Substance name: Boric acid
EC number: 233-139-2 (234-343-4)
CAS number: 10043-35-3 (11113-50-1)

MEMBER STATE COMMITTEE SUPPORT DOCUMENT FOR IDENTIFICATION OF

BORIC ACID

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS CMR PROPERTIES

Adopted on 9 June 2010

CONTENTS

TABLES

Substance Name: Boric acid

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

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

- *Boric acid* is identified as a substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction (category 2)[1].

Summary of how the substance meets the CMR[2] (Cat 1 or 2), PBT[3] or vPvB[4] 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[5]) 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[6] as toxic to reproduction category 2[7], R60-61 (May impair fertility. May cause harm to the unborn child).

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

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

[1] Category in accordance with Annex I to Council Directive 67/548/EEC

[2] CMR means carcinogenic, mutagenic or toxic for reproduction

[3] PBT means persistent, bioaccumulative and toxic

[4] vPvB means very persistent and very bioaccumulative

[5] 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 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (1st ATP)

[6] 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.

[7] 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

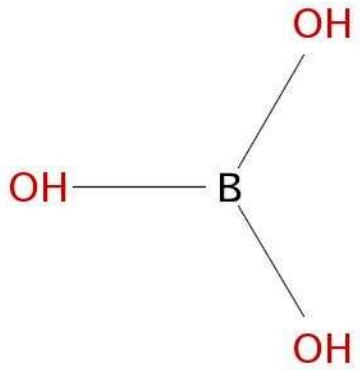
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

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 ($B \leq 0.025$ M). At higher boron concentrations, polynuclear complexes are formed and several dissociation/formation constants apply.	Ingri, 1963
VII, 7.4	Relative Density	4.4	$D_4^{23} = 1.489 \pm 0.006$	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[8] 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

[8] 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 3 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.

9 REFERENCES

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.

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.

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)

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

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.

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.

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

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.

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.

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.

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.

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.

10 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 2: 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/kg bw/day (corresponding to 30, 98, 196, 392, 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 3: 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 boric acid mg/kg bw/day in males) (equivalent to 0, 169, 560, 1120, 2240, 4480 boric acid mg/kg bw/day in females) (equivalent to 0, 34, 71, 142, 284, 568 mg boron/kg bw/day in males) (equivalent to 0, 30, 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	26 mg Boron/kg bw/day	8.8 mg Boron/kg bw/day	Weir, 1962 reviewed in ECHA (2008) and Weir and Fisher (1972)

				At 26 mg Boron/kg bw/day one male exhibited partial testicular atrophy			
Oral in diet	2 years Interim kills after 6 and 12 months	Rat Sprague-Dawley Control groups: 70 Treatment groups: 35 Groups of interim kill: 5	0, 670, 2000, 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)	At 58.5 mg Boron/kg bw/day: reduction of body weight; clinical signs of toxicity, testicular atrophy, reductions in red cell volume and Hb	58.5 mg Boron/kg bw/day	17.5 mg Boron/kg bw/day	Weir, 1966a 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 boric acid/kg bw/day and 216.2 mg boric acid/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 4: 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	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	26.6 mg boron/kg bw/d (LOAEL for males)	26.6 mg boron/kg bw/d (LOAEL)	26.6 mg boron/kg bw/d (LOAEL)	Fail et al., 1991 (NTP, 1990)

		dosed groups			and 25 % reduction in sperm 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 resorption 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 5: 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) 0, 3.3, 6.3, 9.8, 12.9, 25.4 (phase 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	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

					mg/kg bw/d Decreased 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	21.9 mg boron/kg bw/day	21.9 mg boron/kg bw/day	Price et al., 1996b

					toxicity: At the highest dose level: 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.