Annex XV dossier

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS SUBSTANCE OF VERY HIGH CONCERN (SVHC)

Substance Name: Boric acid

EC Number: 233-139-2 / 234-343-4

CAS Number: 10043-35-3 / 11113-50-1

- *It is proposed to identify the substance as an SVHC according to Article 57 (c).*

Submitted by Germany / Slovenia

Version February 2010

CONTENTS

TABLES

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS SUBSTANCE OF VERY HIGH CONCERN

Substance Name: Boric acid

EC Number: 233-139-2 / 234-343-4

CAS number: 10043-35-3 / 11113-50-1

- *It is proposed to identify the substance as an SVHC according to Article 57 (c).*

Summary of how the substance meets the CMR (Cat 1 or 2), PBT or vPvB criteria, or is considered to be a substance of an equivalent level of concern

Pursuant to the first ATP to Regulation (EC) No 1272/2008 (Commission Regulation (EC) No 790/2009) as of 1 December 2010, boric acid will be listed in Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Annex VI, part 3, of Regulation (EC) No 1272/2008[1] as toxic to reproduction category 2[2].

Therefore, this classification of the substance in Commission Regulation (EC) No 790/2009 shows that the substance meets the criteria for classification as carcinogen in accordance with Article 57 (c) of REACH.

Registration number(s) of the substance or of substances containing the substance:

[1] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

[2] This corresponds to a classification as toxic to reproduction 1B in Annex VI, part 3, Table 3.1 of Regulation (EC) No 1272/2008 (list of harmonised classification and labelling of hazardous substances) as amended by the 1st ATP to (EC) No 1272/2008.

JUSTIFICATION

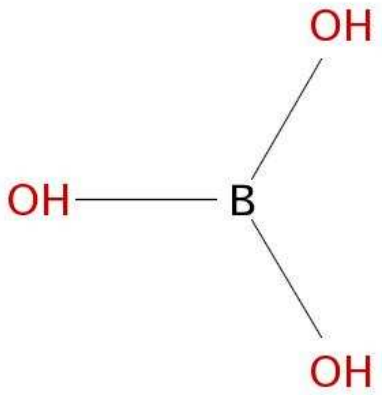
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name: Boric acid
EC Name: Boric acid
CAS Number: 10043-35-3 / 11113-50-1
IUPAC Name: Boric acid

1.2 Composition of the substance

Chemical Name: Boric acid
EC Number: 233-139-2 / 234-343-4
CAS Number: 10043-35-3 / 11113-50-1
IUPAC Name: Boric acid
Molecular Formula: BH_3O_3
Structural Formula:



Molecular Weight: 61.83 g/mol
Typical concentration (% w/w): > 99 % w/w
Concentration range (% w/w): 95 – 100 % w/w

1.3 Physico-chemical properties

Table 1: Summary of 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	4.1	solid	Merck, 1983
VII, 7.2	Melting/freezing point [1)]	4.2	No melting point can be defined in the range 25- 1000°C due to the decomposition of the substance.	Cordia et al., 2003a
VII, 7.3	Boiling point	4.3	not required (due to the decomposition of the substance)	
VII, 7.5	Vapour pressure	4.6	not required (due to the decomposition of the substance)	
VII, 7.7	Water solubility [2)]	4.8	49.20 ± 0.35 g/l at 20 ± 0.5°C (Cordia, 2003) 47.2 g/l at 20°C (Mellor, 1980)	Cordia et al., 2003a Mellor, 1980
VII, 7.8	Partition coefficient n-octanol/water (log value) [3)]	4.7 partition coefficient	-1.09 ± 0.16 (22± 1°C)	Cordia et al., 2003a
IX, 7.16	Dissociation constant [4)]	4.21	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.	Ingri, 1963
VII, 7.4	Relative Density	4.4	D_4^{23} = 1.489 ± 0.006	Cordia et al., 2003a
VII, 7.6	Surface Tension [5)]	4.10	not applicable	
	Thermal stability [6)]	4.19	Boric acid is stable up to approximately 75°C.	Cordia et al., 2003b

1) 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).

2) The difference between the determined water solubility (Cordia et al., 2003a) and the literature value (Mellor, 1980) could be explained by the fact that the two protocol methods used in each case were different.

3) Although not required as this is an inorganic substance, an end point has been derived in Cordia et al., 2003a.

4) At low boron concentrations ($B \leq 0.025$ M) the following equilibrium is found

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

Although at these concentrations, boric acid exists as undissociated boric acid $B(OH)_3$ at

pH < 5, whereas at pH > 12.5 the metaborate ion -$[B(OH)_4]^-$ - becomes the main species in solution. Both species are present at pH 5-12.5 at concentrations $B \leq 0.025$ M.

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 $\leftrightarrow B(OH)_4^-$.

Again, 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 in between 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) ionpair 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.

5) Surface tension is not expected for inorganic substances.

6) It dehydrates on further heating to form metaboric acid and then boric oxide:
$B(OH)_3 \rightarrow HBO_2 + H_2O$ (Temperature range 120 to 180°C)
$HBO_2 \rightarrow 0.5\ B_2O_3 + H_2O$ (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 form a highly viscous liquid whose composition lies between $HBO_2$and B_2O_3. Under these conditions, 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.

2 MANUFACTURE AND USES

Not relevant for this type of dossier.

3 CLASSIFICATION AND LABELLING

3.1 Classification According to the first ATP to Regulation (EC) No 1272/2008

Pursuant to the first ATP to Regulation (EC) No 1272/2008 (Commission Regulation (EC) No 790/2009) as of 1 December 2010, boric acid will be listed in Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Annex VI, part 3, of Regulation (EC) No 1272/2008[3] as follows:

Index Number: 005-007-00-2

Repr. 1B

H360FD (May damage fertility. May damage the unborn child.)

Specific Concentration limits: Repr. 1B; H360FD: C ≥ 5.5 %

According to the first ATP to Regulation (EC) No 1272/2008, the corresponding classification in Annex VI, part 3, Table 3.2 of this Regulation (EC) No 1272/2008 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) will be as follows:

Index Number: 005-007-00-2

Repr. Cat. 2; R60-61 (May impair fertility. May cause harm to the unborn child)

Specific Concentration limits: Repr. Cat. 2; R60-61: C ≥ 5.5 %

3.2 Self classification(s)

None

[3] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

4 ENVIRONMENTAL FATE PROPERTIES

Since this is a dossier targeted to the identification of Boric acid as a CMR substance, environmental fate properties have not been considered.

5 HUMAN HEALTH HAZARD ASSESSMENT

Information on hazard to human health relevant for the assessment as to whether boric acid meets criteria of Article 57 of the REACH-Regulation is provided in section 2 of this report (classification information).

Supplementary information on the toxicological properties of boric acid, which could be relevant for risk assessment, comparative assessment of alternative substances, or for priority setting in the context of recommending substances for the 'Authorisation List' (Annex XIV of the REACH Regulation) can be found in Annex 1 to this report.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not relevant for this type of dossier.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this type of dossier

8 PBT, VPVB AND EQUIVALENT LEVEL OF CONCERN ASSESSMENT

Not relevant for this type of dossier.

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

1 INFORMATION ON EXPOSURE

1.1 Consumer Exposure

1.1.1 Information from Product Registers

Use categories communicated to the Swedish Product Register for boric acid in 2008 (CAS Nr. 10043-35-3 and 11113-50-1, KEMI 2009) include:

- biocides and preservatives (biocides for human hygiene, disinfectants and other biocidical products used in private and public spaces, wood preservative, preservatives for textile, paper, leather, rubber and polymerised materials),
- dental products, veterinary medicines,
- food and fodder additives,
- raw materials (for glass and ceramics, for pharmaceuticals, for production of rubber, intermediates that are not mentioned elsewhere), base oils,
- fertilisers,
- flame retardants,
- detergents, cleaners, stain removers, other decontamination agents,
- paints (including paints with anti-corrosive and paints with flame retardant effects for interior use), pigments for paints and inks, adhesives (water based, for industrial use) and binders, putty, concrete hardener, fireproof cement and concrete,
- fluxing agents for welding, for soldering and for galvanisation, coolants and lubricants (including lubricants for metal processing and for removing metal chips when milling), lubricant additives, soldering metals, soldering products, cutting oil, rolling oil, cast compounds, grinding fluids, hardeners for metal, non-electrolytic metal coatings, metal surface treatment agents, galvano-technical agents, degreasing agents, corrosion inhibitors, rust preventive agents, rust removing agents,
- brake fluids, transmission mediums, hydraulic fluids, refrigerants, cooling medium, material insulating from electricity, inhibitors (protective gas, inert gas)
- catalysts, electrolytes, laboratory chemicals, precipitants, pH-regulating agents, viscosity regulating agents, paper manufacture chemicals, surface treatment products for non-metal, photochemicals (film and other developers, fixatives, others)

Consumer use with boric acid weight concentrations > 5.5% was only communicated for other soldering products, film developer and raw material for pharmaceuticals. Consumer use with Boric Acid weight concentrations <= 5.5% was reported for fertilisers, stain removers, fluxing agents for soldering, brake fluids and transmission mediums, hydraulic fluids, water based paint with flame retardant effect for interior use, film developers and fixatives for photographic film, veterinary medicines, disinfectants and other biocidical products used in private and public spaces, biocides for human hygiene and wood preservatives.

53 Products with boric acid have been identified in the Swiss Product Register, mostly biocides (FOPH 2009). Soldering products contained between 20% and 45% boric acid, fertilisers, photochemicals and soaps and laundry detergents contained below 5% boric acid.

1.1.2 Information from the Transitional Dossier and the RPA report

Consumer Exposure to boric acid has been addressed recently by the Transitional Dossier for boric acid (CAS 10043-35-3) (ECHA 2008a), which also focuses on disodium tetraborate anhydrous (CAS 1330-43-4), disodium tetraborate pentahydrate (CAS 12179-04-03) and disodium tetraborate decahydrate (CAS 1303-96-4). According to this dossier, boric acid is used in a wide range of consumer products due to its consistency-influencing, flame-retardant and preservative properties, for example glass and glass fibres (insulation and textile fibre glass, borosilicate glass, refractories), ceramics (glaze and enamel, tile bodies), starch and casein adhesives, flame retardants (wood products, cellulose insulation, cotton battings in mattresses/futons, fabrics and paper), fertilisers, personal care products (cosmetics, toiletries, pharmaceuticals), biocides (wood preservatives, non professional and professional remedial products), wallboard (plasterboard), paints, water treatment chemicals and fuel additives. Quantitative consumer exposure assessments were provided for exposures to glass wool (during insulation activities), ceramic ware, detergents and fertilisers. A risk characterisation assessment for boron exposure via consumer products was not derived due to the lack of information on other consumer uses, like cellulose insulation, motor oil and non-biocide use in swimming pools. A need for further information was concluded: “The RPA report was not available at the time of the submission of this dossier. This report is expected to provide information on consumer exposure. Therefore, minimal data are available on consumer exposure. In the event that the RPA report does not contain sufficient information, additional consumer exposure information and data will be required if those uses are to be supported by the REACH registration dossier. “

The RPA report (RPA, 2008) on borates in consumer products has been carried out on behalf of the European Commission. It covers boric acid and a number of other boron compounds, principally boric oxide, sodium borate and sodium perborate, which also have been classified as Reprotoxic Category 2. The study approach involved a review of the relevant literature and consultation with the relevant industry stakeholders in the EU in order to identify the range of uses for borates. After exclusion of uses covered by sectorial legislation like Plant Protection Directive, Biocidal Product Directive, Cosmetics Directive, Food Supplements Directive and Medicinal Products Directive and considerations on likelihood of consumer exposure, a shortlist of uses was derived for further evaluations. This shortlist included “uses with potential for significant degree of exposure” (fertiliser mineral, soaps and detergents, other chemical products: anti-freezes, lubricants, brake fluids, metalworking fluids, water treatment chemicals, fuel additives), “uses with potential for possible exposure” (adhesives, paper and pressed panel, paints and coatings, mattresses) and “uses in glass”. The potential of consumer exposure was compared to the tolerable upper intake level (UL) for boron derived by EFSA (EFSA, 2004), which was not surpassed by any single consumer use. (Aggregated exposure from different consumer uses was not in the scope of the RPA report.) Quantitative exposure estimates were provided for fertilisers, detergents, mattresses and starch adhesives. The other uses were discussed on the basis of plausibility argumentations. For example, according to the RPA report, the products identified as examples for data gaps on consumer exposure to boron in the Transitional Dossier (cellulose insulation, anti-freeze, brake fluids, motor oil, and non-biocidal use in swimming pools) will lead to negligible consumer exposure, because they will be handled by consumers only on an occasional (less than weekly) basis. As necessary background information like the boron content of these products is not present, this conclusion might be not valid and more details are necessary to support them.

In the following, consumer exposure estimates from single uses of boric acid are discussed, including uses with quantified exposure estimates from ECHA (2008a) and RPA (2008). As the vapour pressure of boric acid is negligible, inhalation exposure is only expected from uses in particles or aerosols. According to ECHA (2008a) full absorption of boric acid may be supposed for oral and inhalation routes. For dermal absorption an estimate of 0.5% is given, which is mainly based on mean absorption in the in vivo part of the study from Wester et al. (1998). This absorption is used in the following calculations, but caution should be given to the fact, that these results do not apply to damaged skin, and

that even in intact skin there may be a great variability of dermal boric acid absorption. Moreover, the Committee for Risk Assessment the European Chemicals Agency (RAC) is currently discussing an opinion on the use of boric acid and boron compounds in photographic products for consumers, which will also cover dermal absorption of borates. Therefore, the following consumer exposure calculations might need a revision after the publication of the RAC opinion.

1.1.3 Consumer uses under the scope of REACH

1.1.3.1 Detergents

According to HERA (2005), boric acid is used in liquid laundry products in concentrations up to 1% and in automatic dishwashing liquids in concentrations up to 2%. The following assessments for systemic exposure to boric acid from dermal contact to detergents have been provided by HERA (2005). Dermal boric acid intake was calculated as the absorbed content of a thin layer of 0.01 cm thickness on the exposed skin surface area, using a value of 0.4% for dermal absorption in 24 hours derived from Wester (1998) and adapting this value to the much shorter daily exposure times.

For the calculation of systemic boric acid exposure due to hand laundry washing, contact time was assumed as 10 minutes, exposed surface as 1980 cm² (hands and forearms), frequency of tasks per week as typically 4 and maximum 10, boric acid concentration of the diluted product as 0.1 mg/ml, body weight as 60 kg.

Pre-treatment of laundry with the neat product is often done in order to remove spots from the clothes. For the calculation of systemic boric acid exposure due to laundry pretreatment, contact time was assumed as 10 minutes (worst case), exposed surface as 840 cm² (hands), frequency of tasks 1 per day (worst case), boric acid concentration of the neat product as 10 mg/ml, body weight as 60 kg.

For the calculation of systemic boric acid exposure due occasional misuse of liquid laundry detergent for dish washing, contact time was assumed as 45 minutes (worst case), exposed surface as 1980 cm² (hands), frequency of tasks as 1 per week (worst case), boric acid concentration of the diluted product as 0.02 mg/ml, body weight as 60 kg.

Table 2: Exposure estimates for household cleaning products, adopted from HERA (2005)

Scenario	**Worst case** mg /kg bw/day		**Typical case** mg /kg bw/day	
	Boric Acid	**Boron**	**Boric Acid**	**Boron**
Hand laundry washing	1.30E-06	2.30E-07	5.00E-07	1.00E-07
Laundry pretreatment	4.00E-05	7.00E-06		
Misuse of product for hand dishwashing	8.00E-07	1.50E-07		

1.1.3.2 Fertilisers

No representative data have been published on boric acid contents in fertilisers. According to ECHA 2008a, fertilisers for consumer use generally contain 0.02% boron as a concentrate solution or as granules and 0.2 ppm boron in the diluted final working solution. In our research, similar boron contents were found in fertilisers for consumer use. Concentrations in a diluted mixture were 2-7 ppm (Compo 2009). Boric acid concentrations in fertiliser sticks were <1% (Scotts 2005).

RPA (2008) gives boron contents of 2% to 14%, stressing that in some geographic regions, farmers constitute a considerable portion of the local general population, and the purchase of fertilisers is generally open to both, professional farmers and the general public. The authors assessed an occasional oral exposure of 10 mg boron/day from fertilisers. In our research, boric acid fertilisers for professional use with boron contents up to 17.4% were found (Bodenverbesserungs-GmbH, 2009). But use of these agricultural products by the general public may not be very likely, because it requires special agricultural machinery. Moreover, fertilisers will not be ingested in pure form under normal use conditions.

For a diluted fertiliser solution with a boron content of 5 ppm spilled on the area of one hand (428 cm^2 according ConsExpo General Fact Sheet, RIVM 2006), a worse case dermal exposure can be calculated using equations 15-5, 15-6 and 15-7 from ECHA Guidance on consumer exposure estimation (ECHA 2008b). Assuming weekly use, a thickness of the layer on the hand of 0.01 cm, 0.5% dermal absorption and 60 kg body weight, a worst case dermal exposure of 1.5E-6 mg boric acid/kg bw/day or 2.6E-7 mg boron/kg bw/day can be derived. Typical exposure from spilling drops is assumed to be one order of magnitude lower.

Boron intake from hand mouth contact to fertiliser in soil may be possible for playing children of 1-4 years. As soil concentrations of fertiliser are not known, a boron concentration of 5 ppm in a diluted fertiliser mixture is used as a rough estimation. AUH (1995) gives an upper estimate for soil intake by 1 to 4 year old children of 100 mg/day and a median of 20 mg. On this basis, for a child with 10 kg body weight a worst case oral exposure of 2.9E-4 mg boric acid/kg bw/day or 5E-5 mg boron/kg bw/day and a typical oral exposure of 5.7E-5 mg boric acid/kg bw/day or 1E-5 mg boron/kg bw/day can be calculated.

1.1.3.3 Toys

Boric acid is used as a component in slimy toys. Concentrations up to 8% were reported in “silly putty”, which has properties of a cross between play dough and a rubber ball. Playing children may be exposed to boric acid from “silly putty” by the oral and the dermal route.

Release of boric acid in the stomach by stomach acid from an ingested 17-g-package of “silly putty” with 8% boric acid has been simulated according to EN 71-3 (1h in 0.07 N HCl at 37°C after cutting into cubes of 5 mm edge length), which results in the release of up to 0.442 g boric acid or 0.078 g boron (BfR, 2005). If a 20 kg child swallowed accidentally the contents of a commercial 17-g-package of “silly putty”, this release would result in a worst case oral exposure of up to 22.1 mg boric acid/kg bw/day or 3.9 mg boron/kg bw/day. A typical ingestion would be comparable to the assumption of 1 g for modelling clay in the ConsExpo Toys fact Sheet (RIVM 2002), resulting in an oral exposure of up to 1.3 mg boric acid/kg bw/day or 0.227 mg boron/kg bw/day.

Up to 100 mg boric acid corresponding to 17.4 mg boron were released from a 17-g-package of “silly putty” into artificial sweat in a test according to DIN 53160-2 (1 h shaking at pH 6.5 and 37°C, BfR, 2005). This simulation result may be used as an estimate for external dermal exposure to the hands of a playing child. With an uptake fraction of 0.5% through intact skin (ECHA 2008a) and 20 kg body weight, an exposure of up to 0.025 mg boric acid/kg bw/day or 0.036 mg boron/kg bw/day can be calculated.

1.1.3.4 Mattresses

Boric acid is used as a flame retardant in the wadding (or cotton batting) of mattresses, futons and other upholstered furniture. The boric acid concentration in the cotton batting is typically 10% (RPA, 2008). In a study for industry, Murray (2005) provided an upper bound estimate for systemic boron exposure of 0.013 mg/day for adults (corresponding 0.0002 mg/kg bw/day for a 60 kg person) and 0.140 mg/day for children (corresponding 0.014 mg/kg bw/day for a 10 kg child). CPSC (2006) calculated systemic boron exposures of 0.081 mg/day for adults (corresponding to 0.00135 mg/kg bw/day for a 60 kg person) and 0.088 mg/day for children (corresponding to 0.0046 mg/kg bw/day for a 19 kg child).

1.1.3.5 Cellulose Insulation

Boric acid is used as a flame retardant (with also fungicide properties) in cellulose insulation material. In this application, shredded post-consumer recycled paper is mixed with boric acid, other borates or with a mixture of boric acid and other borates. The resulting product is blown into attics and in cavity walls. As this work requires special knowledge and equipment, it is normally not supposed to be done by non-professionals. However, in a study on personal dust monitoring in construction work, manual installation of cellulose insulation was documented with respirable particle concentrations of 2.75 mg/m³ (BTU 2000). With a boric acid concentration of 5% with another 5% disodium decaborate (Seppele 2009), 0.3 days exposure time, 60 kg body weight and an inhalation rate of 33 m³/day (default for a 60 kg person at light exercise according RIVM 2005) an inhalation exposure of 0.004 mg boron/kg bw/day from 0.023 mg boric acid/kg bw/day can be calculated. Another 0.0025 mg boron/kg bw/day derives from disodium decaborate. This kind of consumer exposure will be limited to occasional projects.

1.1.3.6 Glass Wool Insulation

According to the ECHA, 2008a boron content in glass wool is 5% as B_2O_3 or 1.5% as B, with maximal contents of 12% as B_2O_3 (3.6% as boron). In residential buildings, institutions and offices the levels of respirable glass fibres are negligible under normal use conditions. Non-occupational consumer exposure may occur during do-it-yourself installation or removal of glass wool insulation. Fibre concentrations during glass wool insulation work typically range between 0.003 and 1 fibre/cm³ (for a more in depth discussion see ECHA, 2008a). Based on a critical review of studies on exposures to man-made vitreous fibres (IARC, 2002), Jensen (2009) calculated a daily exposure based on a total work day (8 hours) at the occupational limit value of 1 fibre/cm³, 100% retention and 100% solubility of the retained fibres in the lungs. Boron exposure was 0.03–0.06 mg for fibres with a boron content of 1.5% (0.08-0.16 mg for fibres with a maximum boron content of 3.6%). Assuming 60 kg body weight, the daily boron exposure of 0.03-0.06 mg equalizes 0.005–0.01 mg/kg bw/day. An upper limit fibre concentration was used for this calculation and consumer exposure will typically be limited to home improvement projects of about 5 days.

1.1.3.7 Photographic applications

Consumer health risks from boric acid and its compounds in photographic applications are the subject of a request by the European Commission to the Committee for Risk Assessment of the European Chemicals Agency (RAC) according to Art. 77 of the REACH regulation. The RAC opinion still was not adopted at the time this dossier was finalised.

1.1.3.8 Other products

According to RPA (2008) and ECHA (2008a) boric acid is widely used in lubricants, metalworking fluids, water treatment chemicals including swimming pool treatment and fuel additives, and some of these products are placed on the market for use by the general public. Use of boric acid in lubricants may include patented use of boric acid with a crystal dimension of 0.1-40 microns (Erdemir 2000). Consumer exposure to such boric acid nanoparticles may be possible through spilling and hand mouth

contact to fuels, motor oils and greases. Quantitative information on consumer exposure from these uses is still lacking.

1.1.3.9 House dust

House dust represents an aggregate of boron exposure from various sources. No recent data on boron content in house dust were found. In a representative study on settled dust in 3282 living rooms, a median dust sink rate of 4.52 mg/m²/day and a median boron sink rate of 0.13 µg/m²/day were determined (Umweltbundesamt, 2001). These boron contents may derive from different natural sources and from boric acid and borates in products. For a 10 kg child ingesting 100 mg house dust per day by hand mouth contact a worst case external exposure of 0.0003 mg boron/kg bw/day can be calculated from these values. The typical case would be ingestion of 20 mg house dust per day, leading to an external exposure of 0.00006 mg boron/kg bw/day.

1.1.4 Consumer Products under Sectoral Regulation

1.1.4.1 Cosmetics

According to Annex II of the Cosmetics Directive 76/768/EEC, boric acid is permitted in cosmetic products at a maximum of 5% in powders, 0.1% in oral hygiene products and 3% in other products. There are no analytical data or other information indicating the degree to which these limits are exhausted. Assuming 100% exhaustion of the limits, consumer use patterns in SCCP (2006), use of all covered cosmetic products by a 60 kg person, an uptake fraction through intact skin of 0.5% and 100% uptake for lipstick, toothpaste and mouthwash, an internal exposure of 0.1129 mg boric acid/kg bw/day or 0.0197 mg boron/kg bw/day can be calculated. However, as indicated by RPA (2008), use of boric acid in cosmetics is expected to be prohibited according to the Cosmetics Directive, due to its classification as Reprotoxic 1 B by Commission Regulation (EC) No 790/2009.

1.1.4.2 Food Contact Materials:

Glazed Ceramic Ware

Based on data from a study on metal migration from glazed ceramic ware by the Food Standards Agency (Bradley and Castle, 2003), the Transitional Dossier (ECHA 2008a) provides an exposure calculation using a maximal use assumption of items used for eating and drinking (plates, bowls and cups) once each day. For a 60 kg person a maximal boron exposure from glazed ceramic ware of 0.116 mg/day or 0.00193 mg/kg bw/day is calculated. A more typical boron exposure estimation of 0.017 mg/day is based on weekly use.

Glass

The Transitional Dossier (ECHA, 2008a) cites a study on elemental migration from glass in contact with food (GTS, 2002). The migration of boron into water, acetic acid, ethanol, and olive oil from borosilicate glass, soda lime silica glass and lead crystal glass was determined. In most cases, no boron was detected above the reporting limit of 0.03 ppm. Only in one study of 10 samples tested of lead crystal ware using water, one sample resulted in a value above the reporting limit (0.06 ppm).

Other food contact materials

The Commission Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs provides a specific migration limit (SML) for boric acid of 6 mg/kg as boron. Exhausting this limit, a 60 kg person consuming 1 kg food per day would be exposed to 0.1 mg boron/kg bw/day. There are no analytical data or other information indicating the degree to which the SML is exhausted.

1.1.4.3 Biocides

Boric acid has been used on a large scale in biocides as fungicides and insecticides. It has been used in wood preservatives in 0.1-10% solutions to impregnate timber and in dry rot treatment in 10-15% solutions. However, as indicated by RPA (2008), consumer use of boric acid in biocides is expected to be restricted according to the Biocides Directive 98/8/EC, due to its classification as Reprotoxic 1 B by Commission Regulation (EC) No 790/2009.

1.1.4.4 Mineral Water

For mineral waters, boron contents of 0.75 mg/L (mean) and 4.35 mg/L (maximum) have been determined (Moore 1997, cited in BfR (2006a), BfR (2006b) and EFSA (2004)). Assuming a daily mineral water consumption of 2 L of for a 60 kg adult and 100% brand loyality, boron exposures of 0.025 mg/kg bw/day (mean) and 0.145 mg/kg bw/day (maximum) can be calculated. For a 10 kg child consuming 1 L of mineral water per day with 100% brand loyality, exposures would be 0.075 mg/kg bw/day (mean) and 0.435 mg/kg bw/day (maximum).

1.1.4.5 Food Supplements

Boric acid may be used in different forms and formulations as food supplement. The amounts of boron contained in food supplements as borax or boric acid are determined by the individual manufacturers. According to company dossiers, daily intake from boric acid and borax in food supplements is normally in the range of 1-3 mg boron (up to 0.05 mg/kg bw/day) for a 60 kg person, with unlimited duration as the normal recommended dose of boron for self-selection. However, products were available over the counter in EU Member States leading to daily intakes of up to 9 mg boron (higher daily quantities are prescribed by nutritional practitioners to consumers under supervision at levels of up to 9 mg/day). Food supplements for bodybuilders may possibly lead to maximum boron intakes of up to 30 mg/day (0.5 mg/kg bw/day) for a 60 kg person, BfR 2006a.

1.2 Indirect exposure through the Environment

1.2.1 Exposure through diet

According to EFSA (2004), data on boron intake in Europe are limited. Boron intakes in adults in the UK have been estimated by EFSA (2004) from analysis of samples from the 1994 Total Diet Study using consumption data from the 1986/87 Dietary and Nutritional Survey of British Adults as 1.5 mg/day (mean) and 2.6 mg/day (97.5 percentile). For a 60 kg person, these intakes would correspond to 0.025 mg/kg bw/day (mean) and 0.043 mg/kg bw/day (97.5 percentile).

2 INFORMATION ON ALTERNATIVES

No information on alternatives.

3 RISK-RELATED INFORMATION

No information on risks.

4 OTHER INFORMATION

5 REFERENCES

Ausschuss für Umwelthygiene (AUH), 1995: Standards für Expositionsabschätzung. Bericht des Ausschusses für Umwelthygiene. Behörde für Arbeit, Gesundheit und Soziales (Hrsg.), Hamburg 1995 http://www.uke.de/institute/biometrie/downloads/institut-medizinische-biometrie-epidemiologie/AUH.pdf retrieved on 9 November 2009

Aleman CL, Mas RM, Rodeiro I, Noa M, Hernandez C, Menendez R and Gamez R, 1998, Reference database of the main physiological parameters in Sprague-Dawley rats from 6 to 32 months. Laboratory Animals 32: 457-466.

Bodenverbesserungs-GmbH, 2009 : BvG-Bor 17,4 G, Product information. http://www.bvg-rain.de/pdf/bor17,4gneu.pdf , retrieved on 9 November 2009

Bradley E and Castle L, 2003: An investigation of the migration of metals from glazed ceramic ware. Laboratory Report Number FD 01/7. Food Standards Agency, London, cited by ECHA (2008a)

Büro für Technischen Umweltschutz (BTU) 2000: Untersuchung der Staubbelastung an ausgewählten Arbeitsplätzen der hessischen Bauwirtschaft. http://projekte.sozialnetz.de/projekt/NWB/downloads/publikationen/projektbericht.pdf retrieved on 9 November 2009

Bundesinstitut für Risikobewertung (Federal Institute for Risk Assessment, BfR), 2005: Borsäure in Hüpfknete. Gesundheitliche Bewertung Nr. 014/2005 des BfR vom 27. Oktober 2004. http://www.bfr.bund.de/cm/216/borsaeure_in_huepfknete.pdf retrieved on 9 November 2009

Bundesinstitut für Risikobewertung (Federal Institute for Risk Assessment, BfR), 2006a: Addition of boric acid or borax to food supplements. BfR Health Assessment No. 006/2006, 16 November 2005. http://www.bfr.bund.de/cm/245/addition_of_boric_acid_or_borax_to_food_supplements.pdf 9 November 2009

Bundesinstitut für Risikobewertung (Federal Institute for Risk Assessment, BfR), 2006b: Höchstmengen für Bor und Fluorid in natürlichen Mineralwässern sollten sich an Trinkwasserregelungen orientieren. Stellungnahme Nr. 024/2006 des BfR vom 7. Februar 2006 http://www.bfr.bund.de/cm/208/hoechstmengen_fuer_bor_und_fluorid_in_natuerlichen_mineralwaessern_sollten_sich_an_trinkwasserregelungen_orientieren.pdf

COMPO GmbH & Co. KG, 2009: COMPO Hakaphos-Nährsalz, Product Information. http://www.compo-hobby.de/hakaphos-gartenprofi%28hb5%29_produktinfo_09-10_adl_3_4079.file retrieved on 9 November 2009

Commission Directive 2002/72/EC of 6 August 2002 relating to plastic materials and articles intended to come into contact with foodstuffs (OJ L 220/58, 15/8/2002, p.18)

Commission Regulation (EC) No 790/2009 of 10 August 2009 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (OJ L 235/1, 5/9/2009)

Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (OJ L262, 27/9/1976, p169)

Cordia JA, Bal EA, Mak WA and Wils ERJ, 2003a, Determination of some physico-chemical properties of Optibor EP. Rijswijk, The Netherlands: TNO Prins Maurits Laboratory, report PML 2002-C42rr, GLP, Unpublished, confidential data provided by Borax Europe Limited.

Cordia JA, Bal EA, Mak WA and Wils ERJ, 2003b, Determination of some physico-chemical properties of Neobor. Rijswijk, The Netherlands: TNO Prins Maurits Laboratory, report PML 2002-C41rr to C43rr, GLP, Unpublished, confidential data provided by Borax Europe Limited.

CPSC 2006: Quantitative Assessment of Potential Health Effects from the Use of Fire Retardant (FR) Chemicals in Mattresses. Report prepared by the US Consumer Product Safety Commission, dated January 2006, cited by RPA 2008

Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market (OJ L123/1, 24/4/1998, p.1)

Erdemir A: Lubrication with Boric Acid Additives. United States Patent Number 6,025,306. Date of Patent: 15 February 2000.

European Chemicals Agency (ECHA) 2008a: Annex XV transitional reports. Boric acid http://echa.europa.eu/doc/trd_substances/boric_acid/ann_xv_trd/trd_austria_boric_acid.pdf

European Chemicals Agency (ECHA), 2008b: Guidance on information requirements and chemical safety assessment. Chapter R.15: Consumer exposure estimation, Version 1.1, May 2008 http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm retrieved on 9 November 2009

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). (Adopted on 9 July 2004, Request N° EFSA-Q-2003-018.) The EFSA Journal (2004) 80, 1-22.http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178620766601.htm retrieved on 9 November 2009

Federal Office of Public Health (FOPH), 2009: Borsäure Expositionsinformation. Communication to the Federal Institute for Risk Assessment (BfR), 12 December 2009

Fail PA, George JD, Sauls HR, Dennis SW, Seely JC, 1989, Effects of boric acid on reproduction and fertility of rodents Adv Contracept Delivery Syst. 1989; 5: 186-96

Fail PA, George JD, Seely JC, Grizzle TB and Heindel JJ, 1991, Reproductive toxicity of boric acid in Swiss (CD-1) mice: assessment using the continuous breeding protocol. Fund. Appl. Toxicol. 17: 225-239.

Glass Technology Services Ltd (GTS), 2002: Investigation of the Significant Factors in Elemental Migration From Glass in Contact With Food – Final Report. Project code A03029, cited by ECHA (2008a)

Grella P, Tambuscio B and Suma V, 1976, Boric acid and poisoning during pregnancy: Description of one case. Acta Anaestesiol. Ital. 27: 745-748 (in Italian).

Heindel JJ, Price CJ, Field EA, Marr MC Myers CB, Morrissey RE and Schwetz BA, 1992, Developmental toxicity of boric acid in mice and rats. Fund. Appl. Toxicol. 18: 266-272.

HERA, 2005: Human and Environmental Risk Assessment on Ingredients of Household Cleaning Products. Boric acid (CAS No 10043-35-3), Edition 1.0. http://www.heraproject.com/files/27-F-06_HERA_Boric_Acid%20_Jan_2005.pdf retrieved on 9 November 2009

International Agency for Research on Cancer (IARC), 2002: Man-made Vitreous Fibres. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 81, cited by Jensen (2009)

Ingri N, 1963, Equilibrium studies of polyanions containing BIII, SiIV, GeIV and VV. Sven. Kem. Tidskr. 75(4): 199-230.

Jensen, AA, 2009: Risk assessment of boron in glass wool insulation. Environ Sci Pollut Res, 16: 73-78.

KEMI (Swedish Chemicals Agency), 2009, Boric acid exposure information. Communication to the Federal Institute for Risk Assessment (BfR), 17 December 2009

Ku WW, Chapin RE, Wine RN and Gladen BC, 1993, Testicular toxicity of boric acid (BA): Relationship of dose to lesion development and recovery in the F344 rat. Reprod. Toxicol. 7: 305-319.

Matsuzawa T, Nakata M, Goto I, and Tsushima M, 1981, Dietary deprivation induces fetal loss and abortion in rabbits, Toxicology, 22, 255-259

Mellor's Comprehensive Treatise on Inorganic & Theoretical Chemistry, Volume V Boron, Part A: Boron-Oxygen Compounds, 1980, Longman London and New York, ISBN 0-582-46277-0

Merck Index, 10th edition, Windholz, M. (ed.), 1983, Rahway N.J. USA

Moore JA and an Expert Scientific Committee, 1997, An assessment of boric acid and borax using the IEHR evaluative process for assessing human developmental and reproductive toxicity of agents. Repro. Toxicol. 11: 123-160 and NTIS Technical Report PB96-156005, March, 1995.

Murray FJ (2005): Risk Assessment of Mattresses with Borate-Treated Cotton Batting Before and After the Roller Test. Report prepared for Jones Fiber Products dated August 2005, cited by RPA (2008)

NTP (National Toxicology Program), 1987, Toxicology and carcinogenesis studies of boric acid (CAS No. 10043-35-3) in B6C3F1 mice. National Toxicology Program, US Department of Health and Human Services, National Institute of Health (Technical Report Series No. 324).

NTP (National Toxicology Program), 1990, Final report on the Reproductive Toxicity of Boric Acid (CAS NO. 10043-35-3) in CD-1 Swiss Mice. National Toxicology Program, NTP Report # 90-150

Parker JA, Macgregor JA and Schroeder RE, 1986, Diet restriction during gestation in NZW rabbits does not adversely affect fetal outcome, Teratology, 33, 71C

Price CJ, Strong PL, Marr MC, Myers CB and Murray FJ, 1996a, Developmental toxicity

NOAEL and postnatal recovery in rats fed boric acid during gestation. Fund. Appl. Toxicol. 32: 179-193.

Price CJ, Marr MC, Myers CB, Seely JC, Heindel JJ and Schwetz BA, 1996b, The Developmental Toxicity of Boric Acid in Rabbits, Fund. Appl. Toxicol. 34: 176-187.

Risk & Policy Analysts Limited (RPA), 2008: Assessment of the Risk to Consumers from Borates and the Impact of Potential Restrictions on their Marketing and Use. Final Report – November 2008, prepared for European Commission, DG Enterprise and Industry. http://ec.europa.eu/enterprise/newsroom/cf/itemshortdetail.cfm?item_id=3231&lang=de retrieved on 9 November 2009

RIVM, 2002: Bremmer HJ, van Veen MP: Children´s Toys Fact Sheet. To assess the risks for the consumer. RIVM report 612810012/2002 http://www.rivm.nl/bibliotheek/rapporten/612810012.pdf retrieved on 9 November 2009

RIVM, 2005: Delmaar JE, Park MVDZ, van Engelen JGM: ConsExpo 4.0, Consumer Exposure and Uptake Models Program Manual. RIVM report 320104004/2005 http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp retrieved on 9 November 2009

RIVM, 2006: Bremmer HJ, Prud'homme de Lodder LCH, van Engelen JGM: General Fact Sheet. Limiting conditions and reliability, ventilation, room size, body surface area. Updated version for

ConsExpo 4, RIVM report 320104002/2006. http://www.rivm.nl/bibliotheek/rapporten/320104002.pdf retrieved on 9 November 2009

Robbins, WA, Wei, F, Elashoff, DA, Wu, G, Xun, L, and Jia, J (2008), Y:X sperm ratio in boron-exposed men. J. Androl 29, 115-121.

Sayli B.S., 1998, Assessment of fertility and infertility in boron-exposed Turkish subpopulations. Pt. 2. Evidence that Boron has no effect on human reproduction, Biol. Trace Elem. Res. 66: 406-422.

Sayli BS, 2001, Assessment of fertility and infertility in boron-exposed Turkish subpopulations. Pt. 3. Evaluation of fertility among sibs and in 'borate families'. Biol. Trace Elem. Res. 81: 255-267.

Sayli B.S., 2003, Low frequency of Infertility among workers in a borate processing facility, Biol. Trace Elem. Res, 93, 19-30

Scialli, AR, Bonde, JP, Brüske-Hohlsfeld, I, Culver, D, Li, Y and Sullivan, FM 2009, An overview of male reproductive studies of boron with an emphasis on studies of highly exposed Chinese workers. Reproductive Toxicology, in press.

Scientific Committee on Consumer Products (SCCP), 2006: The SCCP´s Notes of Guidance for Testing of Cosmetics Ingredients and their Safety Evaluation. 6th Revision. http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_03j.pdf retrieved 9 November 2009

Scotts CELAFLOR GmbH Co KG, 2005: Sicherheitsdatenblatt für SUBSTRAL Dünger-Stäbchen für Blühpflanzen, überarbeitet am 31-Jän-2005. http://images.raiffeisen.com/Raicom/sdb/4062700000007/7313_200602060941.pdf Retrieved on 9 November 2009

Seppele, 2009: DIN-Sicherheitsdatenblatt zu Thermofloc, P. Seppele GmbH. http://www.thermofloc.com/pruefberichte retrieved on 4 November 2009

Tarasenko NY, Kasparov AA, and Strongina OM, 1972, Effect of boric acid on the generative function in males, Gigiena Truda i Professionalnye Zabolevaniaya, 1972, 11, 13-16

Treinen KA and Chapin RE, 1991, Development of testicular lesions in F344 rats after treatment with boric acid, Toxicol. Appl. Pharmacol. 107: 325-335.

Umweltbundesamt (Ed.) (2001): Friedrich, C, Helm D, Becker K et al.: Umwelt-Survey 1990/92, Band VI: Hausstaub. Deskription der Element- und Biozidgehalte im Hausstaub in der Bundesrepublik Deutschland. WaBoLu-Hefte Nr. 01/2001

Webster RC, Hui X, Hartway T et al., 1998: In vivo Percutaneous Absorption of Boric Acid, Borax and Disodium Octaborate Tetrahydrate in Humans Compared to in Vitro Absorption in Human Skin from Infinite and Finite Doses. Toxicological Sciences 45, 42-51

Weir RJ, 1962, 90 Day dietary administration - rats Boric acid. Hazleton Laboratories Inc., Falls Church, VA. Unpublished report to US Borax Research Corporation, December 12, 1962.

Weir RJ, 1966a, Two-year dietary feeding study - albino rats. Boric acid. Final Report. Hazleton Laboratories Inc., Falls Church, VA, July 8th, 1966 and Addendum to Final Report. Unpublished report to US Borax Research Corporation, April 10, 1967.

Weir RJ, 1966b, Three-generation reproductive study - rats. Boric acid. Final Report. Hazleton Laboratories Inc., Falls Church, VA. Unpublished report to US Borax Research Corporation, July 8, 1966.

Weir RJ, 1966c, Two-year dietary feeding -dogs - Boric acid. Hazleton Laboratories Inc., Falls Church, VA. Unpublished report to US Borax Research Corporation, 8 July 1966.

Weir RJ and Fisher RS, 1972, Toxicologic studies on borax and boric acid. Toxicol. Appl. Pharmacol 23: 351-364.

WHO, 1998, Guidelines for drinking water. Second edition. Geneva, World Health Organisation, 1- 20.

Whorton MD, Haas JL, Trent L. and Wong O, 1994, Reproductive effects of sodium borates on male employees: birth rate assessment. Occup. Environ. Med. 51: 761-767.

Wilding JL, Smith WJ, Yevitch P, Sicks ME, Ryan SG and Punte CL, 1959, The toxicity of boron oxide. Am. Ind. Hyg. J. 20: 284-289.

6 ABBREVIATIONS

GD	Gestational day
LOAEL	Lowest Observed Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
PND	Postnatal day

ANNEX 1

Toxicokinetics (absorption, metabolism, distribution and elimination)

The toxicokinetics of boric acid has been investigated by different uptake routes (oral, dermal, inhalation) in various animal species as well as in humans.

Absorption of boric acid via the oral route is nearly 100%. For the inhalation route also 100% absorption is assumed (based on animal studies performed with boron oxide (Wilding et al., 1959)). 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. Boric acid is not further metabolised. Boric acid is distributed rapidly and evenly through the body, with concentrations in bone 2 - 3 higher than in other tissues. Boron is excreted rapidly, with mean elimination half-lives of 1h in the mouse, 3h in the rat and 13.4 h in humans (range 4 – 27.8 h), and has low potential for accumulation. Differences in renal clearance are the major determinant for the observed species differences. Boric acid is mainly excreted in the urine (ECHA, 2008a).

From a poisoning case with boric acid in a pregnant woman it could be deduced, that boric acid (or borates in general) is able to cross the placenta (Grella et al., 1976).

Table 3: Summary of toxicokinetics of boric acid (taken from ECHA (2008a) with minor modifications)

Absorption	Rapidly and virtually completely absorbed by the oral route Very low absorption through intact skin.
Distribution	Rapidly distributed through body water; no accumulation in tissues. Concentration in bones 2-3 times higher than in other tissues.
Metabolism	No metabolism. Presence in whole blood mainly as boric acid
Excretion	Excreted almost exclusively in the urine. Half-life up to 27.8 hours in humans, 3h in the rat and 1h in the mouse

Repeated dose toxicity

Repeated dose toxicity: oral

Boric acid has been investigated after subchronic and chronic administration to rats, mice and dogs (NTP, 1987; study summaries in ECHA, 2008 and Weir and Fisher, 1972). Although not all of these investigations comply with current test guidelines or GLP principles, the investigations identify the haematological system and the testes as the main targets of toxicity of boric acid. These results are further supported by investigations with other borates (e.g. disodium tetraborate decahydrate).

Key repeat dose studies on boric acid are summarized in Table 3. The dosage in mg/kg was indicated as boron mg/kg bw/d since the boron ion is the toxicologically significant chemical species.

Although not conforming to modern protocols, data on several effects can be obtained from a 90 day study in Sprague-Dawley rats fed 0, 52.5, 175, 525, 1750, 5250 ppm boric acid equivalent to 0, 2.6, 8.8,

26, 88 and 260 mg boron/kg bw/day (10 males and 10 females per group). All animals that received the highest 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 of 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. Although, testicular atrophy is also occasionally seen in young and old un-treated Sprague-Dawley rats (Aleman et al., 1998), the observed effects, one third of the tubules was completely atrophic, while the rest presented an arrest of spermatogenesis usually in the spermatocyte stage, were judged adverse. The NOAEL was determined to be 8.8 mg boron/kg bw/day (Weir, 1962 (summarized in ECHA, 2008 and Weir and Fisher, 1972)).

In a 2 year feeding study on boric acid in Sprague-Dawley rats, testes and blood were identified as major target organs (Weir, 1966a (summarized in ECHA, 2008a and Weir and Fisher, 1972)). Rats were dosed with 0, 670, 2000, and 6690 ppm boric acid, equivalent to 0, 33, 100, 334 mg boric acid/kg bw/day (equivalent to 0, 5.9, 17.5 and 58.5 mg boron/kg bw/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, as well as reductions in body weight were observed in males and females of the highest dose group. Further the scrotum of all males of the high dose group was of shrunken appearance. Decreased red cell volume and haemoglobin were observed in rats treated with boric acid. Blood samples were taken after 1, 2, 3, 6, 12, 18 and 24 months. The observations on haematology over time were not always consistent; however, at the end of the study the values in all dosed animals were reduced compared to control.
Therefore, in the present studies the inconsistencies found after two years can be regarded as coincidental and do not allow a conclusive interpretation. A more in-depth discussion on the haematological findings of this study is given in ECHA (2008a).
Testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months at the highest dose level. Microscopic examination of the tissue revealed atrophied seminiferous epithelium and decreased tubular size in the testes. No effects were observed in control, low and mid dose groups. Based on the testicular atrophy and the haematological effects observed at the highest doses tested (6690 ppm boric acid) a NOAEL for chronic effects equal to 17.5 mg boron/kg bw/day (equivalent to 100 mg boric acid /kg bw/day) can be derived.

In a mouse study carried out for 13/16 weeks, B6C3F1 mice were fed diets containing 0,1200, 2500, 5000, 10000, 20000 ppm boric acid, equivalent to 0, 194, 405, 811, 1622, 3246 mg boric acid/kg bw/day (corresponding to 34, 71, 142, 284, 568 mg B/kg bw/d) in males and 0, 169, 560, 1120, 2240, 4480 mg boric acid (mg boron)/kg bw/day (corresponding to 47, 98, 196, 292, 784 mg boron/kg bw/day) in 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 the end of the 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. Hyperkeratosis and/or acanthosis of the stomach were observed at the highest dose only, in both males and females. Further, extramedullary haematopoiesis of the spleen of minimal to mild severity was observed in all dose groups for both males and females. The numbers of animals per group which displayed this symptom are as follows: 1/10, 3/10, 5/10, 5/10, 10/10, 1/10 in males and 0/10, 2/10, 4/10, 6/10, 10/10, 2/10 in females in the 0, 1200, 2500, 5000, 10000, 20000 ppm groups, respectively. Despite the fact that extramedullary haematopoiesis occurs naturally in mice, there was a dose response relationship evident. The lower incidence at the highest dose can be explained by death of the animals and their bad general condition. In the absence of any haematology data there is no direct evidence of anaemia and since nothing is

reported on occurrence of haemosiderin it can be assumed that it was not present. The incidences in the low dose group of 3/10 (m) and 2/10 (f) are in the range of historical control data from NTP studies. This dose could therefore be seen as the NOAEL in this study. However, since there is no direct evidence of anaemia the effects on testes seen at doses > 5000 ppm are the first adverse effects observed and support a NOAEL of 142 mg B/kg bw/day (NTP, 1987).

Testicular atrophy with some interstitial cell hyperplasia was observed in the top dose in a US National Toxicology Program (NTP) bioassay in B6C3F1 mice fed 0, 2500, 5000 ppm in food for 2 years equivalent to 0, 446 and 1150 mg boric acid/kg bw/day, equivalent to 78.1 and 201.3 mg boron/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. Based on the observed testicular effects a NOAEL of 78.1 mg boron/kg bw/day can be derived (NTP, 1987).

The 90 day dog studies on boric acid (reviewed in Weir and Fisher, 1972) is of limited value and considered inadequate for risk assessment (see ECHA, 2008a), although they support qualitatively that Boron can cause adverse haematological effects and that the main target organ of boron toxicity is the testis. 5 female and male Beagle dogs per group 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 boron/kg/day based on the actual body weight and food consumption data in the study.
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 haemosiderin was also present in reticular cells of the liver and spleen and the proximal tubule of the kidney, indicating increased red blood cell destruction. Additionally a decrease in haematocrit and haemoglobin values was seen in this group for males and females treated with boric acid. A combination of these effects is a clear indication for increased red blood cell destruction even though all the clinical laboratory findings from blood and urine samples were within normal limits and comparable to controls. However, the blood effects observed (HB, HCT, extramedullary haematopoiesis, hemosiderin) are slight and not consistently dose dependent (for a more in-depth discussion of haematological effects see ECHA (2008a).

Two 2 year oral toxicity studies in beagle dogs have been performed with boric acid and the testes were identified as a main target organ. The study had major deficiencies and has been regarded as inadequate for risk assessment, but does confirm the effects seen in other species. Groups of four male dogs were fed boric acid at doses up to 10.9 mg boron/kg bw/day (62.4 mg boric acid/kg bw/day) in one study and 41 mg boron/kg bw/day (233.1 mg boric acid/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. 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 dog was allowed to recover for three weeks. Some recovery was observed. Histopathological changes such as decreased spermatogenesis remained. The NOAEL was deemed to be the equivalent of 10.2 mg B/kg bw/day by the authors (Weir, 1966c (reviewed in ECHA, 2008a and Weir and Fisher, 1972)).

Table 4: Key repeat dose toxicity studies performed with boric acid (adopted from ECHA, 2008a)

Route	Study duration	Species Strain Number of animals (per sex and group)	Dose levels	Results	LO(A)EL	NO(A)EL	Reference
Oral (diet)	13 weeks for control and top dose group, 16 weeks for other dose groups	Mouse, B6C3F1 10	0, 1200, 2500, 5000, 10000, 20000 ppm (equivalent o 0, 194, 405, 811, 1622, 3246 boron mg/kg bw/day in males) (equivalent to 0, 169, 560, 1120, 2240, 4480 boron mg/kg bw/day in females) (equivalent to 0, 34, 71, 142, 284, 568 mg boron/kg bw/day in males) (equivalent to 0, 47, 98, 196, 392, 784 mg boron/kg bw/day)	At ≥ 142 mg Boron/kg bw/d: degeneration and atrophy of the seminiferous tubules At all dose levels extra medullary haematopoiesis of the spleen	≥ 142 mg Boron/kg bw/day in males 196 mg Boron/kg bw/day in females	71 mg Boron/kg bw/day in males 98 mg Boron/kg bw/day in females	NTP, 1987
Oral in diet	90 day	Rat Sprague-Dawley 10	0, 52.5, 175, 525, 1750, 5250 ppm (equivalent to 2.6, 8.8, 26, 88, 260 mg boron/kg bw/day	At ≥ 88 mg Boron/kg bw/day: reduction of body weight; clinical signs of toxicity, testicular atrophy At 26 mg Boron/kg bw/day one male exhibited partial testicular atrophy	26 mg Boron/kg bw/day	8.8 mg Boron/kg bw/day	Weir, 1962 reviewed in ECHA (2008) and Weir and Fisher (1972)
Oral in diet	2 years	Rat	0, 670, 2000,	At 58.5 mg	58.5 mg	17.5 mg	Weir, 1966a

	Interim kills after 6 and 12 months	Sprague-Dawley Control groups: 70 Treatment groups: 35 Groups of interim kill: 5	6690 ppm (equivalent to 0, 33, 100, 334 mg Boric acid/kg bw/day) (equivalent to 0, 5.9, 17.5, 58.5 mg boron acid/kg bw/day)	Boron/kg bw/day: reduction of body weight; clinical signs of toxicity, testicular atrophy, reductions in red cell volume and Hb	Boron/kg bw/day	Boron/kg bw/day	reviewed in ECHA (2008a) and Weir and Fisher (1972)

Other relevant information

Case histories from repeated human exposure to boric acid have not been included in this dossier, because of the several caveats that have been discussed in the Transitional Annex XV dossier (ECHA, 2008a).

Summary and discussion of repeated dose toxicity:

The haematological system and the testes have been identified as the major targets after oral repeat dose exposure to Boric acid. Studies after repeated dermal or inhalation exposure to boric acid are not available. A NOAEL for effects on testes and the blood system of 17.5 mg boron/kg bw/day can be derived (with a LOAEL of 58.5 mg boron/kg bw/day) from two 2-year studies in rats on boric acid. Results obtained with boric acid can be supported by findings obtained from other borates thus indicating that the boron ion is the toxicologically relevant species.

Toxicity for reproduction

Boric acid can impair both fertility and development. From repeat dose studies (see section 5.6 of this dossier) the male reproductive system was identified as a target for the toxic effects of boric acid in rats, mice and dogs. This was confirmed by fertility studies (Fail et al., 1989 (reviewed in Moore et al. 1997)). Fertility studies (which have not performed according to OECD test guidelines) further demonstrated that not only the male, but also the female reproductive system was a target for the toxic effects of boric acid (Weir, 1966b (reviewed in ECHA (2008a) and Weir and Fisher, 1972); NTP, 1990; Fail et al., 1991). In addition, investigations have been performed in order to get a better understanding of male reproductive toxicity (fertility) of boric acid (Treinen and Chapin, 1991; Ku et al., 1993). Key fertility studies are summarized in table 4. Developmental studies with Boric acid have been performed in rats, mice and rabbits. Visceral and skeletal malformations were observed. Key developmental studies are summarized in table 5.

Effects on fertility

In a three generation study in rats groups of 8 males and 16 females were treated with boric acid equivalent to 0, 5.9, 17.5 and 58.8 mg boron/kg bw/day. The high dose P1-generation failed to produce litter. Also when 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 ovaries of high dosed females were examined. Gross necropsy revealed atrophied testes in all P1 males

at 58.8 mg boron/kg bw/day. No information on F1 and F2 generations for this endpoint is available (Weir, 1966b (reviewed in ECHA (2008) and Weir and Fisher, 1972)). The NOAEL was 17.5 mg boron/kg bw/day, however, as also stated in WHO (1998) the small group size (n=8), low control fertility (60%), limited data reported, and inappropriate statistics all limit the applicability of these data for risk assessment. However, as comparable results were obtained with disodium tetraborate decahydrate and effects were seen at equivalent concentrations on the basis of boron equivalents, the results of the study can be utilized in order to complement the picture of the reprotoxic effects of boric acid.

In a continuous breeding study of boric acid in mice (NTP, 1990; Fail et al., 1991), three doses were administered (1000 ppm (26.6 mg boron/kg bw/day), 4500 ppm (111.3 mg boron/kg bw/day) and 9000 ppm (220.9 mg boron/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 boron/kg bw/day, and absent at 221 mg boron/kg bw/day.
For cross over mating only the mid dose group (111.3 mg boron/kg bw/day) could be mated with control animals, since the high dose produced no litter. Indices of fertility for mid dose males with control females, control males with mid dose females and control males with 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 females of the F0-generation is 1000 ppm, this is a LOAEL for males of the F0-generation (motility of epididymal sperms was significantly reduced: 78% ± 3 in controls vs. 69% ± 5 at 1000 ppm). For the F1-generation 1000 ppm can be identified as a LOAEL, based on the 25% reduction of sperm concentration in males and increased uterine and kidney/adrenal weights and the shortened oestrus cycle in females at this dose. Further, though normal in number, the F2-pups had reduced adjusted bodyweights at 1000 ppm, which is therefore also a LOAEL for F2-generation.

Fail et al., (1989) (reviewed in Moore et al. 1997) evaluated the effects of boric acid on male deer mice (*Peromyscus maniculatus*) to test the effects on fertility, reversibility of effect, and to determine if reproductive efficiency was normal in offspring of treated deer mice. Four groups of 30 male deer mice were fed a diet that contained either 4500 or 9000 ppm boric acid for 8 weeks. These doses equal 108.1 mg boron/kg bw/day and 216.2 mg boron/kg bw/day, respectively. Two groups of 30 male deer mice were fed an identical diet to which no boric acid was added and served as controls. At the end of the 8-week exposure period, half of the male deer mice were mated with untreated adult female deer mice for 1 week. Following the mating trial these males were killed and necropsied. The other groups of treated male deer mice were fed a diet containing no boric acid for an additional 9-week period to assess any recovery from the boron treatment. After the 9-week recovery period the male deer mice were mated for 1 week with untreated adult female deer mice, then killed and necropsied. After each mating trial the females were allowed to litter and the resulting pups were counted, sexed, and weighed at birth.
Complete infertility was observed in male deer mice exposed to 38.5 mg boron/kg bw/day for 8 weeks. No decrease in fertility was observed in deer mice that consumed 19.3 mg boron/kg bw/day. Deer mice

at the 38.5 mg boron/kg bw/day level had decreased testicular and epididymal weights. A reduction in the seminiferous index (i.e. a semiquantitative rating of cell types present) was observed at the high dose level. This was felt to account for the resulting decrease in formation of mature sperm. Body and organ weights, seminiferous index, and litter measurements for the lower dose level deer mice were comparable to controls. Following a 9-week period on control diet, mice that consumed 38.5 mg boron/kg bw/day demonstrated a fertility performance similar to untreated mice. Necropsy results and histologic examination of testes were also similar to controls. From this study a NOAEL of 38.5 mg boron/kg bw/day for male fertility effects could be derived.

Two studies were aimed at getting further inside into the effects of Boric acid on the male reproductive system and their reversibility.
Fischer 344 (CDF (F3449/CrlBr) rats received boric acid equivalent to 60.9 mg boron/kg bw/day in the diet for up to 28 days. The treatment group consisted of 36 animals and the control group consisted of 30. Animals were killed and histologically examined after 4, 7, 10, 14, 21 and 28 days of dosing (6 treated and 4 control animals at each time point). The reproductive effects started with reversible inhibition of spermiation. Inhibition of spermiation was already observed after 7 days of treatment and after 28 days extreme epithelial disorganisation and sperm cell loss was evident.
The second part of the study was focussed on hormone analysis. Reduced testosterone levels were observed in the dosed animals, which could be reversed to control levels by treatment with human chorionic gonadotropin and luteinizing hormone releasing hormone. Animals were investigated after 4, 7, 10, 14 and 21 days (Treinen and Chapin, 1991).

In male Fischer 344 (CDF (F3449/CrlBr) rats (6 per group) early effects (severe inhibition of spermiation) were seen after 14 days treatment, at doses around 38 mg boron/kg, (217 mg boric acid/kg bw/day), but at a lower dose of 26 mg boron/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 boron/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 and 68 mg boron/kg bw/day (Ku et al., 1993).

Table 5: Key fertility studies for boric acid (adopted from ECHA (2008))

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**
Oral diet	Predates OECD 3 generation 2 litter per generation	Rat Crl:CD Sprague-Dawley 8 males and 16 females per group	14 weeks pretreatment, then through 3 generations	0, 670, 2000, 6700 boric acid (= 117, 350, 1170 ppm boron) corresponding to 0, 34, 100 and 336 mg boric acid/kg bw/d (0, 5.9, 17.5, 58.5 mg boron/kg bw/d)	Top dose levels caused testes atrophy prior to first mating so no litters were produced. Infertility in males and females of the high dose when mated with untreated animals. No adverse effects in mid and low dose groups in any generation.	2000 ppm (100 mg boric acid/kg bw/d) (17.5 mg boron/kg bw/d)	2000 ppm (100 mg boric acid/kg bw/d) (17.5 mg boron/kg bw/d)	2000 ppm (100 mg boric acid/kg bw/d) (17.5 mg boron/kg bw/d)	Weir and Fisher, 1972
Oral diet	Continuous breeding protocol (NTP)	Mouse, Swiss CD1 40 males and females in control, 20 males and females in dosed groups	1 week premating, 27 weeks in total	0, 1000, 4500, 9000 ppm Equivalent to 0, 26.6, 111,3, 220,9 mg boron/kg bw/d)	Reduced sperm motility (F0) Increased uterine weight and kidney/adrenal weight, shortened oestrus cycle and 25 % reduction in sperm	26.6 mg boron/kg bw/d	26.6 mg boron/kg bw/d	26.6 mg boron/kg bw/d	Fail et al., 1991 (NTP, 1990)

					concentration (F1) Reduced adjusted bodyweight of pups				

Developmental toxicity

In a dietary study groups of Sprague-Dawley rats were dosed with boric acid corresponding to boron levels of either 0, 3.3, 6.3, 9.6, 13.3, or 25 mg boron/kg bw/day from gestational day (GD) 0 to 20 (phase 1) or 0, 3.3, 6.3, 9.8, 12.9, or 25.4 mg boron/kg bw/day from gestational day 0 to 20 (phase 2). In phase 1, which was conducted according to OECD guideline 414, dams killed on gestation day 20 and uterine contents were examined. For the low to high-dose groups, fetal body weights were 99, 98, 97, 94, and 88% of controls, the reduction was significant only in the 13.3 and 25 mg boron/kg bw/day groups. 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). In phase 2, boric acid exposure stopped at birth and dams were allowed to deliver and rear their litters until postnatal day 21. On postnatal day (PND) 0 of phase 2, there were no effects of boric acid on offspring body weight, nor were any differences seen through postnatal day 21. On post natal day 21 the percentage of pups per litter with short rib XIII was elevated only in the 25.3 mg boron/kg bw/day group, but there was no treatment-related increase in wavy rib or extra rib on lumbar 1. 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 PND 21. The NOAELs for developmental toxicity in rat for the prenatal (Phase 1) and postnatal phase (Phase 2) were 9.6 and 12.9 mg boron/kg bw/day, respectively. There was little evidence of maternal toxicity at any of the doses tested (Price et al., 1996a).

In a further rat (Sprague-Dawley) study, average doses were 0, 13.7, 28.5, 57.8 (on GD 0-20) and 94.3 (on GD 6-15) mg boron/kg bw/day (Heindel, et al., 1992). The NOAEL for developmental toxicity in rats was determined to be < 13.7 mg boron/kg bw/day. Prenatal mortality was increased in the highest dose group compared to control (36% resorption per litter versus 4%).

Similar findings were observed in Swiss albino CD-1 mice receiving boric acid equivalent to doses of 0, 43, 79, and 175 mg boron/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 – by 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 boron/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 boron/kg bw/day, the LOAEL was of 79 mg boron/kg bw/day (Heindel et al., 1992).

New Zealand White (NZW) rabbits were administered boric acid once daily by gavage at doses corresponding to 0, 10.9, 21.9 and 43.8 mg boron/kg bw/day during major organogenesis on GD 6-19 (Price et al., 1996b). Rabbits exposed to 43.8 mg boron/kg bw/day on gestation day 6-19 revealed decreased food intake during treatment, relative but not absolute kidney weight increase and vaginal bleeding. At the highest dose, prenatal mortality was increased (90% resorption/litter versus 6% in 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 resorptions was disproportionally high in boric acid-exposed rabbits relative to rabbits with even greater restriction of food intake (Parker et al, 1986; Matsuzawa et al., 1981). Development of the cardiovascular system was particularly 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 were present in 72% of the high-dose fetuses versus 3% in 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 was observed at 43.8 mg boron/kg bw/day (Price et al., 1996b).

Table 6: key developmental studies with boric acid (adopted from ECHA (2008a))

Route of exposure	**Test type** **Method** **Guideline**	**Species** **Strain** **Sex** **No/group**	**Exposure period**	**Doses** **(mg B/kg bw/day)**	**Critical effects**	**NO(A)EL** **maternal**	**NO(A)EL** **Teratogenicity** **Embryotoxicity**	**Reference**
Oral in diet	GLP, FIFRA, Federal Register 54, 3401-34074 Study consists of a prenatal and postnatal development part Prenatal part similar to OECD 414	Rat Sprague-Dawley female 60	GD 0-20 Remark: in Phase 1 (prenatal development), the study was terminated on GD20; in part 2 (postnatal development), the study was terminated in PND 21	0, 3.3, 6.4, 9.6, 13.3, 25.2	Phase 1: reduction of foetal body weight on GD 20 in 13.3 and 25 mg/kg bw/d group, malformations: incidence of short rib XIII or wavy ribs increased. Phase 2: no decreased foetal body weights. Short rib XIII, but no wavy rib or extra rib on lumbar I (PND 21)	No maternal toxicity observed	9.6 mg boron/kg bw/day (foetal skeletal effects)	Price et al., 1996a
Oral in diet	GLP Similar to OECD 414	Rat Sprague-Dawley Female 14 in high dose, 29 in other groups	GD 0-20 for dose groups except the highest GD 6-15 for the highest dose group	0, 13.7, 28.4, 57.8, 94.3	Foetal toxicity: Reduction of foetal body weight from lowest dose on; prenatal mortality increased at the highest dose, malformations: incidence of short rib XIII Maternal toxicity: Altered food intake and increased relative and kidney weight from 13.7 mg/kg bw/d Decreased	13.7 mg B/kg bw/day	< 13.7 mg boron/kg bw/day (foetal body weight decrease) (13.7 mg boron/kb bw/day LOAEL)	Heindel et al., 1992

					body weight gain and gravid uterine weight from 57.8 mg/kg bw/d			
Oral in diet	GLP	Mouse Swiss-Albino CD-1	GD 0-17	0, 43, 79, 175	Foetal toxicity: At 175 mg/kg bw/d: percentage of resorptions per litter increased; from 79 mg/kg bw/d: reduced average foetal body weight per litter Maternal toxicity: decreased body weight, body weight gain and gravid uterine weight at the highest dose level; dose related increase in the incidence of renal tubular dilation	Not identified	43 mg boron/kg bw/day	Heindel et al., 1992
Oral Gavage (vehicle: water)	GLP	Rabbit New Zealand White 30	GD 6-19	0, 10.9, 21.9, 43.8	Foetal toxicity:At the highest dose level: increased incidences of prenatal mortality and of the proportion of pregnant females with no live foetuses; reduced litter size, increased incidence of malformations of the cardiovascular system Maternal toxicity: At the highest dose level:	21.9 mg boron/kg bw/day	21.9 mg boron/kg bw/day	Price et al., 1996b

					Vaginal bleeding, decreased body weight, body weight gain and gravid uterine weight; increased relative kidney weight			

Human data

Investigations of potentially reproductive effects in humans have not been specifically focussed on boric acid alone: available epidemiological studies mainly addressed the effects of exposure to inorganic borates in general. In studies performed among worker populations (Whorton et al., 1994; Tarasenko et al., 1972) or among a highly exposed population (Sayli, 1998; 2001; 2003), no significant adverse effects on reproduction or reproductive outcome have been reported. However, all epidemiological studies performed exhibited methodological deficiencies (for a more in-depth discussion see ECHA (2008a)). In recent studies, lower Y:X ratio in sperm cells have been reported in boron exposed workers (Robbins et al., 2008; Scialli et al. (2009)), which, however, did not correlate with boron concentration in blood. It was concluded, that there was no clear evidence of reproductive toxicity in highly boron-exposed workers (whose exposure levels are nevertheless below the NOAEL which has been derived from animal studies). Thus, epidemiological studies in humans are insufficient to demonstrate the absence of an adverse effect on fertility.

Other relevant information

Summary and discussion of reproductive toxicity

Results from animal experiments demonstrate that boric acid adversely effects fertility and development. Feeding studies in different animal species (rats, mice and dogs) have consistently demonstrated that the male reproductive system is the principle target in experimental animals, although effects on the female reproductive system have also been reported. Testicular damage ranging from mildly inhibited spermiation to complete atrophy has been demonstrated following oral administration of boric acid. Effects on fertility were observed at lower dose levels compared to dose levels, where signs of general toxicity appeared. 17.5 mg boron /kg bw/day was derived as a NOAEL for male and female fertility (ECHA, 2008a).

Developmental toxicity of boric was investigated in the rat, the rabbit and the mouse. In two independent rat studies, the reduction in fetal body weight at 0.1% or 0.2% boric acid in feed from GD 0 to 20 was comparable, maternal toxicity in mice and rats was not striking, since effects on food and water consumption were minimal. Observed weight gain changes seemed to be secondary to developmental toxicity, because body weight gain corrected for gravid uterine weight was not significantly reduced. Studies in rats failed to provide evidence for any treatment related renal pathology. Thus, in the rat, developmental toxicity (decreased foetal weight: at 13.7 mg boron/kg bw/day) occurred in the absence of marked maternal toxicity. For developmental toxicity, a NOAEL of 9.6 mg boron kg bw/day has been derived.

The adverse effects of boric acid on development and fertility observed across species were very similar, both in nature and effective doses. Further, the adverse effects obtained with boric acid are

comparable to those obtained from other borates thus confirming that the Boron ion is the toxicologically active species. The available data on toxicokinetics do not indicate major differences between laboratory animals and humans. It is not known whether there are significant differences in the toxicodynamics between humans and laboratory animal models and in the absence of such knowledge it must be assumed that the effects seen in animals could occur in humans. On the basis of toxicokinetic and toxicodynamic considerations it is assumed that the animal data are relevant to humans. This is further underlined by the fact that (1) there are indications that boric acid is able to cross human placenta and that (2) up to now, epidemiological studies in humans are insufficient to demonstrate the absence of an adverse effect of inorganic borates on fertility.