80	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Allium cepa (Onion (var Riverside Sweet Spanish))	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
Allium cepa (Spanish onion)	NOAEC (Shoot wet weight)	7	Clay-loam soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Allium cepa (Spanish onion)	NOAEC (Shoot length)	7	Clay-loam soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Allium cepa (Spanish onion)	EC20 (Seedling emergence)	7	Artificial soil	Boric acid	11	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: Data suggest hormetic pattern.
Allium cepa (Spanish onion)	EC20 (Seedling emergence)	7	Clay-loam soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: Data suggest hormetic pattern.
Apium graveolens (Celery)	NOEC (dry weight)	Maturity	Outdoor sand solution		15	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<15mg-B/L
Arbutus menziesli Pursh (Madrone)	Threshold (yield reduction)			Not specified	2 to 5.4	mg-extractable B/kg-soil	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Glaubig and Bingham 1985	

Asparagus officinalis (Asparagus)	NOEC (dry weight)	Maturity	Outdoor sand solution		15	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<15mg-B/L
Avena sativa (Oats)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Avena sativa (Oats)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Avena sativa (Oats)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Avena sativa (Oats)	EC20 (Seedling emergence)	5	Artificial and clay-loam soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Beckmannia syzigachne (American sloughgrass)	NOAEC (Shoot wet weight)	24	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Beckmannia syzigachne (American sloughgrass)	EC20 (Seedling emergence)	24	Artificial soil	Boric acid	34	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Beckmannia syzigachne (American sloughgrass)	EC20 (Seedling emergence)	24	Clay-loam soil	Boric acid	73	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Beta vulgaris (Common beet)	NOEC (dry weight)	Maturity	Outdoor sand solution		5 - 10	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Beta vulgaris (Leaf beet)	NOEC (dry weight)	Maturity	Outdoor sand solution		15	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L

Beta vulgaris (Sugar beet (var BPI))	NOEC (dry weight)	Maturity	Outdoor sand solution		10	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Bouteloua gracillus trachycaulum (Grama grass)	NOAEC (Shoot length)	8	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Bouteloua gracillus trachycaulum (Grama grass)	EC20 (Seedling emergence)	8	Artificial soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Bouteloua gracillus trachycaulum (Grama grass)	EC20 (Seedling emergence)	8	Clay-loam soil	Boric acid	6	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: Data suggest hormetic pattern.
Brassica napus (Canola)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	84	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Brassica napus (Canola)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Brassica napus (Canola)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	90	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Brassica napus (Canola)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	119	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Brassica oleracea (Cabbage)	NOEC (dry weight)	Maturity	Outdoor sand solution		5	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L

Brassica oleracea (Cabbage)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Brassica oleracea (Cabbage)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Brassica oleracea (Cabbage)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	47	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Brassica oleracea (Cabbage)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	92	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Brassica oleracea var. Captiata (Cabbage)	Threshold (yield reduction)			Sodium borate	>6.3	mg-extractable B/kg-soil	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Gupta and Cutcliffe 1984	
Brassica rapa (Turnip)	NOEC (dry weight)	Maturity	Outdoor sand solution		15	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Brassica rapa (Turnip)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	0	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Effect seen at lowest added concentration Note: No dose-response pattern observed
Brassica rapa (Turnip)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	84	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Brassica rapa (Turnip)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	17	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	

Brassica rapa (Turnip)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	11	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Brassica sp (Mustard)	NOEC (dry weight)	Maturity	Outdoor sand solution		5	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Bromus ciliatus (Fringed bromegrass)	NOAEC (Shoot length)	13	Clay-loam soil	Boric acid	no data		Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No data - inadequate control response.
Bromus ciliatus (Fringed bromegrass)	EC20 (Seedling emergence)	13	Artificial soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Bromus marginatus (Mountain bromegrass)	NOAEC (Shoot length)	7	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Bromus marginatus (Mountain bromegrass)	EC20 (Seedling emergence)	7	Artificial soil	Boric acid	53	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Bromus marginatus (Mountain bromegrass)	EC20 (Seedling emergence)	7	Clay-loam soil	Boric acid	65	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Calamagrostis canadensis (Bluejoint marsh reed)	NOAEC (Shoot wet weight)	?	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Calamagrostis canadensis (Bluejoint marsh reed)	NOAEC (Shoot length)	?	Clay-loam soil	Boric acid	28	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	

Calamagrostis canadensis (Bluejoint marsh reed)	EC20 (Seedling emergence)	?	Artificial soil	Boric acid	2	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Calamagrostis canadensis (Bluejoint marsh reed)	EC20 (Seedling emergence)	?	Clay-loam soil	Boric acid	33	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Calendula officinalis (Calendula)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
Capsicum frulescens (Redpepper)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
Citrus limona (Lemon)	Threshold (yield reduction)		Solution culture	Boric acid	1	mg-B/L	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Eaton 1944	
Cucumis melo (Muskmelon)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Cucumis sativa(Cucumber)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	28	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Cucumis sativa(Cucumber)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Cucumis sativa(Cucumber)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	1	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Cucumis sativa(Cucumber)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	91	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	

Cynara scolymus (Artichoke)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Daucus carota (Carrot)	NOEC (dry weight)	Maturity	Outdoor sand solution		1 to 5	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
Daucus carota(Carrot)	NOAEC (Shoot wet weight)	6	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Daucus carota(Carrot)	EC20 (Seedling emergence)	6	Artificial soil	Boric acid	44	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Daucus carota(Carrot)	EC20 (Seedling emergence)	6	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: Data suggest hormetic pattern.
Delphinium sp (larkspur)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Eschscholtzia californica (California poppy)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Festuca rubra (Red fescue)	NOAEC (Shoot wet weight)	6	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Festuca rubra (Red fescue)	EC20 (Seedling emergence)	6	Artificial soil	Boric acid	47	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Festuca rubra (Red fescue)	EC20 (Seedling emergence)	6	Clay-loam soil	Boric acid	76	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	

Ficus carica (Fig)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Fragaria sp (Strawberry)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Glycine max (Soybean)	NOAEC (Shoot wet weight)	7	Clay-loam soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Glycine max (Soybean)	NOAEC (Shoot length)	7	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Glycine max (Soybean)	EC20 (Seedling emergence)	7	Artificial soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Glycine max (Soybean)	EC20 (Seedling emergence)	7	Clay-loam soil	Boric acid	21	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Gossipium hirsutum (Cotton)	Threshold (yield reduction)			Boric acid	45	mg-B/kg-bulk soil	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Banuelos et al 1996	
Gossypium hirsutum (Cotton)	NOEC (dry weight)	Maturity	Outdoor sand solution		5	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<10mg-B/L
Helianthus annus (Sunflower)	Threshold (yield reduction)		Field study	Boric acid	1.9 to 2.4	mg-B/kg	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Aitken and McCallum 1988	
Helianthus annus (Sunflower)	**EC50 (growth)**	**14**	**Greenhouse study**	**Boric acid**	**6.74**	**mg-B/kg-dry soil**	**Reliable with restriction**		**Aitken and McCallum 1988**	**Geometric mean of 5 studies**

Helianthus tuberosus (Jerusalem artichoke)	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
Hibiscus cannabimus (Kenaf)	Threshold (yield reduction)			Boric acid	45	mg-B/kg-bulk soil	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Banuelos et al 1996	
Hordeum vulgare (Barley)	Threshold (yield reduction)			Boric acid	8	mg-extractable B/kg-soil	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Riley et al 1994	
Hordeum vulgare (Barley)	NOEC (root/shoot ratio)	85	Greenhouse study	Boric acid	2	mg-B/kg-dry soil	Reliable with restriction		Riley et al 1994	
Hordeum vulgare (Barley)	NOEC (grain yield)	>120	Greenhouse study	Boric acid	4	mg-B/kg-dry soil	Reliable with restriction		Riley et al 1994	
Hordeum vulgare (Barley)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
***Hordeum vulgare* (Barley)**	**NOEC**	**>120**	**Greenhouse study**	**Boric acid**	**1**	**mg-B/kg-dry soil**	**Reliable with restriction**	***Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication***	**Riley et al 1994**	**Cited by the Netherlands (2006) as critical plant study**
Hordeum vulgare (Barley)	NOAEC (Shoot wet weight)	4	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Hordeum vulgare (Barley)	EC20 (Seedling emergence)	4	Artificial soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Hordeum vulgare (Barley)	EC20 (Seedling emergence)	4	Clay-loam soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Hordeum vulgare (Barley)	Tissue residues				0.5 – 1	Mg-B/kd dw soil	Review onle	*No data*	Eisler 1990	Residues of 46-100 mg-B/kg-dw in leaves

Ipomoca batatas (Sweetpotato)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
Koeleria macrantha (June grass)	NOAEC (Shoot wet weight)	9	Clay-loam soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Koeleria macrantha (June grass)	NOAEC (Shoot length)	9	Clay-loam soil	Boric acid	84	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Koeleria macrantha (June grass)	EC20 (Seedling emergence)	9	Artificial soil	Boric acid	27	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Koeleria macrantha (June grass)	EC20 (Seedling emergence)	9	Clay-loam soil	Boric acid	17	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Lactuca sativa (Lettuce (var Big Boston Head))	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Lactuca sativa (Lettuce (var Los Angeles Market))	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Lathyrus odoratus (Sweet pea)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<10mg-B/L
Latuca sativa (Lettuce)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Latuca sativa (Lettuce)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	>112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed

Latuca sativa (Lettuce)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	45	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Latuca sativa (Lettuce)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	74	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Linum usitatissumum (Flax)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	28	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Linum usitatissumum (Flax)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	61	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Linum usitatissumum (Flax)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	98	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Lolium perenne (Perennial ryegrass)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Lolium perenne (Perennial ryegrass)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	69	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: Data suggest hormetic pattern.
Lolium perenne (Perennial ryegrass)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	61	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Lupinus hartwegi (Lupine)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L

Lycoperiscon esculentum (Tomato)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Lycoperiscon esculentum (Tomato)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Lycoperiscon esculentum (Tomato)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	55	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Lycoperiscon esculentum (Tomato)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	31	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Lycoperiscon esculentum (Tomatoe)	Threshold (yield reduction)			Sodium borate	>4	mg-B/kg-bulk soil	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Gupta 1983	
Lycopersicon esculentum (Tomato (var Marglobe))	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<10mg-B/L
Medicago sativa	**NOEC**				**11**	**mg-B/kg-dry soil**	**-**		**Gestring and Soltanpour, 1987**	**Geometric mean of 5 values: 20, 10, 10, 10, 10**
Medicago sativa (Alfalfa)	NOEC (dry weight)	Maturity	Outdoor sand solution		10	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<15mg-B/L
Medicago sativa (Alfalfa)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Medicago sativa (Alfalfa)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data*	Aquaterra Environmental 1998	

								shown.		
Medicago sativa (Alfalfa)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	95	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Medicago sativa (Alfalfa)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	69	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Melilotus indica (Sweetclover)	NOEC (dry weight)	Maturity	Outdoor sand solution		5	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Melilotus indica (Sweetclover)	NOEC (dry weight)	Maturity	Outdoor sand solution		5	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<15mg-B/L
Nicotiana tomentosa (Tobacco)	NOEC (dry weight)	Maturity	Outdoor sand solution		5	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<15mg-B/L
Oxalis bowiel (Oxalis)	NOEC (dry weight)	Maturity	Outdoor sand solution		>25	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<10mg-B/L
Petroseleinum crispum (Parsley)	NOEC (dry weight)	Maturity	Outdoor sand solution		10	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Phaseolus lunatus (Lima bean)	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
Phaseolus uvlgaris (Snap bean)	Threshold (yield reduction)			Sodium borate	> 4	mg-B/kg-bulk soil	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Gupta 1983	
Phaseolus vulgaris (field bean)	**Threshold (yield reduction)**			**Sodium borate**	**1.6 to 3.2**	**mg-extractable B/kg-soil**	**Reliable with restriction**	***Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication***	**Gupta and Cutcliffe 1984**	

Phaseolus vulgaris (field bean)	**NOEC (yield)**	**365**	**Field study**	**Borate 65 (20%B)**	**1.5**	**mg-B/kg-dry soil**	**Reliable with restriction**		**Gupta and Cutcliffe 1984**	
Phaseolus vulgaris (Kidney bean)	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Phleum pratense (Timothy)	NOAEC (Shoot wet weight)	7	Clay-loam soil	Boric acid	28	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Phleum pratense (Timothy)	NOAEC (Shoot length)	7	Clay-loam soil	Boric acid	28	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Phleum pratense (Timothy)	EC20 (Seedling emergence)	7	Artificial soil	Boric acid	35	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Phleum pratense (Timothy)	EC20 (Seedling emergence)	7	Clay-loam soil	Boric acid	77	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Pinus sabiniana (Digger pine, seedlings)	Toxicity – growth reduction, foliar damage		Field study		13-17	mg-B/L soil extract	Review only	*No data*	Eisler 1990	
Pisum sativum (Pea (var American Wonder))	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Pisum sativum (Pea (var Hundredfold))	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Poa pratensis (Kentucky Bluegrass)	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L

Prunus avium (Cherry)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Prunus persica (Peach)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Psium salvium (Pea)	Threshold (yield reduction)			Not specified	20 to 50	mg-B/kg-bulk soil	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Bagheri et al. 1994	
Pyrus communis (Pear)	Toxicity symptoms	6 year	Field (orchard)		82-164	Kg-B/ha	Review only, no data	*Review of literature*	Eisler 1990	Symptoms observed during application and 4 years post-application. Soil B < 2 mg/kg in 5 years and visible toxicity disappeared
Raphanus sativus (Radish (var Early Scarlet))	NOEC (dry weight)	Maturity	Outdoor sand solution		5	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Raphanus sativus (Radish (var Early Scarlet))	NOEC (dry weight)	Maturity	Outdoor sand solution		5	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Raphanus sativus (Radish)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	28	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Raphanus sativus (Radish)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Raphanus sativus (Radish)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	76	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Raphanus sativus (Radish)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	93	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data*	Aquaterra Environmental 1998	Note: Data suggest hormetic pattern.

								shown.		
Rubus sp (Blackberry)	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
Schizachyrium scoparius (Little bluestem)	NOAEC (Shoot wet weight)	10	Clay-loam soil	Boric acid	42	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Schizachyrium scoparius (Little bluestem)	NOAEC (Shoot length)	10	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Schizachyrium scoparius (Little bluestem)	EC20 (Seedling emergence)	10	Artificial soil	Boric acid	92	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: Data suggest hormetic pattern.
Schizachyrium scoparius (Little bluestem)	EC20 (Seedling emergence)	10	Clay-loam soil	Boric acid	104	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: Data suggest hormetic pattern.
Solanum tuberosum (Potato)	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Sorghum vulgare (Milo)	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
***Sorghum vulgare* Sudanese**	**NOEC**				**5**	**mg-B/kg-dry soil**	**-**		**Adriano et al. 1988**	**Cited in Netherlands, 2006. Geometric mean of 3 studies: 4, 4, 8**
Trifolium pratense (Red clover)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	28	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed

Trifolium pratense (Red clover)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	28	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Trifolium pratense (Red clover)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	34	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Trifolium pratense (Red clover)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	8	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Triticum aestivum (Wheat)	NOAEC (Shoot wet weight)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Triticum aestivum (Wheat)	NOAEC (Shoot length)	5	Clay-loam soil	Boric acid	84	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Triticum aestivum (Wheat)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	118	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Triticum aestivum (Wheat)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	112	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Ulma americana (Elm)	NOEC (dry weight)	Maturity	Outdoor sand solution		<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Umbellularia california (California laurel)	Threshold (yield reduction)			Not specified	3 to 4	mg-extractable B/kg-soil	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Glaubig and Bingham 1985	

Vicia atropurpurea (Vetch)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Viola odorata (Violet)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
Viola tricolor (Pansy)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	
Vitis vinifera (Grape (var Malaga))	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Vitis vinifera (Grape (var Sultanina))	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L
Zea mays (Corn)	Threshold (yield reduction)			Sodium borate	2 to 4	mg-B/kg-bulk soil	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Gupta 1983	
Zea mays (Corn)	NOEC (dry weight)	Maturity	Outdoor sand solution		1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<5mg-B/L
Zea mays (Corn)	NOAEC (Shoot wet weight, length)	5	Clay-loam soil	Boric acid	56	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	Note: No dose-response pattern observed
Zea mays (Corn)	EC20 (Seedling emergence)	5	Artificial soil	Boric acid	8	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	
Zea mays (Corn)	EC20 (Seedling emergence)	5	Clay-loam soil	Boric acid	319	mg-B/kg dry soil	Reliable with restriction	*Study meets basic scientific principles but not a peer-reviewed technical publication. Not all data shown.*	Aquaterra Environmental 1998	

Zinnia elegans (Zinnia)	NOEC (dry weight)	Maturity	Outdoor sand solution	<1	mg-B/L	Reliable with restriction	*Peer reviewed publication; study preceeded current methods. Exposure through plant maturity*	Eaton 1944	Deficiency shown at [B]<1mg-B/L

Table 7-9

Terrestrial Soil Micro-organism Toxicity Data

Species	Endpoint Type	Test Duration (days)	Test Conditions	Tested Substance	Endpoint	Value	Reliability Statement	Limitations	Reference	Comments
Arylsufatase in soil	EC60	30 min			270	mg-B/L	Review only, no data	*Insufficient information to evaluate test. Secondary literature citing some other primary source. Only reports an endpoint value or summary*	Crommentijn, 1995	
Aspergillus niger (black mould)	NOEC / LOEC (yield as dry weight)				1200 / 1300	mg-B/L	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Bowen and Gauch 1966	
Dehydrogenase in soil	EC50	1			176	mg-B/L	Review only, no data	*Insufficient information to evaluate test. Secondary literature citing some other primary source. Only reports an endpoint value or summary*	Crommentijn, 1995	
Dehydrogenase in soil	EC50	1	Unenriched and enriched soil	Disodium tetraborate	152 and 363	mg-B/kg-dry soil	Not assignable	study not reviewed	Rogers and Li 1985	Cited in Netherlands, 2006
Neurospora crassa (bread mould)	NOEC / LOEC (yield as				100 / 250	mg-B/L	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical*	Bowen and Gauch 1966	

	dry weight)						*publication*	
Nitrification in soil	EC7	20		54	mg-B/L	Review only, no data	*Insufficient information to evaluate test. Secondary literature citing some other primary source. Only reports an endpoint value or summary*	Crommentijn, 1995
Nitrification in soil	EC10	20	Disodium tetraborate	54	mg-B/kg-dry soil	Not assignable	study not reviewed	Liang and Tabatabai, 1977
Penicillium chrysogenum (fungi)	NOEC / LOEC (yield as dry weight)			500 / 4000	mg-B/L	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Bowen and Gauch 1966
Saccharomyces cerevisia (yeast)	NOEC / LOEC (Growth)			5 / 50	mg-B/L	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Bowen and Gauch 1966
Saccharomyces cerevisia (yeast)	NOEC / LOEC (CO_2 evolution)			<150 / 150	mg-B/L	Reliable with restriction	*Well-done study and report that meets basic scientific principles. Peer-reviewed technical publication*	Bowen and Gauch 1966
Urease in soil	EC13, EC11	2 hr		54, 5.4	mg-B/L	Review only, no data	*Insufficient information to evaluate test. Secondary literature citing some other primary source. Only reports an endpoint value or summary*	Crommentijn, 1995

Table 7-10 Other Terrestrial Organism Toxicity Data

Species	Endpoint Type	Test Duration (days)	Test Conditions	Tested Substance	Endpoint	Value	Reliability Statement	Limitations	Reference	Comments
Apis mellifera (honeybee)	LD50	4		Boric acid	> 363	µg-B/bee	Not assignable	*Insufficient information to evaluate test.*	Atkins 1987	
Apis mellifera (honeybee)	NOEC			Boric acid	87000	mg-B/L	Not assignable	*Insufficient information to evaluate test.*	Ostrovskii 1955	
Anas platyrhynchos (Mallard duck)	LC50	5	Diet	Disodium octaborate	> 2100	mg-B/kg-food	Reliable without restriction	Guideline study	Beavers and Fink 1982c	
Colinus virginianus (Bobwhite quail)	LC50	5	Diet	Boric acid	>983	mg-B/kg-food	Reliable without restriction	Guideline study	Beavers 1984	
Colinus virginianus (Bobwhite quail)	LD50	5	Oral intubation	Disodium octaborate	>527	mg-B/kg-body weight	-		Beavers and Fink 1982a	Cited in SYKE 1998a
Colinus virginianus (Bobwhite quail)	LC50	5	Diet	Disodium octaborate	>2100	mg-B/kg-food	Reliable without restriction	Guideline study	Beavers and Fink 1982b	

Table 7-11. Boron concentrations in soil solution associated with plant growth.

Crop species	Deficiency	Optimum growth [mg B/L]	Toxicity range [mg B/L]	Reference
sensitive		trace – 1	1 - 5	Sprague, 1972; Raymond and Butterwick, 1992
semi-tolerant	< 1	1 – 5	5 – 10	Sprague, 1972
		1 – 4		Raymond and Butterwick, 1992
tolerant	< 5	5 – 10	5 - 25	Sprague, 1972
		4 – 15		Raymond and Butterwick, 1992
general	< 2	2 – 5	5 - 12	Gupta et al. 1985

Table 7-12. Endpoint values used in SSD for aquatic HC_5 derivation

Used by Dyer 2001	Used by BPD 2006	Used by RAR v2	Species	Endpoint (mg-B/L)	Criterion	Source (if not original study)	Original References
X			*Ambystoma jeffersonian*	49.5	LOEC		Laposata & Dunson 1998
X			*Ambystoma maculatum*	49.5	LOEC		Laposata & Dunson 1998
		x	*Anacystis nidulans*	50	NOEC		Martinez et al, 1986
	x	x	*Brachydanio rerio*	5.6	NOEC		Hooftman et al 2000b
X				75	NOEC		Rowe et al. 1998
	x		*Bufo fowleri*	30	NOEC	V.d.Plassche 1999	Raymond & Butterwick 1992
X		x		41	NOEC	Dyer 2001	Species mean value calculated from Birge & Black 1977
	x		*Carassius aurata*	15	NOEC	V.d.Plassche 1999	Raymond & Butterwick 1992
X		x		16.65	NOEC	Dyer 2001	Species mean value calculated from Birge & Black 1977
X	x	x	*Ceriodaphnia dubia*	10	NOEC	V.d.Plassche 1999	Hickey 1989
	x		*Chilomonas paramaecium*	10.6	NOEC	V.d.Plassche 1999	Bringmann & Kuhn 1980a
X	x	x	*Chironomus decorus*	10	NOEC	V.d.Plassche 1999	Maier & Knight 1991
		x	*Chlorella pyrenoidosa*	10	NOEC		Fernandez et al 1984
	x		*Daphnia magna*	6	NOEC	V.d.Plassche 1999	Lewis & Valentine 1981
X				9.12	NOEC	Dyer 2001	Species mean value calculated from Gersich 1984, Lewis & Valentine 1993, Guhl 1992a, Hickey 1989
		x		12.5	NOEC	European Borates Association	Species mean value calculated from Gersich 1984, Lewis & Valentine 1993, Hickey 1989, Hooftman et al 2000a, Gersich & Milazzo 1990
X		x	*Entosiphon sulcatum*	15	NOEC		Guhl 2000
	x		*Ictalurus punctatus*	5	NOEC	V.d.Plassche 1999	Raymond & Butterwick 1992
X		x		13.82	NOEC	Dyer 2001	Species mean value calculated from Birge & Black 1977
		x	*Lemna minor*	60	NOEC		Wang, 1986
	x	x	*Microcystis aeruginosa*	20	NOEC	V.d.Plassche 1999	Bringmann & Kuhn 1978ab
		x	*Micropterus salmoides*	2.89	NOEC	European Borates Association	Species mean value calculated from Birge & Black 1977, Black et al 1993

X				6	NOEC	Dyer 2001	Birge & Black 1977
	x		*Oncorhynchus mykiss*	2	NOEC	V.d.Plassche 1999	Raymond & Butterwick 1992
		x		4.14	NOEC	European Borates Association	Species mean value calculated using LC10 values recalculated by Dyer 2001 from data of Birge & Black 1977, Black et al 1993
X				5.5	LC10	Dyer 2001	Species mean value calculated using LC10 values recalculated from data of Birge & Black 1977
X		x	*Opercularia bimarginata*	10	NOEC		Guhl 2000
X		x	*Paramecium caudatum*	20	NOEC		Guhl 2000
	x		*Pimephales promelas*	14	NOEC	V.d.Plassche 1999	Raymond & Butterwick 1992
	x	x	*Pseudomonas putida*	7.6	NOEC	V.d.Plassche 1999	Schoberl & Huber in ECETOC 1997; originally from Guhl 1992a
X				59.46	NOEC	Dyer 2001	Species mean value calculated from Guhl 1992a, Bringmann & Kuhn 1978
	x		*Rana pipiens*	15	NOEC	V.d.Plassche 1999	Raymond & Butterwick 1992
x		x		29	NOEC	Dyer 2001	Species mean value calculated from Birge & Black 1977
x			*Rana sylvatica*	49.5	LOEC		Laposata & Dunson 1998
x			*Scenedesmus subspicatus*	10	EC0		Guhl 1992a
	x	x		24	EC10	V.d.Plassche 1999	Guhl 1992a in ECETOC, Kopf & Wilk 1995 in ECETOC
	x	x	*Selenastrum capricornutum*	17.5	NOEC		Hanstveit & Oldersma 2000
	x	x	*Spirodella polyrhiza*	6.1	NOEC		Davis et al 2002
		x	*Uronema pardaczi*	23	EC5		Bringmann & Kuhn 1980b
	x			30	NOEC	V.d.Plassche 1999	Bringmann & Kuhn 1980b

8 PBT AND VPVB ASSESSMENT

8.1 Comparison with criteria from annex XIII

Being an inorganic compound, boron does not biodegrade and should therefore be considered as Very Persistent (VP).

Boron is not bioconcentrated, based on the available data that the BCF is less than 2000 L/kg wwt.

The chronic NOEC of boron for marine or freshwater organisms is >).01 mg/B/L and boron is not considered to have endocrine disrupting effects. However, boron is proposed for classification as Toxic for Reproduction category 2, and would be assigned risk phrases R60 and R61. Therefore boron would be considered Toxic (T).

8.2 Assessment of substances of an equivalent level of concern

8.3 Emission characterisation

8.4 Conclusion of PBT and vPvB assessment

Boron should be considered as fulfilling the criteria for Persistence and Toxicity, but not for Bioaccumulation. Therefore boron does not meet the criteria as either PBT or vPvB.

9 EXPOSURE ASSESSMENT

9.1 General discussion on releases and exposure

9.1.1 Summary of the existing legal requirements

9.1.2 Summary of the effectiveness of the implemented risk management measures

9.2 Manufacturing

9.2.1 Occupational exposure

9.2.2 Environmental release

9.3 "Use 1"

For each use include such a sub-chapter. Subsequently, if there is another "Use 2" this will lead to sub-chapter 9.4 "Use 1" including 9.4.1 Human exposure, 9.4.1.1 Occupational exposure, 7.4.1.2 Consumer exposure and 9.4.2 Environmental release. The other sub-chapters will then be renumbered.

SECTION INCOMPLETE

9.3.1 Human exposure

9.3.1.1 Occupational exposure

9.3.1.2 Consumer exposure

9.3.2 Environmental release

9.4 Other sources (for example natural sources)

9.4.1 Human exposure

9.4.1.1 Occupational exposure

9.4.1.2 Consumer exposure

9.4.2 Environmental release

9.5 Environmental exposure assessment

9.5.1 Summary of emissions

9.5.2 Predicted environmental concentrations

9.5.2.1 .

9.5.2.1 Regional concentrations

Atmosphere

Aquatic compartment

Sediment

Soil compartment

9.5.2.2 Local concentrations

Atmosphere

Aquatic compartment

Sediment

Soil compartment

9.5.2.3 Exposure concentrations of man via the environment

9.5.3 Measured levels

Atmosphere

The major source of boron in the atmosphere is from marine evaporation estimated as 1.3 to 4.5 x 10^9 kg-boron per year globally (Argust, 1998, Park and Schlesinger, 2002). Most of this is re-deposited into the oceans or as precipitation in coastal areas. Volcanoes are estimated to contribute about 3 x 10^8 kg-boron per year. Total industrial air emissions are estimated as approximately 1 x 10^7 kg-boron per year, or < 0.6% of total flows (Argust, 1998). Processes such as fibreglass manufacture and ceramics involve high temperatures, so some volatilization of boron is likely. Gomez et al. (2004) reported that boron content of particulates in a ceramic producing region of northeast Spain (average 65 ng/m^3) reflected boron vaporization or volatilization during high temperature ceramic processes. Combustion of coal also may release boron, especially to fly ash.

The total global removal of boron from the atmosphere through both wet and dry deposition has been estimated to be 5.3 to 7.0 million tonnes per year (Argust, 1998). There are limited data available on levels of boron in the atmosphere. 85% of the total atmospheric boron has been reported (Anderson et al 1994) in the gas phase at a level of 16ng/B/m^3 at three continental sites. A more general measurement of atmospheric boron levels comes from the analysis of rain water where levels show wide variation (0.002 to 0.0045 mgB/L in France and 0.1 mgB/L in Japan). An analysis of boron concentrations in rainwater from various regions by Park and Schlesinger (2002) identifies that rainwater from continental sites contain less boron than that from coastal and marine sites. A median value of 6.6 ppb is used with mean values of 4.89 (continental sites) and 10.06 ppb (marine sites).

Aquatic compartment

Extensive environmental monitoring data exists for boron. However, much of the data have been collected as spot samples rather than as part of a more extensive monitoring programme.

There are some areas in Europe where boron levels are high due to local geological conditions and any risk assessment needs to take account of natural background levels. In addition, rainwater, carrying boron from adjacent oceans, may contribute boron to surface waters: by comparing the ratios of ^{11}B and ^{10}B in the Seine River (France) and in sources (perborate, borax from Turkey, borax from the U.S., fertilizer, rainwater, local rocks), Chetelat and Gaillardet (2005) suggested that about 25% of boron in the Seine at Paris was due to rainwater contribution, 10% was due to agricultural-affected waters, and about 65% due to urban effluents. Mean boron discharge at Paris was 4.6 µmol/L or 50 µg-B/L. In the Seine system, geological sources (dissolution of borate from rocks) appeared to contribute less than 1% of total boron except for spring when it reached 10% of total.

A recent analysis of surface water quality data from European countries (Wyness et al., 2003) is summarised in Table 9-1. The study reported the average 95th percentile for every monitoring point, reported as "Mean 95 percentile." This provides a more conservative estimate of the mean concentration than the recommended 90th percentile (ECB, 2003).

Table 9-1. Boron Concentration (µg-B/L) – Summary of data (Wyness et al., 2003)

Country	No. of Monitoring Points	Date Coverage	Total No. Values	Arithmetic Mean	Range	Mean site 95% percentile
Austria	30	1998-2000	712	44	nd-690	80
Belgium	651	1998-2000	5,056	239	25-2,029	410
Denmark	0					
Finland (lakes only)	463	1995	463	3.3	<1-46	44
France	25	1995-2000	1,304	146	nd-2,670	261
Germany	197	1980-95	197	171	nd-1,300	632
Greece	28	1997-99	Not known	144	4-2,330	-
Luxembourg	0					

Ireland	185	1999-2000	185	26	nd-1,630	101
Italy	64	1998-1999	926	114	nd-894	84
Netherlands	9	1986-1999	1,842	111	38-878	218
Portugal	8	1999-2000	129	367	30-3,860	534
Spain	328	1991-2000	4,272	137	nd-7,490	288
Sweden	0					
UK-England	98	1974-2000	22,329	65	nd-1,121	95
UK-Northern Ireland	0					
UK-Scotland	10	1976-1997	3,437	9.7	nd-230	17
UK-Wales	39	1975-1999	4,965	13.0	nd-292	22

Nd = not detected (Wyness et al. does not indicate detection limits.)

Boron data was also collected as part of the GREATER project and this data is summarised in Table 9-2.

Table 9-2. UK Boron monitoring data from the GREATER project

RIVER	**Year**	**No. of sites (No. of samples per site)**	**Range of site Mean boron concs (µg/L)**	**Mean of site mean boron concs (+/- 1 SD[1]) (µg/L)**	**Mean of site 90%ile boron concs (+/- 1 SD[1]) (µg/L)**
R. Aire (UK)	1996-1998	15 (9 -38)	[2] L.D. - 280	247 (+/- 75)	236 (+/- 117)
R,Calder (UK)[3]	1996-1998	18 (18 -27)	26 -417	163 (+/- 94)	274 (+/- 152)
R. Rother (UK)[4]	1996-1998	15 (18 -21)	106 -512	317 (+/- 97)	506 (+/- 178)
R. Went (UK)[5]	1996-1998	8 (19 -24)	179 -530	296 (+/- 108)	442 (+/- 173)

[1] SD is the standard deviation.

[2] L.D. = at the limit of detection (20µg/L). 20 µg/L has been used for the one site to which this applies, in the calculations of overall catchment means. A 90%ile value of 20 µg/L has also been used for this site, in the calculations of overall catchment 90%iles.

[3] Includes 1 small tributary with significant STW effluent influence, and two other tributaries.

[4] Includes 2 tributaries, and also the River Don upstream and downstream of the confluence with the Rother.

[4] Includes 1 small tributary with significant STW effluent influence.

The monitoring data summarised in Table 2-2 has been collected at standard Environment Agency monitoring sites, all of which are located at river sites specifically intended to monitor the effects of inputs from sewage works and other anthropogenic discharges. In the rivers Aire and Calder, the natural upstream and background boron levels are negligible. In the stretch of the river Rother which has been monitored, background boron levels in excess of 100 µg/L are present. These may have resulted from upstream and instream anthropogenic inputs, including leakage from fly ash tipping sites. Background boron levels in excess of 100 µg/L are also present in the river Went, due to exchange with groundwater which has incorporated boron leached from marine sediments exposed in flooded former coal mines. The 90 percentile concentrations from each site (see Fox et al., 2000, Holt et al., 2003) represent the concentrations at low water levels, which are used as a reasonable worst case in environmental risk assessment in Europe. The means of these site-specific 90 percentiles are given in Table 9-2, along with the standard deviations which are due to different boron levels at different sites within the catchment. The means of the 90 percentiles of specific site concentrations are recommended for use in regional risk assessment in Europe (ECB, 2003).

Using recent monitoring data, Heijerick and Van Sprang (2004) used monitoring data to derive the median value of all 90th percentiles that were measured for different sites, rivers/catchments or regions in EU countries. They expressed these as Ambient PEC values, shown in Table 9-3, ranging from 7.4 to 447 µg-B/L. In some cases, the 90th percentiles are calculated from data for river systems within a country because full country-wide data were not available. The use of median is seen as more appropriate than the use of mean (average) values because the median value is less influenced when sites with elevated (possibly contaminated) boron concentrations are present in the data set (Heijerick and Van Sprang, 2004). The highest 90th percentile value from this analysis is 447 µg-B/L.

Heijerick and Van Sprang compared their results with those reported by Wyness et al. (2003, see Table 9-1 above) and noted that the Wyness results were generally a factor of 2 higher. They suggested several reasons for the systematic differences: the Wyness et al. analysis

- was based on 95th percentile values instead of 90th percentile values;
- used the mean of site-specific 95th percentile values instead of the median values;
- did not perform an evaluation of outliers; and
- included older data in all cases, with no preference for using most recent data set.

The highest 95th percentile value in the Wyness et al. analysis was 632 µg-B/L.

Table 9-3 presents additional surface water monitoring data gathered from a range of sources. However, the probabilistic approach of Heijerick and Van Sprang (2004) is the most useful in derivation of PEC values for surface waters in Europe.. The use of this value reflects total uses of borates.

Table 9-3: Data-derived PECs for European Countries (Heijerick and van Sprang, 2004)

Country	**Ambient PEC (µg/L)**
Austria	31.2 µg/L
Belgium Flanders	447 µg B_{total}/L

Rupel catchment	106 µg B/L
Brussels	347 µg B/L
Walloon Region	95.8 µg B/L
Finland	7.4 – 9.3 µg/L
France	167 µg B_{total}/L 97.6 µg B_{diss}/L
Germany	General: 125 – 384 µg/L Baden-Wurttemberg: 60 – 132 µg B/L Large rivers - 1997: 226 µg B/L Large rivers – 1998: 216 µg B/L Bavarian rivers: 58 – 270 µg B/L
Greece	191 – 261 µg B/L
Ireland	47.3 – 62.1 µg B/L
Italy	108.1 µg B/L (Po river)
The Netherlands River Rhine River Meuse	137.1 µg B/L 130.5 µg B/L 140.1 µg B/L
Portugal	356 µg B/L
Spain	--
United Kingdom England Wales Scotland UK – General	 301 (156 – 405) µg B/L 19.7 µg B/L 125 µg B/L 200 µg B/L
Range	**7.4 – 447 µg B/L**

Groundwater

Table 9-4: Additional Reports of Boron Concentrations in Surface Waters

Country	No. sites/ samples	Concentration range (mg/L)	Year	Reference
Austria		< 0.02 – 0.6	1985-1989	Schöller and Bolzer 1989
France	>300	98% < 0.1	1986-89	DDASS de l'Oise, 1990
Germany	7 rivers,17 sites, 360 samples	0.013 – 0.372	1991-95	Metzner *et al* 1999
Italy	19 sites 166 sites 5 sites	< 0.002 < 0.01 – 0.5 0.1- 0.2	1989 1983-84 1997-98	Benfenati *et al* 1992 Tartari and Camusso, 1988 Gandolfi *et al* . 2000
Luxembourg		0.11 – 0.39	1993	Unilever 1994
Netherlands	 22 analyses	0.04 – 0.09 0.09 – 0.145	1981 1992	Mance *et al* 1988 Unilever 1994
Spain	5 sites	0.20- 0.30	1986	Garcia *et al* 1987
Sweden		<0.005 – 0.069 <0.05	1990 1991	Sveriges Geologiska AB Analys, 1991 KM Lab, 1991
England Scotland	15 sites 59 sites (236 samples)	0.011 – 0.311 (mean values) <0.005 – 0.035	1993-96	Neal *et al,* 1998
Switzerland	8 sites	<0.004 – 0.26	1990	EAWAG, 1990

Sediment

Soil compartment

Boron occurs naturally in the soil and levels will reflect rock and soil type, weathering and climate. Sedimentary rocks typically have a higher concentration of boron compared to igneous rocks with rock originating from marine sediments containing borate concentrations of 15-300 mg B/kg while the borate concentration in carbonate sediments is around 10 mg B/kg. (ECETOC 1997). Highly concentrated deposits of boron minerals are generally found in arid areas with a history of volcanism or hydrothermal activity (Woods, 1994). There are many reported ranges of boron concentrations although typically soil boron concentrations range between 10-20 mg B/kg (ECETOC 1997).

TABLE 9-5: SOIL BORON LEVELS (DRY WEIGHT BASIS)

Region	Range	Mean	Reference

US	10- 300 mg/kg	30 mg/kg	Eisler, 2000
Worldwide	45-124 mg/kg	10-20 mg/kg	Eisler , 2000 ECETOC, 1997 (op cit)

A more relevant factor is the bioavailable boron. Most of the B available to plants comes from decomposition of organic matter and from B adsorbed and precipitated on the surfaces of soil particles (Gupta et al., 1985). Typically less than 5% of total soil B is available, with values ranging from 0.4% to 4.7% (Gupta, 1968). Measurement of the soil solution concentration of B would be the preferred method of determining the bioavailable concentration. Two procedures to estimate soil solution concentrations are used: the hot water soluble boron (HWS) and the saturation extract concentration. Neither is seen as universally applicable (Gupta et al., 1985), although the HWS procedure appears to be used more often. Values of HWS boron normally lie between 0.1 mg/L and 3 mg/L (Shorrocks, 1989).

Boron introduced with irrigation water will equilibrate between soil solution and soil particles. The most important factors influencing adsorption are the pH of the system, the amount and type of clay minerals present and the exchangeable minerals in the soil. Soil adsorption of boron is maximal at alkaline pH. Of the clays, illite is the most reactive and kaolinite the least reactive. Liming soils replaces exchangeable aluminium cations with calcium, precipitating aluminium hydroxides which appears to increase B adsorption in limed soils (Gupta et al., 1985).. Goldberg et al. (2000) modelled boron binding to soil as a constant capacitance model, with binding as a function of surface hydroxyl groups on oxides and clay minerals. Boron adsorption was characterized as being maximal around pH 9 and exhibited a parabolic shape around that maximum. The model used boron surface complexation constants that were obtained from easily measured soil properties: soil surface area, organic carbon content, inorganic carbon content and free aluminium oxide content (Goldberg and Su, 2005).

Boron adsorption has been reported as varying from fully reversible to irreversible, depending on soil type and environmental conditions (IPCS 1998). Goldberg and Su (2005) reported that infrared spectroscopy found boron in two types of complexes: inner-sphere complexes with no water between the adsorbed boron and the surface functional groups on the soil minerals and outer-sphere complexes with some water between the adsorbed boron and the surface functional groups on amorphous iron oxide.

Eventually adsorption to soil particles will equal desorption, such that the soil solution concentration will equal the irrigation water concentration. If excess irrigation water is applied, boron will be leached downward below the root zone, minimizing root zone concentrations. If insufficient water is applied, evapotranspiration of soil moisture can result in increased boron concentrations that are phytotoxic in the root zone (Gupta et al., 1985). This pattern is consistent with observations that surface concentrations of boron in arid regions are typically higher than in humid regions: movement of excess precipitation leaches boron downward, away from the root zone, leading to regions with boron deficient soils.

Sewage and sewage sludge

Most boron is not removed by conventional sewage treatment, although there is some evidence to suggest that parts-per-million quantities may be associated with sewage sludge. A review of removal technologies suggested that conventional approaches were not effective at removing boron to sub-parts-per-million concentrations or would be associated with high costs (such as high amounts of sorptive materials, e.g., grams/liter) (Park and Edwards, 2005). While some technologies were seen as meriting further research, none was seen as ready for widespread application.

A limited study looking for evidence of boron removal was done at four water treatment facilities in the UK (Ashact Ltd, 1996). Boron levels were measured at the inlet and outlet of the treatment units such that the same mass of waster was monitored at the inlet and outlet. Significant boron removal was noted at one plant. A mechanism for the removal was not identified.

Removal from wastewater using a weak-base anion exchange resin was reported by Yilmaz et al. (2005) to reach 99% from synthetic wastewater. However, the initial boron concentrations ranged from 250 to 100 mg-B/L, so it is not clear how applicable this study would be to typical wastewater boron concentrations.

Monitoring studies under the GREATER project (Fox et al., 2000; Holt et al 2003; Gandolfi et al., 2000) show mean effluent concentrations in the range 0.5 to 2 mg-B/L, summarized in Table 9-6. Note that more recent data indicate lower concentrations than older data, suggesting an overall reduction in boron loading to sewage. Older reviews (Butterwick et al., 1989) suggested typical effluent values of 2 mg-B/L with levels up to 3 to 5 mg-B/L.

Table 9-6: Examples of boron concentrations in sewage waters

Country	No. sites /samples	Conc range (mg/L)	Mean (mg/L)	Year	Reference
Austria		< 0.02 – 0.8	-		Schöller and Bolzer, 1989; Schöller, 1990
Germany	27 STPs	<1.5-4.5		1973	Dietz, 1975
	1 STP	0.50		1993	Metzner *et al,* 1999
Italy	7 STPs		1.0		Mezzanotte *et al,* 1995
	1 STP	0.23-0.66	0.42		Gandolfi *et al,* 2000
	1 STP	0.67-1.26	1.0		Gandolfi *et al,* 2000
	1 STP	0.73-2.86	1.90		Gandolfi *et al,* 2000
Netherlands	1 STP	0.39-0.75		1994	Feijtel *et al,* 1997
Spain	2 STPs		1.45-3.0		Navarro *et al*, 1992
Sweden	1 STP		0.4		Ahl and Jönssen 1972

UK	8 STPs/203 14 STPs/307 7 STPs/138 6 STPs/156	0.43-0.84 0.22-1.12 0.72-1.16 0.70-1.06	0.53 0.48 0.92 0.93	1996-1998	Fox *et al* 2000 Holt *et al* 2003
Egypt	4 STPs	0.11-1.67	0.08 – 0.2		El Kobbia and Ibrahim, 1989

CONCENTRATION IN DRY SEWAGE SLUDGE

There has always been an assumption that boron is not significantly removed during the sewage treatment process. Nevertheless, some boron is associated with sewage sludge although data is scarce. Results of boron concentrations in sewage sludge from a study of 48 sewage treatment plants in Sweden (Eriksson, 2001) are detailed in Table 9-7.

Table 9-7: Concentration of boron (mg B/kg dw) in sewage sludge

Number of Samples	MEAN	SD	Min	Percentile					Max
				10%	25%	Median	75%	90%	
48	61	81	2	8	18	32	58	150	390

Fujita et al. (2005) reported boron adsorption reaching sludge concentrations of 40 to 600 mg-B/kg-sludge (dry weight) when influent concentrations ranged from 0.3 to 30 mg-B/L. The Freundlich constant for activated sludge was 26 mg/kg and was less than for activated carbon (k=190 mg/kg) and activated alumina (k=440 mg/kg). The adsorption pattern was linear. They suggested that at typical wastewater concentrations in Japan of less than 0.1 mg-B/L, sludge concentrations would likely range from 20 to 60 mg-B/kg. This is in reasonable agreement with the results reported by Eriksson (2001).

Secondary poisoning

9.5.4 Selected environmental concentrations of risk characterisation

Atmosphere

Aquatic compartment

Sediment

Soil compartment

Secondary poisoning

9.6 Combined human exposure assessment

10 RISK CHARACTERISATION

10.1 Human health

10.1.1 Workers

10.1.2 Consumers

10.1.3 Indirect exposure of humans via the environment

10.1.4 Combined exposures

10.2 Environment

10.2.1 Aquatic compartment (including sediment and sewage treatment plant and secondary poisoning)

10.2.2 Terrestrial compartment (including secondary poisoning)

10.2.3 Atmospheric compartment

10.2.4 Microbiological activity in sewage treatment systems

OTHER INFORMATION

It is suggested to include here information on any consultation which took place during the development of the dossier. This could indicate who was consulted and by what means, what comments (if any) were received and how these were dealt with. The data sources (e.g registration dossiers, other published sources) used for the dossier could also be indicated here.

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ANNEX

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Figure 1 vbvnbv

Example 1 hff

Hgkhjfkg

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DRAFT – November 7, 2007

SUBSTANCE EVALUATION REPORT

Substance Name:	**Boric Acid**	**Disodium Tetraborates, anhydrous**
EC Number:	**233-139-2**	**215-540-4**
CAS Number:	**10043-35-3**	**1330-43-4**

Rapporteur Member State : Austria

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CONCLUSION OF THE SUBSTANCE EVALUATION

Substance Name:

EC Number:

CAS number:

Registration dossiers numbers:

Conclusion of the substance evaluation:

INFORMATION ON HAZARD AND RISKS

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

2 MANUFACTURE AND USES

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

This should include the classification (including specific concentration limits) listed in Annex I of Directive 67/548/EEC (including the Index Number)

It is proposed to classify borates with toxic to reproduction category 2 and assign risk phrases R60-61. This is in line with the voting during the TPC-meeting held in February 2007.

3.2 Self classification(s)

This should include the classification, the labelling and the specific concentrations limits. The reason and justification for no classification should be reported here.

It should be stated whether the classification is made according to Directive 67/548/EEC criteria or according to GHS criteria.

Acute Oral Toxicity

No classification is indicated under the current EU guidelines (67/548/EEC). However under the GHS guidelines, both boric acid and disodium tetraborate pentahydrate would be classified as Acute Oral Toxicity Category 5. In addition, the data on disodium tetrahydrate anhydrous, which indicated deaths at 2000 mg/kg bw (2/5 in one study and 4/5 in another study) would suggest that Acute Oral Toxicity Category 5 under GHS classification.

Acute Oral Toxicity Category 5 is not included in the EU proposal for the GHS regulation.

Eye Irritancy

Sodium Tetraborates

Disodium tetraborate decahydrate:
Eye irritant, R36 Under current EU guidelines (67/548/EEC)
GHS Category 2 Irritating to eyes

Disodium tetraborate pentahydrate
Eye irritant, R36 under current EU guidelines (67/548/EEC)
GHS Category 2 Irritating to eyes

Disodium tetraborate anhydrous:
Eye irritant, R36 under current EU guidelines (67/548/EEC)
GHS Category 2 Irritating to eyes
Based on read across from disodium tetraborate pentahydrate and disodium tetraborate decahydrate,

4 ENVIRONMENTAL FATE PROPERTIES

Assessment of the potential for secondary poisoning

5 HUMAN HEALTH HAZARD ASSESSMENT

A number of detailed hazard assessments and reviews of the toxicology of borates have been published (Culver et al, 1994a; ECETOC, 1995; EC, 1996; Murray, 1995; Culver and Hubbard, 1996; Hubbard and Sullivan, 1996, Hubbard, 1998; IPCS, 1998; WHO; 1998; Moore et al., 1998; US FNB, 2001; US EPA, 2004; UK EVM, 2003; EFSA 2004, HERA, 2005).

Most of the simple inorganic borates exist predominantly as un-dissociated boric acid in dilute aqueous solution at physiological and environmental pH, leading to the conclusion that the main species in the plasma of mammals and in the environment is un-dissociated boric acid. Since other borates dissociate to form boric acid in aqueous solutions, they too can be considered to exist as un-dissociated boric acid under the same conditions. See 4.1 Degradation

The majority of toxicological and ecotoxicological studies of borates have involved either boric acid (H_3BO_3) or disodium tetraborate decahydrate (i.e., borax, or $Na_2B_4O_7.10H_2O$). Both acute and longer-term studies have been carried out on these two substances. For the other borates, boric oxide, disodium tetraborate pentahydrate, and disodium tetraborate anhydrous, only acute mammalian toxicity studies have been carried out.

For comparative purposes, dose levels of borates have been expressed in terms of boron (B) equivalents based on the fraction of boron on a molecular weight basis. Conversion factors are given in Table 1 below. These conversion factors are important as some studies express dose in terms of B, whereas other studies express the dose in units of boric acid or disodium tetraborate decahydrate.

Table 5.1 Conversion factors to Boron Equivalents

		Conversion factor for Equivalent dose of B
Boric acid	H_3BO_3	0.175
Disodium tetraborate decahydrate (Borax)	$Na_2B_4O_7 \bullet 10H_2O$	0.113
Disodium tetraborate pentahydrate	$Na_2B_4O_7 \bullet 5H_2O$	0.148
Disodium tetraborate anhydrous	$Na_2B_4O_7$	0.215

5.1 Toxicokinetics (absorption, distribution, metabolism, and elimination)

The toxicokinetics of boric acid; boric oxide; and the sodium tetraborates (anhydrous; pentahydrate and decahydrate) are similar in rats and humans with respect to absorption, distribution, and metabolism (Dourson et al., 1998; Murray, 1998).

Absorption

Oral Absorption

Boric acid and the simple sodium borates given orally are readily and completely absorbed in humans and animals. Animals investigated include rats (Ku et al., 1991), rabbits (Draize & Kelly, 1959), sheep (Brown et al., 1989) and cattle (Owen, 1944; Weeth et al., 1981) as shown by the levels of boron in urine, blood or tissues. In rats fed ^{10}B (boron 10-isotope) at a dose of 20 µg 95% and 4% was recovered from urine and feces respectively within 24 h. Isotope ratios $^{11}B/^{10}B$ measured in the urine changed from the natural abundance of 4.11 to an enriched ratio of 0.951 during the first 3 days after the test meal was fed to rats (Vanderpool et al., 1994). In six adult human volunteers given a single oral dose of 131 mg B (as boric acid dissolved in water), 94% of the administered dose was excreted in the urine over a 96 hour period (Schou et al, 1984). Similar absorption was observed based on urinary excretion of boron in 6 volunteers drinking curative spa water with a high boron content (daily dose of 102 mg B) for two weeks (Job, 1973). In another study, greater than 90% was absorbed in human volunteers taking in 3% boric acid in an aqueous solution or as a waterless emulsifying ointment spread onto biscuits (Jansen, 1984a). In a series of human volunteer studies conducted in the early 1900s, in which large doses of boric acid were repeatedly administered orally, approximately 80% of an administered dose was recovered in the urine, while 1% was recovered in the faeces (Wiley, 1904). Reports involving accidental human ingestion, particularly in infants, where new-born infants died after accidentally ingesting boric acid, provide further evidence of oral absorption (Wong, 1964). After accidental boric acid uptake in 9 patients, the mean half-life of boric acid was determined to be 13.4 hours (range, 4.0 to 27.8) (Litovitz et al. 1988). For human risk assessment purposes 100% oral absorption is assumed.

For the general population, the greatest exposure to boron comes from food. The mean daily intake of boron in the diet is assumed to be near 1.2 mg per day (WHO, 1998). Vegetarian diets (Nielsen, 1992) and consumption of wine and mineral water could raise boron intake (WHO, 1998). A tolerable upper intake level (UL) of boron (sodium borate and boric acid) was derived with 10 mg/person/day for adults based on the most sensitive end-point detected in animals studies; i.e. the NOAEL for decreased fetal body weight in rats following maternal exposure during pregnancy. This UL also applies to pregnant and lactating women. UL values for children were derived by extrapolating from the UL for adults on a body surface area basis, giving values (mg/day) of 3, 4, 5, 7, and 9 for children aged 1-3, 4-6, 7-10, 11-14 and 15-17 years of age, respectively. These UL values apply only to the intake of boron as boric acid and borates (EFSA, 2004b).

Inhalation Absorption

Inhaled sodium borate dust is readily absorbed as demonstrated by the blood and urine levels among groups of workers occupationally exposed to various levels of boron (Culver et al., 1993; 1994b). In rats, inhaled boron oxide (anhydrous boric acid) aerosol was readily absorbed, based on the increased levels of boron excreted in the urine following inhalation exposure. It is not clear if the inhaled amount of boron was absorbed entirely by the respiratory tract Swallowed particles cleared from the respiratory tract may have contributed to systemic uptake. (Wilding et al., 1959). Since born can deposit in the upper respiratory tract, additional excretion studies by this rout would be useful in determining if excretion patterns are similar across all routes of exposure.

Dermal Absorption

Dermal absorption of borates across intact skin is insignificant in all species evaluated, including human new-born infants (no rise in plasma boron levels; Friis-Hansen et al., 1982), adult humans (no increase in boron excretion in urine; Beyer et al., 1983; Hui et al, 1996; Wester et al, 1998), rabbits (Draize and Kelley, 1959), and rats (no or slight increases in urine boron concentration Nielsen, 1970). Borates have been demonstrated to penetrate damaged or abraded skin (Draize and Kelley, 1959; Nielsen, 1970, Stüttgen et al., 1982). Additionally, boric acid has been shown to be well absorbed through mucus membranes (Baselt et al, 2004). However, the use of an ointment-based vehicle may change the absorption though diseased skin compared to an aqueous jelly based vehicle (Nielsen, 1970 and Stüttgen et al, 1982), although the results by Stüttgen et al. (1982) have a number of flaws and are therefore not conclusive.

Skin absorption data was obtained in human volunteers (Hui et al., 1996; Wester et al., 1998). Volunteers were dosed (non-occluded) on a 900 cm2 area (30cm x 30 cm) area of the back with ^{10}B enriched boric acid or sodium tetraborate decahydrate (5% in aqueous solution), or disodium octaborate tetrahydrate and disodium tetraborate decahydrate (10% in aqueous solution). Twenty-four hours later the residual dose was removed by washing. Boron was measured in the urine. The absorption rates are given below.

Table 5.1.1 Dermal Absorption in Humans of boric acid and disodium tetraborate decahydrate

	% Dose Absorbed ± SD	Rate of Absorption Flux $\mu g/cm^2/hr$	Permeability Constant (Kp) (cm/hr)
Boric Acid (5 %)	0.226 ± 0.125	0.009	1.9×10^{-7}
Disodium tetraborate decahydrate (5 %)	0.210 ± 0.194	0.00875	1.8×10^{-7}
Disodium octaborate tetrahydrate (10 %)	0.122 ± 0.10	0.00975	1.0×10^{-7}

SD standard deviation

The total recovery of the applied dose ranged from 48.8 - 63.6%, therefore 36.4-51.2% of the applied dose is not accounted for. The authors suggested that this may be due to loss to outside clothing and bedding. However, part of the lost dose may be located in the body or in the skin at the application site, which in that case should be considered as being absorbed. Based on other data, for instance, the low acute dermal limit studies carried out on sodium tetraborate pentahydrate and sodium tetraborate decahydrate (LD_{50} be > 2000 mg/kg bw) indicate minimal dermal absorption. In an acute dermal limit study on boric acid, the rabbit skin was abraded to increase the absorption. Even in this study there was limited symptoms observed and the acute dermal LD_{50} was > 2000 mg/kg bw. This data could support minimal dermal absorption. However, it could also reflect a low acute dermal toxicity. Wester at al., (1998) reported low dermal absorption in humans.

The percutaneous absorption of disodium tetraborate decahydrate can be read across to disodium tetraborate pentahydrate and disodium tetraborate anhydrous. Disodium tetraborate pentahydrate only slightly less hydrated than

the decahydrate. Anhydrous disodium tetraborate is the anhydrous salt of disodium tetraborate decahydrate and disodium tetraborate pentahydrate. For practical purposes one part of anhydrous disodium tetraborate is equivalent to 1.45 parts of disodium tetraborate pentahydrate; 1.9 parts of disodium tetraborate decahydrate; and in aqueous solution 1.23 parts of boric acid. Anhydrous disodium tetraborate is hygroscopic and takes up water to form a hydrated salt and like the other borates, in solution it will exist as undissociated boric acid. Since anhydrous disodium tetraborate and disodium tetraborate pentahydrate will form the various similar borates in the moistened form that it is applied to the skin, they are unlikely to be absorbed at any greater rate than the other borates tested.

Therefore, based on this study and other data, and using the % dose absorbed plus standard deviation (SD) for boric acid (rounded up), a dermal absorption for borates of 0.5% can be assumed as a worse case estimate.

Distribution

There is no substantiated evidence of boron accumulation in humans or other animals although bone contains higher levels than other tissues and boron is slowly eliminated from bone. (Alexander et al, 1951; Forbes et al., 1954; Forbes and Mitchell, 1957; Jansen et al, 1984b; Ward, 1987; Treinen and Chapin, 1991; Ku et al., 1991;1993; Culver et al., 1994b; Chapin et al, 1997).

Absorbed boron rapidly distributes throughout the body water in humans and animals. In a study of workers occupationally exposed to 10 mg/m^3 of airborne borax (0.22 mg B/kg/day), there was no progressive accumulation of boron in soft tissues during the working week as measured by blood and urine levels (Culver et al., 1993; 1994b). Similarly, Jansen et al. (1984a, b) concluded from pharmacokinetic studies of human volunteers that there was no tendency for boron to accumulate following a single i.v. dose of 600 mg of boric acid (approximately 105 mg B). Tissue levels of boron generally reached steady-state within three to four days among rats fed boric acid in the diet or drinking water for 28 days (Treinen and Chapin, 1991) or 3 – 4 days (Ku et al., 1991). Thus, boron does not accumulate in soft tissues with time in either humans or animals.

A poisoning case with boric acid in a pregnant woman indicated that borates can cross the placenta (Grella et al., 1976). The foetus was delivered early due to accidental poisoning of the mother with boric acid, and since no boric acid fetal blood or amniotic fluid concentrations were measured, it is not possible to conclude that boric acid passed the placenta. No information was presented on possible reproduction parameters.

In both humans and animals, boron levels in soft tissue are comparable to plasma levels, while a greater concentration of boron in bone is observed relative to other tissues. The most complete study of boron distribution conducted to date examined tissue disposition of boron in reproductive organs and other selected tissues in adult male rats fed boric acid, providing approximately 100 mg B/kg bw/day for up to seven days (Ku et al., 1991; 1993). All tissues examined, except bone and adipose tissue, appeared to reach steady state boron levels by three to four days. Bone achieved the highest concentration of boron (2 to 3 times plasma levels), and bone boron levels continued to increase throughout seven days of dietary administration (Ku et al., 1991). In contrast, adipose tissue concentration was approximately 20 % of the plasma level. No other tissues showed any appreciable accumulation of boron over plasma levels. In dogs, an accumulation in the brain, liver and fat was reported after a high single does of 2000 mg (350 mg B)/kg bw boric acid (Pfeiffer et al., 1945). However, the accuracy of the analytical procedures in that study is questionable.

Previous studies also show a greater concentration of boron in bone relative to other tissues in humans (Alexander et al., 1951; Forbes et al., 1954;) and rats (Forbes and Mitchell, 1957). Boron levels in a number of tissues have been measured (Abou-Shakra, 1989; Ciba and Chrusciel, 1992; Ward, 1987; Sabbioni et al., 1990; Shuler et al., 1990; Minoia et al., 1990; 1994). In mice, boron distribution appeared to be homogenous in the tissues examined, except for higher levels in the kidney (bone was not analysed) (Locksley and Sweet, 1954; Laurent-Pettersson et al., 1992), but higher levels were found in bone in another study (Massie et al., 1990). In *vivo* and in *vitro* studies indicate that boric acid has a strong affinity for cis -hydroxyl groups, this effect is reversible and concentration dependent (WHO, 1998). Boric acid can form complexes with various biomolecules. It has an affinity for hydroxyl, amino, and thiol groups (IPCS, 1998). This may explain the higher concentrations of boric acid in bone, owing to the binding of to the cis - hydroxyl groups of hydroxyapetite. Boric acid has been recently added to the list of molecules exerting Histone deacetylase inhibitor activity (HDACi). The study of Di Renzo (Di Renzo et al, 2007) suggested a mechanism for the induction of boric acid related malformations.

Metabolism

Boric acid is not metabolised in either animals or humans, owing to the high energy level required (523kJ/mol) to break the B - O bond (Emsley, 1989). Other inorganic borates convert to boric acid at physiological pH in the aqueous layer

overlying the mucosal surfaces prior to absorption. Additional support for this derives from studies in which more than 90% of administered doses of inorganic borates are excreted in the urine as boric acid. Boric acid is a very weak and exclusively monobasic acid that is believed to act, not as a proton donor, but as a Lewis acid, i.e., it accepts OH-. Because of the high pKa, regardless of the form of inorganic borate ingested (e.g., boric acid, borax or boron associated with animal or plant tissues), uptake is almost exclusively (>98%) as undissociated boric acid.

Elimination

In both humans and animals, boron is excreted in the urine regardless of the route of administration. It is excreted with a half-life of < 24 hours in humans and animals. Boron is slowly eliminated from bone (Chapin et al., 1997).

In humans, 99 % of a single i.v. dose of boric acid was excreted in the urine; the plasma half-life was calculated to be 21 hours using a three compartment toxicokinetic model (Jansen et al., 1984b). Following oral intake of an aqueous solution of boric acid, the urinary recovery was 94 % (Jansen et al., 1984a); more than 50 % of the oral dose was eliminated in the first 24 hours, consistent with the 21 hour half-life in the i.v. study. Sutherland et al. (1998) showed in a boron balance study that only 8% of dietary boron is excreted in faeces. In a previous study, half-lives ranging from 4.0 – 27.8 hours have been reported from nine poisoning cases (Astier et al., 1988; Litovitz et al., 1988).

Elimination half-lives for animals have not been stated explicitly in the scientific literature, but they can be calculated or estimated from the data in the literature. In mice, assuming first order kinetics for elimination, the half-life was estimated to be approximately one hour, and in rat < 12 hours (Farr and Konikowski, 1963; Ku et al. 1991; 1993). In rabbits, 50 to 66% of an orally administered dose of boric acid was excreted in the urine in the first 24 hours after dosing (Draize and Kelley, 1959). A recent study indicated that the half-life may be only 3 hours in both pregnant and non-pregnant rats. The boron clearance in pregnant rats was slightly higher than in non-pregnant rats; however the difference was not statistically significant (Vaziri et al., 2001).

The major determinant of boric acid excretion is expected to be renal clearance since boric acid is excreted unchanged in the urine. Rats and mice generally have faster rates of renal clearance than humans since the glomerular filtration rates as a function of body mass are generally higher in rats and mice than in humans.

Clearances as a function of body surface area of 40.4 ± 3.2 ml/min/1.73m^2 for sodium tetraborate in male rats and 40 ml /min/1.73m^2 for boron in mice (Usuda et al., 1998; Farr and Konikowski, 1963) have been reported, although there are methodological and/or analytical limitations in both studies. In more recent studies boric acid clearance rates in non-pregnant rats and pregnant rats ranged from 29.0 ± 5.7 to 31.0 ± 4.5 and from 32.2 ± 5.1 to 35.6 ± 5.7 ml/min/1.73m^2, respectively (Vaziri et al., 2001).

In humans, Jansen et al (1984b) determined a clearance rate of 55 ml/min/1.73m^2 following an i.v. dose of 600 mg of boric acid (105 mg B). Farr and Konikowski (1963) also reported a similar value of 39 ml/min/1.73m2 in humans given 35 mg B/kg intravenously as sodium pentaborate, although there are methodological and analytical limitations to this 40 year old study. In a more recent study, renal clearance rates in humans were 68.30 ± 35.0ml/min/1.73m^2 for pregnant subjects and 54.31 ± 19.35 ml/min/1.73m^2 for non-pregnant subjects (Pahl et al., 2001). This indicates about 20 –25% greater clearance in pregnant humans.

A comparison of the renal clearance between rats and humans in terms of body surface area indicated that humans clear boric acid slightly faster than rats (~1.7 -1.9 times as fast), while a comparison by bodyweight indicates that humans may clear boric acid more slowly than rats (~ 3 - 4 times slower). (Pahl et al., 2001; Vaziri et al., 2001). The comparison by bodyweight is used for risk assessment purposes.

CONCLUSION

There is little difference between animals and humans in absorption, distribution, and metabolism. A difference in renal clearance is the major determinant in the differences between animals and humans, with the renal clearance in rats approximately 3 times faster than in humans.

Absorption of borates via the oral route is nearly 100%. For the inhalation route also 100% absorption is assumed as worst case scenario. Dermal absorption though intact skin is very low. For risk assessment of borates a dermal absorption of 0.5% is used as a realistic worst case approach. In the blood boric acid is the main species present. Boric acid is not further metabolised. Borates are distributed rapidly and evenly through the body, with concentrations in bone 2 - 3 higher than in other tissues. Boron is excreted rapidly, with elimination half-lives of 1h in the mouse, 3h in the rat and < 27.8 h in humans, and has low potential for accumulation. Boric acid is mainly excreted in the urine.

Table 5.1.2 Summary of Toxicokinetics of Inorganic Borates in rats and humans

Absorption	• Readily absorbed orally and by inhalation (of respirable particles) • No dermal absorption (< 0.5%) except through mucus and severely damaged skin
Distribution	• Rapidly distributed through body water • With the exception of bone - no accumulation in tissues
Metabolism	• Not metabolised • Exists mainly as boric acid in whole blood
Elimination	• Excreted almost exclusively in the urine • Half-life < 27.8 hours in humans • Renal clearance is approximately 3 times faster in rats than humans based on a body weight comparison

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Studies in animals

The borates are in general of low acute oral toxicity in mammals, including rats and mice. An accidental poisoning case in cows and a further study in goats do not suggest that these species are more sensitive to the effects of borates with respect to acute toxicity (Sisk et al., 1988; 1990). The rat LD50 values for the various borates are given below. No substantial differences in acute oral toxicity were seen in mice and dogs in the limited studies available. However, dogs exhibit an emetic effect in response to high doses of borates. The LD50 in dogs was determined to be > 3980 mg boric acid/kg (697 mg B) and > 6150 mg disodium tetraborate decahydrate (695 mg B) /kg (administered in a capsule). The dogs vomited shortly after treatment at all doses (158 mg boric acid (28 mg B)/kg and 246 mg disodium tetraborate decahydrate (28 mg B)/kg were the lowest doses tested) (Keller, 1962; Weir & Fisher, 1972). The main symptoms of toxicity seen in all species tested were CNS depression, ataxia and convulsions.

Two limit dose studies were conducted on disodium tetraborate anhydrous. The first study, rats were dosed at 200 (43 mg B) and 2000 mg (430 mg B) /kg/ bw. At 2000 mg (430 mg B)/kg 2/5 male rats died. Slight body weight loses were recorded for both animals. Clinical signs indicated soft faeces, soiling of anogenital area, lethargy, hunched posture, ptosis, hypothermia and wasted appearance. In surviving males, signs of soft faeces, soiling of anogenital area and hunched posture were apparent but had resolved by day 4, but an unkempt appearance was noted between day 7 and termination (day 15). Piloerection and anogenital soiling was noted in 4 females of the same group, and these recovered by day 3. The only pathological effects observed were a distended stomach and darkened lungs in one rat that died and an enlarged liver, dark inflated lungs and red fluid in the thoracic cavity of the second rat that died. At 200 mg (43 mb B)/kg, apart from one male rat with an unkempt appearance no other clinical signs were observed. At 200 mg(43 mg B)/kg, no animals died and the only observation seen was an unkempt appearance in one male and one female at intervals during the second week. The LD50 was estimated to be > 200 mg(43 mg B)/kg bw Males; >2000 mg (430 mg B)/kg Females. The second study was conducted to confirm that the LD50 is above 2000 mg (430 mg B)/kg/bw. Rats were dosed at 1600 (344 mg B) and 2500 mg (538 mg B)/kg. No deaths occurred at either dose. No effects were observed at 1600 mg (344 mg B)/kg. At 2500 mg (538 mg B)/kg, piloerection observed in one animal that recovered by day 2. No other adverse effects were observed (Denton 1995, 1996). Based on the data in the first study, it is likely that the LD50 is lower than 5000 mg (1075 mg B)/kg/bw.

Table 5.2.1 Acute Oral Toxicity Studies

Route	Method Guideline	Species Strain Sex no/group	Dose levels duration of exposure	Value LD_{50} /LC_{50}	Remarks	Reference
Boric Acid						
Oral	[1] No specific guidelines were available at the time of this study.	Rat: Sprague Dawley 5/group	2000; 2520; 3160; 3980;5010 and 6310 mg/kg bw	LD_{50} males + females = 3765 mg /kg bw (659 mg B/kg)	Other data supports a range of 2660 – 4100 mg/kg	Keller, 1962 Weir & Fisher, 1972; Preiffer et al., 1945
Disodium Tetraborate Anhydrous						
Oral	OECD 401	Rat: Crl:CD.BR 5/group	1600; 2500 mg/kg bw	> 2500 mg (538 mg B)/kg bw males		Denton. (1996).

Disodium Tetraborate Pentahydrate						
Oral	US EPA-FIFRA guidelines	Rat: Sprague Dawley 5/group	1000; 1495; 2236; 3344 5000 mg/kg bw	3305 (2403 - 4207) mg/kg (489 mg B/kg)		Reagan and Becci (1985a)
Disodium Tetraborate Decahydrate						
Oral	[1]Unknown	Rat: Sprague Dawley 5/group	4000; 4500; 5000; 5500; 6000; 6500; 7000 mg/kg bw	5560 (5150 - 6000) mg/kg (628 mg B/kg)		Meyding and Foglhian (1961),

[1]Although only old data is available for boric acid and for disodium tetraborate decahydrate, there are a number of studies in rats (and mice and dogs), which confirm the low acute oral toxicity of the borates. Further testing is therefore not justified in the interests of protecting laboratory animals.

Studies in humans

There is a large database of accidental or intentional poisoning incidents for humans. Humans display different acute symptoms compared with most animals. In the literature, the human oral lethal dose is regularly quoted as 2-3 g boric acid for infants, 5-6 g boric acid for children and 15-30 g boric acid for adults. This data is largely unsubstantiated. In most cases it is difficult to make a good quantitative judgment particularly since medical intervention occurred in most cases and there were often other unrelated medical conditions (Culver and Hubbard, 1996). Of 784 more recent reports of accidental ingestion, none were reported as fatal and 88.3% were asymptomatic. The estimated dose range was 10 mg to 88.8 g (Litovitz et al, 1988). However, a single intake of 30 g of boric acid was fatal in one case (Yoshitaka et el., 1993). Symptoms of acute effects may include nausea, vomiting, gastric discomfort, skin flushing, excitation, convulsions, depression and vascular collapse. Currently, sodium borate (borax) is frequently used in household cleaning products, wood preservatives, fungicide. In addition it is found as household pesticides to control ants, flies and cockroaches. Boric acid toxicity and fatalities predominantly occur in infants and young children, which in contrast to adults do not require large amounts of borate. Concluding, that the toddler population is currently at risk (e.g refer to recent case report Hamilton, 2007).

5.2.2 Acute toxicity: inhalation

Studies in animals

Low acute inhalation toxicity was observed in those borates tested. In an inhalation study in which rats were exposed to boric acid at actual concentrations of 2.12 mg (0.37 mg B)/L (highest attainable concentration) for 4 hours no deaths were observed (Wnorowski, 1997).

Studies in rats with disodium tetraborate decahydrate (Wnorowski, 1994a) and disodium tetraborate pentahydrate (Wnorowski, 1994b) revealed LC50's of >2.03 (0.23 mg B) and 2.04 mg (0.30 mg B)/L (2g/m3) respectively. Although no test was carried out on disodium tetraborate anhydrous, it can be assumed that this would also have low acute inhalation toxicity.

Table 5.2.2 Acute Inhalation Toxicity Studies

Route	Method Guideline	Species Strain Sex no/group	Dose levels duration of exposure	Value LD_{50} /LC_{50}	Remarks	Reference
Boric Acid						
Inhalation	OECD Guide-line 403 "Acute Inhalation Toxicity" (USEPA.FIFRA 40 CFR Part 160.	Rat : Sprague Dawley 5/group	Analytical concentration 2120 ±140 mg/m³ 4 hours	≥ 2120 mg (371 mg B)/m³		Wnorowski, (1997)
Disodium Tetraborate Anhydrous						
Read across to Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate						
Disodium Tetraborate Pentahydrate						
Inhalation	OECD 403	Rat: Sprague Dawley 5/group	2g/m^3 nominal 4 Hours	>2.04.mg (0.30 mg B)/L (2g/m^3)		Wnorowski, (1994 b)
Disodium Tetraborate Decahydrate						
Inhalation	OECD 403	Rat : Sprague Dawley 5/group	2g/m^3 nominal 4 Hours	>2.03.mg 0.23 mg B)/L (2g/m^3)		Wnorowski, (1994a),

5.2.3 Acute toxicity: dermal

Studies in animals

The acute dermal toxicity of borates is low, being >2000 mg/kg bw for all borates tested. Although no test was carried out on disodium tetraborate anhydrous, it can be assumed that this would also have low acute dermal toxicity.

Table 5.2.3 Acute Dermal Toxicity Studies

Route	Method Guideline	Species Strain Sex no/group	Dose levels duration of exposure	Value LD_{50} /LC_{50}	Remarks	Reference
Boric Acid						
Dermal	FIFRA (40 CFR 163) Acceptable protocol at the time	Rabbits; New Zealand White 5/group	Dosage to 2 g/kg bw: 24 hours	≥ 2 g/kg bw (0.35 g B/kg)		Weiner et al.,. (1982).
Disodium Tetraborate Anhydrous						
Read across to Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate						
Disodium Tetraborate Pentahydrate						
Dermal	[1]US EPA-FIFRA guidelines	Rabbits; New Zealand White 5/group	2000 mg/kg bw	>2000 mg/kg bw (296 mg B/kg)		Reagan and Becci, 1985b
Disodium Tetraborate Decahydrate						
Dermal	[1]US EPA-FIFRA guidelines	Rabbits; New Zealand White 5/group	2000 mg/kg bw	>2000 mg/kg bw (226 mg B/kg)		Reagan and Becci, 1985c

[1] This study was carried out to comply with US EPA-FIFRA guidelines at the time and carried out by the US Food and Drug Laboratories to GLP. Although it is not to modern protocols the data is consistent with other borate data and further testing is not warranted in the interests of animal welfare and protecting laboratory animals

Studies in humans

Several poisoning cases have been reported in humans. Many were the result of accidental use as an antiseptic for irrigating body cavities, treating wounds or as a treatment for conditions such as epilepsy. Such medical uses are now obsolete. Also, accidental misuse in the preparation of baby formula (1 – 14 g in boric acid in the formula) and the topical use of pure boric acid powder for infants has led to poisonings in the past. This database is reviewed in several papers of data from poisoning centres as well as a detailed review of the literature cases from the mid 1800s to the 1970s by Kliegel (Kliegel, 1980; Wong et al. 1964, Litovitz et al, 1988; Goldbloom and Goldbloom, 1953; Valdes-Dapena and Arey, 1962).

5.2.4 Acute toxicity: other routes

Studies in animals

The acute intravenous LD_{50} s of a 5 % aqueous solution of boric acid were 1.78 g/kg and 1.33 g/kg in mice and rats respectively and the subcutaneous LD_{50} s were 2.07 g/kg and 1.2 g/kg for mice and guinea pigs respectively (Pfeiffer et al., 1945).

5.2.5 Summary and discussion of acute toxicity

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are of low acute toxicity. Although the acute oral studies were not of modern standards and were performed prior to the introduction of GLP, they are reproducible across a number of studies and species and of acceptable quality. For acute dermal and acute inhalation some studies do meet the modern GLP standard. For all the borates the acute toxicity results are: LD_{50} oral rat > 2000 mg/kg; LD_{50} dermal rat > 2000 mg/kg; LC_{50} inhalation rat > 2 mg/l.

Table 5.2.5 Summary of Acute Toxicity Data

Route	Value LD_{50} /LC_{50}	Reference
Boric Acid		

Oral	3765 (2660 – 4100) mg/kg	Keller (1962); Weir & Fisher, (1972); Pfeiffer et al., (1945)
Inhalation	≥ 2120 mg/m³	Wnorowski, 1997
Dermal	≥ 2 g/kg bw	Weiner et al., (1982).
Disodium Tetraborate Anhydrous		
Oral	> 2500 mg/kg bw males	Denton, (1995).
Inhalation	>2.mg/L (2g/m^3)	Read across from Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate
Dermal	>2000 mg/kg bw	
Disodium Tetraborate Pentahydrate		
Oral	3305 (2403 - 4207) mg/kg	Reagan and Becci (1985a)
Inhalation	>2.04.mg/L (2g/m^3)	Wnorowski, , (1994 a)
Dermal	>2000 mg/kg bw	Reagan and Becci, (1985b)
Disodium Tetraborate Decahydrate		
Oral	5560 (5150 - 6000) mg/kg	Meyding and Foglhian (1961),
Inhalation	>2.03.mg/L (2g/m^3)	Wnorowski, (1994b)
Dermal	>2000 mg/kg bw	Reagan and Becci, 1985c

No classification is indicated under the current EU guidelines (67/548/EEC). However under the GHS guidelines, both boric acid and disodium tetraborate pentahydrate would be classified as Acute Oral Toxicity Category 5. In addition, the data on disodium tetrahydrate anhydrous, which indicated deaths at 2000 mg (430 mg B)/kg bw (2/5 in one study and 4/5 in another study) would suggest that Acute Oral Toxicity Category 5 under GHS classification.

5.3 Irritation

5.3.1 Skin

Studies in animals

In a study in rabbits, boric acid did not cause skin irritation when applied to the intact or abraded skin at a dose of 0.5 g. Similarly, in studies in rabbits, sodium tetraborate decahydrate (Reagan and Becci, 1985e) and sodium tetraborate pentahydrate (Reagan and Becci, 1985d) did not cause skin irritation at doses of 0.5 g. In an earlier study in white rabbits, 5 ml of 10% boric acid (w/v) in water applied to abraded skin demonstrated very mild irritation with a primary irritation score of 2.5. In the same study, 10 ml of 5% borax (Disodium Tetraborate Decahydrate) in water (w/v) resulted in very mild irritation with a primary irritation score of 2.3. However, in the same study in Guinea pigs, neither boric acid nor borax was irritating when applied on abraded skin, with primary irritation scores less than 2 (Roudabush 1964). Although no test was carried out on disodium tetraborate anhydrous, it can be assumed that this would also not cause skin irritation.

Boric acid and disodium tetraborate decahydrate are used at concentrations of 5% in cosmetics in the US and in talc in Europe, up to 3% in other cosmetics in Europe and up to 0.5% in oral hygiene products in Europe and elsewhere (Beyer et al., 1983; EC, 2000).

Table 5.3.1 Skin Irritation Data

Species	Method	Average score 24, 48, 72 h		Reversibility yes/no	Result	Reference
		Erythema	Edema			
Boric Acid						
White Rabbits	21 CFR 191.11				PII 2.5 Mildly Irritating Abraded Skin	Roudabush et al. (1964)
Rabbits; New Zealand White	FIFRA (40 CFR 163) Acceptable protocol at the time	0.105	0	yes	Non irritant	Weiner et al. (1982).
Disodium Tetraborate Anhydrous						
Read across from Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate – Non Irritant						

Disodium Tetraborate Pentahydrate						
Rabbit	[1]US EPA-FIFRA guidelines	0	0		Non Irritant	Reagan and Becci, (1985d)
Disodium Tetraborate Decahydrate						
White Rabbits	21 CFR 191.11				PII 2.3 Mildly Irritating Abraded Skin	Roudabush et al. (1964)
Rabbit	[1]US EPA-FIFRA guidelines	0	0		Non Irritant	Reagan and. Becci (1985e),

[1] This study was carried out to comply with US EPA-FIFRA guidelines at the time and carried out by the US Food and Drug Laboratories to GLP. Although it is not to modern protocols the data is consistent with other borate data and further testing is not warranted in the interests of animal welfare and protecting laboratory animals

5.3.2 Eye

Studies in animals

Boric Acid

Boric acid induced conjunctivae redness and chemosis and minor effects on the iris. The effects were reversible within 7 days. (Doyle, 1989a)

Table 5.3.2 -1 Eye irritation Boric Acid

Species	Method	Average Score				Result	Reversibility yes/no	Reference
		Cornea	Iris	Conjunctiva				
				Redness	Chemosis			
Rabbits; New Zealand White	FIFRA (40 CFR 158, 162); TSCA (40 CFR 798).	0.00	0.11	0.94	0.56	Non irritant	Yes	Doyle, 1989a

Disodium Tetraborate Pentahydrate
A number of eye irritancy studies have been carried on disodium tetraborate pentahydrate (Reagan and Becci, 1985f, Wnorowski, 1996 and Cerven, 2000), which involved testing various batches of substance and under varying conditions, all indicating eye irritation. However the key study was carried out at the request of the US EPA to confirm that the eye irritation previously seen was caused by the glassy nature of the crystals of substance and not a chemical effect of irritation (Cerven, 2000). To confirm this, the sample was ground to a fine powder before instillation to reduce the glassy, sharp crystals in the sample (0.08 ml dosed). As a result for this study the US EPA accepted that the effects were mechanical downgraded its classification according to US FIFRA to Toxicity II (40 CFR 156) by ocular administration (Corneal involvement or irritation clearing in 8-21 days).

Disodium Tetraborate Decahydrate
Two studies have been carried out both indicating eye irritancy (Reagan and Becci, 1985g; Doyle, 1989b). In the second study, regarded as the key study the sample was ground to a fine powder to reduce the glassy, sharp crystals in the sample.

Disodium Tetraborate Anhydrous
While no data has been obtained for disodium tetraborate anhydrous, it can be assumed that it should be an eye irritant based on the data obtained with the hydrated disodium tetraborates.

Table 5.3.2 -2 Eye irritation Data: Disodium Tetraborates

Species	Method	Average Score				Result	Reversibility yes/no	Reference
		Cornea	Iris	Conjunctiva				
				Redness	Chemosis			
Disodium Tetraborate Anhydrous								

Read across from Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate – Irritant								
Disodium Tetraborate Pentahydrate								
Rabbit	FIFRA (40 CFR 158, 430); EPA OPPTS 870.2400	0.22	0.22	2.8	1.89	Irritant	Yes	Cerven, (2000).
Disodium Tetraborate Decahydrate								
Rabbit	FIFRA (40 CFR 158, 162); TSCA (40 CFR 798).	0.72	0.61	1.70	2.11	Irritant	Yes	Doyle, (1989b)

Studies in humans

Disodium tetraborate decahydrate and disodium tetraborate pentahydrate are used as a buffer in eyewashes. In addition, in normal handling and use the large glassy crystals would not be able to enter the eye easily and in addition over 50 years of occupational exposure to all borate has indicated no adverse effects on the human eye.

5.3.3 Respiratory tract

Studies in animals

Acute inhalation studies in rats with disodium tetraborate decahydrate, disodium tetraborate and boric acid (Wnorowski, 1994ab, 1997) revealed LC50's > 2 g/m^3. During the initial 1.5 h of exposure to boric acid (Wnorowski, 1997) ocular and nasal discharge, hunched posture and hypoactivity were noticed. Recovery from these symptoms was noticed by day two (all rats). Within several hours of exposure to disodium tetraborate pentahydrate nasal discharge (2 male rats) was observed (recovery day 6). Exposure to disodium tetraborate decahydrate 2 rats (female, male) nasal discharge was noticed (recovery day 7) (Wnorowski, 1994ab). There is no data from animal studies on boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate that indicated respiratory irritation. A rat 28-day inhalation toxicity study on boric acid was requested to better characterize the effects of repeated inhalation exposure (US EPA, 2006).

Studies in humans

Some older studies on workers exposed occupationally to borax dust reported eye irritation, dry mouth, nose or throat, sore, nose bleeding, throat and productive cough (reported in Garabrant et al.1984, 1985). However there were severe limitations to this data (See ANNEX 1).

Several studies were investigating acute and chronic symptoms associated with boron dust, including irritation, during routine industrial activities (Eisen, et al, 1991; Hui et al, 1992; Hu et al, 1992; Wegman et al, 1994; Woskie et al, 1994). Acute irritant effects are well documented in human workers exposed to borates (EPA, 2004; Wegman 2004, Garabrant 1984, 1985). Wegman *et* al (Wegman et al, 1994) examined work-related chronic abnormality in pulmonary function and work-related acute irritant symptoms (Table 5.3.3 -1) associated with exposure to boron dust in mining and processing operations. Borax in this study refers to any one or mixtures of disodium tetraborate (disodium tetraborate decahydrate, disodium tetraborate pentahydrate, disodium tetraborate anhydrous). In addition to the use of hourly surveys, subjects were provided a means of adding a mark to the exposure monitor each time they experienced an acute irritant symptom. A personal direct-reading aerosol monitor (the MINIRAM, Miniature Real-time Aerosol Monitor) was used in conjunction with a datalogger system. This device permitted each subject to record the actual time of symptom onset. At the hourly survey, the technician would ask whether the marker had been used, and if so, for what symptom. Five acute respiratory symptoms were investigated to establish a dose-response-relationship: nose, eye and throat irritation; sneezing; nose bleeds; coughing and breathlessness. A severity scale with 13 categories was introduced and provided reproducible and reliable results. Exposed subjects experienced more frequent irritations than unexposed. Average daily exposure (6-h time weighted average) for the exposed group was 5.72 mg/m^3 of total dust (0.44 mg/m^3 B); 79% of the group had daily exposures higher than 1.0 mg/m^3. The majority of exposures were between 1.0 and 10.0 mg/m^3. A total of 68% of the exposed subject-days included at least one 15-min interval when exposure exceeded 10.0 mg/m^3. The epidemiological analyses of the irritant symptoms indicate that exposure-response relationships are present and related to exposure for each of the specific symptoms. The exposure – response trends were statistically significant ($p < 0.05$), except eye irritation. In comparison to control group exposed subjects had a rate ratio (RR) for nose irritation (RR 8.8), eye irritation (RR 5.2), throat irritation (RR 2.9), breathlessness (RR 7.1) and coughing (RR 1.7). The most striking difference was for nasal irritation where 23% of the exposed group reported at least two incident symptoms as compared to none of the unexposed. Associations persisted after taking account of smoking, age and the presence of common cold. Sodium borate exposure in this plant was associated with irritant effects that included nasal, eye and throat irritation, cough and breathlessness (Wegman et al, 1994). Concerning respiratory irritations among those exposed workers, non-smokers had higher rate ratios than smokers for nasal and eye irritation, and lower ratios for

throat irritations, cough, and breathlessness. Reduction of forced expiratory volume 1 sec (FEV1) was observed among smokers who had heavy cumulative sodium borate exposure (≥80 mg/m3-year), but not among less-exposed smokers and non-smokers (Wegman, 1994). In this study, no nosebleeds were reported.

NOAEL derivation for respiratory irritation by boric acid and borates has been performed by the BAuA, in march 2007 (BAuA, 2007) The German, federal institute for occupational safety and health assumed a NOAEL based on the Wegman study (1994) of 1-2 mg/m^3, according to the lowest exposed group (1-4 mg/m^3) having just mild effects. According to Cluver et al (1994) the exposure values obtained by Wegman *et* al were underestimated. The corrected NOAEL for respiratory irritation (sodium borate) is 3 mg/m^3 .It has been assumed that, at a concentration of 0.5 mg B/m^3 no local adverse irritating effect of boric acid and borates will be expected. Within the report the following equivalent concentrations are stated: boric acid 2.6 mg/m^3, sodium-tetraborate anhydrous 2.1 mg/m^3, sodium-tetraborate pentahydrate 3.0 mg/m^3, andsodium-tetraborate decahydrate 4.0 mg/m^3.

In contrast, the time-weighted average (TWA) values according to the National Institute for Occupational Safety and Health (NIOSH, 2005) to protect irritation of eyes and respiratory system are: sodium-tetraborate, anhydrouse 1 mg/m^3, sodium-tetraborate pentahydrate, 1 mg/m^3, sodium-tetraborate decahydrate 5 mg/m^3. Regulations, guidelines applicable on TWA values are available http://www.atsdr.cdc.gov/toxprofiles/tp26-c8.pdf.

The Agency for Toxic Substances and Disease Registry (ATSDR, 2007) has derived an acute-duration inhalation minimal risk level (MRL) of 0.01 mg B/m^3. It is based on a LOAEL of 0.44 mg B/m^3 for eye, nasal and throat irritation, cough, and breathlessness in workers (Wegman et al., 1994) and an assessment factor of 30 (3 for the use of a minimal LOAEL and 10 for human variability).

An approach to determine the acceptable exposure limits based on measurement of responses of 12 male volunteers to measured amounts of various dusts was investigated by Cain et al;., 2004 in a human study in which the sensory perception of dusts of sodium tetraborate pentahydrate (Na2B4O7·5H2O), calcium sulphate (CaSO4), and calcium oxide (CaO) was investigated. The study was designed to investigate the chemesthetic feel of sodium tetraborate pentahydrate and to help determine, if possible, where the continuum from ill defined feel through to irritation occurs. Twelve subjects were exposed to 5, 10, 20, 30 and 40 mg/m^3 sodium tetraborate pentahydrate dust particles (mass median aerodynamic diameter 7.11 µm) for 20 min while performing moderate exercise (i.e., riding an exercise bike set at a load of 60 watts). Exposure to carbon dioxide vapour was used to set a reference scale for subjects to judge the feel of the stimulus materials. During exposure, subjects judged level of feel or irritation in the eye, nose, and throat (nasopharynx) at 5-min intervals. The subjects indicated the absence of any feel or irritation by a judgement of zero. At the intervals indicated, heart rate, oxygen saturation, minute ventilation and respiration rate were recorded as well. During the study subjects registered time-dependent feel from exposures principally in the nose, secondarily in throat and hardly in eyes. At 10 mg/m^3 (1.5 mg B/m^3) sodium-tetraborate pentahydrate a mild irritating effect was observed, but not at 5 mg/m^3 (0.75 mg B/m^3) sodium-tetraborate pentahydrate. In general, the number of subjects who participated in this study was relatively small (n=12). **The NOAEL determined was 0.7 mg boron /m^3. At the LOAEL 1.5 mg boron /m^3 respiratory symptoms of irritation of nose and throat and increased nasal secretion were observed (Cain et al., 2004).** A further study has been carried out on boric acid (Cain et al., 2007). A similar effect compared to sodium-tetraborate pentahydrate was obtained at 10 mg/m^3 boric acid, but a flatter dose response curve was obtained. The doses at 2.5 and 5 mg/ m^3 resulted in a lower reduced effect; nevertheless the effect itself was described to be lower. Both Cain studies are of limited value due to the small numbers of participants.

Table 5.3.3-1 Acute Inhalation Studies – Human

Route	Exposure	NOAEL mg B/m^3	LOAEL mg B/m^3	Symptoms	Remarks	Reference
Sodium Borates (Sodium tetraborate pentahydrate)						
Inhalation	once, 20 min	0.7	1.5	Irritation of nose and throat; increased nasal secretion	only 12 male volunteers	Cain et al. 2004
Sodium Borates						
Inhalation	6hr / day TWA		0.44*	Nasal and throat irritation; cough and		Wegman et al. 1994

				breathlessness		

*Used to derive an acute duration inhalation minimal risk level of 0.01 mg boron/m^3; exposure level divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability); TWA time weighted average.

The only chronic effects of sodium borate particulate exposures were examined by pulmonary function at the beginning and end of a 7-year study period. No association was found between the FEV_1 and sodium borate exposure (Wegman et al., 1994).. In this study approximately 50% of subjects were lost to follow up, so an assessment of chronic respiratory effects was not possible.

5.3.4 Summary and discussion of irritation

Skin Irritation

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not skin irritants.

Eye Irritation

Boric acid induced conjunctivae redness and chemosis and minor effects on the iris. The effects were reversible within 7 days.

No classification is indicated under the current EU guidelines (67/548/EEC) or under the GHS guidelines.

Both disodium tetraborate decahydrate and disodium tetraborate pentahydrate induced eye irritation. This could be due to the glassy crystalline nature of these compounds however it is not possible to exclude eye irritation is the result of a non mechanical action.

Disodium tetraborate pentahydrate should be classified as an eye irritant R36 current EU guidelines (67/548/EEC) is indicated by the conjunctivae redness and oedema in two out of three animals and under GHS as Category 2 Irritating to eyes, based on redness >2.0 and also Oedema >2 reversible in 14 days.

Disodium tetraborate decahydrate should be classified as an eye irritant; R36 under current EU guidelines (67/548/EEC) is indicated by the iris and conjunctivae oedema and under GHS as Category 2 Irritating to eyes, based on iris**,** conjunctivae redness and oedema which does not reverse by 7 days.

Based on read across from disodium tetraborate pentahydrate and disodium tetraborate decahydrate, disodium tetraborate anhydrous should also be classified as an eye irritant R36 current EU guidelines (67/548/EEC) under GHS as Category 2 Irritating to Eyes.

Respiratory tract

No classification is necessary under the current EU guidelines (67/548/EEC) and under the GHS guidelines.

The effects observed do not constitute a 'serious irritation to the respiratory tract'. In the earlier studies (Hui et al., 1992; Hu et al., 1992; Wegman et al, 1994) the workers reported minor effects on the nose and throat and to a lesser extent the eye. The number of workers affected was very low; there were a number of confounding factors in the study and the data cannot be substantiated or related to a specific dose in controlled studies. No effects on lung function were observed. The data indicates that the effects that the workers identified were 'chemesthetic' i.e. the feel of dusts on the sensory system and do not denote specific chemical irritancy at normal exposures. This was reinforced in the Cain study (Cain et al 2004; 2007) where the level of effect was not significant irritancy and most likely due to the physical exposure to a dust rather than a specific chemical effect with no significant respiratory effects at 14-15 mg/m3 sodium borate.

The conclusions for both studies indicate that the effects noticed cannot specifically be attributed to an irritant effect based on the chemical nature of the borate tested. The level of effect was not significant irritancy. Moreover, under normal handling and use conditions the effects were not really apparent and do not constitute irritant effects. The effects are most likely due to the physical exposure to a dust rather than a specific chemical effect. Therefore the available evidence does not support classification as R37.

Under GHS, respiratory irritants are included in Cat. 3 Specific Target Organ/Systemic Toxicity (Single Exposure, STOT) that is specially designed for Transient Target organ effects. The effects observed in the human studies do not fulfil the criteria for a respiratory irritant under GHS[1]. The effects observed do not impair function, and they are not accompanied by serious symptoms and the later studies indicate no effect on lung function. Therefore no classification under GHS is necessary.

5.4 Corrosivity

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not corrosive.

5.5 Sensitisation

5.5.1 Skin

Studies in animals

Boric acid, disodium tetraborate decahydrate and disodium tetraborate pentahydrate were tested in a Buehler method skin sensitisation test (Wnorowski, 1994 e, f, g). They were applied at a concentration of 95% (powder moistened with water) during both the induction and challenge phase of the test. No signs of skin sensitisation were observed.

Studies in humans

The data indicate that these borates are not sensitisers. In addition there is no evidence of skin sensitisation in humans exposed occupationally to borates has been reported (Bruze et al., 1995).

Table 5.6.1 Sensitisation Data

Active substance	Species	Method	Number of animals sensitised/total number of animals	Result	Reference
Boric Acid	Guinea Pig	Buehler Test OECD Guide-line 406 "Skin Sensitisation"	0	Non sensitiser	Wnorowski, (1994e),
Disodium Tetraborate Anhydrous	Read across from Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate – Non sensitiser				
Disodium tetraborate pentahydrate	Guinea Pig	Buehler Test OECD Guide-line 406 "Skin Sensitisation"	0	Non sensitiser	Wnorowski, (1994f),
Disodium tetraborate decahydrate	Guinea Pig	Buehler Test OECD Guide-line 406 "Skin Sensitisation"	0	Non sensitiser	Wnorowski, (1994g),

[1] *GHS Vol II (27.06.2007) 3.8.2.2 Substances of Category 3: Transient target organ effects, 3.8.2.2.1 Criteria for respiratory tract irritation The criteria for classifiying substances as Category 3 for respirator are:(a) Respiratory irritant effects (characterized by localized redness, edema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. It is recognized that this evaluation is based primarily on human data; (b) Subjective human observations could be supported by objective measurements of clear respiratory tract irritation (RTI) (e.g. electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids; (c) The symptoms observed in humans should also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of "irritation" should be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of this classification endpoint; (d) There are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. Such animal studies shall be considered as part of weight of evidence evaluation. (e) This special classification would occur only when more severe organ effects including in the respiratory system are not observed.*

5.5.2 Respiratory system

There is no data to suggest that boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are respiratory sensitisers.

5.5.3 Summary and discussion of sensitisation

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are neither skin nor respiratory sensitisers.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

Studies in animals

A number of sub-chronic and chronic studies on boric acid and disodium tetraborate decahydrate were carried out in rats, mice and dogs. In some cases these studies are research studies (e.g. Dixon et al, 1976; Seal and Weeth, 1980; Lee et al., 1978; Treinen and Chapin, 1991; Ku et al., 1993), but most support that the main target organs of boron toxicity are testis and blood. Some of the studies are further described in section 5.9.1.

In a 30/60 day study in rats of disodium tetraborate decahydrate administered in drinking water (0, 500, 1000, 2000 ppm equivalent to 0, 25, 50, 100 mg B/kg bw/day) no reduction of bodyweight or organ weights were observed, with the exception of significantly reduced epididymal weights in all dosed groups after 30 days. After 60 days the weight of testes and liver at 50 and 100 mg B/kg bw/day was also reduced. At these doses a significant loss of spermatocytes and spermatogenic cells and testicular atrophy (60 days > 30 days) concomitant with reduced enzyme activities of hyaluronidase, SDH (dehydrogenase of sorbitol) and LDH-X (lactate dehydrogenase isoenzyme X) and increased enzyme activities of G3P-DH (glyceraldehye-3-phosphate dehydrogenase) and M-DH (malate dehydrogenase) were observed, correlating well with dose and duration of exposure. Plasma levels of FSH (follicle stimulating hormone) were increased in all treated groups, with both a dose-response and an exposure time-response apparent. LH (luteinizing hormone) and testosterone levels were not significantly altered. The NOAEL in this study was 25 mg B/kg bw/day (Dixon et al., 1979).

In male rats fed disodium tetraborate decahydrate for either 30 or 60 days at 60 or 125-131 mg B/kg bw/day (NOAEL, 50 mg B/kg bw/day) testis weight was reduced, testicular germ cells were depleted, selected testicular enzymes were affected and fertility was reduced. Hyaluronidase, SDH, and LDH-X were significantly decreased; and G3P-DH and M-DH were significantly increased at 100 and 200 mg b/kg bw/day. Further, an increase in plasma FSH levels correlated well with germinal depletion and both effects were dose and time dependent. As might be expected, while recovery from inhibition of spermiation occurred at the lower doses, there was no recovery from testicular atrophy when the germ cells were lost. (Lee et al., 1978). More details on fertility effects observed in this study are described in section 5.9.1.

In another study male Long-Evans rats (15/dose) were also administered disodium tetraborate decahydrate in drinking water for 70 days at levels of 0, 150 and 300 mg B/l, which is assumed to correspond to a total boron intake of 23.7 and 47.4 mg/kg low/d, based on a bodyweight of 350 g and water intake of 49 ml/d (US EPA IRIS 2004). Reduced body weight and reduced weight of testes and spleen were seen at the mid dose. Haematocrit was reduced (6.8%) and spermatogenesis was impaired at 47 mg b/kg bw/d (Seal and Weeth 1980)

Although not conforming to modern protocols, data on several effects can be obtained from a 90 day study in rats fed 0, 52.5, 175, 525, 1750, 5250 ppm equivalent boron (as boric acid) equal to 0, 2.6, 8.8, 26, 88 and 260 mg B/kg bw/day. All the animals in the top dose died by week 6. Animals at the top two doses displayed rapid respiration, hunched position, bloody nasal discharge, urine stains on the abdomen, inflamed eyes, desquamation and swollen paws and tail. These animals exhibited reduced food consumption and body weight gain. At 88 mg B/kg bw/day, in females, reduced weight for livers, spleens and ovaries were observed, while for males only the kidney and adrenal weights were reduced. The adrenals in 4 males at 88 mg B/kg bw/day displayed minor increases in lipid content and size of the cells in the zona reticularis. All the male rats at 88 mg B/kg bw/day had atrophied testis, a histologically complete atrophy of the spermatogenic epithelium and a decrease in the size of the seminiferous tubules. One male at 26 mg B/kg bw/day exhibited partial testicular atrophy. The NOAEL was determined to be 8,8 mg B/kg bw/day. In an analogous 90 day study on disodium tetraborate decahydrate similar effects were observed, however, in this study the dose response

relation was less clear. Atrophied testes were seen at 2.6 and 88 mg B/kg bw/days but not at 8.8 or 26 mg B/kg bw/day (Weir, 1962). At the latter dose, however, spermatogenic arrest was described (Weir, 1962b). In a third rat-90 day study on disodium tetraborate decahydrate, no adverse effects were observed at levels up to 26 mg B/kg bw/day (Weir,1963).

In a mouse study carried out for 13 or 16 weeks, mice were fed diets containing 0,1200, 2500, 5000, 10000, 20000 ppm boric acid, equivalent to 0, 194 (34), 405 (71), 811 (142), 1622 (284), 3246 (568) mg boric acid (mg B)/day males and 0, 169 (47), 560 (98), 1120 (196), 2240 (392), 4480 (784) mg boric acid (mg B)/day females. At the highest dose level (20000 ppm) 8/10 males and 6/10 females died and 1/10 males from the 10000 ppm group died before end of study. Symptoms included nervousness, haunched appearance, dehydration, foot lesions and scaly tails. A reduction in mean bodyweights was observed in the 5000, 10000 and 20000 ppm groups. Incidences of extramedullary haematopoiesis of spleen observed of minimal to mild severity in all dose groups for both males and females and hyperkeratosis and/or acanthosis of the stomach observed at the highest dose only in both males and females. In the absence of any haematology data there is no direct evidence of anaemia. In addition extramedullary haematopoiesis of the spleen occurs naturally in mice. At doses > 5,000 ppm (142 mg B/kg bw for the male), degeneration or atrophy of the seminiferous tubules was observed (NTP 1987).

The 90 day dog studies on both boric acid and disodium tetraborate decahydrate are of limited value and considered inadequate for risk assessment although they provide support for the target organs being the testis and blood (see Annex 2). Dogs were dosed with dietary levels of 0, 0.01, 0.1, 1.0 % boric acid equivalent to 0, 0.4, 4.4, and 33 mg B/kg/day and 0, 0.0154, 0.154, 1.54 % disodium tetraborate decahydrate equivalent to of 0, 0.4, 4.1, and 38 mg B/kg/day, based on the actual body weight and food consumption data in the study. Unfortunately, the published report of these studies does not accurately reflect the original study reports (Paynter, 1963 a;b; Weir & Fisher, 1972). At the mid-dose testes of all males showed an ‘artifactual distortion’ of the outer third of the glands which might be a substance related effect, since it was observed in all males of this dose, but not in males from control and low dose groups. The spermatogenic epithelium was intact at this dose. In the high dose animals severe atrophy of the testes was observed. A slight degree of extramedullary haematopoiesis was present in the spleen of the test animals somewhat more consistently than in the control animals. At the highest dose hemosiderin was also present in reticular cells of the liver and spleen and the proximal tubule of the kidney, indicating increased red blood cell distruction. Additionally a decrease in haematocrit and haemoglobin values (min 9% and max 28%) was seen in this group for males and females treated with boric acid or disodium tetraboratedecahydrate. According to Muller (2006) the combination of these effects on the blood system has to be considered as adverse, even though all the clinical laboratory findings from blood and urine samples were within normal limits and comparable to controls. Apart from the death of one dog in the high dose group of the disodium tetraborate decahydrate study, which may not be attributable to the substance, no further clinical signs were observed.

Long term chronic feeding studies have been carried out on boric acid and/or disodium tetraborate decahydrate in mice, rats and dogs:

Testicular atrophy with some interstitial cell hyperplasia was observed in the top dose in a US National Toxicology Program (NTP) bioassay in mice fed 0, 2500, 5000 ppm in food for 2 years equivalent to 0, 446 and 1150 mg boric acid/kg bw/d, equivalent to 78.1 and 201.3 mg B/kg bw/day. Splenic extramedullary haematopoiesis occurs naturally in mice. An incidence was reported in males as 3/48, 11/49, 10/48, and in females as 10/49, 11/34, 7/50 in the control, low- and high-dose groups, respectively. There is no other mention or discussion about extramedullary haematopoiesis in the rest of the report, so it was not regarded as an important finding (NTP, 1987).

In 2 year oral toxicity studies in dogs for both boric acid and disodium tetraborate decahydrate the testes were identified as a main target organ. These studies had major deficiencies and are inadequate for risk assessment, but do confirm the effects seen in other species. Dogs were fed 0, 0.033, 0.067, 0.20, 0.67% boric acid equivalent to 0, 1.7, 3.8, 10.9, and 41 mg B/kg/day and 0, 0.051, 0.103, 0.309, 1.03% disodium tetraborate decahydrate equivalent to 0, 1.9, 3.6, 9.6, and 38 mg B/kg/day, based on the actual body weight and food consumption data in the study. No significant clinical findings were observed (Weir, 1966 e,f; 1967 a,b). These studies are further discussed in section 5.9.1 – Effects on Fertility.

In a 2 year feeding study in rats again on boric acid and disodium tetraborate decahydrate testes and blood were identified as major target organs (Weir, 1966a;b). Rats were dosed with , 0; 670 (117); 2000 (350); 6690 (1170) ppm boric acid (boron equivalents) equivalent to 0, 33 (5.9), 100 (17.5), 334 (58.5) mg boric acid (B)/kg bw per day and 0, 1030 (117), 3080 (350), 10300 (1170) ppm disodium tetraborate decahydrate (as boron equivalents) equivalent to 0,52 (5.9), 155 (17.5), 516 (58.5)mg borax/kg/day or 0, 5.9, 17.5 or 58.5 mg B/kg/day. Clinical signs included coarse hair coats, hunched position, and inflamed bleeding eyes, desquamation of the skin of the tail and the pads of the paws which were also swollen, marked respiratory involvement, shrunken appearance of the scrotum were observed in all

males of the high dose group. In addition a reduction in body weight was observed in males and females in the high dose group accompanied by decreased food consumption.
Decreased red cell volume and haemoglobin were observed in boric acid and disodium tetraborate decahydrate treated rats. Blood samples were taken after 30, 60, 90, 180, 365, and 545 days and at the end of the study. The observations over time were not always consistent, however, at the end of the study the values in all dosed animals were reduced compared to control. Significant reduction of red cell volume and haemoglobin was mainly observed in high dosed males treated with boric acid (at the end of the study 5% to 21% and 7% to 19 % reduction compared to control, were observed for red blood cell volume and haemoglobin, respectively), but also in the females treated with boric acid a significant reduction of haemoglobin at all dose groups was detected at the last measurement (between 8% and 13%). For disodium tetraborate decahydrate blood of the high dosed animals showed reduced values for both endpoints in males and females at several time points. As described in Muller at al. (2006) reduction of haemoglobin of 20% is a stand alone adverse effect, reductions of 10% must be supported by further effects like extramedullary haematopoiesis or haemosiderin deposition. However, these endpoints were not examined in the study and since only 5 animals per group were sampled the statistical power is low.
Testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months at the highest dose level with both boric acid and disodium tetraborate decahydrate. Microscopic examination of the tissue revealed atrophied seminiferous epithelium and decreased tubular size in the testes. No effects were observed in the control and low dose groups.
Based on the clinical and haematological effects and the testicular atrophy observed at the highest doses tested (6690 ppm boric acid, equivalent to 334 (58.5) mg boric acid (B)/kg bw per day and 10300 ppm (equivalent to borax intake of 516 (58.5) mg disodium tetraborate decahydrate (B) /kg bw/day) the NOAEL for the effects of boron is 17.5 mg B/kg bw/day (equivalent to 100mg boric acid or 155 mg disodium tetraborate decahydrate/kg bw/day).

Studies in humans

In humans multiple exposures (high levels > 1g) results in various symptoms which may appear singly or together and include dermatitis, alopecia, loss of appetite, nausea, vomiting, diarrhoea, and focal or generalised central nervous system irritation or convulsions. Much data comes from the mid 1800s to around 1940, when boric acid and disodium tetraborate decahydrate were used systematically for a variety of medical conditions including amenorrhea, malaria, epilepsy, urinary tract infection and exudative pleuritis (Kliegel, 1980). Daily oral doses in adults ranged from 1-14 g per day. Repeated doses in the 6-0 g/day range were given for as long as several weeks. In one extreme case a 28 year old women ingested around 0.5 g of boric acid (in baby powder) every day for two years and suffered anaemia, which reversed on ceasing ingestion (Adelhardt and Fogh, 1983). Doses greater than 3 –5 g/day regularly caused vomiting and/or diarrhoea in the first instance often accompanied by dermatitis and appetite suppression. As the dose became higher and the dosing period longer, symptoms included alopecia, disseminated maculopapular eruption followed by widespread desquamation, focal or generalised central nervous system irritation, and convulsions. The symptoms of dermatitis, nausea, diarrhoea and vomiting symptoms also occurred in some patients receiving doses of 2 g boric acid/day (29 mg boric acid/kg/day) and above. In one such case, reduction of the dose from 2 g/day of boric (29 mg boric acid/kg/day) acid to 1g/day (14 mg boric acid/kg/day) resulted in resolution of the effects (vomiting and dermatitis). In all cases where withdrawal of treatment was reported, recovery occurred with no lasting effects. The lowest recorded adult dose causing symptoms was 2 g/day boric acid (Kliegel, 1980).

Table 5.6.1-1 Key Repeated dose toxicity studies

Route	duration of study	Species Strain Sex no/group	dose levels	Results	LO(A)EL	NO(A)EL	Reference
Boric Acid							
Oral in diet	13 weeks for control and top dose group, 16 weeks for other dose groups	Mouse, B6C3F1 10/sex/ group	0, 1200, 2500, 5000, 10000, 20000 ppm of boric acid. Equivalent to 0, 194, 405, 811, 1622, 3246 mg boric acid/kg bw/day in males & 0, 169, 560, 1120, 2240, 4480 mg boric acid/kg bw per day in	At ≥ 142 mg B/kg bw/day: degeneration and atrophy of the seminiferous tubules was observed. At all dose levels extra medullary haematopoiesis of the spleen	≥ 142mg B/kg bw/day in males 196 mg B/kg bw/day in females	71 mg B/kg bw/day in males 98 mg B/kg bw/day	National Toxicology Program (NTP) Technical Report Series No. 324, 1987

			females Equivalent to 0, 34, 71, 142, 284, 568 mg B/kg bw/day in males & 0, 47, 98, 196, 392, 784 mg B/kg bw per day in females.				
Oral in diet	90 days	Rat Sprague Dawley Treatment: 10/sex/group	0, 52.5, 175, 525, 1750, 5250 ppm Equivalent to 2.6, 8.8, 26, 88 and 260 mg B/kg bw/d.	At ≥ 88 mg B/kg bw/day: Reduction bodyweight; clinical signs of toxicity; testicular atrophy At 26 mg B/kg bw/day on male exhibited partial testicular atrophy	26 mg B/kg bw/day	8.8 mg B/kg bw/day	Weir, 1962
Oral in diet	2 year, interim kills at 6 and 12 months	Rat Sprague Dawley controls: 70/sex Treatment: 35/sex/group Interim kills with 5/sex/group	0, 670, 2000, 6690 ppm Equivalent to 0, 33, 100, 334 mg boric acid/kg bw/day Equivalent to 5.9, 17.5, 58.5 B/kg bw/day	58.5 mg B/kg bw/day: Reduction bodyweight; clinical signs of toxicity; testicular atrophy, reductions in red cell volume and Hb	58.5 mg B/kg bw/day	17.5 B/kg bw/day	Weir, 1966a
Disodium tetraborate decahydrate							
Oral in drinking water	30 and 60 days	Rat, Sprague Dawley male 18/group	0, 500, 1000, 2000 ppm Equivalent to 25, 50, 100 mg B/kg bw/day	Significant reduction in epididymal weight in all dose groups after 30 days In all dosed groups increase of plasma FSH levels and decrease of diameter of the seminiferous tubules. 60 days: reductions in testes and liver weights ≥ 50 mg B/kg bw/day; 60 days > 30 days: significant loss of germinal elements and testicular atrophy ≥ 50 mg B/kg bw/day Changes of testicular enzyme activities ≥ 50 mg B/kg bw/day	25 mg B/kg bw/day	-	Dixon et al. (1979)
Oral In diet	90 day	Rat Sprague Dawley Treatment: 10/sex/group	0, 52.5, 175, 525, 1750, 5250 ppm Equivalent to 2.6, 8.8, 26, 88 and 260 mg B/kg bw/d.	2.6 & 88 mg B/kg bw/day: atrophied testes (not seen at 8.8 & 26 mg B/kg bw/day) 26 mg B/kg bw/day: Spermatogenic arrests	-	-	Weir, 1962 b
Oral in diet	2 years	Rat, Sprague Dawley male and female 70/sex/ group in controls; 35/sex/group treated	0, 1030, 3080, 10300 ppm, Equivalent to 0, 5.9, 17.5 or 58.5 mg B/kg/day	58.5 mg B/kg bw/day: Reduction bodyweight; clinical signs of toxicity; reductions in red cell volume and Hb; testicular atrophy	58.5 mg B/kg bw/day	17.5 mg B/kg bw/day	Weir, 1966 b.

5.6.2 Repeated dose toxicity: inhalation

No data on boric acid or the disodium tetraborates

5.6.3 Repeated dose toxicity: dermal

No data on boric acid or the disodium tetraborates

5.6.4 Other relevant information

5.6.5 Summary and discussion of repeated dose toxicity:

A number of studies on boric acid or disodium tetraborate decahydrate in diet or via drinking water for periods of 30 days to two years in rats, mice and dogs indicated that the main target organs for boron toxicity are the testis and blood. Other effects observed at high doses include rapid respiration, hunched position, bloody nasal discharge; urine stains on the abdomen, inflamed bleeding eyes, desquamation and swollen paws and tail, reduced food consumption and body weight gain. Treatment with boric acid and disodium tetraborate decahydrate disrupted spermiation, induced degeneration of testicular tubules and caused testicular atrophy. For effects on the blood system extramedullary haematopoiesis, reduced red cell volume and haemoglobin values and deposition of haemosiderin in spleen, liver and proximal tubules of the kidney were described.
A NOAEL for effects on testes and the blood system of 17.5 mg B/kg bw/day can be derived (with a LOAEL of 58.5 mg B/kg bwday) from a two year study in rats. However, it has to be considered that effects on testes were also observed at lower doses in other studies, including a low quality dog study (NOAEL: 0.4 mg B/kg bw/day; LOAEL: 4.4 mg B/kg bw/day for effects on testis; while slight extramedullary haematopoiesis was present in all dosed groups, hemosiderin and reductions in red cell volume and haemoglobin was only seen in the high dose: 33 mg B/kg bw/day).

5.7 Mutagenicity

5.7.1 In vitro data

A number of *in vitro* mutagenicity studies, including bacterial mutation assays in *Salmonella typhimurium* and *Escherichia coli*, gene mutation in mammalian cells (L5178Y mouse lymphoma, V79 Chinese hamster cells, C3H/10T1/2 cells), bacterial DNA-damage assay, unscheduled DNA synthesis (hepatocytes), chromosomal aberration and sister chromatid exchange in mammalian cell (Chinese hamster ovary, CHO cells) have been carried out on boric acid and one study on disodium tetraborate decahydrate. No evidence of mutagenic activity was observed (NTP, 1987; Haworth et al., 1983; Landolph, 1985; Bakke, 1991; Stewart, 1991).

Table 5.8.1 Key In Vitro Mutagenicity data with boric acid

Test system Method Guideline	organism/ strain(s)	concentrations tested (give range)	Result		Remark give information on cytotoxicity and other	Reference
			+ S9	- S9		
US EPA 40 CRF Part 158; FIFRA, Section 158.340, Guideline 84-2. Comparable to OECD 471	S. typhimurium: TA 1535, TA 1537, TA 97, TA 98, TA 100, TA 1538	10; 50; 100; 1000; 2500 µg/plate	-	-		Stewart, 1991,
40 CFR Part 158 US-EPA-FIFRA, Section 156.340; Complies with OECD 476	Mouse lymphoma L5178Y cells	0, 1.2, 1.7, 2.45, 3.5, and 5.0 mg/ml boric acid	-	-	Concentration related cytoxicity (60% reduction over controls at 5 mg/m)l	Rudd, 1991
1985; NTP protocol. resembles OECD 473	Chinese hamster Ovary (CHO)	With S9: 1000;1600;2000; 2500 µg/ml Without S9: 500; 1500; 2000 µg/ml	-	-		National Toxicology Program (NTP).1987

5.7.2 In vivo data

No mutagenic activity was seen *in vivo* in a mouse bone marrow micronucleus study on boric acid (O'Loughlin, 1991). Ten mice per sex per dosage group orally dosed with boric acid in sterile deionized water at dosage levels of 900, 1800 and 3500 mg/kg/day; which were considered to be the maximum practical doses that could be given. The percentage of PCEs among RBCs was not altered significantly by the treatment with boric acid. All boric acid treated groups, when compared to with the sterile deionized water control group, had micronucleus counts approximately equal to that of the negative control groups and did not differ statistically from controls at $p < 0.05$. Average micronucleus incidences in male and female mice treated with boric acid were 0.18% and 0.21%, respectively. Male and female mice treated with deionized water alone averaged background micronucleus incidences of 0.23% and 0.25%, respectively.

5.7.3 Human data

No data available

5.7.4 Other relevant information

No data available

5.7.5 Summary and discussion of Mutagenicity

All the data *in vitro* indicate no mutagenic activity. In addition the single *in vivo* study on boric acid also indicated no mutagenic activity.

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not mutagenic.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

Studies in animals

In long term feeding studies on boric acid and disodium tetraborate decahydrate in both rats, no carcinogenic effects were observed (Weir, 1966a,b; Weir and Fisher, 1972). Effects observed in the rat studies included lowered food consumption, retarded body weight gain, course hair coats, hunched position, swollen pads, inflamed bleeding eyes and changes in haematological parameters at the highest doses (58.5 mg B/kg bw/day). In the 2-year rat studies, only 10 animals/sex of the control and high-dose group were macroscopically and histologically examined. Animals in the low and mid-dose groups were not examined. Only 1-2 animals/sex/dose/time were examined in the 2-year studies in dogs, which limit the conclusions that can be made regarding carcinogenicity in dogs.

Testicular atrophy with some interstitial cell hyperplasia were the critical effects seen in a US National Toxicology Program (NTP) bioassay in mice fed 0, 2500, 5000 ppm in food equivalent to 0, 446 (75 mg B) and 1150 mg boric acid (200 mg B)/kg bw/d. Splenic extramedullary haematopoiesis occurs naturally in mice. An incidence was reported in males as 3/48, 11/49, 10/48, and in females 10/49, 11/34, 7/50 in the control, low- and high-dose groups, respectively. There is no other mention or discussion about extramedullary haematopoiesis in the rest of the report, so it was not regarded as an important finding.

No carcinogenic effects were observed at doses of boric acid of 75 mg B/kg bw/day and 200 mg B/kg bw/day (NTP, 1987). Effects on survival rate and reduced body weight gain were seen at the high doses. The testicular effects noted in these studies are discussed in more detail in Toxicity to Reproduction.

Table 5.9.1 Key Carcinogenicity study with Boric acid (mouse)

Route	Species Strain Sex no/group	dose levels frequency of application	Tumours	Reference

Oral in diet	Mouse B6C3F1 50/sex/group	0, 2500, 5000 ppm in food equivalent to 0, 446 (75 mg B) and 1150 mg boric acid (200 mg B)/kg bw/d 103 weeks	No evidence of carcinogenicity was found. At both doses: In males haematopoiesis in the spleen. Other effects in testes: At the high dose increased testicular atrophy and interstitial cell hyperplasia, variable loss of spermatogenia, and various stages of spermatogenesis from the seminiferous tubules.	National Toxicology Program (NTP) 1987.

5.8.2 Carcinogenicity: inhalation

No data

5.8.3 Carcinogenicity: dermal

No data

5.8.4 Carcinogenicity: human data

No data

5.8.5 Other relevant information

5.8.6 Summary and discussion of carcinogenicity

The studies carried out are not to modern standards, nor to GLP. In the 2-year rat studies, only 10 animals/sex of the control and high-dose group were macroscopically and histologically examined. Animals in the low and mid-dose groups were not examined. Only 1-2 animals/sex/dose/time were examined in the 2-year studies in dogs, which limit the conclusions that can be made regarding carcinogenicity in dogs. However, they are well performed and reported and are adequate to evaluate the carcinogenicity of boric acid and sodium borates. It can be concluded that that boric acid and sodium borates are not carcinogenic and there is no concern for a carcinogenic effects in humans.

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not carcinogenic.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

Studies in animals

Effects on the testis have been observed in both sub-chronic and chronic studies in three species: rats, mice and dogs. Further, a three generation study in rats and a continuous breeding study in mice showed effects on male and female fertility (Fail et al., 1991; Weir, 1966 c, d). A comparison of the key NOAELs and LOAELs for reproduction studies is given in the Table 5.9.1.1. The effects tend to be similar in all three species, although most data comes from rat studies.

In a 30/60 day study in rats of disodium tetraborate decahydrate administered in drinking water (0, 500, 1000, 2000 ppm equivalent to 0, 25, 50, 100 mg B/kg bw/day) no reduction of bodyweight or organ weights were observed, with the exception of significantly reduced epididymal weights in all dosed groups after 30 days. After 60 days the weight of testes and liver at 50 and 100 mg B/kg bw/day was also reduced. At these doses a significant loss of germinal elements and testicular atrophy (60 days > 30 days) concomitant with reduced enzyme activities of hyaluronidase, SDH and LDH-X and increased enzyme activities of G3P-DH and M-DH (malate dehydrogenase) were observed, correlating well with dose and duration of exposure. Plasma levels of FSH were increased in all treated groups, with both a dose-response and an exposure time-response apparent. LH and testosterone levels were not significantly altered. The NOAEL in this study was 25 mg B/kg bw/day (Dixon et al., 1979).

In male rats fed disodium tetraborate decahydrate for either 30 or 60 days at 60 or 125-131 mg B/kg bw/day (NOAEL, 30 mg B/kg bw/day) testis weight was reduced, testicular germ cells were depleted, selected testicular enzymes were affected and fertility was reduced. Hyaluronidase, sorbitol dehydrogenase, and lactic acid dehydrogenase isozyme-X were significantly decreased; and glyceraldehyde-3-phosphate dehydrogenase and malate dehydrogenase were significantly increased at 100 and 200 mg b/kg bw/day. Further, an increase in plasma FSH levels correlated well with germinal depletion and both effects were dose and time dependent. As might be expected, while recovery from inhibition of spermiation occurred at the lower doses, there was no recovery from testicular atrophy when the germ cells were lost. The serial mating studies in 5 males from each group indicate that the boron induced infertility is attributable to germ cell depletion. Germinal aplasia, elevated FSH-levels and infertility persisted at least for 8 months following cessation of boron exposure for the high dose 60 day group, but was reversible in the lower and shorter dosed groups (Lee et al., 1978).

The reproductive effects in rats treated with boric acid start with reversible inhibition of spermiation. Inhibition of spermiation was already observed after 7 days of treatment with doses of 61 mg B/kg bw in the diet and after 28 days extreme epithelial disorganisation and sperm cell loss was evident. Reduced testosterone levels were observed in the dosed animals, which could be reversed to control levels by treatment with hCG and LHRH. Animals were investigated after 4, 7, 10, 14 and 21 days (Treinen and Chapin, 1991).

Early effects (severe inhibition of spermiation) were seen after 14 days treatment, at doses around 38 mg B/kg, (217 mg boric acid/kg bw/day), but at a lower dose of 26 mg B/kg (149 mg boric acid/kg bw/day) the effects seen by histopathological analysis including staging, took about 28 days to manifest. The severely inhibited spermiation at 38 mg B/kg bw/day was resolved by 16 weeks posttreatment, but areas of focal atrophy were detected that did not recover posttreatment. Also no signs of recovery from atrophy were observed at doses of 52 & 68 mg B/kg bw/day (Ku et al., 1993).

In rat 90 day studies of boric acid all the male rats at 1750 ppm B (88mg B/kg bw/day) had atrophied testis and histologically complete atrophy of the spermatogenic epithelium and a decrease in the size of the seminiferous tubules. One male at 525 ppm (26 mg B kg bw/day) exhibited partial testicular atrophy (Weir 1962, Weir & Fisher, 1972). Similar results were observed in a study with disodium tetraborate decahydrate (Weir 1962b).

In a three generation study in rats groups of 8 males and 16 females were treated with boric acid or disodium tetraborate decahydrate equivalent to 0, 5.9, 17.5 and 58.8 mg B/kg bw/day. The high dose P1-generation failed to produce litter. Even if females of that group were mated with untreated males they had no offspring, indicating that the female reproduction was affected. A decreased ovulation in the majority of ovaries examined in that group was mentioned not to be sufficient to explain the observed infertility. Only overies of high dosed females were examined. Gross necropsy revealed atrophied testes in all P1 males at 58,8 mg B/kg bw/day. No information on F1 and F2 generations for this endpoint is available (Weir, 1966c, d; Weir and Fisher, 1972). The NOAEL was 17.5 mg B/kg bw/day.

Similar results were seen in two-year rat studies of boric acid and disodium tetraborate decahydrate at 58.5 mg B/kg bw/day conducted at the same dose range as the above described three generation study (Weir 1966 a,b; Weir and Fisher, 1972). Testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months at the highest dose level (58.5 mg B/kg bw/day) with both boric acid and disodium tetraborate decahydrate. Microscopic examination of the tissue revealed atrophied seminiferous epithelium and decreased tubular size in the testes. No effects were observed in the control and low dose groups. The NOAEL was 17.5 mg B/kg bw/day.

Fewer data are available for mice and dogs, but the results support the findings in rats:

In a continuous breeding study of boric acid in mice (NTP, 1990; Fail et al., 1991), the three administered doses were 1000 ppm (26,6 mg B/kg bw/day), 4500 ppm (111,3 mg B/kg bw/day) and 9000 ppm (220,9 mg B/kg bw/day). A dose-related effect on the testis (testicular atrophy and effects on sperm, motility, morphology and concentration) was noted; fertility was partially reduced at 111 mg B/kg bw/day, and absent at 221 mg B/kg bw/day.
For cross over mating only the mid dose group (111,3 mg B/kg bw/day) could be mated with control animals, since the high dose produced no litter. Indices of fertility for mid dose males x control females, control males x mid dose females and control males x control females were 5%, 65% and 74%, respectively. The according indices of mating (incidence of copulatory plugs) were 30%, 70% and 79%. This indicates that the primary effect was seen in males, however, slight effects were also noted in females. Live pup weight (adjusted for litter size) was significantly reduced compared to control litters, the average dam weight was significantly lower on postnatal day 0 compared to control dams and the average gestational period of the mid dose females was 1 day longer than in control females.
In task 4 of this continuous breeding study control animals and low-dose F1 animals were mated because in the 9000 ppm groups no litters and in the 4500 ppm group only 3 litters were produced. While mating, fertility and reproductive

competence were un-altered compared to control, the adjusted pup-weight (F2) was slightly but significantly decreased. F1 females had significantly increased kidney/adrenal and uterus weights and the oestrus cycle was significantly shorter compared to control females. In F1 males a reduction in sperm concentration was observed, but no other sperm parameters were influenced.
While in this study the NOAEL for the F0-generation is 1000 ppm (only motility of epididymal sperms was significantly reduced: 78% ± 3 in controls vs. 69% ± 5 at 1000 ppm) this is not a true NOAEL for F1 animals, because of the observed increase of uterine and kidney/adrenal weights and the shortened oestrus cycle in females and the 25% reduction of sperm concentration in males. Further, though normal in number, the F2-pups had reduced adjusted bodyweights.

Data in dogs derives from two very limited 90 day and two-year dietary studies. Dogs were dosed for 90 days with dietary levels of 0, 0.01, 0.1, 1.0% boric acid equivalent to 0, 0.4, 4.4, and 33 mg B/kg/day and 0, 0.0154, 0.154, 1.54% disodium tetraborate decahydrate equivalent to of 0, 0.4, 4.1, and 38 mg B/kg/day, based on the actual body weight and food consumption data in the study. Unfortunately, the published report of these studies does not accurately reflect the original study reports (Paynter, 1963 a;b; Weir and Fisher, 1972). At the mid-dose testes of all males showed 'artifactual distortion' of the outer third of the glands which might be a substance related effect, since it was observed in all males of this dose, but not in males from control and low dose groups. The spermatogenic epithelium was intact at this dose. In the high dose animals severe atrophy of the testes was observed. The data from the 90 day studies on boric acid and disodium tetraborate decahydrate has been considered inadequate for risk assessment and only used as supporting evidence of a reproductive effect and not to contribute to the determination of the NOAEL (EFSA, 2004; US EPA, 2004; US FNB, 2001; IPCS, 1998; ECETOC, 1995; IEHR, 1997; UK EVM, 2003). In particular the 90 day studies had many limitations and are considered not suitable for risk assessment. These limitations are further detailed in Annex 2.

In the two year dog studies on both boric acid and disodium tetraborate decahydrate, the actual dietary intake was reported in the original study reports allowing a more accurate measure of the dietary intake than presented in the published paper, in which the authors estimated the dietary intakes from standard intake figures. Groups of only four male dogs were fed either boric acid or disodium tetraborate decahydrate at doses up to 10.9 mg B/kg bw/day (62.4 mg boric acid/kg bw/day) and 9,6 mg B/kg bw/day (84.7 mg disodium tetraborate decahydrate/kg bw/day) in one study and 41 mg B/kg bw/day (233.1 mg boric acid/kg bw/day) and 39 mg B/kg bw/day (373.2 mg disodium tetraborate decahydrate/kg bw/day) in a second study. The animals were sacrificed at various time periods such that observations were reported on only 1 or 2 animals. At the highest dose, testicular atrophy was observed, however the effects in the only one disodium tetraborate decahydrate treated dog investigated at 38 weeks were less severe than those seen in the control dog. Testicular atrophy was present in three out of four control dogs, so that the significance of the effect in the treated animals is difficult to assess. One boric acid treated and one disodium tetraborate decahydrate treated dog were allowed to recover for three weeks. Some recovery was observed in each dog. Histopathological changes such as decreased spermatogenesis remained which was less obvious in the disodium tetraborate decahydrate treated dog. The NOAEL was deemed to be the equivalent of 10.2 mg B/kg bw/day by the authors (Weir, 1966 e,f; 1967 a, b; Weir and Fisher, 1972). Although this data is inadequate for risk assessment, it does confirm the effects seen in other species.

Table 5.9.1.1 Comparison of NOAELs and LOAELs for Reproductive Effects

Species	Study type or duration	NOAEL	LOAEL	Effect at LOAEL	Reference
Rat, Sprague Dawley	30 and 60 days, 18 per group	-	25 mg B/kg bw/day	Significant reduction in epididymal weight in all dose groups after 30 days In all dosed groups increase of plasma FSH levels and decrease of diameter of the seminiferous tubules. 60 days: reductions in testes and liver weights ≥ 50 mg B/kg bw/day; 60 days > 30 days: significant loss of germinal elements and testicular atrophy ≥ 50 mg B/kg bw/day Changes of testicular enzyme activities ≥ 50 mg B/kg bw/day	Dixon et al., 1979

Rat, Sprague Dawley	30 and 60 days, 18 per group Serial mating for 12 / 20 weeks	30 mg B/kg bw/day	60 mg B/kg be/day	Testis weight reduced and atrophy, Testicular germ cells depleted, Changes in testicular enzyme activities, Increased FSH levels, Reduced fertiliy (irreversible during the study in the high dose group, 60days)	Lee et al., 1978
Rat, Fischer 344	9 week dietary study, 6 per group	-	26 mg B/kg bw/day	Mild reversible inhibition of spermiation	Ku et al., 1993
Rat, Sprague Dawley	3-generation dietary study, 8 males and 16 females/group	17.5 mg B/kg bw/day	58.5 mg B/kg bw/day	Testicular atrophy reduced fertility (no offsping from high dose females mated with untreated males)	Weir, 1966c,d Weir and Fisher, 1972
Rat, Sprague Dawley	2 year dietary study, 70/control/sex, 35/group/sex	17.5 mg B/kg bw/day	58.5 mg B/kg bw/day	Testicular atrophy with atrophied seminiferous epithelium;	Weir, 1966, a,b Weir and Fisher, 1972
Mouse, Swiss CD-1	Continuous breeding dietary study, 40 males and females in control, 20 males and females in dosed groups	-	26.6 mg B/kg bw/day	Reduced sperm motility (F0) Increased uterine weight and kidney/adrenal weight, shortened oestrus cycle and 25% reduction in sperm concentration (F1) Reduced adjusted bodyweight of pups (F2)	Fail et al., 1991 (NTP, 1990)

Table 5.9.1.2 Fertility Studies

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Exposure Period	Doses	Critical effect	NO(A)EL Parental		NO(A)EL F1		NO(A)EL F2		Reference
Fertility Study of Boric acid in Rats						m	f	m	f	m	f	
Oral diet	Predates OECD 3generation 2litter per generation study	Rat Crl:CD Sprague Dawley 8 males 16 females/group	14 weeks pre-treatment then through three generations	0, 670, 2000 or 6700 ppm boric acid (0, 117, 350 and 1,170 ppm boron) in the diet, equivalent to 0, 34 (5.9), 100 (17.5) and 336 (58.5) mg boric acid (mg B)/kg bw	Top dose level caused testes atrophy prior to first mating so no litters produced. No adverse effects in mid and low dose groups in any generation.	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	*Weir R J (1966d).*
Fertility Study of Borax in Rats												
Oral diet	Predates OECD 3generation 2litter per generation study	Rat Crl:CD Sprague Dawley 8 males 16 females per group	14 weeks pre-treatment then through three generations	0, 1030, 3080 or 10300 ppm borax (0, 117, 350 and 1,170 ppm boron) in the diet, equivalent to 0, 50 (5.9), 155 (17.5) and 518 (58.5) mg borax (mg B)/kg bw respectively	Top dose level caused testes atrophy prior to first mating so no litters produced. No adverse effects in mid and low dose groups in any generation.	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	*Weir R J (1966c)*

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Exposure Period	Doses	Critical effect	LOAEL F0	NOAEL F0	LOAEL F1		LOAEL F2		Reference
Fertility Study of Boric acid in Mice						m	f	m	f	m	f	
Oral diet	Continuous breeding protocol (NTP)	Mouse, Swiss CD1 40 males and females in control, 20 mles and females in dosed groups	1 week pre-mating	0, 1000, 45000, 9000 ppm, Equivalent to 0, 26.6, 111.3, 220.9 mg B/kg bw/day	Reduced sperm motility (F0) Increased uterine weight and kidney/adrenal weight, shortened oestrus cycle and 25% reduction in sperm concentration (F1) Reduced adjusted bodyweight of pups (F2)	26.6 mg B/kg be/day	26.6 mg B/kg be/day	26.6 mg B/kg be/day	26.6 mg B/kg be/day	26.6 mg B/kg be/day	26.6 mg B/kg be/day	*Fail et al., 1991 (NTP, 1990)*

See Also Table 5.6.1.1

5.9.2 Developmental toxicity

Studies in animals

Only boric acid has been tested in developmental studies. Visceral and skeletal malformations were observed dose and species dependent in rats, mice and rabbits. Rats were more sensitive than mice and rabbits Price et al., 1996ab, Heindel1992). The studies by Price et al. (1996a) and Heindel et al. (1992) in rats were chosen as critical developmental studies because they were well-conducted studies of a sensitive endpoint that identified both a NOAEL and LOAEL. A comparison of the key NOAELs and LOAELs for developmental studies is given in the Table 5.9.2-1.

In two separate dietary studies performed in the same laboratory, groups of rats were given dose levels of 3.3, 6.3, 9.6, 13.3, 25 or 0; 3.3; 6.3; 9.8; 12.9; 25.4. At non-maternally toxic doses, there was a reduction on foetal weight and skeletal malformations (increase in incidence of wavy ribs and short rib XIII, decreased incidence of rudimentary extra rib on lumbar 1). The NOAELs for developmental toxicity in rat for the prenatal (Phase 1) and postnatal phase (Phase 2) were 9.6 and 12.9 mg B/kg bw/day, respectively. Maternal liver weight (absolute and relative to body weight) and maternal right kidney weight (absolute) were not affected. Relative kidney weight was increased at 25 mg B/kg bw/day in the diet on gd 20, with no treatment-related effects on post natal day 21. There was little evidence of maternal toxicity at any of the doses tested (Price et al., 1996a).

Average doses for rats were 0, 13.7, 28.5, 57.8 (on gestation day 0-20) and 94.3 (gestation day d 6-15) mg B/kg bw/day (Heindel, et al., 1992). The NOAEL for developmental toxicity in rats was determined to be < 13.7 mg B/kg bw/day. Prenatal mortality was increased in the highest dose group compared to control (36% resorption per litter versus 4%). The reduction in fetal body weight from independent studies at 0.1% or 0.2% boric acid in feed from gd 0 to 20 was comparable (Price et al., 1996a; Heindel et al., 1992).

Similar findings were observed in mice receiving estimated doses of 0, 43, 79, and 175 mg B/kg bw/day on gestation days 0-20 in feed (Heindel et al, 1992). Maternal toxicity was indicated by mild renal lesions and at the highest dose increases in the relative kidney weight and food and water intake. A NOAEL for maternal toxicity was not reached in the mouse study. The key developmental effects in mice observed were similar to those seen in rats, which were investigated in the same study as well, i.e. a reduction in foetal body weight at the mid dose (79 mg B/kg) and an increase in skeletal malformations (missing lumbar vertebrae, fused vertebral arches and short rib XIII) and resorptions at the highest dose, where slight maternal toxicity was recorded. The NOAEL for developmental effects in mice was 43 mg B/kg bw/day , the LOAEL was of 79 mg B/kg bw/day (Heindel et al., 1992). Maternal toxicity in mice and rats were not striking (Heindel et al., 1992), since the effects on food and water consumption were minimal. Weight gain seemed to be secondary to developmental toxicity (i.e. body weight gain corrected for gravid uterine weight was not significant reduced). Both studies (mice/rat) failed to provide evidence for any treatment related renal pathology (Price et al., 1996a). Neither the incidence nor the severity of the minimal nephropathy was dose related. In rat, developmental toxicity (decreased foetal weight: at 13.7 mg B/kg bw/day) occurred in the absence of marked maternal toxicity.

New Zealand White (NZW) rabbits were administered once daily at doses of 0, 10.9, 21.9 and 43.8 mg B/kg bw/day by gavage during major organogenesis on gestation days (gd) 6-19 (Price et al, 1996b). Rabbits exposed to 43.8 mg B/kg bw/day on gestation day 6-19 were associated with decreased food intake (during treatment), relative but not absolute kidney weight increase and vaginal bleeding. Prenatal mortality at the highest dose was increased (90% resorption/litter versus 6% controls). In this dose group 14 live fetuses (6 live litters) were available for evaluation, compared to 153-175 live fetuses (18-23 live litters) in the other groups. The resoprtion rate was consistent with other studies, but the incidence of resoprtions was disproportional high in boric acid-exposed rabbits relative to rabbits with even greater restriction of food intake (Parker et al, 1986; Matsuzaea et al, 1981). Development of the cardiovascular system was particular sensitive. The types of malformations (primarily cardiovascular) were dissimilar to those reported after diet restriction in other rabbit studies. Decreased maternal food intake may have been a contributing factor, but cannot be solely responsible for the range and severity of adverse developmental effects observed at the high dose of boric acid. Malformed fetuses/litters increased in 72% of the high-dose fetuses versus 3% of controls. The only skeletal effect observed was a decreased incidence of rudimentary extra rib on lumbar 1 which was not considered biologically significant. Mild maternal effects, but severe developmental toxicity were observed at 43.8 mg B/ kg bw/day (Price et al., 1996b).

Table 5.9.2-1 Comparison of NOAELs and LOAELs for Developmental Effects

Species	mg/Boron/kg bw/day			Effect at LOAEL	Reference
	Maternal NOAEL	NOAEL	LOAEL		
Rat	No maternal toxicity observed	9.6 * 12.9**	13.3* 25.3**	Decreased foetal body weight; skeletal malformations (short rib XIII, wavy rib, extra rib on lumbar I)	Price et al., 1996a
Rat	13.7*	< 13.7	13.7	Decreased foetal body weight, skeletal malformations (short rib XIII)	Heindel et al., 1992
Mice	Not identified**	43	79	Decreased foetal body weight, skeletal malformations	Heindel et al., 1992
Rabbits	21.9	21.9	43.8	Mild maternal toxicity; resorptions; Visceral malformations: cardiovascular system (interventricular septal defect)	Price et al., 1996b

* prenatal (Phase 1); **postnatal (Phase 2)

Table 5.9.2-2 Key Developmental studies with Boric acid

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Exposure Period	Doses (mg boron/ kg body weight per day)	Critical effects fetuses	NO(A)EL maternal	NO(A)EL Teratogenicity Embryotoxicity	Reference
Oral in diet	GLP, FIFRA, Federal Register 54, 3401-34074	Rat Female Sprague-Dawley and Male Cr1:CD (SD) BR VAF/ Plus	Day 0-20 of gestation (Exposure limited to gd 0-20)	Phase 1: (gd 0-20) 0; 3.3; 6.3; 9.6; 13.3; 25.0 Phase 2: (pnd 0-21) 0; 3.3; 6.3; 9.8; 12.9; 25.4	Phase 1: Reduction of foetal body weight on gd 20 in 13.3 and 25 mg/kg bw/day, malformations: incidence of short rib XIII or wavy ribs increased. Phase 2: No decreased foetal body weights effect. Short rib XIII, but no wavy rib or extra rib on lumbar I (pn d 21)	No maternal toxicity observed	NOAEL for foetal skeletal effects is 9.6 mg B/kg bw/day	Price et al, 1996a
Oral in diet	GLP	Rat Female Sprague-Dawley and Male Cr1:CD (SD) BR VAF/ Plus	Day 0-20 of gestation (highest dose to one group on Day 6-15 of gestation)	0; 13.7; 28.5; 57.8; 94.3;	Reduction of foetal body weight, malformations: Incidence of short rib XIII	13.7 mg/kg bw/day	< 13.7 mg/kg bw/day, foetal body weight decrease	Heindel et al., 1992
Oral in diet	GLP	Mice Swiss albino CD-1	Day 0-17 of gestation	0, 43, 79, 175	Reduced bodyweight; skeletal malformations including short rib XIII.	Not identified	43 mg B /kg bw/day	Heindel et al, 1992.
Oral Gavage in water	GLP	Rabbits NZW 30 per group	Day 6-19 of gestation, termination on gd 30	0, 10.9, 21.9 ,43.8	Prenatal mortality increased, malformations increased primarily cardiovascular defects (interventricular septal)	43.8 mg B/kg bw/day	21.9 mg B/kg bw/day	Price et al, 1996b

Phase 1/2: prenatal/postnatal period; gd gestation day; pnd postnatal day

Studies in humans

The investigated developmental toxicity of boron in animals indicates that fetuses of pregnant women may be the susceptible group; those fetuses of women who are experiencing renal insufficiency may represent a sensitive sub-population.
The potential reproductive effects of inorganic borate exposure to a population of workers at a large mining and production facility was assessed using the Standardised Birth Ratio (SBR), a measure of the ratio of observed to

expected births. A total of 542 workers completed a reproductive questionnaire. The average exposure for the highest exposure group was 28.4 mg B/day (approximately 0.4 mg B/kg bw/day) for two or more years. The average duration of exposure was 16 years. The number of offspring was actually greater than the US national average, indicating no adverse effects on reproduction in these workers (Whorton et al., 1994). It should be noted that the comparison with the US national average may dilute the effect that the socio-economic status plays on the number of offspring.

In a study of a highly exposed population in Turkey, where exposure comes mainly from naturally high levels of B in drinking water (up to 29 mg B/l) as well as from mining and production, no adverse effect has been reported on fertility over three generations (Sayli, 1998; 2001). Sayli et al. compared fertility in the residents of two Turkish villages with high levels of boron in their drinking water (8.5 to 29 mg B/L and 2.05 to 2.5 mg B/L), with there nearby villages with low boron levels (0.03 to 0.40 mg B/L). The authors compared the reproductive history of families living in the high boron region with families in the low boron region by identifying married adults who provided information about each spouse's family pedigrees covering three generations. In the high boron region, 159 three-generation kindreds containing 1068 families were ascertained. In the low-boron region, 154 three-generation kindreds containing 610 families were ascertained. No significant difference in fertility was noted between the high and low exposure groups. The gender ration (M:F) of offspring was 0.89 in the high exposure region compared to 1.04 in the low boron region, although the difference was not statistically significant ($p > 0.05$) (Sayli, 1998; 2001). The commission Working Group of Specialized Experts in the field of Reprotoxicity (Ispra, October 5-6, 2004) concluded that the epidemiological studies are insufficient to demonstrate the absence of an adverse effect on fertility.

The University of California Los Angeles (Wendie A. Robbins) is funded by the NIOSH to investigate the relation between workplace exposure to boron-containing compounds and adverse male reproductive effects. The aim of an ongoing study is to contribute critical information on four exposure levels at which boron causes adverse effects on human male reproduction.

5.9.3 Other relevant information

5.9.4 Summary and discussion of reproductive toxicity

Effects on Fertility

A dose related effect on the testis was observed in rats and mice with confirmation from limited studies in dogs. Effects in rats start with reversible inhibition of spermiation after 14 days (at 39 mg B/kg bw/day) and 28 days (at 26 mg B/kg bw/day). At doses equal to and above 26 mg B/kg bw/day testicular atrophy, degeneration of seminiferous tubules and reduced sperm counts were observed. Three fertility studies (two in rats, one in mice) indicate that the effects on testes are the main cause for reduced fertility. However, slight effects were also seen when treated female mice were mated with control males (e.g. significantly reduced live pup weight, adjusted for litter size). Additionally, female rats treated with 58.8 mg B/kg bw/day produced no offspring when mated with control males.

A NOAEL of 17.5 mg B/kg bw/day can be derived from a two year study (Weir, 1966a,b) and a three generation study in rats (Weir, 1966c,d). However, the continuous breeding study (Fail et al., 1991) in which only a LOAEL could be derived has to be considered too, since this study is more reliable than Weir (1966c, d), due to higher animal numbers per group and quality of examinations. Further, it has to be considered that effects on spermiation and testicular histology were observed at much lower doses in dogs (NOAEL: 0.4 mg B/k bw/day; LOAEL: 4.4 mg B/kg bw/day, Paynter, 1963a,b), even though those studies are of low quality (ANNEX 2).

In can be summarised that the dose-response curve is quite steep with a NOAEL at 17.5 mg B/kg bw/day, reversible effects at 26/39 mg B/kg bw/day and serious, irreversible effects at 58.5 mg B/kg bw/day.

Developmental Effects

Developmental effects have been observed in three species, rats, mice and rabbits. The most sensitive species being the rat with a NOAEL of 55 mg/kg bw/day (9.6 mg B/kg bw/day). This is based on a reduction in mean foetal body weight/litter, increase in wavy ribs and an increased incidence in short rib XIII at 76 mg/kg bw/day (13.3 mg B/kg bw/day). The reduction in foetal body weight and skeletal malformations had reversed, with the exception of short rib XIII, by 21 days post natal. At maternally toxic doses, visceral malformations observed included enlarged lateral ventricles and cardiovascular effects.

The NOAEL for this endpoint is 9.6 mg B/kg bw/day corresponding to 55 mg boric acid/kg bw/day; 85 mg disodium tetraborate decahydrate/kg, 65 mg disodium tetraborate pentahydrate/kg and 44.7 mg disodium tetraborate anhydrous/kg.

5.10 Other effects

Essentiality in animals

Boron has been suggested to be critical for normal reproduction and embryonic development in some animal species. Low boron culture conditions have resulted in abnormal development and increased malformations in frog (Xenopus laevis) embryos (Fort et al., 1998, 1999) and mechanisms for this essentiality are beginning to be revealed (Fort 2002). Survival of rainbow trout and zebrafish was impaired in low-B conditions (Eckhert, 1998, Rowe and Eckhert, 1999). Such effects have not been found consistently in rodent models (Lanoue et al., 1998, 1999). Like many essential elements, it is likely that boric acid exhibits a "U-shaped" dose response curve in some animals, as demonstrated by Rowe et al. (1998). Growth of vitamin D3-deficient chicks was stimulated by supplementation of boron (3 mg-B/kg-diet) in a low-B basal diet (Hunt and Nielsen 1981). Boron supplementation in pig diets (5 mg-b/kg-diet) decreased the inflammatory response to an intradermal injection of phytohemagglutinin in pigs, altered plasma lipid metabolites, and tended to increase the production of cytokines following a stress (Armstrong et al., 2001, Armstrong et al., 2000, Armstrong and Spears 2003). In rats, maternal exposure to a low boron diet was associated with a reduction in embryo implantation sites (Lanoue et al, 1998a). In vitro exposures of mouse embryos to low B growth medium showed reduced blastocyst formation and increased embryo degeneration (Lanoue et al.1998b).

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

The guidelines for developing DNELS (under RIP3.2.2) are not yet finalised therefore this section cannot be finalised until these guidelines are available. However the critical NOAEL can be identified. As soon as the DNEL guidelines are available the issue of the DNELs can be addressed more thoroughly.

Identification of the Critical NOAEL

Boron is an ubiquitous element found widely distributed in the environment.

It is an essential micronutrient for plants, and there is evidence to indicate that B is of nutritional importance, if not essential, for mammals. Boron is essential for normal reproduction and embryonic development in frogs and fish (Fort et al., 1999, 2002; Rowe et al., 1998), and mechanisms for this essentiality are beginning to be revealed (Fort 2002).

Boric acid and sodium borates have low acute toxicity. They are not skin irritants, nor skin sensitisers. Some borates cause eye irritancy in animals due to the glassy nature of the crystals, but in 50 years of occupational exposure no adverse ocular effects have been seen in humans. Borates are absorbed orally and by inhalation. They are very poorly absorbed dermally except through mucus and severely damaged skin. Dermal absorption has been shown to be <0.5% on human studies. They are not carcinogenic or mutagenic.

In human cases of poisoning, via accidental oral intake, acute and chronic symptoms of nausea, vomiting and diarrhoea occur. As the dose became higher and the dosing period longer, symptoms included alopecia, disseminated maculopapular eruption followed by widespread desquamation, focal or generalised central nervous system irritation, and convulsions.

The most critical endpoints of toxicity are considered to be (1) effects on the testis and fertility in males and (2) developmental effects (in particular, foetal weight reduction). The effects seen occur in three species, rats, mice and dogs for reproductive effects; rats, mice and rabbits for developmental effects. Visceral and skeletal malformations were observed dose and species dependent. Rats were more sensitive than mice and rabbits, which were also studied for developmental toxicity (Price et al., 1996ab, Heindel et al. 1992). The critical lowest No Observed Adverse Effect (NOAEL) level for the purposes of risk assessment is 9.6 mg B/kg bw/day (54 mg boric acid/kg bw/day; 85 mg/kg bw/day disodium tetraborate decahydrate; 65 mg/kg bw/day disodium tetraborate pentahydrate; 45 mg/kg bw/day disodium tetraborate anhydrous), based on developmental effects.

5.11.1 Overview of typical dose descriptors for all endpoints

Acute Toxicity

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are of low acute toxicity. For all the borates the acute toxicity results are: LD_{50} oral rat > 2000 mg/kg; LD_{50} dermal rat > 2000 mg/kg; LC_{50} inhalation rat > 2 mg/l.

Skin Irritation

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not skin irritants. Moreover boric acid and disodium tetraborate decahydrate are used at concentrations of 5% in cosmetics in the US and in talc in Europe, up to 3% in other cosmetics in Europe (Beyer et al., 1983; EC, 2000).

Eye Irritation

Boric acid induced conjunctivae redness and chemosis and minor effects on the iris. The effects were reversible within 7 days. Both disodium tetraborate decahydrate and disodium tetraborate pentahydrate induced eye irritation. This could be due to the glassy crystalline nature of these compounds however it is not possible to exclude eye irritation is the result of a non mechanical action. Disodium tetraborate pentahydrate is classified as an eye irritant R36 current EU guidelines (67/548/EEC) is indicated by the conjunctivae redness and oedema in two out of three animals and under GHS as Category 2A Irritating to eyes, based on redness >2.0 and also Oedema >2 reversible in 14 days. Disodium tetraborate decahydrate is classified as an eye irritant; R36 under current EU guidelines (67/548/EEC) is indicated by the iris and conjunctivae oedema and under GHS as Category 2A Irritating to eyes, based on iris, conjunctivae redness and oedema which does not reverse by 7 days.

Respiratory tract

The toxicology database for boric acid is not considered complete at this time. A rat 28-day inhalation toxicity study on boric acid was requested to better characterize the effects of repeated inhalation exposure (US EPA, 2006). So far, no chronic respiratory effect was obtained because no reliable animal studies are present for boric acid and borates. Additionally, epidemiological studies were not able to detect chronic effects in humans. In contrast, several studies were investigating acute symptoms associated with work-related boron dust. The epidemiological analyses indicate an exposure-response relationship for the irritant symptoms. It is assumed, that at a concentration of at X mg B/m^3 no local adverse irritating effect will be expected.

Sensitisation

Boric acid, disodium tetraborate decahydrate and disodium tetraborate pentahydrate were tested in a Buehler method skin sensitisation test (Wnorowski, 1994 e, f, g). They were applied at a concentration of 95% (powder moistened with water) during both the induction and challenge phase of the test. No signs of skin sensitisation were observed .The data indicate that these borates are not sensitisers. In addition there is no evidence of skin sensitisation in humans exposed occupationally to borates has been reported (Bruze et al., 1995).

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are neither skin nor respiratory sensitisers.

Repeated Dose Toxicity

A number of studies on boric acid or disodium tetraborate decahydrate in diet or via drinking water for periods of 30 days to two years in rats, mice and dogs indicated that the main target organs for boron toxicity are the testis and blood. Other effects observed at high doses include rapid respiration, hunched position, bloody nasal discharge; urine stains on the abdomen, inflamed bleeding eyes, desquamation and swollen paws and tail, reduced food consumption and body weight gain. Treatment with boric acid and disodium tetraborate decahydrate disrupted spermiation, induced degeneration of testicular tubules and caused testicular atrophy. For effects on the blood system extramedullary haematopoiesis, reduced red cell volume and haemoglobin values and deposition of haemosiderin in spleen, liver and proximal tubules of the kidney were described.
A NOAEL for effects on testes and the blood system of 17.5 mg B/kg bw/day can be derived (with a LOAEL of 58.5 mg B/kg bwday) from a two year study in rats. However, it has to be considered that effects on testes were also observed at lower doses in other studies, including a low quality dog study (ANNEX 2, NOAEL: 0.4 mg B/kg bw/day; LOAEL: 4.4 mg B/kg bw/day for effects on testis; while slight extramedullary haematopoiesis was present in all dosed groups, hemosiderin and reductions in red cell volume and haemoglobin was only seen in the high dose: 33 mg B/kg bw/day).

Mutagenicity studies

All data from the conducted in vitro studies indicate no mutagenic activity. In addition the single in vivo study on boric acid also indicated no mutagenic activity. Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not mutagenic.

Carcinogencity

In long term feeding studies on boric acid and disodium tetraborate decahydrate in both rats, no carcinogenic effects were observed (Weir, 1966a,b; Weir and Fisher, 1972). No carcinogenic effects were observed in mice at doses of boric acid of 75 mg B/kg bw/day and 200 mg B/kg bw/day (NTP, 1987). It can be concluded that that boric acid and sodium borates are not carcinogenic and there is no concern for a carcinogenic effects in humans.

Reproductive Toxicity

Effects on Fertility

A dose related effect on the testis was observed in rats and mice with confirmation from limited studies in dogs. Effects in rats start with reversible inhibition of spermiation after 14 days (at 39 mg B/kg bw/day) and 28 days (at 26 mg B/kg bw/day). At doses equal to and above 26 mg B/kg bw/day testicular atrophy, degeneration of seminiferous tubules and reduced sperm counts were observed. Three fertility studies (two in rats, one in mice) indicate that the effects on testes are the main cause for reduced fertility. However, slight effects were also seen when treated female mice were mated with control males (e.g. significantly reduced live pup weight, adjusted for litter size). Additionally, female rats treated with 58.8 mg B/kg bw/day produced no offspring when mated with control males.

A NOAEL of 17.5 mg B/kg bw/day can be derived from a two year study (Weir, 1966a,b) and a three generation study in rats (Weir, 1966c,d). However, the continuous breeding study (Fail et al., 1991) in which only a LOAEL could be derived has to be considered too, since this study is more reliable than Weir (1966c, d), due to higher animal numbers per group and quality of examinations. Further, it has to be considered that effects on spermiation and testicular histology were observed at much lower doses in dogs (NOAEL: 0.4 mg B/k bw/day; LOAEL: 4.4 mg B/kg bw/day, Paynter, 1963a,b), even though those studies are of low quality (ANNEX 2).

Developmental Effects

Developmental effects have been observed in three species, rats, mice and rabbits. The most sensitive species being the rat with a NOAEL of 55 mg/kg bw/day (9.6 mg B/kg bw/day). This is based on a reduction in mean foetal body weight/litter, increase in wavy ribs and an increased incidence in short rib XIII at 76 mg/kg bw/day (13.3 mg B/kg bw/day). The reduction in foetal body weight and skeletal malformations had reversed, with the exception of short rib XIII, by 21 days post natal. At maternally toxic doses, visceral malformations observed included enlarged lateral ventricles and cardiovascular effects. The NOAEL for this endpoint is 9.6 mg B/kg bw/day corresponding to 55 mg boric acid/kg bw/day; 85 mg disodium tetraborate decahydrate/kg, 65 mg disodium tetraborate pentahydrate/kg and 44.7 mg disodium tetraborate anhydrous/kg.

Human Data

A no effect level for humans based on the acute single intake and chronic, but daily single intake, symptoms of nausea, vomiting and diarrhoea can be established at about 1 g of boric acid/day (2.5 mg B/kg/day). The level at which adverse effects of anorexia, indigestion and exfoliative dermatitis will be seen is 5.0 mg boric acid/kg/day.

5.11.2 Correction of dose descriptors if needed (for example route-to-route extrapolation)

Since borates are assumed to be 100% absorbed by inhalation and oral exposure there is no need to further scale for inhalation and the oral NOAEL should be used as the basis for deriving a DNEL for borates.

5.11.3 Application of assessment factors

Assessment factor		Default value systemic effects
Interspecies	- correction for differences in metabolic rate per body weight	3
	- remaining differences	1
Intraspecies	- worker	5
	- general population	10
Exposure duration	- subacute to sub-chronic	na
	- sub-chronic to chronic	na
	- subacute to chronic	na
Dose-response	- issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity of effect	1
Quality of whole database	- issues related to completeness and consistency of the available data	1
	- issues related to reliability of the alternative data	1

The proposed assessment factor changes from the default is to the Systemic Effects Allometric scaling where the default of 4 for metabolic rate from rats to man can be reduced to 3 for borates based on a comparison of the renal clearance between rats and humans which indicated that humans may clear boric acid 3 times more slowly than rats (Pahl et al., 2001; Vaziri et al., 2001). The main difference between rats and humans is renal clearance.

As there are no other major differences between rats and humans then the extra factor of 2.5 can be disregarded since there are no metabolic differences between the species.

Since the data is based on reproductive effects there is no need for adjustments for duration of exposure.

5.11.4 Selection/ identification of the critical DNEL(s)/ the leading health effect

Based on the critical lowest No Observed Adverse Effect (NOAEL) level of 9.6 mg B/kg/day (54 mg boric acid/kg/day; 85 mg disodium tetraborate decahydrate; 65 mg disodium tetraborate pentahydrate; 45 mg disodium tetraborate anhydrous) in rats based on developmental effects; an interspecies assessment factor of 3, intraspecies assessment factors of 5 for workers and 10 for general population, the proposed critical DNELs are 0.640 mg B/kd/d for workers, and 0.320 mg B/kg/d for general population.

Summary of Adjustment factors for borates

	NOAEL mg B/kg/d	Interspecies		Total InterSp	Intraspecies		Total AF	DNEL mg B/kg/d	OEL Workers mg B/m3
		AS	Other		Worker	GPop			
Worker	9.6	3	1	3	5	1	15	0.640	4.48*
General Pop	9.6	3	1	3	1	10	30	0.320	

*Estimate based on 8 hours exposure and 10 m^3 inhalation and 60 kg adults.

AS = factor for allometric scaling AF = assessment factor

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

7 ENVIRONMENTAL HAZARD ASSESSMENT

8 PBT AND VPVB ASSESSMENT

9 EXPOSURE ASSESSMENT

10 RISK CHARACTERISATION

REFERENCES

[click to insert references classed alphabetically by author. For details on referencing, see explanatory note]

European Food Standards Agency (EFSA), 2004, Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Boron (Sodium Borate and Boric Acid). The EFSA Journal (2004) 80, 1-22. (Request N° EFSA-Q-2003-018) (adopted on 9 July 2004)

ANNEX 1

Drawbacks of the Garabrant at al. (1984, 1985) studies

- There is no indication of the temporal relationship between when a symptom was experienced and when the questionnaire was administered. It could have been days, weeks or months. Recall reliability can be in doubt.
- There is no assurance that the time when air samples were taken was relevant to the time symptoms were experienced. In the information on boric acid, the eight air samples upon which irritant effects were assessed had been collected in a plant that was no longer in existence at the time the symptom study was done.
- And even though the air samples were obtained for the purpose of representing exposure of a group of workers, there were too few (probably less than 6) to provide statistical power.
- The air samples used in the study may represent dust, but give no information about borate exposure.
- The respiratory irritation and complaints of dryness of mouth, nose and mouth and eye irritation are hardly surprising from a group involved in physical exertion in the high desert environment of the Mojave Desert.

ANNEX 2

Quality Assessment of the 90-Day Dog Studies of Boric Acid and Borax (Paynter, 1963a;b; Weir & Fisher, 1972)

- The test system is unsuitable because the age of the dogs is not identified in these studies. Age is a critical factor in a study that purports to evaluate male reproductive toxicity. Because the investigators did not know the ages of the dogs and because the dogs appear to be of varying ages, the test system is highly inappropriate for assessing male reproductive toxicity. The development of the testes is age-dependent. If a dog is either too young or too old, testicular endpoints may be affected by age. This deficiency alone should render these studies as unsuitable for quantitative risk assessment for endpoints of male reproductive toxicity.

- For unexplained reasons, the weight of the dogs varied significantly at the start of the experiment. The weight range of the male and female dogs at the start of the study was 6.0-10.4 and 4.2-11.5 kg, respectively. It is a generally accepted scientific principle that the animals used on a study should have similar body weights. The large difference in body weight at the beginning of the study calls into further question the age (and suitability) of the test system (animals).

- The test system is unsuitable because the source of the dogs is unknown. Although the authors state that purebred beagles were used, the source of the beagles is not stated in the 90-day studies (or in any of the Weir and Fisher studies). It was common practice in the 1960s to obtain dogs for research from dog pounds. In fact, some of the control dogs for other studies in the Weir and Fisher series were described by the authors as "mongrels."

- The test system is unsuitable because the dogs may not have been housed properly. The report states that the dogs in the 90-day studies were housed individually in metal cages. Yet, a female dog became pregnant during the course of another Weir and Fisher dog study, in which the authors stated that the dogs were housed individually in metal cages. This finding strongly suggests irregularities in the housing of the dogs. If two dogs housed individually can cohabitate, it also raises questions about the possibility of "individually-housed" dogs gaining access to the wrong diets.

- The test system is unsuitable because confounding factors, including previous exposure to reproductive toxicants, were not identified. The dogs used for this study may have been exposed to other chemicals, including chemicals that cause male reproductive toxicity, prior to placement on this study. Since the source of the dogs is unknown, there are no records on exposures to chemicals, drugs, and pesticides prior to the being placed on this study. Also, it was common practice in the 1960s to use the same dogs for more than one set of experiments. According to the

FDA Redbook (FDA, 2000), "Healthy animals that have not been subjected to previous experimental procedures should be used" for toxicity studies.

- The test system is unsuitable because at least one of the dogs (female control dog #4996) was missing a left kidney. It is not clear whether the missing kidney was due to a congenital defect or to previous surgery. At any rate, it is highly unusual to select a dog with only one kidney for a controlled experiment.

- The test system is unsuitable because the study report says the dogs were treated with a vermifuge "as needed" during the course of the study. Vermifuge is a type of anti-helminthic agent, which has been placed on California's Proposition 65 list of chemicals "known to the state" to cause reproductive toxicity based on studies of developmental toxicity. Based on a literature search, there is no publically available evidence that vermifuge has ever been tested for effects on male reproduction. According to the US FDA Redbook (US FDA, 2000), "Generally, it is not possible to treat animals for infection during the course of a study without the risk of interaction between the treatment drug and the test substance." In addition, the dogs were "vaccinated against canine distemper, infectious canine hepatitis, and rabies.

- The dogs on the study were administered "Wayne Dog Feed" *ad libitum* throughout the study. In addition, the dogs were also given a 100 gram ration of canned meat (Hill Packing Company) 5 days per week. This ration was apparently given because the Wayne dog food with boric acid and borax was not well tolerated. First, it is not clear what role, if any, the canned meat ration had on overall food consumption, because the consumption of the canned meat was not recorded. Second, the canned meat was not analysed for chemical impurities that might affect male reproduction.

- The reporting of the methods and results is insufficient because the statistical test methods are not described. The level of statistical significance (i.e., the *p* value) is not reported.

- The reporting of the results of the histopathology is insufficient, because no individual data are reported. It is not possible to determine which specific dogs exhibited histopathological findings. The authors simply reported the results for the entire group. The absence of detailed pathology reports on each individual dog, and the absence of any report on the findings in the controls, is a very severe limitation in the interpretation of these studies.

- The histological description of the testes in the 90-day dog studies is incomplete and inadequate by today's standards. The standards described in the FDA Redbook (FDA, 2000) were not met. According to the FDA Redbook (FDA, 2000): "A thorough histological evaluation of the testis should include an examination of the interstitial compartment and the seminiferous tubule compartment. A histopathological evaluation of the intertubular cell compartment of the testis should include a general assessment of the Leydig cells, the blood vessels, and the cell types other than the Leydig cells typically found in the intratubular space. The general appearance of the seminiferous tubules should be noted. This should be followed by an examination of the seminiferous tubule compartment to detect any disruption in the normal sequence of the events that occurs during the normal process of spermatogenesis. The seminiferous epithelium should then be carefully observed to detect any of the following: presence of multinucleated cells, missing germ cell layers, increased germ-cell degeneration, abnormal development in germ cells, sperm release delay or failure, presence of germ cells in the seminiferous tubule lumen, and any changes in the Sertoli cells (vacuolization, sloughing, or nuclear changes). The general condition of the boundary layer should be noted."

- Another abnormality in the test results is that many test results always ended in the numbers 0 or 5. For example, food consumption was always reported as a value that ended with either 0 or 5. Similarly, the BUN results all end in either 0 or 5. One possible explanation is that the instruments for measuring food consumption and BUN only measured whole numbers and half numbers. Interestingly, the testes weights of 15/15 boric acid-exposed dogs always ended in either 0 or 5. In contrast, only 2/5 of the control dogs ended in either a 0 or 5. This suggests that the method of weighing the testes of the control dogs may have been different from that used to weigh the testes of exposed dogs.

- The test system is unsuitable because the dog is not an appropriate model for evaluating male reproductive effects. No regulatory agency recommends using the dog as a species for evaluating male reproductive toxicity.

- The reporting of the method of preparing the test diets is inadequate: "The test material was added to the diet on a weight/weight basis and thoroughly mixed in a large volume blender. The report does not state whether the blending was performed wet or dry. The report describes no analysis to ensure that the actual concentration of test material was consistent with the nominal concentration. The report does not describe any effort to determine

whether the concentration of the test material in the diet was homogenous. This is a major flaw in the test system, since there is no verification of exposure to the test material. If the diets were not homogenous, the concentration of the test material in the diet given to the dogs may have varied from day to day. Dog diets are normally in chunks or pellets and, therefore, not easy to mix. Unlike rats, dogs cannot be satisfactorily fed a powdered diet.

- The results of the 90-day dog studies are called into question by the results of the 2-year dog studies conducted by Weir and Fisher. The effects seen at the mid-dose in the 90-day studies were not observed in the 2-year dog studies.

- The reporting of the results is insufficient because the average boron equivalent intake doses given at the bottom of Table 1 (Paynter, 1963a;b) does not match the average of the individual data provided. The average dose should be the average of the calculated dose for each of the 13 weeks of the study. But, the average dose reported is consistently lower than the average of the calculated dose for each of the 13 weeks of the study. For example, for male dog #4925, the reported average boron intake dose in Table 1 is 3.3 mg B/kg-d, but the average of the 13 weekly doses for this same dog is 5.2 mg B/kg-d. Likewise in the Borax study, dog #4984 reported average boron intake dose in Table 1 is 3.2 mg B/kg-d but the average of the 13 weekly doses for this same dog is 5.0 mg B/kg-d. This raises the serious possibility that the dose levels were incorrectly calculated in this study.

- The reporting of the results is inadequate because the body weight of individual dogs at week 13 (the end of the study) in Table 1 (Paynter, 1963a;b) do not match the same dog's body weight at autopsy (Table 5). Not only are the results of the body weights different between the two tables, but there is an inconsistent pattern to the difference in body weights. All of the control male dogs weighed less in Table 5 compared to Table 1. In contrast, only one of the mid- and high-dose male dogs weighed less in Table 5 compared to Table 1. If the body weights in Table 1 had been used instead of the body weights in Table 5 to calculate the relative weight of the testes, the relative testicular weight of the control group would have been less than originally reported, and the relative testicular weight of the mid- and high-dose groups would have been higher than originally reported. This observation calls into question the significance of the reported decrease in testicular weight, particularly at the mid-dose. These findings suggest that different dose groups of animals were weighed by different persons or on different scales. An alternative explanation is that different groups were autopsied on different days. Since the boric acid and borax studies were conducted simultaneously and incorporated a common control group, a large number of dogs would have been autopsied on a single day if all the dogs had been autopsied on the same day of the study. In fact, in the 90-day study, 70 male and female dogs would have been required to be autopsied on the same day. It is doubtful whether the same person could have conducted 70 autopsies of dogs on the same day.

Conclusions

The Weir and Fisher 90-day dog studies should be classified as Category 4 under the TGD Guidelines because the studies have an "unsuitable test system or conditions" and "insufficient reporting of methods and/or results data." Studies in rats and other species demonstrate that Boron can cause testicular toxicity and this is not in dispute. The 90-day dog studies, while adequate qualitatively to support this conclusion, are wholly inadequate to serve as the critical studies in quantitative risk assessment.

Figure 1 vbvnbv

Example 1 hff

Hgkhjfkg

DRAFT – October 19, 2007

SUBSTANCE EVALUATION REPORT

Substance Name:	**Boric Acid**	**Disodium Tetraborates**
EC Number:	**233-139-2**	**215-540-4**
CAS Number:	**10043-35-3**	**1330-43-4, 12179-04-3, 1303-96-4**

Rapporteur Member State : Austria

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TABLES

FIGURES

EXAMPLES

CONCLUSION OF THE SUBSTANCE EVALUATION

Substance Name:

EC Number:

CAS number:

Registration dossiers numbers:

Conclusion of the substance evaluation:

INFORMATION ON HAZARD AND RISKS

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

[click here to insert text]

1.1 Name and other identifiers of the substance

Chemical Name:

EC Name:

CAS Number:

IUPAC Name:

1.2 Composition of the substance

For each constituent/ impurity/ additive, fill in the following table (which should be repeated in case of more than one constituent). The information is particularly important for the main constituent(s) and for the constituents (or impurity) which influence the outcome of the dossier.

Chemical Name:

EC Number:

CAS Number:

IUPAC Name:

Molecular Formula:

Structural Formula:

Molecular Weight:

Typical concentration (% w/w):

Concentration range (% w/w):

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1		
VII, 7.2	Melting/freezing point	3.2		
VII, 7.3	Boiling point	3.3		
VII, 7.4	Relative density	3.4 density		
VII, 7.5	Vapour pressure	3.6		
VII, 7.6	Surface tension	3.10		
VII, 7.7	Water solubility	3.8		
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient		
VII, 7.9	Flash point	3.11		
VII, 7.10	Flammability	3.13		
VII, 7.11	Explosive properties	3.14		
VII, 7.12	Self-ignition temperature			
VII, 7.13	Oxidising properties	3.15		
VII, 7.14	Granulometry	3.5		
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17		
XI, 7.16	Dissociation constant	3.21		
XI, 7.17,	Viscosity	3.22		
	Auto flammability	3.12		
	Reactivity towards container material	3.18		
	Thermal stability	3.19		
	[enter other property or delete row]			

Table 1: Summary of physico- chemical properties

2 MANUFACTURE AND USES

2.1 Manufacture

2.2 Identified uses

2.3 Uses advised against

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

This should include the classification (including specific concentration limits) listed in Annex I of Directive 67/548/EEC (including the Index Number)

3.2 Self classification(s)

This should include the classification, the labelling and the specific concentrations limits. The reason and justification for no classification should be reported here.

It should be stated whether the classification is made according to Directive 67/548/EEC criteria or according to GHS criteria.

Acute Oral Toxicity

No classification is indicated under the current EU guidelines (67/548/EEC). However under the GHS guidelines, both boric acid and disodium tetraborate pentahydrate would be classified as Acute Oral Toxicity Category 5. In addition, the data on disodium tetrahydrate anhydrous, which indicated deaths at 2000 mg/kg bw (2/5 in one study and 4/5 in another study) would suggest that Acute Oral Toxicity Category 5 under GHS classification.

Eye Irritancy

Sodium Tetraborates

Disodium tetraborate decahydrate:
Eye irritant, R36 Under current EU guidelines (67/548/EEC)
GHS Category 2A Irritating to eyes

Disodium tetraborate pentahydrate
Eye irritant, R36 under current EU guidelines (67/548/EEC)
GHS Category 2A Irritating to eyes

Disodium tetraborate anhydrous:
Eye irritant, R36 under current EU guidelines (67/548/EEC)
GHS Category 2A Irritating to eyes
Based on read across from disodium tetraborate pentahydrate and disodium tetraborate decahydrate,

4 ENVIRONMENTAL FATE PROPERTIES

4.1 Degradation

4.1.1 Stability

Corresponds to IUCLID 4.1

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

4.1.2.2 Screening tests

4.1.2.3 Simulation tests

4.1.3 Summary and discussion of persistence

4.2 Environmental distribution

4.2.1 Adsorption/desorption

Corresponds to IUCLID 4.4.1

4.2.2 Volatilisation

Corresponds to IUCLID 4.4.2

4.2.3 Distribution modelling

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

4.3.1.2 Measured bioaccumulation data

4.3.2 Terrestrial bioaccumulation

4.3.3 Summary and discussion of bioaccumulation

4.4 Secondary poisoning

Assessment of the potential for secondary poisoning

5 HUMAN HEALTH HAZARD ASSESSMENT

A number of detailed hazard assessments and reviews of the toxicology of borates have been published (Culver et al, 1994a; ECETOC, 1995; EC, 1996; Murray, 1995; Culver and Hubbard, 1996; Hubbard and Sullivan, 1996, Hubbard, 1998; IPCS, 1998; WHO; 1998; Moore et al., 1998; US FNB, 2001; US EPA, 2004; UK EVM, 2003; EFSA 2004, HERA, 2005).

Most of the simple inorganic borates exist predominantly as un-dissociated boric acid in dilute aqueous solution at physiological and environmental pH, leading to the conclusion that the main species in the plasma of mammals and in the environment is un-dissociated boric acid. Since other borates dissociate to form boric acid in aqueous solutions, they too can be considered to exist as un-dissociated boric acid under the same conditions. See 4.1 Degradation

The majority of toxicological and ecotoxicological studies of borates have involved either boric acid (H_3BO_3) or disodium tetraborate decahydrate (i.e., borax, or $Na_2B_4O_7.10H_2O$). Both acute and longer-term studies have been carried out on these two substances as well as ecotoxicological studies. For the other borates, boric oxide, disodium tetraborate pentahydrate, and disodium tetraborate anhydrous, only acute mammalian toxicity studies have been carried out.

For comparative purposes, dose levels of borates have been expressed in terms of boron (B) equivalents based on the fraction of boron on a molecular weight basis. Conversion factors are given in Table 1 below. These conversion factors are important as some studies express dose in terms of B, whereas other studies express the dose in units of boric acid or disodium tetraborate decahydrate. The B equivalents used are a generic designation rather than a designation of the element boron.

Table 5.1 Conversion factors to Boron Equivalents

		Conversion factor for Equivalent dose of B
Boric acid	H_3BO_3	0.175
Disodium tetraborate decahydrate (Borax)	$Na_2B_4O_7 \bullet 10H_2O$	0.113
Disodium tetraborate pentahydrate	$Na_2B_4O_7 \bullet 5H_2O$	0.148
Disodium tetraborate anhydrous	$Na_2B_4O_7$	0.215

5.1 Toxicokinetics (absorption, distribution, metabolism, and elimination)

The toxicokinetics of boric acid; boric oxide; boric oxide and the sodium tetraborates (anhydrous; pentahydrate and decahydrate) are similar in rats and humans with respect to absorption, distribution, and metabolism (Dourson et al., 1998; Murray, 1998).

Absorption

Oral Absorption

Boric acid and the simple sodium borates given orally are readily and completely absorbed in humans and animals. Animals investigated include rats (Ku et al., 1991), rabbits (Draize & Kelly, 1959), sheep (Brown et al., 1989) and cattle (Owen, 1944; Weeth et al., 1981) as shown by the levels of boron in urine, blood or tissues. In rats fed ^{10}B (boron 10-isotope) at a dose of 20 µg 95% and 4% was recovered from urine and feces respectively within 24 h. Isotope ratios $^{11}B/^{10}B$ measured in the urine changed from the natural abundance of 4.11 to an enriched ratio of 0.951 during the first 3 days after the test meal was fed to rats (Vanderpool et al., 1994). In six adult human volunteers given a single oral dose of 131 mg B (as boric acid dissolved in water), 94% of the administered dose was excreted in the urine over a 96 hour period (Schou et al, 1984). Similar absorption was observed based on urinary excretion of boron in 6 volunteers drinking curative spa water with a high boron content (daily dose of 102 mg B) for two weeks (Job, 1973). In another study, greater than 90% was absorbed in human volunteers taking in 3% boric acid in an aqueous solution or as a waterless emulsifying ointment spread onto biscuits (Jansen, 1984a). In a series of human volunteer studies conducted in the early 1900s, in which large doses of boric acid were repeatedly administered orally, approximately 80% of an administered dose was recovered in the urine, while 1% was recovered in the faeces (Wiley, 1904). Reports involving accidental human ingestion, particularly in infants, where new-born infants died after accidentally ingesting boric acid,

provide further evidence of oral absorption (Wong, 1964). After accidental boric acid uptake in 9 patients, the mean half-life of boric acid was determined to be 13.4 hours (range, 4.0 to 27.8) (Litovitz et al. 1988). For human risk assessment purposes 100% oral absorption is assumed.

Inhalation Absorption

Inhaled sodium borate dust is readily absorbed as demonstrated by the blood and urine levels among groups of workers occupationally exposed to various levels of boron (Culver et al., 1993; 1994b). In rats, inhaled boron oxide (anhydrous boric acid) aerosol was readily absorbed, based on the increased levels of boron excreted in the urine following inhalation exposure. It is not clear if the inhaled amount of boron was absorbed entirely by the respiratory tract (Wilding et al., 1959).

Dermal Absorption

Dermal absorption of borates across intact skin is insignificant in all species evaluated, including human new-born infants (no rise in plasma boron levels; Friis-Hansen et al., 1982), adult humans (no increase in boron excretion in urine; Beyer et al., 1983; Hui et al, 1996; Wester et al, 1998), rabbits (Draize and Kelley, 1959), and rats (no or slight increases in urine boron concentration Nielsen, 1970). Borates have been demonstrated to penetrate damaged or abraded skin (Draize and Kelley, 1959; Nielsen, 1970, Stüttgen et al., 1982). However, the use of an ointment-based vehicle may prevent or reduce the absorption though diseased skin compared to an aqueous jelly based vehicle (Nielsen, 1970 and Stüttgen et al, 1982), although the results by Stüttgen et al. (1982) have a number of flaws and are therefore not conclusive.

Skin absorption data was obtained in human volunteers (Hui et al., 1996; Wester et al., 1998). Volunteers were dosed (non-occluded) on a 900 cm2 area (30cm x 30 cm) area of the back with ^{10}B enriched boric acid or sodium tetraborate decahydrate (5% in aqueous solution), or disodium octaborate tetrahydrate and disodium tetraborate decahydrate (10% in aqueous solution). Twenty-four hours later the residual dose was removed by washing. Boron was measured in the urine. The absorption rates are given below.

Table 5.1.1 Dermal Absorption in Humans of boric acid and disodium tetraborate decahydrate

	% Dose Absorbed ± SD	Rate of Absorption Flux $\mu g/cm^2/hr$	Permeability Constant (Kp) (cm/hr)
Boric Acid (5 %)	0.226 ± 0.125	0.009	1.9×10^{-7}
Disodium tetraborate decahydrate (5 %)	0.210 ± 0.194	0.00875	1.8×10^{-7}
Disodium octaborate tetrahydrate (10 %)	0.122 ± 0.10	0.00975	1.0×10^{-7}

The total recovery of the applied dose ranged from 48.8 - 63.6%, therefore 36.4-51.2% of the applied dose is not accounted for. The authors suggested that this may be due to loss to outside clothing and bedding. However, part of the lost dose may be located in the body or in the skin at the application site, which in that case should be considered as being absorbed. Based on other data, for instance, the low acute dermal limit studies carried out on sodium tetraborate pentahydrate and sodium tetraborate decahydrate (LD_{50} be > 2000 mg/kg bw) indicate minimal dermal absorption. In an acute dermal limit study on boric acid, the rabbit skin was abraded to increase the absorption. Even in this study there was limited symptoms observed and the acute dermal LD_{50} was > 2000 mg/kg bw. This data supports minimal absorption, which is supported by the results of the human percutaneous absorption study (Wester et al., 1998).

The percutaneous absorption of disodium tetraborate decahydrate can be read across to disodium tetraborate pentahydrate and disodium tetraborate anhydrous. Disodium tetraborate pentahydrate only slightly less hydrated than the decahydrate. Anhydrous disodium tetraborate is the anhydrous salt of disodium tetraborate decahydrate and disodium tetraborate pentahydrate. For practical purposes one part of anhydrous disodium tetraborate is equivalent to 1.45 parts of disodium tetraborate pentahydrate; 1.9 parts of disodium tetraborate decahydrate; and in aqueous solution 1.23 parts of boric acid. Anhydrous disodium tetraborate is hygroscopic and takes up water to form a hydrated salt and like the other borates, in solution it will exist as undissociated boric acid. Since anhydrous disodium tetraborate and disodium tetraborate pentahydrate will form the various similar borates in the moistened form that it is applied to the skin, they are unlikely to be absorbed at any greater rate than the other borates tested.

Therefore, based on this study and other data, and using the % dose absorbed plus SD for boric acid (rounded up), a dermal absorption for borates of 0.5% can be assumed as a worse case estimate.

Distribution

There is no substantiated evidence of long term boron accumulation in humans or other animals although bone contains higher levels than other tissues and is slowly eliminated from bone. (Alexander et al, 1951; Forbes et al., 1954; Forbes and Mitchell, 1957; Jansen et al, 1984b; Ward, 1987; Treinen and Chapin, 1991; Ku et al., 1991;1993; Culver et al., 1994b ; Chapin et al, 1997).

Absorbed boron rapidly distributes throughout the body water in humans and animals. In a study of workers occupationally exposed to 10 mg/m^3 of airborne borax (0.22 mg B/kg/day), there was no progressive accumulation of boron in soft tissues during the working week as measured by blood and urine levels (Culver et al., 1993; 1994b). Similarly, Jansen et al. (1984a, b) concluded from pharmacokinetic studies of human volunteers that there was no tendency for boron to accumulate following a single i.v. dose of 600 mg of boric acid (approximately 105 mg B). Tissue levels of boron generally reached steady-state within three to four days among rats fed boric acid in the diet or drinking water for 28 days (Treinen and Chapin, 1991) or 3 – 4 days (Ku et al., 1991). Thus, boron does not accumulate in soft tissues with time in either humans or animals.

A poisoning case with boric acid in a pregnant woman indicated that borates can cross the placenta (Grella et al., 1976). The foetus was delivered early due to accidental poisoning of the mother with boric acid, and since no boric acid fetal blood or amniotic fluid concentrations were measured, it is not possible to conclude that boric acid passed the placenta. No information was presented on possible reproduction parameters.

In both humans and animals, boron levels in soft tissue are comparable to plasma levels, while a greater concentration of boron in bone is observed relative to other tissues. The most complete study of boron distribution conducted to date examined tissue disposition of boron in reproductive organs and other selected tissues in adult male rats fed boric acid, providing approximately 100 mg B/kg bw/day for up to seven days (Ku et al., 1991; 1993). All tissues examined, except bone and adipose tissue, appeared to reach steady state boron levels by three to four days. Bone achieved the highest concentration of boron (2 to 3 times plasma levels), and bone boron levels continued to increase throughout seven days of dietary administration (Ku et al., 1991). In contrast, adipose tissue concentration was approximately 20 % of the plasma level. No other tissues showed any appreciable accumulation of boron over plasma levels. In dogs, an accumulation in the brain, liver and fat was reported after a high single does of 2000 mg (350 mg B)/kg bw boric acid (Pfeiffer et al., 1945). However, the accuracy of the analytical procedures in that study is questionable.

Previous studies also show a greater concentration of boron in bone relative to other tissues in humans (Alexander et al., 1951; Forbes et al., 1954;) and rats (Forbes and Mitchell, 1957). Boron levels in a number of tissues have been measured (Abou-Shakra, 1989; Ciba and Chrusciel, 1992; Ward, 1987; Sabbioni et al., 1990; Shuler et al., 1990; Minoia et al., 1990; 1994). In mice, boron distribution appeared to be homogenous in the tissues examined, except for higher levels in the kidney (bone was not analysed) (Locksley and Sweet, 1954; Laurent-Pettersson et al., 1992), but higher levels were found in bone in another study (Massie et al., 1990). In vivo and in vitro studies indicate that boric acid has a strong affinity for cis -hydroxyl groups. This may explain the higher concentrations of boric acid in bone, owing to the binding of to the cis -hydroxyl groups of hydroxyapetite.

Metabolism

Boric acid is not metabolised in either animals or humans, owing to the high energy level required (523kJ/mol) to break the B - O bond (Emsley, 1989). Other inorganic borates convert to boric acid at physiological pH in the aqueous layer overlying the mucosal surfaces prior to absorption. Additional support for this derives from studies in which more than 90% of administered doses of inorganic borates are excreted in the urine as boric acid. Boric acid is a very weak and exclusively monobasic acid that is believed to act, not as a proton donor, but as a Lewis acid, i.e., it accepts OH-. Because of the high pKa, regardless of the form of inorganic borate ingested (e.g., boric acid, borax or boron associated with animal or plant tissues), uptake is almost exclusively (>98%) as undissociated boric acid.

Excretion

In both humans and animals, boron is excreted in the urine regardless of the route of administration. It is excreted with a half-life of < 24 hours in humans and animals. Boron is slowly eliminated from bone (Chapin et al., 1997).

In humans, 99 % of a single i.v. dose of boric acid was excreted in the urine; the plasma half-life was calculated to be 21 hours using a three compartment toxicokinetic model (Jansen et al., 1984b). Following oral intake of an aqueous solution of boric acid, the urinary recovery was 94 % (Jansen et al., 1984a); more than 50 % of the oral dose was eliminated in the first 24 hours, consistent with the 21 hour half-life in the i.v. study. Sutherland et al. (1998) showed in a boron balance study that only 8% of dietary boron is excreted in faeces. In a previous study, half-lives ranging from 4.0 – 27.8 hours have been reported from nine poisoning cases (Astier et al., 1988; Litovitz et al., 1988).

Elimination half-lives for animals have not been stated explicitly in the scientific literature, but they can be calculated or estimated from the data in the literature. In mice, assuming first order kinetics for elimination, the half-life was estimated to be approximately one hour, and in rat < 12 hours (Farr and Konikowski, 1963; Ku et al. 1991; 1993). In rabbits, 50 to 66% of an orally administered dose of boric acid was excreted in the urine in the first 24 hours after dosing (Draize and Kelley, 1959). A recent study indicated that the half-life may be only 3 hours in both pregnant and non-pregnant rats. The boron clearance in pregnant rats was slightly higher than in non-pregnant rats; however the difference was not statistically significant (Vaziri et al., 2001).

The major determinant of boric acid excretion is expected to be renal clearance since boric acid is excreted unchanged in the urine. Rats and mice generally have faster rates of renal clearance than humans since the glomerular filtration rates as a function of body mass are generally higher in rats and mice than in humans.

Clearances as a function of body surface area of 40.4 ± 3.2 ml/min/1.73m^2 for sodium tetraborate in male rats and 40 ml /min/1.73m^2 for boron in mice (Usuda et al., 1998; Farr and Konikowski, 1963) have been reported, although there are methodological and/or analytical limitations in both studies. In more recent studies boric acid clearance rates in non-pregnant rats and pregnant rats ranged from 29.0 ± 5.7 to 31.0 ± 4.5 and from 32.2 ± 5.1 to 35.6 ± 5.7 ml/min/1.73m^2, respectively (Vaziri et al., 2001).

In humans, Jansen et al (1984b) determined a clearance rate of 55 ml/min/1.73m^2 following an i.v. dose of 600 mg of boric acid (105 mg B). Farr and Konikowski (1963) also reported a similar value of 39 ml/min/1.73m2 in humans given 35 mg B/kg intravenously as sodium pentaborate, although there are methodological and analytical limitations to this 40 year old study. In a more recent study, renal clearance rates in humans were 68.30 ± 35.0ml/min/1.73m^2 for pregnant subjects and 54.31 ± 19.35 ml/min/1.73m^2 for non-pregnant subjects (Pahl et al., 2001). This indicates about 20 –25% greater clearance in pregnant humans.

A comparison of the renal clearance between rats and humans in terms of body surface area indicated that humans clear boric acid slightly faster than rats (~1.7 -1.9 times as fast), while a comparison by bodyweight indicates that humans may clear boric acid more slowly than rats (~ 3 - 4 times slower). (Pahl et al., 2001; Vaziri et al., 2001). The comparison by bodyweight is used for risk assessment purposes.

CONCLUSION

There is little difference between animals and humans in absorption, distribution, and metabolism. A difference in renal clearance is the major determinant in the differences between animals and humans, with the renal clearance in rats approximately 3 times faster than in humans.

Absorption of borates via the oral route is nearly 100%. For the inhalation route also 100% absorption is assumed. Dermal absorption though intact skin is very low. For risk assessment of borates a dermal absorption of 0.5% is used as a realistic worst case approach. In the blood boric acid is the main species present. Boric acid is not further metabolised. Borates are distributed rapidly and evenly through the body, with concentrations in bone 2 - 3 higher than in other tissues. Boron is excreted rapidly, with elimination half-lives of 1h in the mouse, 3h in the rat and < 27.8 h in humans, and has low potential for accumulation. Boric acid is mainly excreted in the urine.

Table 5.1.2 Summary of Toxicokinetics of Inorganic Borates in rats and humans

Absorption	• Readily absorbed orally and by inhalation (of respirable particles) • No dermal absorption (< 0.5%) except through severely damaged skin
Distribution	• Rapidly distributed through body water • With the exception of bone - no accumulation in tissues
Metabolism	• Not metabolised • Exists mainly as boric acid in whole blood
Excretion	• Excreted almost exclusively in the urine • Half-life < 24 hours • Renal clearance is approximately 3 time faster in rats than humans based on a body weight comparison

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Studies in animals

The borates are in general of low acute oral toxicity in mammals, including rats and mice. An accidental poisoning case in cows and a further study in goats do not suggest that these species are more sensitive to the effects of borates with respect to acute toxicity (Sisk et al., 1988; 1990). The rat LD50 values for the various borates are given below. No substantial differences in acute rat toxicity were seen in mice and dogs in the limited studies available. However, dogs exhibit an emetic effect in response to high doses of borates. The LD50 in dogs was determined to be > 3980 mg boric acid/kg (697 mg B) and > 6150 mg disodium tetraborate decahydrate (695 mg B) /kg (administered in a capsule). The dogs vomited shortly after treatment at all doses (158 mg boric acid (28 mg B)/kg and 246 mg disodium tetraborate decahydrate (28 mg B)/kg were the lowest doses tested) (Keller, 1962; Weir & Fisher, 1972). The main symptoms of toxicity seen in all species tested were CNS depression, ataxia and convulsions.

Two limit dose studies were conducted on disodium tetraborate anhydrous. The first study, rats were dosed at 200 (43 mg B) and 2000 mg (430 mg B) /kg/ bw. At 2000 mg (430 mg B)/kg 2/5 rats male rats died. Slight body weight loses were recorded for both animals. Clinical signs indicated soft faeces, soiling of anogenital area, lethargy, hunched posture, ptosis, hypothermia and wasted appearance. In surviving males, signs of soft faeces, soiling of anogenital area and hunched posture were apparent but had resolved by day 4, but an unkempt appearance was noted between day 7 and termination (day 15). Piloerection and anogenital soiling was noted in 4 females of the same group, and these recovered by day 3. The only pathological effects observed were a distended stomach and darkened lungs in one rat that died and an enlarged liver, dark inflated lungs and red fluid in the thoracic cavity of the second rat that died. At 200 mg (43 mb B)/kg, apart from one male rat with an unkempt appearance no other clinical signs were observed. At 200 mg(43 mg B)/kg, no animals died and the only observation seen was an unkempt appearance in one male and one female at intervals during the second week. The LD50 was estimated to be > 200 mg(43 mg B)/kg bw Males; >2000 mg (430 mg B)/kg Females. The second study was conducted to confirm that the LD50 is above 2000 mg (430 mg B)/kg/bw. Rats were dosed at 1600 (344 mg B) and 2500 mg (538 mg B)/kg. No deaths occurred at either dose. No effects were observed at 1600 mg (344 mg B)/kg. At 2500 mg (538 mg B)/kg, piloerection observed in one animal that recovered by day 2. No other adverse effects were observed (Denton 1995, 1996). Based on the data in the first study, it is likely that the LD50 is lower than 5000 mg (1075 mg B)/kg/bw.

Table 5.2.1 Acute Oral Toxicity Studies

Route	Method Guideline	Species Strain Sex no/group	Dose levels duration of exposure	Value LD_{50} /LC_{50}	Remarks	Reference
Boric Acid						
Oral	[1] No specific guidelines were available at the time of this study.	Rat: Sprague Dawley 5/group	2.0; 2.52; 3.16; 3.98;5.01 and 6.31 g/kg bw	LD_{50} males + females = 3765 mg /kg bw (659 mg B/kg)	Other data supports a range of 2660 – 4100 mg/kg	Keller, 1962 Weir & Fisher, 1972; Preiffer et al., 1945
Disodium Tetraborate Anhydrous						
Oral	OECD 401	Rat: Crl:CD.BR 5/group	1600; 2500 mg/kg bw	> 2500 mg (538 mg B)/kg bw males		Denton. (1996).
Disodium Tetraborate Pentahydrate						
Oral	US EPA-FIFRA guidelines	Rat: Sprague Dawley 5/group	1000; 1495; 2236; 3344 5000 mg/kg bw	3305 (2403 - 4207) mg/kg (489 mg B/kg)		Reagan and Becci (1985a)
Disodium Tetraborate Decahydrate						
Oral	[1]Unknown	Rat: Sprague Dawley 5/group	4.0; 4.5; 5.0; 5.5; 6.0; 6.5; 7.0 grams/kg bw	5560 (5150 - 6000) mg/kg (628 mg B/kg)		Meyding and Foglhian (1961),

[1]Although only old data is available for boric acid and for disodium tetraborate decahydrate, there are a number of studies in rats (and mice and dogs), which confirm the low acute oral toxicity of the borates Further testing is therefore not justified in the interests of protecting laboratory animals.

Studies in humans

There is a large database of accidental or intentional poisoning incidents for humans. Many were the result of accidental use as an antiseptic for irrigating body cavities, treating wounds or as a treatment for conditions such as epilepsy. Such medical uses are now obsolete. Also, accidental misuse in the preparation of baby formula (1 – 14 g in boric acid in the formula) and the topical use of pure boric acid powder for infants has led to poisonings in the past. This database is reviewed in several papers of data from poisoning centres as well as a detailed review of the literature cases from the mid 1800s to the 1970s by Kliegel (Kliegel, 1980; Wong et al. 1964, Litovitz et al, 1988; Goldbloom and Goldbloom, 1953; Valdes-Dapena and Arey, 1962). Humans display different acute symptoms compared with most animals. In the literature, the human oral lethal dose is regularly quoted as 2--3 g boric acid for infants, 5-6 g boric acid for children and 15-30 g boric acid for adults. This data is largely unsubstantiated. In most cases it is difficult to make a good quantitative judgment particularly since medical intervention occurred in most cases and there were often other unrelated medical conditions (Culver and Hubbard, 1996). Of 784 more recent reports of accidental ingestion, none were reported as fatal and 88.3% were asymptomatic. The estimated dose range was 10 mg to 88.8 g (Litovitz et al, 1988). However, a single intake of 30 g of boric acid was fatal in one case (Yoshitaka et el., 1993). Symptoms of acute effects may include nausea, vomiting, gastric discomfort, skin flushing, excitation, convulsions, depression and vascular collapse.

5.2.2 Acute toxicity: inhalation

Studies in animals

Low acute inhalation toxicity was observed in those borates tested. In an inhalation study in which rats were exposed to boric acid at actual concentrations of 2.12 mg (0.37 mg B)/L (highest attainable concentration) for 4 hours no deaths were observed (Wnorowski, 1997).

Studies in rats with disodium tetraborate decahydrate (Wnorowski, 1994a) and disodium tetraborate pentahydrate (Wnorowski, 1994b) revealed LC50's of >2.03 (0.23 mg B) and 2.04 mg (0.30 mg B)/L (2g/m3) respectively. Although no test was carried out on disodium tetraborate anhydrous, it can be assumed that this would also have low acute inhalation toxicity.

Table 5.2.2 Acute Inhalation Toxicity Studies

Route	Method Guideline	Species Strain Sex no/group	Dose levels duration of exposure	Value LD_{50} /LC_{50}	Remarks	Reference
Boric Acid						
Inhalation	OECD Guide-line 403 "Acute Inhalation Toxicity" (USEPA.FIFRA 40 CFR Part 160.	Rat : Sprague Dawley 5/group	Analytical concentration 2120 ±140 mg/m³ 4 hours	≥2120 mg (371 mg B)/m³		Wnorowski, (1997)
Disodium Tetraborate Anhydrous						
Read across to Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate						
Disodium Tetraborate Pentahydrate						
Inhalation	OECD 403	Rat: Sprague Dawley 5/group	2g/m³ nominal 4 Hours	>2.04.mg (0.30 mg B)/L (2g/m³)		Wnorowski, (1994 b)
Disodium Tetraborate Decahydrate						
Inhalation	OECD 403	Rat : Sprague Dawley 5/group	2g/m³ nominal 4 Hours	>2.03.mg 0.23 mg B)/L (2g/m³)		Wnorowski, (1994a),

5.2.3 Acute toxicity: dermal

Studies in animals

The acute dermal toxicity of borates is low, being >2000 mg/kg bw for all borates tested. Although no test was carried out on disodium tetraborate anhydrous, it can be assumed that this would also have low acute dermal toxicity.

Table 5.2.3 Acute Dermal Toxicity Studies

Route	Method Guideline	Species Strain Sex no/group	Dose levels duration of exposure	Value LD_{50} /LC_{50}	Remarks	Reference
Boric Acid						
Dermal	FIFRA (40 CFR 163) Acceptable protocol at the time	Rabbits; New Zealand White 5/group	Dosage to 2 g/kg bw: 24 hours	≥ 2 g/kg bw (0.35 g B/kg)		Weiner et al.,. (1982).
Disodium Tetraborate Anhydrous						
Read across to Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate						
Disodium Tetraborate Pentahydrate						
Dermal	[1]US EPA-FIFRA guidelines	Rabbits; New Zealand White 5/group	2000 mg/kg bw	>2000 mg/kg bw (296 mg B/kg)		Reagan and Becci, 1985b
Disodium Tetraborate Decahydrate						
Dermal	[1]US EPA-FIFRA guidelines	Rabbits; New Zealand White 5/group	2000 mg/kg bw	>2000 mg/kg bw (226 mg B/kg)		Reagan and Becci, 1985c

[1] This study was carried out to comply with US EPA-FIFRA guidelines at the time and carried out by the US Food and Drug Laboratories to GLP. Although it is not to modern protocols the data is consistent with other borate data and further testing is not warranted in the interests of animal welfare and protecting laboratory animals

5.2.4 Acute toxicity: other routes

Studies in animals

The acute intravenous LD_{50} s of a 5 % aqueous solution of boric acid were 1.78 g/kg and 1.33 g/kg in mice and rats respectively and the subcutaneous LD_{50} s were 2.07 g/kg and 1.2 g/kg for mice and guinea pigs respectively (Pfeiffer et al., 1945).

5.2.5 Summary and discussion of acute toxicity

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are of low acute toxicity. Although the acute oral studies were not of modern standards and were performed prior to the introduction of GLP, they are reproducible across a number of studies and species and of acceptable quality. For acute dermal and acute inhalation some studies do meet the modern GLP standard. For all the borates the acute toxicity results are: LD_{50} oral rat > 2000 mg/kg; LD_{50} dermal rat > 2000 mg/kg; LC_{50} inhalation rat > 2 mg/l.

Table 5.2.5 Summary of Acute Toxicity Data

Route	Value LD_{50} /LC_{50}	Reference
Boric Acid		
Oral	3765 (2660 – 4100) mg/kg	Keller 1962; Weir & Fisher, 1972; Pfeiffer et al., 1945
Dermal	≥ 2 g/kg bw	Weiner et al., (1982).
Inhalation	≥2120 mg/m³	Wnorowski, 1997
Disodium Tetraborate Anhydrous		
Oral	> 2500 mg/kg bw males	Denton, (1995).
Dermal	>2000 mg/kg bw	Read across from Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate
Inhalation	>2.mg/L (2g/m³)	
Disodium Tetraborate Pentahydrate		
Oral	3305 (2403 - 4207) mg/kg	Reagan and Becci (1985a)
Dermal	>2000 mg/kg bw	Reagan and Becci, (1985b)
Inhalation	>2.04.mg/L (2g/m³)	Wnorowski, , (1994 a)
Disodium Tetraborate Decahydrate		
Oral	5560 (5150 - 6000) mg/kg	Meyding and Foglhian (1961),
Dermal	>2000 mg/kg bw	Reagan and Becci, 1985c
Inhalation	>2.03.mg/L (2g/m³)	Wnorowski, (1994b),

No classification is indicated under the current EU guidelines (67/548/EEC). However under the GHS guidelines, both boric acid and disodium tetraborate pentahydrate would be classified as Acute Oral Toxicity Category 5. In addition, the data on disodium tetrahydrate anhydrous, which indicated deaths at 2000 mg (430 mg B)/kg bw (2/5 in one study and 4/5 in another study) would suggest that Acute Oral Toxicity Category 5 under GHS classification.

5.3 Irritation

5.3.1 Skin

Studies in animals

In a study in rabbits, boric acid did not cause skin irritation when applied to the intact or abraded skin at a dose of 0.5 g. Similarly, in studies in rabbits, sodium tetraborate decahydrate (Reagan and Becci, 1985e) and sodium tetraborate pentahydrate (Reagan and Becci, 1985d) did not cause skin irritation at doses of 0.5 g. In an earlier study in white rabbits, 5 ml of 10% boric acid (w/v) in water applied to abraded skin demonstrated very mild irritation with a primary irritation score of 2.5. In the same study, 10 ml of 5% borax (Disodium Tetraborate Decahydrate) in water (w/v) resulted in very mild irritation with a primary irritation score of 2.3. However, in the same study in Guinea pigs, neither boric acid nor borax was irritating when applied on abraded skin, with primary irritation scores less than 2 (Roudabush 1964). Although no test was carried out on disodium tetraborate anhydrous, it can be assumed that this would also not cause skin irritation.

Boric acid and disodium tetraborate decahydrate are used at concentrations of 5% in cosmetics in the US and in talc in Europe, up to 3% in other cosmetics in Europe and up to 0.5% in oral hygiene products in Europe and elsewhere (Beyer et al., 1983; EC, 2000).

Table 5.3.1 Skin Irritation Data

Species	Method	Average score 24, 48, 72 h		Reversibility yes/no	Result	Reference
		Erythema	Edema			
Boric Acid						
White Rabbits	21 CFR 191.11				PII 2.5 Mildly Irritating Abraded Skin	Roudabush et al. (1964)
Rabbits; New Zealand White	FIFRA (40 CFR 163) Acceptable protocol at the time	0.105	0	yes	Non irritant	Weiner et al. (1982).
Disodium Tetraborate Anhydrous						
Read across from Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate – Non Irritant						
Disodium Tetraborate Pentahydrate						
Rabbit	[1]US EPA-FIFRA guidelines	0	0		Non Irritant	Reagan and Becci, (1985d)
Disodium Tetraborate Decahydrate						
White Rabbits	21 CFR 191.11				PII 2.3 Mildly Irritating Abraded Skin	Roudabush et al. (1964)
Rabbit	[1]US EPA-FIFRA guidelines	0	0		Non Irritant	Reagan and. Becci (1985e),

[1] This study was carried out to comply with US EPA-FIFRA guidelines at the time and carried out by the US Food and Drug Laboratories to GLP. Although it is not to modern protocols the data is consistent with other borate data and further testing is not warranted in the interests of animal welfare and protecting laboratory animals

5.3.2 Eye

Studies in animals

Boric Acid

Boric acid induced conjunctivae redness and chemosis and minor effects on the iris. The effects were reversible within 7 days. (Doyle, 1989a)

Table 5.3.2 -1 Eye irritation Boric Acid

Species	Method	Average Score				Result	Reversibility yes/no	Reference
		Cornea	Iris	Conjunctiva				
				Redness	Chemosis			
Rabbits; New Zealand White	FIFRA (40 CFR 158, 162); TSCA (40 CFR 798).	0.00	0.11	0.94	0.56	Non irritant	Yes	Doyle, 1989a

Disodium Tetraborate Pentahydrate
A number of eye irritancy studies have been carried on disodium tetraborate pentahydrate (Reagan and Becci, 1985f, Wnorowski, 1996 and Cerven, 2000), which involved testing various batches of substance and under varying conditions, all indicating eye irritation. However the key study was carried out at the request of the US EPA to confirm that the eye irritation previously seen was caused by the glassy nature of the crystals of substance and not a chemical effect of irritation (Cerven, 2000). To confirm this, the sample was ground to a fine powder before instillation to reduce the glassy, sharp crystals in the sample (0.08 ml dosed). As a result for this study the US EPA accepted that the effects were mechanical downgraded its classification according to US FIFRA to Toxicity II (40 CFR 156) by ocular administration (Corneal involvement or irritation clearing in 8-21 days).

Disodium Tetraborate Decahydrate
Two studies have been carried out both indicating eye irritancy (Reagan and Becci, 1985g; Doyle, 1989b). In the second study, regarded as the key study the sample was ground to a fine powder to reduce the glassy, sharp crystals in the sample.

Disodium Tetraborate Anhydrous
While no data has been obtained for disodium tetraborate anhydrous, it can be assumed that it should be an eye irritant based on the data obtained with the hydrated disodium tetraborates.

Table 5.3.2 -2 Eye irritation Data: Disodium Tetraborates

Species	Method	Average Score				Result	Reversibility yes/no	Reference
		Cornea	Iris	Conjunctiva				
				Redness	Chemosis			
Disodium Tetraborate Anhydrous								
Read across from Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate – Irritant								
Disodium Tetraborate Pentahydrate								
Rabbit	FIFRA (40 CFR 158, 430); EPA OPPTS 870.2400	0.22	0.22	2.8	1.89	Irritant	Yes	Cerven, (2000).
Disodium Tetraborate Decahydrate								
Rabbit	FIFRA (40 CFR 158, 162); TSCA (40 CFR 798).	0.72	0.61	1.70	2.11	Irritant	Yes	Doyle, (1989b)

Studies in humans

Disodium tetraborate decahydrate and disodium tetraborate pentahydrate are used as a buffer in eyewashes. In addition, in normal handling and use the large glassy crystals would not be able to enter the eye easily and in addition over 50 years of occupational exposure to all borate has indicated no adverse effects on the human eye.

5.3.3 Respiratory tract

Studies in animals

There is no data from animal studies on boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate that indicated respiratory irritation.

Studies in humans

Some older studies on workers exposed occupationally to borax dust reported eye irritation, dry mouth, nose or throat, sore throat and productive cough (reported in Garabrant et al.1984, 1985). However there were severe imitations to this data.

1) There is no indication of the temporal relationship between when a symptom was experienced and when the questionnaire was administered. It could have been days, weeks or months. Recall reliability can be in doubt.
2) There is no assurance that the time when air samples were taken was relevant to the time symptoms were experienced. In the information on boric acid, the eight air samples upon which irritant effects were assessed had been collected in a plant that was no longer in existence at the time the symptom study was done.
3) Air samples were not obtained for epidemiological analysis and cannot be relied upon to represent exposure of a group of workers.
4) And even though the air samples were obtained for the purpose of representing exposure of a group of workers, there were too few (probably less than 6) to provide statistical power.
5) The air samples used in the study may represent dust, but give no information about borate exposure.
6) The respiratory irritation and complaints of dryness of mouth, nose and mouth and eye irritation are hardly surprising from a group involved in physical exertion in the high desert environment of the Mojave Desert.
7) The fact that workers could tolerate the full shift extreme exposure levels reported by NIOSH casts doubt on the irritant characteristics of borates.

To investigate these claims further, a field study by Wegman and associates sought to establish a relationship between level of exposure to borates and various acute symptoms, including irritation, during routine industrial activities (Eisen, et al, 1991; Hui et al, 1992; Hu et al, 1992; Wegman et al, 1994; Woskie et al, 1994). In addition to the use of hourly surveys, subjects were provided a means of adding a mark to the exposure monitor each time they experienced an acute irritant symptom. A personal direct-reading aerosol monitor (the MINIRAM, Miniature Real-time Aerosol Monitor) was used in conjunction with a datalogger system. This device permitted each subject to record the actual time of symptom onset. At the hourly survey, the technician would ask whether the marker had been used, and if so, for what symptom. Only mild respiratory effects were reported that included nasal, eye and throat irritation, cough and breathlessness (Wegman et al, 1994). Wegman and associates also found that smokers reported symptoms less frequently than non-smokers and old workers less frequently than younger workers. Concerning respiratory irritations among exposed workers, non-smokers had higher rate ratios than smokers for nasal and eye irritation, and lower ratios for throat irritations, cough, and breathlessness. Reduction of forced expiratory volume 1 sec (FEV1) among smokers who had heavy cumulative sodium borate exposure (≥80 mg/m3-year), but not among less-exposed smokers and non-smokers (Wegman, 1994). However, the study design introduces bias as the workers clearly are aware that they are working with borates and the fact that a study is being carried out would tend to make them more vigilant and over interpret symptoms that may just be due to physical effects of the dust. The findings indicated that an exposure response relationship was present for investigated symptoms. Of the 2490 reporting periods, there were 136 cases where both the button was pressed and the severity recorded by the technician. In these cases, the exposures were not different from the other 2086 cases when neither the button was pressed nor the severity recorded. This indicates that there was no real irritant effect. Other confounding factors acknowledged by Wegman et al., 1994, are that the severity scale had not been used on other irritant-exposure environments and that true sensory irritants increase in severity rapidly with increasing exposure levels which did not occur in this study. The reported irritation increased only to mild levels and did not increase at all with additional exposure, indicating that the borate dust is not a sensory irritant. The results more closely resembled the expected effects associated with an inert dust. The data indicates that the effects that the workers identified were ‘chemesthetic’ i.e. the feel of dusts on the sensory system and do not denote specific chemical irritancy at normal exposures.

Chronic effects of sodium borate particulate exposures were examined by pulmonary function at the beginning and end of a 7-year study period. No association was found between the FEV_1 and sodium borate exposure (Wegman et al., 1994).

An approach to determine more precisely the acceptable exposure limits based on measurement of responses of 12 male volunteers to measured amounts of various dusts was investigated by Cain et al;., 2004) in a human study in which the sensory perception of dusts of sodium tetraborate pentahydrate (Na2B4O7·5H2O), calcium sulphate (CaSO4), and calcium oxide (CaO) was investigated. The study was designed to investigate the chemesthetic feel of sodium tetraborate pentahydrate and to help determine, if possible, where the continuum from ill defined feel through to irritation occurs. Twelve subjects were exposed to 5, 10, 20, 30 and 40 mg/m^3 sodium tetraborate pentahydrate dust particles for 20 min while performing moderate exercise (i.e., riding an exercise bike set at a load of 60 watts). Exposure to carbon dioxide vapour was used to set a reference scale for subjects to judge the feel of the stimulus materials. During exposure, subjects judged level of feel or irritation in the eye, nose, and throat (nasopharynx) at 5-min intervals. The subjects indicated the absence of any feel or irritation by a judgement of zero. At the intervals indicated, heart rate, oxygen saturation, minute ventilation and respiration rate were recorded as well. The level of effect was not significant irritancy and most likely due to the physical exposure to a dust rather than a specific chemical effect. The results indicated no significant respiratory effects at 14 -15 mg/m^3 sodium borate (Cain et al., 2004). This level would also be protective for ocular irritation. This value would also be compatible with the previously published results of the field studies on borate workers by Wegman and colleagues. Therefore the data supports a limit of 10 mg/m^3 (the general nuisance level) for all borates. A further study has been carried out on boric acid which reinforces these results (Cain et al., 2007).

5.3.4 Summary and discussion of irritation

Skin Irritation

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not skin irritants. Moreover boric acid and disodium tetraborate decahydrate are used at concentrations of 5% in cosmetics in the US and in talc in Europe, up to 3% in other cosmetics in Europe (Beyer et al., 1983; EC, 2000).

Eye Irritation

Boric acid induced conjunctivae redness and chemosis and minor effects on the iris. The effects were reversible within 7 days.

No classification is indicated under the current EU guidelines (67/548/EEC) or under the GHS guidelines.

Both disodium tetraborate decahydrate and disodium tetraborate pentahydrate induced eye irritation. This could be due to the glassy crystalline nature of these compounds however it is not possible to exclude eye irritation is the result of a non mechanical action.

Disodium tetraborate pentahydrate is classified as an eye irritant R36 current EU guidelines (67/548/EEC) is indicated by the conjunctivae redness and oedema in two out of three animals and under GHS as Category 2A Irritating to eyes, based on redness >2.0 and also Oedema >2 reversible in 14 days.

Disodium tetraborate decahydrate is classified as an eye irritant; R36 under current EU guidelines (67/548/EEC) is indicated by the iris and conjunctivae oedema and under GHS as Category 2A Irritating to eyes, based on iris**,** conjunctivae redness and oedema which does not reverse by 7 days.

Based on read across from disodium tetraborate pentahydrate and disodium tetraborate decahydrate, disodium tetraborate anhydrous is also classified as an eye irritant R36 current EU guidelines (67/548/EEC) under GHS as Category 2A Irritating to Eyes.

It should be noted that disodium tetraborates are used in eye washes up to 5 % (Beyer 1983).

Respiratory tract

No classification is necessary under the current EU guidelines (67/548/EEC) and under the GHS guidelines.

The effects observed do not constitute a ‘serious irritation to the respiratory tract’. In the later studies (Hui et al., 1992; Hu et al., 1992; Wegman et al, 1994) the workers reported minor effects on the nose and throat and to a lesser extent the eye. The number of workers affected was very low; there were a number of confounding factors in the study and the data cannot be substantiated or related to a specific dose in controlled studies. No effects on lung function were observed. The data indicates that the effects that the workers identified were ‘chemesthetic’ i.e. the feel of dusts on the sensory system and do not denote specific chemical irritancy at normal exposures. This was reinforced in the Cain

study (Cain et al 2004; 2007) where the level of effect was not significant irritancy and most likely due to the physical exposure to a dust rather than a specific chemical effect with no significant respiratory effects at 14-15 mg/m3 sodium borate.

The conclusions for both the studies indicate that the effects noticed cannot specifically be attributed to an irritant effect based on the chemical nature of the borate tested. The level of effect was not significant irritancy. Moreover, under normal handing and use conditions the effects were not really apparent and do not constitute irritant effects. The effects are most likely due to the physical exposure to a dust rather than a specific chemical effect. Therefore the available evidence does not support classification as R37.

Under GHS, respiratory irritants are included Cat. 3 Specific Target Organ/Systemic Toxicity (Single Exposure, STOT) that is specially designed for Transient Target organ effects. The effects observed in the human studies do not fulfil the criteria for a respiratory irritant under GHS[1]. The effects observed do no impair function, and they are not accompanied by serious symptoms and later studies indicate no effect on lung function. Therefore no classification under GHS is necessary.

5.4 Corrosivity

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not corrosive.

5.5 Sensitisation

5.5.1 Skin

Studies in animals

Boric acid, disodium tetraborate decahydrate and disodium tetraborate pentahydrate were tested in a Buehler method skin sensitisation test (Wnorowski, 1994 e, f, g). They were applied at a concentration of 95% (powder moistened with water) during both the induction and challenge phase of the test. No signs of skin sensitisation were observed.

Studies in humans

The data indicate that these borates are not sensitisers. In addition there is no evidence of skin sensitisation in humans exposed occupationally to borates has been reported (Bruze et al., 1995).

Table 5.6.1 Sensitisation Data

Active substance	Species	Method	Number of animals sensitised/total number of animals	Result	Reference
Boric Acid	Guinea Pig	Buehler Test OECD Guide-line 406 "Skin Sensitisation"	0	Non sensitiser	Wnorowski, (1994e),
Disodium Tetraborate	Read across from Disodium Tetraborate Pentahydrate and Disodium Tetraborate Decahydrate – Non				

[1] *GHS Rev1 2005 guidelines 3.8.2.2.1 Criteria for respiratory tract irritation*
The criteria for respiratory tract irritation as Category 3 are:
(a) Respiratory irritant effects (characterized by localized redness, edema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. It is recognized that this evaluation is based primarily on human data;
(b) Subjective human observations could be supported by objective measurements of clear respiratory tract irritation (RTI) (e.g. electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids;
(c) The symptoms observed in humans should also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of "irritation" should be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of this classification endpoint;

Anhydrous	sensitiser				
Disodium tetraborate pentahydrate	Guinea Pig	Buehler Test OECD Guide-line 406 "Skin Sensitisation"	0	Non sensitiser	Wnorowski, (1994f),
Disodium tetraborate decahydrate	Guinea Pig	Buehler Test OECD Guide-line 406 "Skin Sensitisation"	0	Non sensitiser	Wnorowski, (1994g),

5.5.2 Respiratory system

There is no data to suggest that boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are respiratory sensitisers.

5.5.3 Summary and discussion of sensitisation

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are neither skin nor respiratory sensitisers.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

Studies in animals

A number of repeated dose studies in which rats were fed boric acid or disodium tetraborate decahydrate in their diet or drinking water for periods of 70 - 90 days indicated that the main target organ for toxicity is the testis. (e.g. Dixon et al, 1976; Seal and Weeth, 1980; Lee et al., 1978; Treinen and Chapin, 1991; Ku et al., 1993; Weir & Fisher, 1972; NTP, 1987). In some case the studies are research studies, but all support that the main target organ as the testis.

Other clinical effects were observed in sub chronic studies include 90 days studies in rats, mice and dogs, as well as testicular effects which are further described in 5.9.1 Effects on Fertility.

In a 90 day study in rats of disodium tetraborate decahydrate administered in drinking water, no biologically significant reduction in body or organ weights, clinical chemistry or FSH and LH levels were found, with a NOAEL of 0.84 mg B/kg bw/d (Dixon et al, 1976). Reduced body weight, reduced testes weight, and spermatogenesis were impaired at 47 mg b/kg bw/d, LOAEL of mg B/kg bw/d in a 70 day study of disodium tetraborate decahydrate administered in drinking water (Seal and Weeth 1980).

Although not conforming to modern protocols, data on other effects can be obtained from a 90 day study in rats fed 0, 52.5, 175, 525, 1750, 5250 ppm equivalent boron (as boric acid) equal to 0, 2.6, 8.8, 26, 88 and 260 mg B/kg bw/day. All the animals in the top dose died by week 6. Animals at the top two doses displayed rapid respiration, hunched position, bloody nasal discharge, urine stains on the abdomen, inflamed eyes, desquamation and swollen paws and tail. These animals exhibited reduced food consumption and body weight gain. At 1750 ppm, in females, reduced weight for livers, spleens and ovaries were observed, while for males only the kidney and adrenal weights were reduced. The adrenals in 4 males at 1750 ppm displayed minor increases in lipid content and size of the cells in the zona reticularis. All the male rats at 1750 ppm had atrophied testis a histologically complete atrophy of the spermatogenic epithelium and a decrease in the size of the seminiferous tubules. One male at 525 ppm exhibited partial testicular atrophy. However, no effects were observed at this dose in a 90 day study in rats on disodium tetraborate decahydrate and in subsequent two years studies. The NOAEL was determined to be 26 mg B/kg bw/day. (Weir 1962; 1963; Weir and Fisher, 1972).

In a mouse study carried out for 13 or 16 weeks, mice were fed diets containing 0,1200, 2500, 5000, 10000, 20000 ppm boric acid, equivalent to 0, 194 (34), 405 (71), 811 (142), 1622 (284), 3246 (568) mg boric acid (mg B)/day males and 0, 169 (47), 560 (98), 1120 (196), 2240 (392), 4480 (784) mg boric acid (mg B)/day females. At the highest dose level

(20000 ppm) 8/10 males and 6/10 females died and 1/10 males from the 10000 ppm group died before end of study. Symptoms included nervousness, haunched appearance, dehydration, foot lesions and scaly tails. A reduction in mean bodyweights was observed in the 5000, 10000 and 20000 ppm groups. Incidences of extra medullary haematopoiesis of spleen observed of minimal to mild severity in all dose groups for both males and females and hyperkeratosis and/or acanthosis of the stomach observed at the highest dose only in both males and females. In the absence of any haematology data there is no direct evidence of anaemia and the effect is only minimal to mild. In addition extramedullary haematopoiesis of the spleen occurs naturally in mice. At doses > 5,000 ppm (142 mg B/kg bw for the male), degeneration or atrophy of the seminiferous tubules was observed (NTP 1987).

The 90 day dogs studies on both boric acid and disodium tetraborate decahydrate are of limited value and considered inadequate for risk assessment of the effects on fertility although they provide support for the target organ being the testis (see section 5.9.1. and Annex 1). Dogs were dosed with dietary levels of 0, 0.01, 0.1, 1.0% boric acid equivalent to 0, 0.4, 4.4, and 33 mg B/kg/day and 0, 0.0154, 0.154, 1.54% disodium tetraborate decahydrate equivalent to of 0, 0.4, 4.1, and 38 mg B/kg/day, based on the actual body weight and food consumption data in the study (Paynter, 1963 a;b; Weir & Fisher, 1972). Apart from the death of one dog in the high dose group of the disodium tetraborate decahydrate study, which may not be attributable to the substance, and testicular atrophy, no other clinical signs apart from minor haematological effects were observed. A small decrease in haematocrit and haemoglobin values was seen in the highest does groups, but all the clinical laboratory findings from blood and urine samples were within normal limits and comparable to controls. A slight degree of splenic extramedullary haematopoiesis was also observed, which was also seen in the controls. The authors proposed that the stimulus to frequent withdrawal of blood for examination may have linked to the heamatopoiesis. Hemosiderin was also present in reticular cell of the liver and spleen and the proximal tubule of the kidney. No statistical evaluation was carried out on any of the data. These effects are not considered significant due to (1) the varied nature of the observations, (2) the known flaws in the study (see Annex 1) and (3) the findings of Muller et al, 2006 that small effects on haematological parameters in the absence of other clinical findings do not lead to a conclusion this is a significant effect. The authors themselves were not sure of the significance of the findings.

Long term chronic feeding studies have been carried out on boric acid and/or disodium tetraborate decahydrate in mice, rats and dogs. Testicular atrophy with some interstitial cell hyperplasia was the critical effect seen in a US National Toxicology Program (NTP) bioassay in mice fed 0, 2500, 5000 ppm in food equivalent to 0, 446 and 1150 mg boric acid/kg bw/d. Splenic extramedullary haematopoiesis occurs naturally in mice. An incidence was reported in males as 3/48, 11/49, 10/48, and in females 10/49, 11/34, 7/50 in the control, low- and high-dose groups, respectively. There is no other mention or discussion about extramedullary haematopoiesis in the rest of the report, so it was not regarded as an important finding (NTP, 1987).

In 2 year oral toxicity studies in dogs for both boric acid and disodium tetraborate decahydrate the testes were identified as a major target organ. These studies had major deficiencies and are inadequate for risk assessment, but do confirm the effects seen in other species. Dogs were fed 0, 0.033, 0.067, 0.20, 0.67% boric acid equivalent to 0, 1.7, 3.8, 10.9, and 41 mg B/kg/day and 0, 0.051, 0.103, 0.309, 1.03% disodium tetraborate decahydrate equivalent to 0, 1.9, 3.6, 9.6, and 38 mg B/kg/day, based on the actual body weight and food consumption data in the study. No significant clinical findings were observed (Weir and Fisher, 1966 e;f; 1967 a,b). These studies are further discussed in section 5.9.1 – Effects on Fertility.

In a 2 year feeding study in rats again on boric acid and disodium tetraborate decahydrate the testes were identified as a major target organ (Weir, 1966a;b). Rats were dosed with , 0; 670 (117); 2000 (350); 6690 (1170) ppm boric acid (boron equivalents) equivalent to 0, 33 (5.9), 100 (17.5), 334 (58.5) mg boric acid (B)/kg bw per day and 0, 1030 (117), 3080 (350), 10300 (1170) ppm disodium tetraborate decahydrate (as boron equivalents) equivalent to 0, 52 (5.9), 155 (17.5) , 516(58.5)mg borax/kg/day or 0, 5.9, 17.5 or 58.5 mg B/kg/day. Clinical signs included coarse hair coats, hunched position, and inflamed bleeding eyes; desquamation of the skin of the tail and the pads of the paws which were also swollen; marked respiratory involvement, shrunken appearance of the scrotum were observed in all males of the high dose group. In addition a reduction in body weight was observer in males and females in the high dose group accompanied by decreased food consumption.

With boric acid significantly decreased red cell volume and haemoglobin were observed in the high dose group males with occasional, significant reductions in these parameters were in males of the low- and mid-dose groups. Similar results were observed with disodium tetraborate decahydrate at many intervals during the study which were occasionally different from the control and the low and intermediate test groups, but are not considered meaningful due to the inconsistencies of occurrence and lack of dose effect trend. However these are not regarded as treatment related as indicated in the Muller et al, 2006; that small effects on haematological parameters in the absence of other clinical

findings and do not constitute a serious effect. In addition, since only 5 animals per group were sampled the statistical power is low.

Testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months at the highest dose level with both boric acid and disodium tetraborate decahydrate. Microscopic examination of the tissue revealed atrophied seminiferous epithelium and decreased tubular size in the testes. No effects were observed in the in the control and low dose groups.

Based on the clinical effects and the testicular atrophy observed at the highest doses tested (6690 ppm boric acid, equivalent to 334 (58.5) mg boric acid (B)/kg bw per day and 10300 ppm (equivalent to borax intake of 516 (58.5) mg disodium tetraborate decahydrate (B) /kg bw/day) the NOAEL for the effects of boron is 17.5 mg B/kg bw/day (equivalent to 100mg boric acid or 155 mg disodium tetraborate decahydrate/kg bw/day).

Studies in humans

In humans multiple exposures (high levels > 1g) results in various symptoms which may appear singly or together and include dermatitis, alopecia, loss of appetite, nausea, vomiting, diarrhoea, and focal or generalised central nervous system irritation or convulsions. Much data comes from the mid 1800s to around 1940, when boric acid and disodium tetraborate decahydrate were used systematically for a variety of medical conditions including amenorrhea, malaria, epilepsy, urinary tract infection and exudative pleuritis (Kliegel, 1980). Daily oral doses in adults ranged from 1-14 g per day. Repeated doses in the 6 10 g/day range were given for as long as several weeks. In one extreme case a 28 year old women ingested around 0.5 g of boric acid (in baby powder) every day for two years and suffered anaemia, which reversed on ceasing ingestion (Adelhardt and Fogh, 1983). Doses greater than 3 –5 g/day regularly caused vomiting and/or diarrhoea in the first instance often accompanied by dermatitis and appetite suppression. As the dose became higher and the dosing period longer, symptoms included alopecia, disseminated maculopapular eruption followed by widespread desquamation, focal or generalised central nervous system irritation, and convulsions. The symptoms of dermatitis, nausea, diarrhoea and vomiting symptoms also occurred in some patients receiving doses of 2 g boric acid/day (29 mg boric acid/kg/day) and above. In one such case, reduction of the dose from 2 g/day of boric (29 mg boric acid/kg/day) acid to 1g/day (14 mg boric acid/kg/day) resulted in resolution of the effects (vomiting and dermatitis). In all cases where withdrawal of treatment was reported, recovery occurred with no lasting effects. The lowest recorded adult dose causing symptoms was 2 g/day boric acid (Kliegel, 1980).

In children, where low levels can be estimated (Gordon et al, 1973 and O'Sullivan and Taylor, 1983), infants aged from 6 to 19.5 weeks ingested borax (as a honey-borax mixture which had been applied to pacifiers) for periods of 4 to 12 weeks. The mean intake was 0.98 g boric acid/day (range 0.55g to 2 g) for a 10 kg child. The effects seen, which disappeared on withdrawal of the honey borax mixture, relate to effects on CNS such as convulsions, generalised seizures and focal seizures. There were no dermal effects. Minor occurrences of vomiting and loose stools were also described.

Table 5.6.1-1 Key Repeated dose toxicity studies

Route	duration of study	Species Strain Sex no/group	dose levels frequency of application	Results	LO(A)EL	NO(A)EL	Reference
Boric Acid							
Oral in diet	13 weeks for control and top dose group, 16 weeks for other dose groups	Mouse, B6C3F1 10/sex/ group	0, 1200, 2500, 5000, 10000, 20000 ppm of boric acid. Equivalent to 0, 194 (34), 405 (71), 811 (142), 1622 (284), 3246 (568) mg boric acid (mg B)/kg bw/day males; and 0, 169 (47), 560 (98), 1120 (196), 2240 (392), 4480 (784) mg boric acid (mg B)/kg bw per day females. 5 days/week	At ≥ 5000 ppm: degeneration and atrophy of the seminiferous tubules was observed. At all dose levels extra medullary haematopoiesis of the spleen, but in the absence of any haematology and natural occurrence in mice, not considered serious	5000 ppm equivalent to 811 *mg boric acid/kg bw(≥ 142mg B/kg bw*	2500 ppm, equivalent to 405(71) mg boric acid(B)/kg bw/day	National Toxicology Program (NTP) Technical Report Series No. 324, 1987

Oral in diet	90 days	Rat Sprague Dawley Treatment: 10/sex/group	0, 52.5, 175, 525, 1750, 5250 ppm equivalent boron; 2.6, 8.8, 26, 88 and 260 mg B/kg bw/d.	At ≥ 1750 ppm: Reduction bodyweight; clinical sign of toxicity; testicular atrophy, extramedullary haematopoiesis, reductions in red cell volume and Hb	1750 ppm, equal to 88 mg B/kg bw/day	525 ppm, equal to 26 mg B/kg bw/day	Weir, 1962
Oral in diet	2 year, interim kills at 6 and 12 months	Rat Sprague Dawley controls: 70/sex Treatment: 35/sex/group Interim kills with 5/sex/group	0, 670, 2000, 6690 ppm, equivalent to 0, 33 (5.9), 100 (17.5), 334 (58.5) mg boric acid (B)/kg bw/day	6690 ppm: Reduction bodyweight; clinical sign of toxicity; in males testicular atrophy and reductions in red cell volume and Hb	6690ppm, equivalent to 334(58.5) mg boric acid (B)/kg bw/day	2000 ppm equivalent to 100 (17.5) boric acid (B)/kg bw/day	Weir, 1966a
Disodium tetraborate decahydrate							
Oral in diet	2 years	Rat, Sprague Dawley male and female 70/sex/ group in controls; 35/sex/group treated	Disodium tetraborate decahydrate: 0, 1030, 3080, 10300 ppm, equivalent to 0, 52, 155, 516 mg borax/kg/day or 0, 5.9, 17.5 or 58.5 mg B/kg/day	10300 ppm: Reduction bodyweight; clinical signs of toxicity; reductions in red cell volume and Hb; testicular atrophy	10300 ppm, equivalent to 516 (58.5) mg disodium tetraborate decahydrate (B)/kg bw	3080 ppm, equivalent to 155 (17.5) mg disodium tetraborate decahydrate (B)/kg bw.	Weir, 1966 b.

5.6.2 Repeated dose toxicity: inhalation

No data on boric acid or the disodium tetraborates

5.6.3 Repeated dose toxicity: dermal

No data on boric acid or the disodium tetraborates

5.6.4 Other relevant information

5.6.5 Summary and discussion of repeated dose toxicity:

A number of studies in which rats were fed boric acid or disodium tetraborate decahydrate in their diet or drinking water for periods of 70 days to two years in rats, mice and dogs indicated that the main target organ for toxicity is the testis. Other effects observed at high doses include rapid respiration, hunched position, bloody nasal discharge; urine stains on the abdomen, inflamed bleeding eyes, desquamation and swollen paws and tail, reduced food consumption and body weight gain. Boric acid induced testicular atrophy and minor haematological effects. The minor haematological findings observed are not regarded as serious treatment related effects. As indicated in Muller et al, 2006, the small effects on haematological parameters in the absence of other clinical findings and do not constitute a serious effect and do not impact on the determination of the NOAEL.

Based on the clinical effects and the testicular atrophy the lowest NOAEL for the effects of boron is 17.5 mg B/kg bw/day (equivalent to 100mg boric acid or 155 mg disodium tetraborate decahydrate/kg bw/day).

5.7 Mutagenicity

5.7.1 In vitro data

A number of *in vitro* mutagenicity studies, including bacterial mutation assays in *Salmonella typhimurium* and *Escherichia coli*, gene mutation in mammalian cells (L5178Y mouse lymphoma, V79 Chinese hamster cells, C3H/10T1/2 cells), bacterial DNA-damage assay, unscheduled DNA synthesis (hepatocytes), chromosomal aberration and sister chromatid exchange in mammalian cell (Chinese hamster ovary, CHO cells) have been carried out on boric acid and one study on disodium tetraborate decahydrate. No evidence of mutagenic activity was observed (NTP, 1987; Haworth et al., 1983; Landolph, 1985; Bakke, 1991; Stewart, 1991).

Table 5.8.1 Key In Vitro Mutagenicity data with boric acid

Test system Method Guideline	organism/ strain(s)	concentrations tested (give range)	Result		Remark give information on cytotoxicity and other	Reference
			+ S9	- S9		
US EPA 40 CRF Part 158; FIFRA, Section 158.340, Guideline 84-2. Comparable to OECD 471	S. typhimurium: TA 1535, TA 1537, TA 97, TA 98, TA 100, TA 1538	10; 50; 100; 1000; 2500 µg/plate	-	-		Stewart, 1991,
40 CFR Part 158 US-EPA-FIFRA, Section 156.340; Complies with OECD 476	Mouse lymphoma L5178Y cells	0, 1.2, 1.7, 2.45, 3.5, and 5.0 mg/ml boric acid	-	-	Concentration related cytoxicity (60% reduction over controls at 5 mg/m)l	Rudd, 1991
1985; NTP protocol. resembles OECD 473	Chinese hamster Ovary (CHO)	With S9: 1000;1600;2000; 2500 µg/ml Without S9: 500; 1500; 2000 µg/ml	-	-		National Toxicology Program (NTP).1987

5.7.2 In vivo data

No mutagenic activity was seen *in vivo* in a mouse bone marrow micronucleus study on boric acid (O'Loughlin, 1991). Ten mice per sex per dosage group orally dosed with boric acid in sterile deionized water at dosage levels of 900, 1800 and 3500 mg/kg/day; which were considered to be the maximum practical doses that could be given. All boric acid treated groups, when compared to with the sterile deionized water control group, had micronucleus counts approximately equal to that of the negative control groups and did not differ statistically from controls at $p < 0.05$. Average micronucleus incidences in male and female mice treated with boric acid were 0.18% and 0.21%, respectively. Male and female mice treated with deionized water alone averaged background micronucleus incidences of 0.23% and 0.25%, respectively.

5.7.3 Human data

No data available

5.7.4 Other relevant information

No data available

5.7.5 Summary and discussion of Mutagenicity

All the data *in vitro* indicate no mutagenic activity. In addition the single *in vivo* study on boric acid also indicated no mutagenic activity.

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not mutagenic.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

Studies in animals

In long term feeding studies on boric acid and disodium tetraborate decahydrate in both rats and dogs, no carcinogenic effects were observed (Weir, 1966a,b; Weir and Fisher, 1972). Effects observed in the rat studies included lowered food consumption, retarded body weight gain, course hair coats, hunched position, swollen pads, inflamed bleeding eyes and changes in haematological parameters at the highest doses (58.5 mg B/kg bw/day). In the 2-year rat studies, only 10 animals/sex of the control and high-dose group were macroscopically and histologically examined. Animals in the low and mid-dose groups were not examined. Only 1-2 animals/sex/dose/time were examined in the 2-year studies in dogs, which limit the conclusions that can be made regarding carcinogenicity in dogs. Testicular effects were observed in both rats and dogs.

Testicular atrophy with some interstitial cell hyperplasia were the critical effects seen in a US National Toxicology Program (NTP) bioassay in mice fed 0, 2500, 5000 ppm in food equivalent to 0, 446 (75 mg B) and 1150 mg boric acid (200 mg B)/kg bw/d. Splenic extramedullary haematopoiesis occurs naturally in mice. An incidence was reported in males as 3/48, 11/49, 10/48, and in females 10/49, 11/34, 7/50 in the control, low- and high-dose groups, respectively. There is no other mention or discussion about extramedullary haematopoiesis in the rest of the report, so it was not regarded as an important finding.

No carcinogenic effects were observed at doses of boric acid of 75 mg B/kg bw/day and 200 mg B/kg bw/day (NTP, 1987). Effects on survival rate and reduced body weight gain were seen at the high doses. The testicular effects noted in these studies are discussed in more detail in Toxicity to Reproduction.

Table 5.9.1 Key Carcinogenicity study with Boric acid (mouse)

Route	Species Strain Sex no/group	dose levels frequency of application	Tumours	Reference
Oral in diet	Mouse B6C3F1 50/sex/group	0, 2500, 5000 ppm in food equivalent to 0, 446 (75 mg B) and 1150 mg boric acid (200 mg B)/kg bw/d 103 weeks	No evidence of carcinogenicity was found. At both doses: In males haematopoiesis in the spleen. Other effects in testes: At the high dose increased testicular atrophy and interstitial cell hyperplasia, variable loss of spermatogenia, and various stages of spermatogenesis from the seminiferous tubules.	National Toxicology Program (NTP) 1987.

5.8.2 Carcinogenicity: inhalation

No data

5.8.3 Carcinogenicity: dermal

No data

5.8.4 Carcinogenicity: human data

No data

5.8.5 Other relevant information

5.8.6 Summary and discussion of carcinogenicity

The studies carried out are not to modern standards, nor to GLP. In the 2-year rat studies, only 10 animals/sex of the control and high-dose group were macroscopically and histologically examined. Animals in the low and mid-dose groups were not examined. Only 1-2 animals/sex/dose/time were examined in the 2-year studies in dogs, which limit the conclusions that can be made regarding carcinogenicity in dogs. However, they are well performed and reported and are adequate to evaluate the carcinogenicity of boric acid and sodium borates. It can be concluded that that boric acid and sodium borates are not carcinogenic and there is no concern for a carcinogenic effects in humans.

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not carcinogenic.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

Studies in animals

Effects on the testis have been observed in both sub-chronic and chronic studies in three species: rats, mice and dogs. In rats, a single dose of 88 mg B/kg bw was found to cause reversible disruption of tubular spermiation (Linder et al., 1990), although no such effects were observed after a single dose of 350 mg B/kg (2000 mg boric acid/kg) (Bouissou and Castagnol, 1965). In the acute toxicity study by Bouissou and Castagnol, 250 pubescent male rats in groups of 50 were dosed at 1, 2, 3, 4 and 5 g boric acid/kg bw. No rats died in the 1 (175 mg B) and 2 g (350 mg B)/kg dose groups. After 130 days, all the surviving animals were able to breed. No histopathological examination was conducted on testes from the 1 (175 mg B) of 2 g boric acid (350 mg B)/kg treatment groups.

A comparison of the key NOAELs and LOAELs for reproduction studies is given in the Table 5.9.1.1. The effects tend to be similar in all three species, although most data comes from rat studies. The reproductive effects in rats at lower doses and shorter time periods start with reversible inhibition of spermiation. Inhibition of spermiation was already observed after 7 days of treatment with doses of 61 mg B/kg bw in the diet and after 28 days extreme epithelial disorganisation and sperm cell loss was evident (Treinen and Chapin, 1991). Early effects (severe inhibition of spermiation) were seen after 14 days treatment, at doses around 39 mg B/kg, (217 mg boric acid/kg bw/day), but at a lower dose of 26 mg B/kg (149 mg boric acid/kg bw/day) the effects seen by histopathological analysis including staging, take about 28 days to manifest (Ku et al., 1993). Effects were observed in rats 30 days after gavage treatment of boric acid at 35 and 140 mg B/kg bw, (Caujolle et al. 1962). In rat 90 day studies all the male rats at 1750 ppm B (88mg B/kg bw/day) had atrophied testis and histologically complete atrophy of the spermatogenic epithelium and a decrease in the size of the seminiferous tubules. One male at 525 ppm (26.3 mg B kg bw/day) exhibited partial testicular atrophy (Weir 1966a,b; 1963, Weir & Fisher, 1972).

Higher doses lead to testicular atrophy, degeneration of seminiferous tubules, reduced sperm count and a reduction in fertility (as indicated by no litters being produced) as seen in a three generation study of boric acid and disodium tetraborate decahydrate in rats at 58.5 mg B/kg bw/day (Weir, 1966c, d; Weir and Fisher, 1972). The NOAEL was 17.5 mg B/kg bw/day.

Similar results were seen in two-year rat studies of boric acid and disodium tetraborate decahydrate at 58.5 mg B/kg bw/day. (Weir 1966 a,b; Weir and Fisher, 1972). Testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months at the highest dose level (58.5 mg B/kg bw/day) with both boric acid and disodium tetraborate decahydrate. Microscopic examination of the tissue revealed atrophied seminiferous epithelium and decreased tubular size in the testes. No effects were observed in the in the control and low dose groups. The NOAEL was 17.5 mg B/kg bw/day. In male rats fed disodium tetraborate decahydrate for either 30 or 60 days at 100 or 200 mg B/kg bw/day (NOAEL, 50 mg B/kg bw/day) testis weight was reduced, testicular germ cells were depleted, selected testicular enzymes were affected and fertility was reduced (Lee et al., 1978). Hyaluronidase, sorbitol dehydrogenase, and lactic acid dehydrogenase isozyme-X were significantly decreased; and glyceraldehyde-3-phosphate dehydrogenase and malate dehydrogenase were significantly increased at 100 and 200 mg b/kg bw/day. As might be expected, while recovery from inhibition of spermiation occurred at the lower doses, there was no recovery from testicular atrophy when the germ cells were lost.

Fewer data are available for mice and dogs, but the results confirm the findings in rats. In a continuous breeding study of boric acid in mice, a dose-related effect on the testis (testicular atrophy and effects on sperm, motility, morphology and concentration) was noted; fertility was partially reduced at 111 mg B/kg bw/day, and absent at 221 mg B/kg bw/day. Effects on females were minimal. Fertility parameters evaluated in females included uterine weights, evaluation of vaginal smears, histopathology of reproductive organs, mating index, and fertility index. The LOAEL was 27 mg B/kg bw/day (154 mg boric acid /kg bw/day); although at this dose the motility of epididymal sperm was slightly affected without any effect on fertility (Fail et al., 1991). These results are consistent with those in rats.

Data in dogs derives from two very limited 90 day and two-year dietary studies. Dogs were dosed for 90 days with dietary levels of 0, 0.01, 0.1, 1.0% boric acid equivalent to 0, 0.4, 4.4, and 33 mg B/kg/day and 0, 0.0154, 0.154, 1.54% disodium tetraborate decahydrate equivalent to of 0, 0.4, 4.1, and 38 mg B/kg/day, based on the actual body weight and food consumption data in the study. Unfortunately, the published report of these studies does not accurately reflect the original study reports (Paynter, 1963 a;b; Weir and Fisher, 1972). The data from the 90 day studies on boric acid and disodium tetraborate decahydrate has been considered inadequate for risk assessment and only used as supporting evidence of a reproductive effect and not to contribute to the determination of the NOAEL (EFSA, 2004; US EPA, 2004; US FNB, 2001; IPCS, 1998; ECETOC, 1995; IEHR, 1997; UK EVM, 2003). In particular the 90 day studies had many limitations and are considered not suitable for risk assessment. These limitations are further detailed in Annex 1.

In the two year dog studies on both boric acid and disodium tetraborate decahydrate, the actual dietary intake was reported in the original study reports allowing a more accurate measure of the dietary intake than presented in the published paper, in which the authors estimated the dietary intakes from standard intake figures. Groups of only four male dogs were fed either boric acid or disodium tetraborate decahydrate at doses up to 10.2 mg B/kg bw/day (62.4 mg boric acid/kg bw/day and 84.7 mg disodium tetraborate decahydrate/kg bw/day) in one study and 39.5 mg B/kg bw/day (233.1 mg boric acid/kg bw/day and 373.2 mg disodium tetraborate decahydrate/kg bw/day) in a second study. The animals were sacrificed at various time periods such that observations were reported on only 1 or 2 animals. At 39.5 mg B/kg bw/day, testicular atrophy was observed, however the effects in the only one disodium tetraborate decahydrate treated dog investigated at 38 weeks were less severe than those seen in the control dog. Also, testicular atrophy was present in three out of four control dogs, so that the significance of the effect in the treated animals is difficult to assess. One boric acid treated and one disodium tetraborate decahydrate treated dog were allowed to recover for three weeks. Some recovery was observed in each dog. Minor histopathological changes such as decreased spermatogenesis remained which was less obvious in the disodium tetraborate decahydrate treated dog. The NOAEL was deemed to be the equivalent of 10.2 mg B/kg bw/day by the authors (Weir, 1966 e,f; 1967 a, b; Weir and Fisher, 1972). Although this data is inadequate for risk assessment, it does confirm the effects seen in other species. Due to the acute toxic effects of borates in dogs, had the LOAEL doses been administered as a single dose (i.e. by gavage) then vomiting would have occurred and the study would not have been possible.

Table 5.9.1.1 Comparison of NOAELs and LOAELs for Reproductive Effects

Species	Study type or duration	NOAEL	LOAEL	Effect at LOAEL	Reference
		mg B/kg bw/day			
Rat	9 week dietary study	-	26	Mild reversible inhibition of spermiation	Ku et al., 1993
	3-generation dietary study and 2	17.5	58.5	Testicular atrophy; reduced fertility	Weir, 1966, a,b,c,d

	year dietary study				Weir and Fisher, 1972
Mouse	Continuous breeding dietary study	-	27	Reduced sperm motility	Fail et al., 1991
Dog	2 year dietary study	10.2	39.4	Testicular atrophy (also present in control animals)	Weir, 1966e,f; 1967a,b

Table 5.9.1.2 Key Fertility Studies

Route of exposure	Test type Method Guideline	Species Strain Sex no/group	Exposure Period	Doses	Critical effect	NO(A)EL Parental		NO(A)EL F1		NO(A)EL F2		Reference
Fertility Study of Boric acid in Rats						m	f	m	f	m	f	
Oral diet	Predates OECD 3generation 2litter per generation study	Rat Crl:CD Sprague Dawley 8 males 16 females/group	14 weeks pre-treatment then through three generations	0, 670, 2000 or 6700 ppm boric acid (0, 117, 350 and 1,170 ppm boron) in the diet, equivalent to 0, 34 (5.9), 100 (17.5) and 336 (58.5) mg boric acid (mg B)/kg bw	Top dose level caused testes atrophy prior to first mating so no litters produced. No adverse effects in mid and low dose groups in any generation.	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	2000 ppm = 100 mg/kg bw boric acid= 17.5 mgB/kg bw	*Weir R J (1966a).*
Fertility Study of Borax in Rats												
Oral diet	Predates OECD 3generation 2litter per generation study	Rat Crl:CD Sprague Dawley 8 males 16 females per group	14 weeks pre-treatment then through three generations	0, 1030, 3080 or 10300 ppm borax (0, 117, 350 and 1,170 ppm boron) in the diet, equivalent to 0, 50 (5.9), 155 (17.5) and 518 (58.5) mg borax (mg B)/kg bw respectively	Top dose level caused testes atrophy prior to first mating so no litters produced. No adverse effects in mid and low dose groups in any generation.	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw	*Weir R J (1966b)*

See Also Table 5.6.1.1

5.9.2 Developmental toxicity

Studies in animals

Only boric acid has been tested in developmental studies. Effects were observed at high doses in rats, mice and rabbits. A comparison of the key NOAELs and LOAELs for developmental studies is given in the Table 5.9.2-1.
The majority of studies have been carried out in rats. In two separate dietary studies performed in the same laboratory, groups of rats were given dose levels of approximately 3.3, 6.3, 9.6, 13.7, 25, 28 and 59 mg B/kg bw/day on gestation days 0-20 and 94 mg B/kg bw/day on gestation days 6-15 in feed. At non-maternally toxic doses, there was a reduction on foetal weight and some skeletal variations and malformations (increase in wavy ribs and short rib XIII and a decreased incidence of rudimentary extra rib on lumbar 1) which, had reversed by postnatal day 21 at 13.7 and also, with the exception of short rib XIII, had reversed at 28.6 mg B/kg bw/day in a study designed to look at postnatal recovery (Price et al., 1990, 1994, 1996). At higher maternally toxic doses, other indications of developmental effects were observed, including resorptions and visceral malformations (enlarge lateral ventricles; cardiovascular effects; anophthalmia and microphthalmia and short and curly tails) (Price et al., 1990, 1994 1996; Heindel et al., 1992). The NOAELs for maternal toxicity and developmental effects in the rat were 13.6 mg B/kg bw/day and 9.6 mg B/kg bw/day, respectively (Price et al. 1990,1991,1996). A reduction in food intake and an increase in relative liver and kidney weight and a reduction in maternal body weight gain at higher doses indicated maternal toxicity.

Similar findings were observed in mice receiving estimated doses of 0, 43, 79, and 175 mg B/kg bw/day on gestation days 0-20 in feed. Maternal toxicity was indicated by mild renal lesions and at the highest dose increases in the relative kidney weight and food intake. A NOAEL was not determined for maternal toxicity. The key developmental effects observed were similar to those seen in rats i.e. a reduction in foetal body weight at the mid dose (79 mg B/kg) and an increase in skeletal variations and malformations (missing lumbar vertebrae, fused vertebral arches and short rib XIII) and resorptions at the highest, more maternally toxic dose. The NOAEL for developmental effects in mice was 43 mg B/kg bw/day (Heindel et al., 1992); however, this dose was also a maternally toxic dose.

In rabbits receiving estimated doses of 0, 11, 22 and 44 mg B/kg bw/day by gavage on gestation days 6-19 maternal toxicity was indicated by effects such as an increase in relative kidney weight, decrease food intake (30% reduction in average daily intake during treatment relative to controls), vaginal bleeding and an increase in corrected weight gain. Developmental effects were seen only at the top dose, where the majority of the embryos were resorbed and malformations were primarily visceral (major heart and/or great vessel defects). The only skeletal effect observed was a decreased incidence of rudimentary extra rib on lumbar 1 which was not considered biologically significant. The NOAEL for both maternal and developmental toxicity in the rabbit was 21.8 mg B/kg bw/day (Price et al., 1991).

Table 5.9.2-1 Comparison of NOAELs and LOAELs for Developmental Effects, Figures in mg boron.kg

Species	mg/B/kg bw/day			Effect at LOAEL	Reference
	Maternal NOAEL	NOAEL	LOAEL		
Rat	13.6	9.6	13.6	Decreased foetal body weight; minor skeletal variations	Price et al., 1990, 1994, 1996
Mouse	No NOAEL	43	79	Maternal toxicity; decreased foetal body weight; some skeletal variations	Heindel et al., 1992
Rabbit	21.8	21.8	43.5	Maternal toxicity; resorptions; Visceral malformations (cardiovascular defects)	Price et al., 1991

Table 5.9.2-2 Key Developmental studies with Boric acid

Route of exposure	Test type Method Guideline	Species Strain Sex	Exposure Period	Doses	Critical effects dams	NO(A)EL maternal toxicity	NO(A)EL Teratogenicity Embryotoxicity	Reference

		no/group			fetuses			
Oral in diet	OECD 414	Rat Crl:CD VAF/ Plus (Sprague Dawley) 28-32 per group	Day 0-20 of gestation	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	Dams: no toxicity. Fetuses: Reduced bodyweight; short 13th rib; wavy rib; not seen postnatally	2000ppm, equal to 143 mg/kg bw boric acid or 25 mg B/kg bw	750ppm, equal to 55 mg boric acid/kg bw/day or 9.6 mg B/kg bw/day	Price et al., (1994).
Oral in diet		Mice Swiss albino CD-1	All gestation (Day 0-17)	0,0.1,0.2 , 0.4% equivalent to 0, 248 (43), 452 (79) and 1,002 (175) mg boric acid (mg B)/kg bw/day	Dams: Reduced bodyweight gain; increased relative kidney weight and food intake at all doses; mild renal lesions at all doses. Fetuses: Reduced bodyweight; skeletal malformations including short 13th rib.	No identified	0.2 % equal to , 248 mg boric acid or 43mg B /kg bw/day	Heindel et al, 1992.
Oral gavage	OECD 414	Rabbit NZW 30 per group	Day 6-19 of gestation	Gavage 0, 62.5, 125 or 250 mg/kg bw/day, equivalent to 0, 10.9, 21.8 and 43.5 mg B/kg bw/day	Dams: Reduced bodyweight and food intake at high dose level with abortions and resorptions Fetuses: Resorptions and cardiovascular malformations at high dose level.	125mg/kg bw/day, or 21.8 mgB/kg bw/day.	125mg/kg bw/day, or 21.8 mgB/kg bw/day	Price et al 1994

Studies in humans

The potential reproductive effects of inorganic borate exposure to a population of workers at a large mining and production facility was assessed using the Standardised Birth Ratio (SBR), a measure of the ratio of observed to expected births. A total of 542 workers completed a reproductive questionnaire. The average exposure for the highest exposure group was 28.4 mg B/day (approximately 0.4 mg B/kg bw/day) for two or more years. The average duration of exposure was 16 years. The number of offspring was actually greater than the US national average, indicating no adverse effects on reproduction in these workers (Whorton et al., 1994). It should be noted that the comparison with the US national average may dilute the effect that the socio-economic status plays on the number of offspring.

In a study of a highly exposed population in Turkey, where exposure comes mainly from naturally high levels of B in drinking water (up to 29 mg B/l) as well as from mining and production, no adverse effect has been reported on fertility over three generations (Sayli, 1998; 2001). Sayli et al. compared fertility in the residents of two Turkish villages with high levels of boron in their drinking water (8.5 to 29 mg B/L and 2.05 to 2.5 mg B/L), with there nearby villages with low boron levels (0.03 to 0.40 mg B/L). The authors compared the reproductive history of families living in the high boron region with families in the low boron region by identifying married adults who provided information about each spouse's family pedigrees covering three generations. In the high boron region, 159 three-generation kindreds containing 1068 families were ascertained. In the low-boron region, 154 three-generation kindreds containing 610 families were ascertained. No significant difference in fertility was noted between the high and low exposure groups.

The gender ration (M:F) of offspring was 0.89 in the high exposure region compared to 1.04 in the low boron region, although the difference was not statistically significant ($p > 0.05$) (Sayli, 1998; 2001).

5.9.3 Other relevant information

5.9.4 Summary and discussion of reproductive toxicity

Effects on Fertility

A dose related effect on the testis was observed in rats and mice with confirmation from limited studies in dogs. Effects start with reversible inhibition of spermiation after 14 days treatment, at doses around 39 mg B/kg, (217 mg boric acid/kg bw/day) although at a lower dose of 26 mg B/kg (149 mg boric acid/kg bw/day) the effects take about 28 days to manifest. Higher doses (58.5 mg B/kg bw/day and above) lead to testicular atrophy, degeneration of seminiferous tubules, reduced sperm count and a reduction in fertility. No recovery from testicular atrophy was observed when the germ cells were lost.

The NOAEL for this endpoint is 17.5 mg B/kg corresponding to 100 mg boric acid/kg/day; 155 mg disodium tetraborate decahydrate/kg , 118 mg disodium tetraborate pentahydrate/kg and 81 mg disodium tetraborate anhydrous/kg.

Developmental Effects

Developmental effects have been observed in three species, rats, mice and rabbits. The most sensitive species being the rat with a NOAEL of 55 mg/kg bw/day (9.6 mg B/kg bw/day). This is based on a reduction in mean foetal body weight/litter, increase in wavy ribs and an increased incidence in short rib X111 at 76 mg/kg bw/day (13.3 mg B/kg bw/day). The reduction in foetal body weight and some skeletal variations which, with the exception of short rib XIII, had reversed by 21 days post natal. At maternally toxic doses, visceral malformations observed included enlarged lateral ventricles and cardiovascular effects.

The NOAEL for this endpoint is 9.6 mg B/kg corresponding to 55 mg boric acid/kg/day; 85 mg disodium tetraborate decahydrate/kg, 65 mg disodium tetraborate pentahydrate/kg and 45 mg disodium tetraborate anhydrous/kg.

5.10 Other effects

Essentiality in animals

Boron has been found to be critical for normal reproduction and embryonic development in several animal species. Low boron culture conditions have resulted in abnormal development and increased malformations in frog (Xenopus laevis) embryos (Fort et al., 1998, 1999) and mechanisms for this essentiality are beginning to be revealed (Fort 2002). Survival of rainbow trout and zebrafish was impaired in low-B conditions (Eckhert, 1998, Rowe and Eckhert, 1999). Such effects have not been found consistently in rodent models (Lanoue et al., 1998, 1999). Like many essential elements, it is likely that boric acid exhibits a "U-shaped" dose response curve in animals, as demonstrated by Rowe et al. (1998). Growth of vitamin D3-deficient chicks was stimulated by supplementation of boron (3 mg-B/kg-diet) in a low-B basal diet (Hunt and Nielsen 1981). Boron supplementation in pig diets (5 mg-b/kg-diet) decreased the inflammatory response to an intradermal injection of phytohemagglutinin in pigs, altered plasma lipid metabolites, and tended to increase the production of cytokines following a stress (Armstrong et al., 2001, Armstrong et al., 2000, Armstrong and Spears 2003). In rats, maternal exposure to a low boron diet was associated with a reduction in embryo implantation sites (Lanoue et al, 1998a). In vitro exposures of mouse embryos to low B growth medium showed reduced blastocyst formation and increased embryo degeneration (Lanoue et al.1998b).

Nutritional Importance in Humans

Boron has not been established to be an essential nutrient for humans and no specific biochemical function for boron has been identified in higher animals or man (FNB, 2001). Recommended intakes for boron have not been established (SCF, 1993; FNB, 2001). There is also wide database of references relating to the nutritional importance of boron. Several authors have proposed a role for boron in the metabolism of vitamin D and estrogen (Nielsen, 1998; Nielsen and Penland, 1999; Samman et al., 1998). In addition, dietary boron deprivation studies in both rats and humans have consistently found an effect of boron intake on brain electrophysiology and, in humans, on performance of tasks measuring eye-hand coordination, attention, and short-term memory (Penland, 1998). Although to date insufficient data is available to confirm the essentiality in humans, the U.S. Food and Nutrition Board in 2001, published a Tolerable Upper Intake Level (UL) for boron of 20 mg/day, which confirms the nutritional importance for humans. In addition the UK Expert Committee on Minerals and Vitamins and the European Food Standards Agency (EFSA) also determined an acceptable daily intake for boron (0.16 mg /kg/day) (UK Expert Group on Minerals and Vitamins, 2002, EFSA 2004). A tolerable upper intake level (UL) of boron (sodium borate and boric acid) was derived with 10 mg/person/day for adults based on the most sensitive end-point detected in animals studies; i.e. the NOAEL for decreased fetal body weight in rats following maternal exposure during pregnancy. This UL also applies to pregnant and lactating women. UL values for children were derived by extrapolating from the UL for adults on a body surface area basis, giving values (mg/day) of 3, 4, 5, 7, and 9 for children aged 1-3, 4-6, 7-10, 11-14 and 15-17 years of age, respectively. These UL values apply only to the intake of boron as boric acid and borates (EFSA, 2004b).

Significant advances in the search for essentiality of boron have been made recently in the discovery of a "Quorum sensing" cell-cell communication auto inducer molecule containing a borate-sugar diester (Chen et al., 2002); the B transporter membrane protein, BOR1, identified in plant roots of Arabidopsis thaliana (Takano et al., 2002);); the incidence of esophageal cancer has been reported to be significantly higher in a low boron region, compared to an area with boron exposure (Kibblewhite et al, 1984); a case-control study that found no significantly elevated risk of prostate cancer in an occupational cohort with boron exposure (Rooney et al.,, 1993; Zhang et al., 2001) and the identification of a role for boron in the inhibition of human prostate cancer cell proliferation (Barranco and Eckert, 2004). Data on boron intake in EU countries are limited (EFSA-Q-2003-018 (adopted on 8 July 2004). The World Health Organization provisional guideline value for boron in drinking water is 0.5 mg/l (WHO 2006).

Conclusions

A no effect level for humans based on the acute single intake and chronic, but daily single intake, symptoms of nausea, vomiting and diarrhoea can be established at about 1 g of boric acid/day (2.5 mg B/kg/day). The level at which adverse effects of anorexia, indigestion and exfoliative dermatitis will be seen is 5.0 mg boric acid/kg/day. Although chronic absorption data at these levels is not available in the literature for infants, their responses at high doses are similar enough to the human adult to assume that children are not more sensitive to the effects of borates.

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

The guidelines for developing DNELS (under RIP3.2.2) are not yet finalised therefore this section cannot be finalised until these guidelines are available. However the critical NOAEL can be identified. As soon as the DNEL guidelines are available the issue of the DNELs can be addressed more thoroughly.

Identification of the Critical NOAEL

Boron is an ubiquitous element found widely distributed in the environment and is a normal component of a healthy diet. It is an essential micronutrient for plants, and there is evidence to indicate that B is of nutritional importance, if not essential, for mammals. Boron is essential for normal reproduction and embryonic development in frogs and fish (Fort et al., 1999, 2002; Rowe et al., 1998), and mechanisms for this essentiality are beginning to be revealed (Fort 2002).

Boric acid and sodium borates have low acute toxicity. They are not skin irritants, nor skin sensitisers. Some borates cause eye irritancy in animals due to the glassy nature of the crystals, but in 50 years of occupational exposure no adverse ocular effects have been seen in humans. Borates are absorbed orally and by inhalation. They are very poorly absorbed dermally except through severely damaged skin. Dermal absorption has been shown to be <0.5% on human studies. They are not carcinogenic or mutagenic.

In human cases of poisoning, via accidental oral intake, acute and chronic symptoms of nausea, vomiting and diarrhoea occur. As the dose became higher and the dosing period longer, symptoms included alopecia, disseminated maculopapular eruption followed by widespread desquamation, focal or generalised central nervous system irritation, and convulsions.

The most critical endpoints of toxicity are considered to be (1) effects on the testis and fertility in males and (2) developmental effects (in particular, foetal weight reduction). The effects seen occur in three species, rats, mice and dogs for reproductive effects; rats, mice and rabbits for developmental effects. There is good agreement between these species, which indicates that there is little species variation in the response. This may be due to the lack of metabolism of boric acid and borates, which tends to reduce interspecies variation. The critical lowest No Observed Adverse Effect (NOAEL) level for the purposes of risk assessment is 9.6 mg B/kg/day (54 mg boric acid/kg/day; 85 mg disodium tetraborate decahydrate; 65 mg disodium tetraborate pentahydrate; 45 mg disodium tetraborate anhydrous), based on developmental effects.

5.11.1 Overview of typical dose descriptors for all endpoints

Acute Toxicity

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are of low acute toxicity. For all the borates the acute toxicity results are: LD_{50} oral rat > 2000 mg/kg; LD_{50} dermal rat > 2000 mg/kg; LC_{50} inhalation rat > 2 mg/l.

Skin Irritation

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not skin irritants. Moreover boric acid and disodium tetraborate decahydrate are used at concentrations of 5% in cosmetics in the US and in talc in Europe, up to 3% in other cosmetics in Europe (Beyer et al., 1983; EC, 2000).

Eye Irritation

Boric acid induced conjunctivae redness and chemosis and minor effects on the iris. The effects were reversible within 7 days. Both disodium tetraborate decahydrate and disodium tetraborate pentahydrate induced eye irritation. This could be due to the glassy crystalline nature of these compounds however it is not possible to exclude eye irritation is the result of a non mechanical action. Disodium tetraborate pentahydrate is classified as an eye irritant R36 current EU guidelines (67/548/EEC) is indicated by the conjunctivae redness and oedema in two out of three animals and under GHS as Category 2A Irritating to eyes, based on redness >2.0 and also Oedema >2 reversible in 14 days. Disodium tetraborate decahydrate is classified as an eye irritant; R36 under current EU guidelines (67/548/EEC) is indicated by the iris and conjunctivae oedema and under GHS as Category 2A Irritating to eyes, based on iris, conjunctivae redness and oedema which does not reverse by 7 days.

Respiratory tract

There is no data from animal studies on boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate that indicated respiratory irritation. Some older studies on workers exposed occupationally to borax dust reported eye irritation, dry mouth, nose or throat, sore throat and productive cough (reported in Garabrant et al.1984, 1985). However there were severe imitations to this data.

Sensitisation

Boric acid, disodium tetraborate decahydrate and disodium tetraborate pentahydrate were tested in a Buehler method skin sensitisation test (Wnorowski, 1994 e, f, g). They were applied at a concentration of 95% (powder moistened with water) during both the induction and challenge phase of the test. No signs of skin sensitisation were observed .The data indicate that these borates are not sensitisers. In addition there is no evidence of skin sensitisation in humans exposed occupationally to borates has been reported (Bruze et al., 1995).

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are neither skin nor respiratory sensitisers.

Repeated Dose Toxicity

A number of studies in which rats were fed boric acid or disodium tetraborate decahydrate in their diet or drinking water for periods of 70 days to two years in rats, mice and dogs indicated that the main target organ for toxicity is the

testis. Other effects observed at high doses include rapid respiration, hunched position, bloody nasal discharge; urine stains on the abdomen, inflamed bleeding eyes, desquamation and swollen paws and tail, reduced food consumption and body weight gain. Boric acid induced testicular atrophy and minor haematological effects. The haematological findings observed are not regarded as serious treatment related effects. Based on the clinical effects and the testicular atrophy the lowest NOAEL for the effects of boron is 17.5 mg B/kg bw/day (equivalent to 100mg boric acid or 155 mg disodium tetraborate decahydrate/kg bw/day).

Mutagenicity studies

All the data in vitro studies conducted indicate no mutagenic activity. In addition the single in vivo study on boric acid also indicated no mutagenic activity. Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not mutagenic.

Carcinogencity

In long term feeding studies on boric acid and disodium tetraborate decahydrate in both rats and dogs, no carcinogenic effects were observed (Weir, 1966a,b; Weir and Fisher, 1972). No carcinogenic effects were observed in mice at doses of boric acid of 75 mg B/kg bw/day and 200 mg B/kg bw/day (NTP, 1987). It can be concluded that that boric acid and sodium borates are not carcinogenic and there is no concern for a carcinogenic effects in humans.

Reproductive Toxicity

Effects on Fertility

A dose related effect on the testis was observed in rats and mice with confirmation from limited studies in dogs. Effects start with reversible inhibition of spermiation after 14 days treatment, at doses around 39 mg B/kg, (217 mg boric acid/kg bw/day) although at a lower dose of 26 mg B/kg (149 mg boric acid/kg bw/day) the effects take about 28 days to manifest. Higher doses (58.5 mg B/kg bw/day and above) lead to testicular atrophy, degeneration of seminiferous tubules, reduced sperm count and a reduction in fertility. The NOAEL for this endpoint is 17.5 mg B/kg corresponding to 100 mg boric acid/kg/day; 155 mg disodium tetraborate decahydrate/kg , 118 mg disodium tetraborate pentahydrate/kg and 81 mg disodium tetraborate anhydrous/kg.

Developmental Effects

Developmental effects have been observed in three species, rats, mice and rabbits. The most sensitive species being the rat with a NOAEL of 55 mg/kg bw/day (9.6 mg B/kg bw/day). This is based on a reduction in mean foetal body weight/litter, increase in wavy ribs and an increased incidence in short rib X111 at 76 mg/kg bw/day (13.3 mg B/kg bw/day). The reduction in foetal body weight and some skeletal variations which, with the exception of short rib XIII, had reversed by 21 days post natal. At maternally toxic doses, visceral malformations observed included enlarge lateral ventricles and cardiovascular effects. The NOAEL for this endpoint is 9.6 mg B/kg corresponding to 55 mg boric acid/kg/day; 85 mg disodium tetraborate decahydrate/kg, 65 mg disodium tetraborate pentahydrate/kg and 45 mg disodium tetraborate anhydrous/kg.

Human Data

A no effect level for humans based on the acute single intake and chronic, but daily single intake, symptoms of nausea, vomiting and diarrhoea can be established at about 1 g of boric acid/day (2.5 mg B/kg/day). The level at which adverse effects of anorexia, indigestion and exfoliative dermatitis will be seen is 5.0 mg boric acid/kg/day.

5.11.2 Correction of dose descriptors if needed (for example route-to-route extrapolation)

Since borates are assumed to be 100% absorbed by inhalation and oral exposure there is no need to further scale for inhalation and the oral NOAEL should be used as the basis for deriving a DNEL for borates.

5.11.3 Application of assessment factors

Assessment factor		Default value systemic effects
Interspecies	- correction for differences in metabolic rate per body weight	3
	- remaining differences	1
Intraspecies	- worker	5
	- general population	10
Exposure duration	- subacute to sub-chronic	na
	- sub-chronic to chronic	na
	- subacute to chronic	na
Dose-response	- issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity of effect	1
Quality of whole database	- issues related to completeness and consistency of the available data	1
	- issues related to reliability of the alternative data	1

The proposed assessment factor changes from the default is to the Systemic Effects Allometric scaling where the default of 4 for metabolic rate from rats to man can be reduced to 3 for borates based on a comparison of the renal clearance between rats and humans which indicated that humans may clear boric acid 3 times more slowly than rats (Pahl et al., 2001; Vaziri et al., 2001). The main difference between rats and humans is renal clearance.

As there are no other major differences between rats and humans then the extra factor of 2.5 can be disregarded since there are no metabolic differences between the species.

Since the data is based on reproductive effects there is no need for adjustments for duration of exposure.

5.11.4 Selection/ identification of the critical DNEL(s)/ the leading health effect

Based on the critical lowest No Observed Adverse Effect (NOAEL) level of 9.6 mg B/kg/day (54 mg boric acid/kg/day; 85 mg disodium tetraborate decahydrate; 65 mg disodium tetraborate pentahydrate; 45 mg disodium tetraborate anhydrous) in rats based on developmental effects; an interspecies assessment factor of 3, intraspecies assessment factors of 5 for workers and 10 for general population, the proposed critical DNELs are 0.640 mg B/kd/d for workers, and 0.320 mg B/kg/d for general population.

Summary of Adjustment factors for borates

	NOAEL mg B/kg/d	Interspecies		Total InterSp	Intraspecies		Total AF	DNEL mg B/kg/d	OEL Workers mg B/m3
		AS	Other		Worker	GPop			
Worker	9.6	3	1	3	5	1	15	0.640	4.48*
General Pop	9.6	3	1	3	1	10	30	0.320	

*Estimate based on 8 hours exposure and 10 m^3 inhalation and 60 kg adults.

AS = factor for allometric scaling AF = assessment factor

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

No Human Heath Hazards

6.2 Flammability

No Human Heath Hazards

6.3 Oxidising potential

No Human Heath Hazards

7 ENVIRONMENTAL HAZARD ASSESSMENT

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Short-term toxicity to fish

Long-term toxicity to fish

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Long-term toxicity to aquatic invertebrates

7.1.1.3 Algae and aquatic plants

7.1.1.4 Sediment organisms

7.1.1.5 Other aquatic organisms

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

7.1.2.1 PNEC water

7.1.2.2 PNEC sediment

7.2 Terrestrial compartment

7.2.1 Toxicity test results

7.2.1.1 Toxicity to soil macro organisms

7.2.1.2 Toxicity to terrestrial plants

7.2.1.3 Toxicity to soil micro-organisms

7.2.1.4 Toxicity to other terrestrial organisms

Toxicity to birds

Toxicity to other above ground organisms

7.2.2 Calculation of Predicted No Effect Concentration (PNEC_soil)

7.3 Atmospheric compartment

7.4 Microbiological activity in sewage treatment systems

7.4.1 Toxicity to aquatic micro-organisms

7.4.2 PNEC for sewage treatment plant

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

7.6 Conclusion on the environmental classification and labelling

8 PBT AND VPVB ASSESSMENT

8.1 Comparison with criteria from annex XIII

8.2 Assessment of substances of an equivalent level of concern

8.3 Emission characterisation

8.4 Conclusion of PBT and vPvB assessment

9 EXPOSURE ASSESSMENT

9.1 General discussion on releases and exposure

9.1.1 Summary of the existing legal requirements

9.1.2 Summary of the effectiveness of the implemented risk management measures

9.2 Manufacturing

9.2.1 Occupational exposure

9.2.2 Environmental release

9.3 "Use 1"

For each use include such a sub-chapter. Subsequently, if there is another "Use 2" this will lead to sub-chapter 9.4 "Use 1" including 9.4.1 Human exposure, 9.4.1.1 Occupational exposure, 7.4.1.2 Consumer exposure and 9.4.2 Environmental release. The other sub-chapters will then be renumbered.

9.3.1 Human exposure

9.3.1.1 Occupational exposure

9.3.1.2 Consumer exposure

9.3.2 Environmental release

9.4 Other sources (for example natural sources)

9.4.1 Human exposure

9.4.1.1 Occupational exposure

9.4.1.2 Consumer exposure

9.4.2 Environmental release

9.5 Environmental exposure assessment

9.5.1 Summary of emissions

9.5.2 Predicted environmental concentrations

9.5.2.1 Regional concentrations

Atmosphere

Aquatic compartment

Sediment

Soil compartment

9.5.2.2 Local concentrations

Atmosphere

Aquatic compartment

Sediment

Soil compartment

9.5.2.3 Exposure concentrations of man via the environment

9.5.3 Measured levels

Atmosphere

Aquatic compartment

Sediment

Soil compartment

Secondary poisoning

9.5.4 Selected environmental concentrations of risk characterisation

Atmosphere

Aquatic compartment

Sediment

Soil compartment

Secondary poisoning

9.6 Combined human exposure assessment

10 RISK CHARACTERISATION

10.1 Human health

10.1.1 Workers

10.1.2 Consumers

10.1.3 Indirect exposure of humans via the environment

10.1.4 Combined exposures

10.2 Environment

10.2.1 Aquatic compartment (including sediment and sewage treatment plant and secondary poisoning)

10.2.2 Terrestrial compartment (including secondary poisoning)

10.2.3 Atmospheric compartment

10.2.4 Microbiological activity in sewage treatment systems

OTHER INFORMATION

It is suggested to include here information on any consultation which took place during the development of the dossier. This could indicate who was consulted and by what means, what comments (if any) were received and how these were dealt with. The data sources (e.g registration dossiers, other published sources) used for the dossier could also be indicated here.

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[click to insert references classed alphabetically by author. For details on referencing, see explanatory note]

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ANNEX 1

Quality Assessment of the 90-Day Dog Studies of Boric Acid and Borax (Paynter, 1963a;b; Weir & Fisher, 1972)

- The test system is unsuitable because the age of the dogs is not identified in these studies. Age is a critical factor in a study that purports to evaluate male reproductive toxicity. Because the investigators did not know the ages of the dogs and because the dogs appear to be of varying ages, the test system is highly inappropriate for assessing male reproductive toxicity. The development of the testes is age-dependent. If a dog is either too young or too old, testicular endpoints may be affected by age. This deficiency alone should render these studies as unsuitable for quantitative risk assessment for endpoints of male reproductive toxicity.

- For unexplained reasons, the weight of the dogs varied significantly at the start of the experiment. The weight range of the male and female dogs at the start of the study was 6.0-10.4 and 4.2-11.5 kg, respectively. It is a generally accepted scientific principle that the animals used on a study should have similar body weights. The large difference in body weight at the beginning of the study calls into further question the age (and suitability) of the test system (animals).

- The test system is unsuitable because the source of the dogs is unknown. Although the authors state that purebred beagles were used, the source of the beagles is not stated in the 90-day studies (or in any of the Weir and Fisher studies). It was common practice in the 1960s to obtain dogs for research from dog pounds. In fact, some of the control dogs for other studies in the Weir and Fisher series were described by the authors as "mongrels."

- The test system is unsuitable because the dogs may not have been housed properly. The report states that the dogs in the 90-day studies were housed individually in metal cages. Yet, a female dog became pregnant during the course of another Weir and Fisher dog study, in which the authors stated that the dogs were housed individually in metal cages. This finding strongly suggests irregularities in the housing of the dogs. If two dogs housed individually can cohabitate, it also raises questions about the possibility of "individually-housed" dogs gaining access to the wrong diets.

- The test system is unsuitable because confounding factors, including previous exposure to reproductive toxicants, were not identified. The dogs used for this study may have been exposed to other chemicals, including chemicals that cause male reproductive toxicity, prior to placement on this study. Since the source of the dogs is unknown, there are no records on exposures to chemicals, drugs, and pesticides prior to the being placed on this study. Also, it was common practice in the 1960s to use the same dogs for more than one set of experiments. According to the FDA Redbook (FDA, 2000), "Healthy animals that have not been subjected to previous experimental procedures should be used" for toxicity studies.

- The test system is unsuitable because at least one of the dogs (female control dog #4996) was missing a left kidney. It is not clear whether the missing kidney was due to a congenital defect or to previous surgery. At any rate, it is highly unusual to select a dog with only one kidney for a controlled experiment.

- The test system is unsuitable because the study report says the dogs were treated with a vermifuge "as needed" during the course of the study. Vermifuge is a type of anti-helminthic agent, which has been placed on California's Proposition 65 list of chemicals "known to the state" to cause reproductive toxicity based on studies of developmental toxicity. Based on a literature search, there is no publically available evidence that vermifuge has ever been tested for effects on male reproduction. According to the US FDA Redbook (US FDA, 2000), "Generally, it is not possible to treat animals for infection during the course of a study without the risk of interaction between the treatment drug and the test substance." In addition, the dogs were "vaccinated against canine distemper, infectious canine hepatitis, and rabies.

- The dogs on the study were administered "Wayne Dog Feed" *ad libitum* throughout the study. In addition, the dogs were also given a 100 gram ration of canned meat (Hill Packing Company) 5 days per week. This ration was apparently given because the Wayne dog food with boric acid and borax was not well tolerated. First, it is not clear what role, if any, the canned meat ration had on overall food consumption, because the consumption of the canned meat was not recorded. Second, the canned meat was not analysed for chemical impurities that might affect male reproduction.

- The reporting of the methods and results is insufficient because the statistical test methods are not described. The level of statistical significance (i.e., the *p* value) is not reported.

- The reporting of the results of the histopathology is insufficient, because no individual data are reported. It is not possible to determine which specific dogs exhibited histopathological findings. The authors simply reported the results for the entire group. The absence of detailed pathology reports on each individual dog, and the absence of any report on the findings in the controls, is a very severe limitation in the interpretation of these studies.

- The histological description of the testes in the 90-day dog studies is incomplete and inadequate by today's standards. The standards described in the FDA Redbook (FDA, 2000) were not met. According to the FDA Redbook (FDA, 2000): "A thorough histological evaluation of the testis should include an examination of the interstitial compartment and the seminiferous tubule compartment. A histopathological evaluation of the intertubular cell compartment of the testis should include a general assessment of the Leydig cells, the blood vessels, and the cell types other than the Leydig cells typically found in the intratubular space. The general appearance of the seminiferous tubules should be noted. This should be followed by an examination of the seminiferous tubule compartment to detect any disruption in the normal sequence of the events that occurs during the normal process of spermatogenesis. The seminiferous epithelium should then be carefully observed to detect any of the following: presence of multinucleated cells, missing germ cell layers, increased germ-cell degeneration, abnormal development in germ cells, sperm release delay or failure, presence of germ cells in the seminiferous tubule lumen, and any changes in the Sertoli cells (vacuolization, sloughing, or nuclear changes). The general condition of the boundary layer should be noted."

- Another abnormality in the test results is that many test results always ended in the numbers 0 or 5. For example, food consumption was always reported as a value that ended with either 0 or 5. Similarly, the BUN results all end in either 0 or 5. One possible explanation is that the instruments for measuring food consumption and BUN only measured whole numbers and half numbers. Interestingly, the testes weights of 15/15 boric acid-exposed dogs always ended in either 0 or 5. In contrast, only 2/5 of the control dogs ended in either a 0 or 5. This suggests that the method of weighing the testes of the control dogs may have been different from that used to weigh the testes of exposed dogs.

- The test system is unsuitable because the dog is not an appropriate model for evaluating male reproductive effects. No regulatory agency recommends using the dog as a species for evaluating male reproductive toxicity.

- The reporting of the method of preparing the test diets is inadequate: "The test material was added to the diet on a weight/weight basis and thoroughly mixed in a large volume blender. The report does not state whether the blending was performed wet or dry. The report describes no analysis to ensure that the actual concentration of test material was consistent with the nominal concentration. The report does not describe any effort to determine whether the concentration of the test material in the diet was homogenous. This is a major flaw in the test system, since there is no verification of exposure to the test material. If the diets were not homogenous, the concentration of the test material in the diet given to the dogs may have varied from day to day. Dog diets are normally in chunks or pellets and, therefore, not easy to mix. Unlike rats, dogs cannot be satisfactorily fed a powdered diet.

- The results of the 90-day dog studies are called into question by the results of the 2-year dog studies conducted by Weir and Fisher. The effects seen at the mid-dose in the 90-day studies were not observed in the 2-year dog studies.

- The reporting of the results is insufficient because the average boron equivalent intake doses given at the bottom of Table 1 (Paynter, 1963a;b) does not match the average of the individual data provided. The average dose should be the average of the calculated dose for each of the 13 weeks of the study. But, the average dose reported is consistently lower than the average of the calculated dose for each of the 13 weeks of the study. For example, for male dog #4925, the reported average boron intake dose in Table 1 is 3.3 mg B/kg-d, but the average of the 13 weekly doses for this same dog is 5.2 mg B/kg-d. Likewise in the Borax study, dog #4984 reported average boron intake dose in Table 1 is 3.2 mg B/kg-d but the average of the 13 weekly doses for this same dog is 5.0 mg B/kg-d. This raises the serious possibility that the dose levels were incorrectly calculated in this study.

- The reporting of the results is inadequate because the body weight of individual dogs at week 13 (the end of the study) in Table 1 (Paynter, 1963a;b) do not match the same dog's body weight at autopsy (Table 5). Not only are the results of the body weights different between the two tables, but there is an inconsistent pattern to the difference in body weights. All of the control male dogs weighed less in Table 5 compared to Table 1. In contrast, only one

of the mid- and high-dose male dogs weighed less in Table 5 compared to Table 1. If the body weights in Table 1 had been used instead of the body weights in Table 5 to calculate the relative weight of the testes, the relative testicular weight of the control group would have been less than originally reported, and the relative testicular weight of the mid- and high-dose groups would have been higher than originally reported. This observation calls into question the significance of the reported decrease in testicular weight, particularly at the mid-dose. These findings suggest that different dose groups of animals were weighed by different persons or on different scales. An alternative explanation is that different groups were autopsied on different days. Since the boric acid and borax studies were conducted simultaneously and incorporated a common control group, a large number of dogs would have been autopsied on a single day if all the dogs had been autopsied on the same day of the study. In fact, in the 90-day study, 70 male and female dogs would have been required to be autopsied on the same day. It is doubtful whether the same person could have conducted 70 autopsies of dogs on the same day.

Conclusions

The Weir and Fisher 90-day dog studies should be classified as Category 4 under the TGD Guidelines because the studies have an "unsuitable test system or conditions" and "insufficient reporting of methods and/or results data." Studies in rats and other species demonstrate that Boron can cause testicular toxicity and this is not in dispute. The 90-day dog studies, while adequate qualitatively to support this conclusion, are wholly inadequate to serve as the critical studies in quantitative risk assessment.

Figure 1 vbvnbv

Example 1 hff

Hgkhjfkg

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