Committee for Risk Assessment

RAC

Annex 1

Background document

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

Boric Acid

EC numbers: 233-139-2 [1], 234-343-4 [2]

CAS numbers: 10043-35-3 [1], 11113-50-1 [2]

CLH-O-0000003738-64-03

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

Adopted

14 March 2014

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Boric Acid

EC Number: **233-139-2**

CAS Number: **10043-35-3**

Index Number: **005-007-00-2**

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Boric acid***
EC number:	***233-139-2***
CAS number:	***10043-35-3***
Annex VI Index number:	***005-007-00-2***
Degree of purity:	**≥ *99 % w/w***
Impurities:	***None specified***

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Repr. 1B - H360FD C ≥ 5,5%	Repr. Cat 2; R60-61 C ≥ 5,5%
Current proposal for consideration by RAC	Repr. 2 - H361d C ≥ 5,5%	Repr. Cat 3; R63 C ≥ 5,5%
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Repr. 2 - H361d C ≥ 5,5%	Repr. Cat 3; R63 C ≥ 5,5%

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	None		None	Not evaluated
2.2.	Flammable gases	None		None	Not evaluated
2.3.	Flammable aerosols	None		None	Not evaluated
2.4.	Oxidising gases	None		None	Not evaluated
2.5.	Gases under pressure	None		None	Not evaluated
2.6.	Flammable liquids	None		None	Not evaluated
2.7.	Flammable solids	None		None	Not evaluated
2.8.	Self-reactive substances and mixtures	None		None	Not evaluated
2.9.	Pyrophoric liquids	None		None	Not evaluated
2.10.	Pyrophoric solids	None		None	Not evaluated
2.11.	Self-heating substances and mixtures	None		None	Not evaluated
2.12.	Substances and mixtures which in contact with water emit flammable gases	None		None	Not evaluated
2.13.	Oxidising liquids	None		None	Not evaluated
2.14.	Oxidising solids	None		None	Not evaluated
2.15.	Organic peroxides	None		None	Not evaluated
2.16.	Substance and mixtures corrosive to metals	None		None	Not evaluated
3.1.	Acute toxicity - oral	None		None	Not evaluated
	Acute toxicity - dermal	None		None	Not evaluated
	Acute toxicity - inhalation	None		None	Not evaluated
3.2.	Skin corrosion / irritation	None		None	Not evaluated
3.3.	Serious eye damage / eye irritation	None		None	Not evaluated
3.4.	Respiratory sensitisation	None		None	Not evaluated
3.4.	Skin sensitisation	None		None	Not evaluated
3.5.	Germ cell mutagenicity	None		None	Not evaluated
3.6.	Carcinogenicity	None		None	Not evaluated
3.7.	Reproductive toxicity	Repr 2 - H361d	C ≥ 5,5 %	Repr 1B - H360FD Repr. 1B; H360FD: C ≥ 5,5 %	
3.8.	Specific target organ toxicity – single exposure	None		None	Not evaluated
3.9.	Specific target organ toxicity – repeated exposure	None		None	Not evaluated
3.10.	Aspiration hazard	None		None	Not evaluated
4.1.	Hazardous to the aquatic environment	None		None	Not evaluated
5.1.	Hazardous to the ozone layer	None		None	Not evaluated

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Pictogram: GHS08
Signal word: Warning

Hazard statements: H361d: Suspected of damaging the unborn child
Precautionary statements: No precautionary statements are proposed since precautionary statements are not included in Annex VI of Regulation EC no. 1272/2008.

Proposed notes assigned to an entry: None

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	None		None	Not evaluated
Oxidising properties	None		None	Not evaluated
Flammability	None		None	Not evaluated
Other physico-chemical properties	None		None	Not evaluated
Thermal stability	None		None	Not evaluated
Acute toxicity	None		None	Not evaluated
Acute toxicity – irreversible damage after single exposure	None		None	Not evaluated
Repeated dose toxicity	None		None	Not evaluated
Irritation / Corrosion	None		None	Not evaluated
Sensitisation	None		None	Not evaluated
Carcinogenicity	None		None	Not evaluated
Mutagenicity – Genetic toxicity	None		None	Not evaluated
Toxicity to reproduction – fertility	None		Repr. Cat. 2; R60: C ≥ 5,5 %	
Toxicity to reproduction – development	Repr. Cat 3; R63	C ≥ 5,5 %	Repr. Cat. 2; R61: C ≥ 5,5 %	
Toxicity to reproduction – breastfed babies. Effects on or via lactation	None		None	Not evaluated
Environment	None		None	Not evaluated

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: Xn
R-phrases: R63 Possible risk of harm to the unborn child
S-phrases: (2-)36/37

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Boric acid (Index No. 005-007-00-2) was classified as Repr. 1B; H360FD: C ≥ 5,5 %, in 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.

2.2 Short summary of the scientific justification for the CLH proposal

A joint REACH registration dossier was available for boric acid when this CLH proposal was prepared. ECHA's dissemination website suggests two joint registration dossiers are available, but this is misleading and is a function of how information is extracted from dossiers for dissemination. The information from the joint REACH registration dossier was considered during preparation of the CLH proposal for boric acid.

Developmental and reproductive toxicity effects were observed in laboratory animals. Effects on the testis have been observed in both sub-chronic and chronic studies in three species: rats, mice and dogs. For comparative purposes, exposures to boric acid, disodium tetraborate, boric oxide and disodium octaborate referred collectively as "borates" are expressed in terms of boron (B) equivalents based on the fraction of boron in the source substance on a molecular weight basis. The effects tend to be similar in all three species, although most data comes from rat studies with a NOAEL of 17.5 mg B/kg/day (100 mg boric acid/kg bw/day). Developmental effects have been observed in three species, rats, mice and rabbits, the most sensitive species being the rat with a NOAEL of 9.6 mg B/kg bw/day (55 mg boric acid/kg bw/day).

Boron deprivation has also been shown to have detrimental effects on fertility in animals, indicating that boron plays an essential role in normal reproduction in animals. Boron deprivation has also been shown to produce detrimental effects to embryo and fetus, including malformations, indicating that boron is essential for normal prenatal development in animals. Boron is recognized as an essential element in plants and a biologically important substance, in animals.

In contrast to the laboratory animal data, studies in humans have not demonstrated adverse effects of high boron exposures. In humans effects on fertility were studied in several highly exposed populations. At a U.S. Borax mine and production facility in Southern California no adverse effects on reproduction were seen in workers exposed up to an average of 28.4 mg B/day (ca. 0.4 mg B/kg bw/day). In a population living in a boron rich region of Turkey (up to 29 mg B/L well water) no effects on fertility were seen over three generations. Chinese boron workers were studied by a research team from the Beijing University of Science and Technology and the China National Environmental Monitoring Centre in collaboration with the University of California at Los Angeles. The boron worker group average exposure was 42 mg B/day (SD 58). Sperm count, sperm concentration, motility, morphology, percentage of DNA strand breakage and sperm aneuploidy and diploidy were not significantly different across the three boron exposure comparison groups. The highest exposed workers were exposed to about 5 mg B/kg/day, which is more than 100 times greater than the average daily exposure of the general population. A recent study of workers in Turkey was conducted to investigate the reproductive effects of boron exposure in workers employed in boric acid production plant in Turkey. Boron concentrations were determined in biological samples (blood, urine, semen), in workplace air, in food, and in water sources. The mean calculated daily boron exposure of the highly exposed group was 14.45 ± 6.57 (3.32–35.62) mg B/day. As with the Chinese study, there were no negative effects observed for boron exposure on

the reproductive toxicity indicators (concentration, motility, morphology of the sperm cells and blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone).

Although these appear to be the highest documented occupational exposures, they are only about one third to one quarter of the NOAEL for testis effects in rodents. However, this shows that humans are not significantly more sensitive to this type of toxic effect than rodents. This can be seen when comparing the NOAEL for fertility effects in the rat and the human NOAEL (highest occupational exposures in the Chinese workers study). The NOAEL in rats is 17.5 mg B/kg/day; divided by the human NOAEL of 2.08 mg B/kgday (based on 125 mg B/day and 60 kg person; Scialli et al. 2010) results in a ratio of only 8.75, over 10 times lower than the default safety factor of 100 often used in risk assessments.

The Chinese and Turkish semen studies in highly exposed workers are a major source of information as to human reproductive toxicity. Not only are these the most exposed workers with exposures measured directly from food, drink and inhalation, but the Chinese and Turkish workers studies are the most sensitive studies that have been carried out as semen analysis was performed, a very sensitive detection system for testicular damage. In addition to the absence of effects on male fertility in humans, there is no evidence of developmental effects in humans attributable to boron in studies of populations with high exposures to boron. Epidemiological studies of human developmental effects have shown an absence of effects in exposed borate workers and populations living in areas with high environmental levels of boron. In a case control study from Hungary the difference in congenital abnormalities in children born to mothers in the study group that received boric acid treatment during pregnancy for infectious diseases of the genital organs compared to the control group was not statistically significant.

Occupational exposures in the studies in Chinese, Turkish and USA workers were lower than laboratory exposures of animals, but the highest of these likely describe the upper limits of exposures in production of boron-containing products. The Chinese exposures were higher than would be expected from production processes because 34 % of workers reported eating in contaminated areas. It is unlikely that in the future workplace exposures will be as high. It is also unlikely that non-occupational exposures will approach the 42 mg B/day found in the Chinese workers. The highest non-occupational exposure found were populations in Northern Chile in which estimated intake of boron was 21 to 27 mg B/day, which correlated to naturally high boron concentrations in local rivers.

A review of evidence for the essentiality of dietary boron shows that boron is biologically important in humans. A World Health Organization (WHO) expert committee concluded that boron is “probably essential” for humans. The U.S. Food and Nutrition Board in 2001 published a Tolerable Upper Intake Level (UL) for boron of 20 mg/day. Also, the UK Expert Group on Vitamins and Minerals and the European Food Safety Authority also regarded boron as nutritionally important and determined an acceptable daily intake for boron (0.16 mg B/kg/day). A U-shaped correlation between boron intake and health can therefore be expected.

Beneficial effects of boron have been reported for bone health, cell membrane function, psychomotor skills, cognitive processes of attention and memory, response to estrogen therapy, control of inflammatory disease, enzyme regulation, energy metabolism, macroscale mineral metabolism, and potential anticarcinogenic properties. Epidemiological studies indicate that boron exposure in drinking water is associated with lower incidences of some types of cancer including prostate, lung, cervical and esophageal cancer.

A low intrinsic hazard of boron in humans is supported by the lack of an endocrine-related mechanism for the fertility and developmental effects in laboratory animals, the numerous studies showing the physiological importance for boron, evidence for the homeostatic control of boron in

humans and mammals, and that boron meets the criteria of essentiality. A low U.S. EPA Toxicological Priority Index (ToxPi) score, the fact that boric acid is not mutagenic and is not carcinogenic in either mice or rats support the conclusion that boric acid is not an endocrine active substance.

Based on a total weight of evidence, Repr. Category 2 (H361d: Suspected of damaging the unborn child) is considered the appropriate classification. Extensive evaluations of sperm parameters in highly exposed workers have demonstrated no effects on male fertility in humans. While no developmental effects have been seen in highly exposed populations, epidemiological studies of developmental effects are not as robust as the fertility studies, warranting the Repr. Category 2 H361d. This classification based upon the developmental endpoint accommodates for both the positive findings in laboratory animals and the absence of relevant effects in humans.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Classification: Repr. 1B; H360FD
Labelling: GHS08
Danger
H360FD
SCL: ≥5,5 %

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Classification: Repr. Cat. 2; R60-61
Labelling: T
R: 60-61
S: 53-45
SCL: ≥5,5 %

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Tabel 5. Notified classification and labelling according to CLP criteria
Source: http://echa.europa.eu/information-on-chemicals/cl-inventory-database

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Number of Notifiers	Joint Entries	View
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)					
Repr. 1B	H360	H360		GHS08 Dgr	Repr. 1B: C ≥ 5.5%		849		
Repr. 1B	H360	H360		GHS08 Dgr			141		
Repr. 1B	H360	H360		GHS08 Dgr	Repr. 1B: C ≥ 5.5%		86		
Repr. 1B	H360	H360		GHS08 Dgr	Repr. 1B: C ≥ 5.5%		84		

Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 5.5%		43
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 5%		29
Repr. 1B	H360	H360	GHS08 Dgr			28
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ca. 5.5%		26
		H360	Dgr	Repr. 1B: C ≥ 5.5%		24
Repr. 1B	H360	H360	GHS08 Dgr	Carc. 1B: C ≥ 5.5%		20
Repr. 1A	H360	H360				18
			GHS08 Dgr			
Repr. 1B	H360	H360	Dgr			18
Repr. 1B	H360	H360	GHS08 Dgr			7
Repr. 1B	H360	H360	GHS08 Dgr			4
Repr. 1B	H360	H360	GHS08 Dgr			4
Repr. 1B	H360	H360	GHS08 Dgr			4
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 5.5%		3
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: 5.5% ≤ C < 100%		3
		H360	GHS08 Dgr		Note D Note F	2
Repr. 1B	H360	H360	GHS08 Dgr			2
Repr. 1B	H360		GHS08 Dgr	Repr. 1B: C ≥ 5.5%		2
Skin Irrit. 2	H315	H315				
Repr. 1B	H360	H360	GHS08 Dgr			2
STOT SE 1	H370	H370				
STOT RE 1	H372	H372				
Not Classified						1
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: 5.5% ≤ C ≤ 100%		1
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 5.5%		1
Repr. 1B	H360	H360	GHS08 Dgr			1
Repr. 1A	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 5.5%		1
Repr. 1B	H360	H360	GHS08 Dgr			1
Repr. 1B	H360	H360	GHS08 Dgr			1
Repr. 1B	H360	H360	GHS08 Dgr			1
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 5.5%	Note B	1
Repr. 1B	H360	H360	GHS08 Dgr	Repr. 1B: C ≥ 5.5%		1
Repr. 1B	H360		GHS08 Dgr			1
Repr. 1B	H360	H360	GHS08 Dgr			1
STOT SE 3	H335	H335	GHS07 Wng			1
Repr. 1B	H360	H360	GHS08 Dgr			1

2.4.2 Current self-classification and labelling based on DSD criteria

Not applicable (see section 2.3)

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Recitial 2 of the 30th ATP to Directive 67/548/EEC as published in the EU Official Journal, 15 September 2008 stated that "*The classification and labelling of the substances listed in this Directive should be reviewed if new scientific knowledge becomes available. In this respect, considering recent preliminary, partial and not peer-reviewed information submitted by industry, special attention should be paid to further results of epidemiological studies on the Borates concerned by this Directive including the ongoing study conducted in China…*" Extensive evaluation of the Chinese semen studies has now taken place and hence a further review of the classification and labelling of boric acid is appropriate in light of the findings of these studies.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

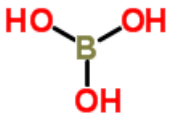
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 6: Substance identity

EC number:	233-139-2
EC name:	Boric acid
CAS number (EC inventory):	10043-35-3
CAS number:	10043-35-3
CAS name:	Boric acid
IUPAC name:	Boric acid
CLP Annex VI Index number:	005-007-00-2
Molecular formula:	BH_3O_3
Molecular weight range:	61.833

Structural formula:



1.2 Composition of the substance

Table 7: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Boric acid	99.5 % (w/w)	≥ 99 % (w/w)	

Current Annex VI entry: boric acid

Table 8: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks

Current Annex VI entry: None specified

Table 9: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks

Current Annex VI entry: None specified

1.2.1 Composition of test material

Boric acid (CAS# 10043-35-3) and disodium tetraborate decahydrate (CAS# 1303-96-4) were tested in studies in laboratory animals for reproductive effects. Only boric acid has been tested in developmental studies in laboratory animals.

For epidemiological studies the actual borate substances that workers and study populations were exposed to could not be determined. Most of the simple inorganic borates exist predominantly as undissociated boric acid in dilute aqueous solution at physiological and environmental pH, leading to the conclusion that the main species in the plasma of mammals is un-dissociated boric acid. Since other borates dissociate to form boric acid in aqueous solutions, they too can be considered to exist as un-dissociated boric acid under the same conditions. Since only boric acid and the borate anion are present at environmentally and physiologically relevant conditions, read across between the different boron substances can be done on the basis of boron (B) equivalents. For complete epidemiological studies, exposures are based on analytical measurements of boron in the environment, personal dust samples, blood, urine, food and water.

Justification for read-across of different borate substances

For comparative purposes, exposures to boric acid, disodium tetraborate, boric oxide and disodium octaborate referred collectively as "borates" are expressed in terms of boron (B) equivalents based on the fraction of boron in the source substance on a molecular weight basis. NOAELs are determined on a boron equivalent basis. As noted previously, only boric acid and the borate anion are present at environmentally and physiologically relevant concentrations. Read-across between the different boron substances can be done on the basis of boron (B) equivalents. Conversion factors are given in Table 10 below.

Table 10: Conversion factors to boron equivalents

Substance	**Formula**	**Conversion factor for equivalent dose of B (multiply by)**
Boric acid	H_3BO_3	0.1748
Boric Oxide	B_2O_3	0.311
Disodium tetraborate anhydrous	Na_2B4O_7	0.2149
Disodium tetraborate pentahydrate	$Na_2B4O_7•5H_2O$	0.1484
Disodium tetraborate decahydrate	$Na_2B4O_7•10H_2O$	0.1134
Disodium octaborate tetrahydrate	$Na_2B_8O_{13}·4H_2O$	0.2096

1.3 Physico-chemical properties

Table 11: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	white odorless crystalline solid	Cordia JA et al. (2003)	Measured
Melting point	> 1000 ºC	Cordia JA et al (2003)	Measured, EU Method A1
Freezing point	> 171 ºC	Kirk-Othmer (1992)	Measured, ASTM E537-76 (Differential Thermal Analysis)
Boiling point			According to Annex VII, section 7.3, column 2 of Regulation No. 1907/2006, a boiling point study is not required for solids that melt above 300 °C. Boric acid has a melting point greater than 1000 °C. Boric acid starts to give off water and decomposes at above 100°C first forming metaboric acid and is converted into boric oxide (B_2O_3). This has a boiling point of 2200°C.
Relative density	1.49 at 23 ºC 1.52 at 14 ºC	Cordia JA et al. (2003) Kirk-Othmer (1992)	Measured, EU Method A3 Measured, EU Method A3
Vapour pressure	0.000099 Pa at 25 ºC	Tremain S (1998)	Measured, EU Method A4
Surface tension			According to Annex VII, section 7.6, column 2 of Regulation No. 1907/2006, surface tension is not required unless the surface activity is expected or is a desired property of the material. Based on the structure surface activity is not expected for an inorganic substance and is not a desired property of boric acid, therefore the test is not required.
Water solubility	49.2 g/L at 20 ºC 48.37 g/L at 20 ºC	Cordia JA et al. (2003) Spruit WET (2006)	Measured, EU Method A6 Measured, EU Method A6
Partition coefficient n-octanol/water	Log Kow = - 1.09 at 22 °C	Cordia JA et al. (2003)	Measured, EU Method A8
Flash point			According to Annex VII, section 7.9, column 2 of Regulation No. 1907/2006, flash-point does not need to be conducted if the substance is inorganic. Boric acid is an inorganic substance and therefore the study is not required.

Flammability	Non flammable	Younis S (2010)	Measured, EU Method A.10 (Flammability (Solids)), the United Nations Document, Recommendations of the Transport of Dangerous Goods, Manual of Tests and Criteria (Test N.1.) and HSE Code of Physio-Chemical Properties 1982
Explosive properties	Not explosive		Potential explosive properties are indicated by the presence of certain reactive groups in the molecule. The molecular structure of boric acid indicates that such groups are not present. No reactive or unstable groups are present and it does not contain any functional groups quoted in the "Manual of Tests and Criteria" (fourth revised edition, appendix 6, table A6.1) or in Bretherick's-Handbook (6th Edition, Volume 2) as indicating explosive properties. It can therefore be concluded by expert judgment that the molecular structure does not indicate that this substance will explode under the conditions of the test as described in Test Guideline A.14 of EC Directive 92/69/EEC and therefore testing is not required.
Auto flammability	Not a self heating substance Not classified as a pyrophoric solid	Younis S (2010)	Measured, United Nations Recommendations on the Transportation of Dangerous Goods, Manual of Tests and Criteria for substances of Class 4, Division 4.2
Oxidising properties	Not oxidising		Experimental techniques are available for classification of a substance or mixture as oxidising. These are described in EC test A17 (solids) and EC test A21 (liquids). However, Test A17 need not be carried out when examination of the structural formula establishes beyond reasonable doubt that the substance has no oxidising properties. The supplement to the A17 method describes situations in which experimental assessment of necessary. The contents of this supplement are outlined below. Compounds which have no highly electronegative atom - oxygen, fluorine, chlorine, bromine - are not likely to

			possess oxidising properties. Similarly, where these elements are present but the atoms are only bonded to carbon and/or hydrogen, then oxidising properties are unlikely. A substance may have oxidising properties when: • The electronegative atoms which are present constitute a high proportion of the molecule and are bound to elements in a high oxidation state; • The electronegative atoms are bonded to each other or to electronegative elements such as iodine, nitrogen, sulfur or phosphorous. As the ability to predict the reactivity of chemical compounds from their structure is still limited, the best approach is by analogy with existing compounds. A functional groups table provides a list of oxidising compounds and reactive groups which increase the oxidising power. However, this list is not exhaustive. If the substance meets one of the above criteria. The lack of any reactive group listed may not be sufficient to justify not performing the A17 test. For organic substances only, the oxygen balance (OB) calculation may be useful as a criteria combined with an examination of the chemical structure as a mean of predicting oxidising properties. For organic substance CXHYOZ of molecular weight M, the OB is calculated as follows: Oxygen balance = -1600(2X + Y/2 - Z) / Mol. wt. Although experts think that the OB calculation is a possible approach, there is currently no consensus on the criteria that should be used. For the moment, judicial judgment will be required to use the OB value on a case by case basis. In any case, if theoretical considerations are used to exclude performance of the A17 test, the reasons and all relevant information should be clearly

			stated in the technical dossier. Assessment of oxidising properties of boric acid: Examining the structural formula, the following observations can be made: The molecule does not contain any functional groups listed. Although this list is not exhaustive, this is a significant observation as most commonly occurring oxidising functional groups are contained within the list. According to the two criteria quoted, oxidising properties can exist when: • The electronegative atoms which are present constitute a high proportion of the molecule and are bound to elements in a high oxidation state. In the case of boric acid, the proportion of electronegative atoms in the molecule is high (7 oxygen atoms out of an overall atom count of 13). However, all oxygen atoms are bound to boron atoms. • The electronegative atoms are bonded to each other or to other electronegative elements such as iodine, nitrogen, sulfur or phosphorous. In the case of boric acid the electronegative atoms are not bound to one another or to any other electronegative elements. Assessment against these two criteria indicates strongly that the molecule will not have oxidising properties. In every respect of the oxidising solids exemption procedure, the material does not show any evidence of possessing oxidising properties. On the basis of this exercise, the material should be considered as not oxidising and should not be subjected to experimental testing. The material meets all criteria for exemption from testing and has a structure not at all conducive with that required to exhibit oxidising tendencies.

Granulometry	d50 = 74.395 µm	Younis S (2010)	Measured, BS ISO 13320-1:1999 and CIPAC MT 187; and equivalent to OECD TG 110
Stability in organic solvents and identity of relevant degradation products			According to Annex IX, section 7.15, column 2 of Regulation No. 1907/2006, stability in organic solvents and identity of relevant degradation products is not required if the substance is inorganic. Boric acid is an inorganic substance and therefore the study is not required.
Dissociation constant	pKa = 8.94 at 20 °C	Younis S (2010)	Measured, OECD TG 112 At low boron concentrations (B ≤ 0.025 M) the following equilibrium is found $B(OH)_3 + 2H_2O$«$[B(OH)_4]^- + H_3O^+$ pKa = 9.0 at 25 °C pKa = 8.94 at 20°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 ≤ 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: $B(OH)_3$ «polynuclear anions«$B(OH)_4^-$. Again, pH<5, boron is mainly present as $B(OH)_3$ and in alkaline solution at pH>12.5, boron is mainly present as $B(OH)_4^-$. At 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).
Viscosity			This substance is a solid and therefore in accordance with REACH Annex XI, testing does not appear scientifically necessary.
Additional physico-chemical information: corrosive to metals	The percentage mass losses on steel and aluminium were found	Younis S (2010)	Measured, Test C.1, UN Transport of Dangerous Goods Recommendations, Fourth

	to be < 13.5 % over 7 days, however the maximum pit depth on the aluminium coupons was > 120 µm. The saturated solution of boric acid was therefore a candidate for classification as a corrosive substance of UN Class 8, Packing group III (according to the UN Transport of Dangerous Goods Recommendations).		Revised Edition.
Additional physico-chemical information: emission of flammamble gas in contact with water	It was determined that boric acid should not be classified as a material of Class 4.3 according to the UN recommendations on the Transportation of Dangerous Goods.	Younis S (2010)	Meausered, Test performed according to UN Recommendation on the Transportation of Dangerous Goods, Manual of Tests and Criteria for substances of Class 4, Division 4.3
Additional physico-chemical information: flammability of a dust cloud	In both the spatula test and the ignition tube test the sample melted to a clear liquid emitting small quantity of grey smoke, which ignited with a small green, non-sustaining flame. On completion of testing a white material remained.	Rowe SM (2003)	Measured, spatula test and the ignition tube test
Additional physico-chemical information: dustiness	The dustiness of boric acid granular (d50 mm 0.608) and boric acid powder (d50 mm 0.051) were assessed according to CIPAC method MT 171. Boric acid granular did not produce significant amounts of dust and was nearly dust free. Boric acid powder did produce a significant amount of dust and was classified as dusty.	Foster B (2010)	Measured, CIPAC method MT 171 - Dustiness of granular products

2 MANUFACTURE AND USES

2.1 Manufacture

Boric acid is manufactured usually by reacting the mined calcium or sodium borate with acid e.g. sulphuric acid. The resulting liquor is clarified, and then crystallised. The product is separated from the liquor by filtration, centrifugation etc. Product is washed to remove adhering impurities.

2.2 Identified uses

Boric acid is used in industrial fluids – metalworking fluids, water treatment chemicals, fuel additives, welding, brazing, soldering fluxes, paints and coatings. This substance is also added in metallurgy process to prevent oxidation of metal surfaces.

Boric acid is used to produce insulation, textile, fiber glass and borosilicate glass.

Boric acid is added to adhesives derived from starch to achieve increased viscosity, quicker tack and better fluid properties.

Boric acid makes long-lasting protection against wood destroying organisms therefore is the active substance in biocides.

The enzyme stabilizing features of boric acid results in its addition to detergents, cosmetics and pharmaceuticals.

Boric acid and other borates used in fertilizers deliver an essential micronutrient for plants.

The substance is also used in photographic applications, laboratory chemicals, automotive lubricants and fluids.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Table 12: Summary of toxicokinetics (absorption, metabolism, distribution and elimination): non human information.

Method	Results	Remarks	Reference
rat (Sprague-Dawley) female oral: gavage Exposure regime: Single administration Doses/conc.: Renal clearance study: 0.3, 3.0 or 30 mg boric acid/kg bw; 0.052, 0.52 and 5.2 mg boron /kg respectively by gavage. Plasma half-life study: 30 mg boric acid/kg.	Main ADME results: excretion: Renal clearance: 3.1 ml/min/kg for non-pregnant rats, 3.2 ml/min/kg for pregnant rats. The difference in clearance is not statistically significant. Clearance independent of dose up to 30 mg /kg bw. (5.24 mg B/k). Toxicokinetic parameters: Half-life 1st: The plasma half-life of boric acid in non-pregnant and pregnant rats given boric acid by gavage was 2.93 ± 0.24 and 3.23 ± 0.28 hours, respectively. Metabolites identified: no Details on metabolites: Boric acid is not metabolised.	1 (reliable without restriction) key study experimental result **Test material (EC name): boric acid** **CAS No: 10043-35-3** **Analytical purity > 90%**	Vaziri ND & Ovesisi F (2000) Vaziri ND, Oveisi F, Culver DB, Pahl MV, Andersen ME, Strong PL & Murray J (2001)
No data	Boric acid and borates are not metabolised in humans or animals. The metabolism of boric acid is not possible owing to the high energy level required (523 kJ/mol) to break the B-O bond. Other inorganic borates convert to boric acid at physiological pH in the aqueous layer overlying the mucosal surfaces prior to absorption. Additional support for this derives from studies in which more than 90 % of administered doses of inorganic borates are excreted in the urine as boric acid. Boric acid is a very weak and exclusively monobasic acid that is believed to act, not as a proton donor, but as a Lewis acid,	4 (not assignable) **Test material (EC name): boric acid CAS No: 10043-35-3 and other borates** **purity unknown**	Emsley (1989)

	accepting OH-. Because of the high pKa, regardless of the form of inorganic borate ingested (e.g. boric acid, borax (disodium tetraborate decahydrate) or boron associated with animal or plant tissues), uptake is almost exclusively (> 98 %) as undissociated boric acid. In vivo and in vitro studies indicate that boric acid has a strong affinity for cis-hydroxyl groups. This may explain the higher concentrations of boric acid in bone owing to the binding of to the cis-hydroxyl groups of hydroxyapetite.		
rabbit Dermal and oral Exposure regime: Dermal applications: Boric acid on the first day of the week and of daily exposures to the boric acid preparations on the succeeding 4 days. Oral applications: Daily for 4 consecutive days. Doses/conc.: Dermal applications: USP boric acid crystals (powdered): 4000 mg/kg 12 % boric acid in talcum: 500 mg/kg 5 % boric acid in talcum: 200 5 % aqueous solution: 200 mg/kg USP XIV boric acid ointment: 400 mg/kg Boroglycerin glycerite: 200 mg/kg Oral application: 100, 200, 500, 600 and 700 mg/kg.	Main ADME results: absorption: Boric acid is readily and completely absorbed in rabbits given borates orally. In rabbits, 50 to 66 % of an orally administered dose of boric acid was excreted in the urine in the first 24 hours after dosing. absorption: Dermal absorption of borates across intact skin is insignificant in all species evaluated. Borates penetrated damaged or abraded skin. Transfer: not determined Metabolites identified: no Details on metabolites: Boric acid is not metabolised.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Draize JH & Kelley EA (1959)
mouse (Swiss) male intravenous Exposure regime:	Main ADME results: excretion: Assuming first order kinetics for elimination, the half-life for elimination in the mouse was estimated to be approximately one hour.	2 (reliable with restrictions) supporting study experimental result	Farr LE & Konikowski T. (1963)

Single exposure Doses/conc.: 0.01 mL/g, averaging 0.21 mL per mouse at a molar ratio of boron to glucose of 2:1. Group 1: 100 µg/0.01 mL Group 2: 25 µg/0.01 mL	excretion: In mice, boron is cleared at a rate of 40 ml/min/1.73 m^2 (volume of plasma cleared per minute per 1.73 square metres of body surface). Metabolites identified: not measured Details on metabolites: Boric acid is not metabolised.	**Test material (EC name): sodium pentaborate** **CAS No: 12007-92-0** **purity unknown**	
rat (Wistar) male oral: gavage Exposure regime: Single administration. Doses/conc.: Experiment 1, urine collection: 0, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg/L as boron. Experiment 2, blood collection: 500 mg/L as boron, containing 0.4 mg of boron/100 g bw.	Toxicokinetic parameters: Absorption half-life: 0.608 ± 0.432 h; elimination half life t1/2 = 4.64 ± 1.19 h; volume of distribution, Vd = 142.0 ± 30.2 mL/100 g bw; total clearance, Ctox = 0.359 ± 0.0285 mL/min per 100 g bw. Tmax: 1.76 ± 0.887 h Metabolites identified: not measured Details on metabolites: Boric acid is not metabolised.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): disodium tetraborate decahydrate** **CAS No: 1303-96-4** **Analytical purity > 99%**	Usuda K, Kono K, Orita Y, Dote T, Iguchi K, Nishiura H, Tominaga, Tagawa T, Goto E & Shirai Y. (1998)
rat (Fischer 344) oral: feed Exposure regime: Up to 4 weeks Doses/conc.: 9000 ppm w/w boric acid	Main ADME results: distribution: Tissue levels of boron generally reach steady-state within three to four days among rats fed boric acid in the diet or drinking water for 28 days Metabolites identified: not measured Details on metabolites: Boric acid is not metabolised.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Treinen KA & Chapin RE. (1991)
rat (Fischer 344) male oral: feed Exposure regime: Nine weeks Doses/conc.: 3000, 4500, 6000 and 9000 ppm boric acid; 545, 788, 1050 and 1575 ppm boron (< 0.2, 26, 38, 52, 68 mg	Main ADME results: distribution: Mean (± SD) testis B levels over the 9 week period were 5.6 ± 0.8, 8.8 ±0.7, 11.9 ± 1.4 and 15.1 ± 1.9 µg/g for 3000, 4500, 6000 and 9000 ppm BA respectively. Toxicokinetic parameters: Mean (± SD) serum B levels (weeks 1, 4 and 9) were 6.7 ± 1.0, 10.3 ± 0.6, 13.3 ± 0.7 and 17.3 ± 2.2 µg/g for 3000, 4500, 6000 and 9000 ppm BA respectively.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Ku WW, Chapin RE, Wine RN & Gladen BC. (1993a)

B/kg bw/day) respectively.	Metabolites identified: no Details on metabolites: Boric acid is not metabolised.		
rat (Fischer 344) male oral: feed Exposure regime: Daily for 7 days Doses/conc.: 0 and 9000 ppm (1575 ppm boron); 93 – 96 mg B/kg bw/day.	Main ADME results: absorption: Boric acid is readily and completely absorbed in rats given borates orally. distribution: All tissues examined, except bone and adipose tissue, appeared to reach steady state boron levels by three to four days. distribution: Bone achieved the highest concentration of boron (2 to 3 times plasma levels), and bone boron levels continued to increase throughout seven days of dietary administration. Toxicokinetic parameters: Half-life 1st: A half-life of < 12 hours can be estimated assuming first order kinetics. Metabolites identified: no Details on metabolites: Boric acid is not metabolised.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Ku WW, Chapin RE, Moseman RF, Brink RE, Pierce KD & Adams KY. (1991)
rat (Wistar) female dermal Exposure regime: Single application Doses/conc.: Aqueous boric acid jell: 2.5 % boric acid w/v; 2 mL applied Oleaginous boric acid ointment: 2.8 % boric acid; 2 mL applied	Main ADME results: absorption: Dermal absorption of borates across intact skin is insignificant in rats. absorption: Borates have been demonstrated to penetrate damaged or abraded skin. However, the use of an ointmentbased vehicle may prevent or reduce the absorption through diseased skin compared to an aqueous jelly based vehicle. Metabolites identified: no Details on metabolites: Boric acid is not metabolised.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Nielsen GH (1970)
rat (Fischer 344) male/female oral: feed Exposure regime: Study 1: Daily for 9 weeks Study 2: Daily for 12 weeks Doses/conc.: Study 1: 3000, 4500, 600 and 9000 ppm boric acid; 545, 788, 1050	Main ADME results: distribution: Mean (± SEM) for both studies combined showed mean levels of B in male bone in the 0, 200, 1000, 3000, 4500, 6000 and 9000 ppm groups were 0.78, 3.03, 9.79, 27.2, 43.0, 54.4 and 662 µg B/g, respectively. Femur break stress, vertebral yield load, vertebral break load, vertebral yield stress, vertebral break stress and vertebral modulus of elasticity were significantly affected by boron at all dose levels.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Chapin RE, Ku WW, Kenney MA, McCoy H, Gladen B, Wine RN, Wilson R & Elwell MR (1997)

and 1575 ppm boron (< 0.2, 26, 38, 52, 68 mg B/kg bw/day) respectively. Study 2: 200, 1000, 3000 and 9000 ppm	Metabolites identified: no Details on metabolites: Boric acid is not metabolised.		
rat oral: unspecified Exposure regime: Single application. Doses/conc.: 20 µg ^{10}B	Main ADME results: excretion: During the 3 days after a ^{10}B oral dose, 95 % of the ^{10}B was recovered from the urine and 4 % from the feces. excretion: Urinary isotope ratios, $^{11}B/^{10}B$, changed from a natural abundance of 4.1140 to an enriched value of 0.9507, a 77 % change. distribution: The ^{10}B label in perfused rat livers peaked within 3 hr (>90 % recovery" 56 % change in $^{11}B/^{10}B$) and returned to a natural abundance ratio within 24 hr. Metabolites identified: no Details on metabolites: Boric acid is not metabolised.	2 (reliable with restrictions) supporting study experimental result **Test material (Common name): Boron** **purity unknown**	Vanderpool RA, Hoff D & Johnson PE (1994)
Various, including rats, rabbits, sheep, cattle and humans. oral, dermal or inhalation. Exposure regime: No data Doses/conc.: In humans: 131 mg B (as boric acid dissolved in water); or daily dose of 102 mg B.	Main ADME results: absorption: Boric acid and sodium borates are readily and completely absorbed in humans and animals given borates orally. distribution: Animals investigated include rats (Ku et al., 1991), rabbits (Draize & Kelly, 1959), sheep (Brown et al., 1989) and cattle (Owen, 1944; Weeth et al., 1981) as shown by the levels of boron in urine, blood or tissues. absorption: Borates have been demonstrated to penetrate damaged or abraded skin (Draize and Kelley, 1959; Nielsen, 1970, Stuttgen et al., 1982). absorption: However, the use of an ointment-based vehicle may prevent or reduce the absorption through diseased skin compared to an aqueous jelly based vehicle (Nielsen, 1970 and Stuggen et al, 1982), although the results by Stuggen et al, 1982 have a number of flaws. Metabolites identified: not measured Details on metabolites: Boric acid is not metabolised.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): Boric acid (CAS No. 10043-35-3) and sodium borate (CAS No. unknown)** **Purity unknown**	Beyer KH, Bergfeld WF, Berndt WO, Boutwell RK, Carlton W, Hoffmann DK & Schroeter AL (1983) Brown TF, McCormick ME, Morris DR & Zeringue LK. (1989) Owen EC. (1944) Schou JS, Jansen JA & Aggerbeck B (1984) Stuttgen G, Siebel T & Aggerbeck B (1982) Weeth HJ, Speth CF & Hanks DR (1981) Wilding JL, Smith WJ, Yevitch P, Sicks ME, Ryan SG & Punte CL (1959) Wiley H. (1904) Wong LC,

			Heimbach MD, Truscott DR & Buncan BD. (1964)
Various, including rats and humans Exposure regime: No data Doses/conc.: Various, including: Humans: 10 mg/m^3 of airborne disodium tetraborate decahydrate (0.22 mg B/kg/day) Rats: Boric acid, providing approximately 100 mg B/kg bw/day for up to seven days.	Transfer: Bone achieved the highest concentration of boron. Toxicokinetic parameters: No data Metabolites identified: not measured Details on metabolites: Boric acid is not metabolised. Evaluation of results: no bioaccumulation potential based on study results	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): Boron, boric acid (CAS No. 10043-35-3) and disodium tetraborate decahydrate (CAS No. 1303-96-4)** **purity unknown**	Alexander GV, Nusbaum RE & MacDonald NS (1951) Ciba J & Chrusciel A. (1992) Forbes RM & Mitchell HH. (1957) Forbes RM, Cooper AR & Mitchell HH. (1954) Krause C, Chutsch M, Henke M, Leiske M, Meyer E, Schultz C, Schwartz E & Wolter R. (1991) Laurent-Pettersson M, Delpech B & Thellier M (1992) Locksley HB & Sweet (1954) Sabbioni E, Nicolaou GR, Pietra R, Beccaloni E, Conni E, Alimonti A & Caroli S. (1990) Shuler TR, Pootrakul P, Yamasukon P & Neilsen FH (1990) Ward NL (1987)
Various, including mice, rats and humans. Various, including i.v. and oral. Exposure regime: Various, including a single i.v. dose to humans.	Transfer: not determined Toxicokinetic parameters: Half-life 1st: < 24 h in both animals and humans Metabolites identified: not measured Details on metabolites: Boric acid is not metabolised.	2 (reliable with restrictions) supporting study experimental result **Test material (Common name): Boric acid (CAS No. 10043-35-3) and disodium tetraborate (CAS**	Astier A, Baud F & Fourneir A (1988) Jansen JA, Schou JS, & Aggerbeck B (1984) Litovitz TL, Klein-Schwartz W, Oderda GM & Schmitz BF. (1988)

		1303-96-4) **purity unknown**	Sutherland B, Strong PL & King JC. (1998)
rat (Sprague-Dawley) male/female oral: gavage Exposure regime: Single administration Doses/conc.: 1000 mg/kg (200 mg/mL at a dosing volume of 5 mL/kg). The dose was calculated based on the most recent individual animal body weight. equivalent or similar to OECD Guideline 417 (Toxicokinetics)	Main ADME results: distribution: Pancreas tissue had the highest level of zinc, ranging from 72.7 to 76.8 µg/mg tissue, followed by liver and femur tissue. Kidney tissue had the highest level of boron ranging from 14 to 32.7 µg/mg tissue followed by femur tissue. excretion: Urinary excretion for zinc reached a maximum rate range of 20.4 to 44.9 µg/24 h. Urinary excretion of boron reached a maximum rate range of 16245 to 20981 µg/24 h. excretion: A negligible amount of intake zinc was recovered from urine. Total recovery of boron in urine was 57.8 % (males) to 60.8 % (females) during the 0 - 72 h post-dose collection period (groups combined per sex). excretion: 5 % or less of intake boron was recovered from faeces between 0 and 24 h post-dose. Total recovery of zinc in faeces was 59.3 % (males) to 79.4 % (females) during the 0 - 72 h post-dose collection period (groups combined per sex) Toxicokinetic parameters: Tmax: 5 - 6 h after administration. Cmax: 9.63 - 11.7 µg/mL for zinc and 26.7 to 27 µg/mL for boron were reached before concentrations decreased ot background levels by 72 h post-dose. AUC: AUC0-∞ ranged from 9201 to 10396 min*µg/mL for zinc and 26023 to 32687 min*µg/mL for boron. CL/F (total body clearance) was 1.75 to 1.98 L/h/kg for zinc and 0.275 to 0.346 L/h/kg for boron. Vz/F was 18.7 to 21.8 L/kg for zinc and 1.97 to 3.48 L/kg for boron. Half-life 1st: T1/2 ranged from 5.0 to 7.7 h for both zinc and boron. Half-life 1st: T1/2a ranged from 0.79 to 1.7 h for zinc and from 5.1 to 5.2 h for boron. Half-life 1st: T1/2 ranged from 10.1 to 15.1 h for zinc and from 5.1 to 7.4 h for boron. Metabolites identified: not measured Evaluation of results: no bioaccumulation potential based on study results	1 (reliable without restriction) key study experimental result **Test material Dodecaboron tetrazinc docosaoxide heptahydrate CAS No: 138265-88-0)** **Purity: >98%**	Muzzio M (2010)

4.1.2 Human information

Table 13: Summary of toxicokinetics (absorption, metabolism, distribution and elimination): human information.

Method	Results	Remarks	Reference
Study type: In vivo percutaneous absorption study in humans. Details on study design: Males and females aged 22 - 50 with 8 people per group were exposed to the test substance. Urine was sampled as well as T-shirts worn and skin washings sampled. Endpoint addressed: dermal absorption Endpoint addressed: basic toxicokinetics	No adverse toxic or clinical signs were observed. There was no skin irritation. Recovery compound: BA -76.5 %; disodium tetraborate decahydrate 72 %; disodium octaborate tetrahydrate 78.5 %. Since the skin was washed 10 times and less 1 % was found in the last wash, it is assumed that most of the substance unaccounted for was in lost to outside clothing (over the T-shirt) and bedding during the 24 hour dosing period. Boric acid percent dose absorbed was 0.226 ± 0.125, with flux and permeability constant calculated at 0.0094 μg/cm^2/hr and 1.9 x 10-7 cm/hr, respectively. Borax (disodium tetraborate decahydrate) percent dose absorbed was 0.210 ± 0.194, with flux and permeability constant calculated at 0.00875 μg/cm^2/hr and 1.8 x 10^{-7} cm/hr, respectively. disodium octaborate tetrahydrate percent dose absorbed was 0.122 ± 0.108, with flux and permeability constant calculated at 0.010 μg/cm^2/hr and 1.0 x 10^{-7} cm/hr, respectively.	1 (reliable without restriction) key study **Test material (EC name): boric acid (CAS No. 10043-35-3), disodium tetraborate decahydrate (CAS No. 1303-96-4) , disodium octaborate tetrahydrate (CAS No. 12280-03-4)** **purity unknown**	Hui, X, Wester, RC & Maibach, HI. (1996) Wester RC, Hui X, Hartway T, Maibach HI, Bell K, Schell MJ, Northington, Strong P & Culver BD (1998)
Study type: Percutaneous absorption through human skin in vitro. Details on study design: In vitro diffusion from aqueous solution was determined in receptor fluid accumulation over a 24 h period. Human cadaver skin (dermatomed) was clamped onto an AMIE Systems in-line cell in a flow-through apparatus, with 1 cm^2 surface area of skin exposed. Receptor fluid was pumped at a rate of 3 mL/hr and collected every 4 h to 24 h. After 24 h the skin	Percent doses absorbed for boric acid were 1.2 for 0.005 % dose, 0.28 for 0.5 % dose and 0.70 % for 5 % dose. Skin surface and soap washed removed 72.4 ± 9.1, 86.0 ± 5.9 and 81.9 ± 2.9 % doses after the 24 h dosing interval. The final wash removed 1.2 ± 2.0 % dose, thus the washing procedure was essentially complete. These absorption amounts translated into flux values of 0.25, 0.58 and 14.58 mg/cm^2/h and permeability constants (Kp) of 5.0 x 10^{-4}, 1.2 x 10^{-4} and 2.9 x 10^{-4} /cm/hr. The above doses were at a standard 1000 μL/cm^2 dosing solutions. When the 5 % dose was applied at 2 μL/cm^2 (in vivo dosing volume), flux decreased some 200-fold to 0.07 mg/cm^2/hr and Kp of 1.4 x 10 $^{-6}$ cm/hr. Borax (disodium tetraborate decahydrate) dosed at 5 %/1000 μL/cm^2 had 0.41 % dose absorbed. Skin surface wash recovery was 87.7 ± 5.9 % dose. Flux was 8.5 μg/cm^2/h, and Kp was 1.7 x 10^{-4} cm/h. Disodium octaborate tetrahydrate dosed at 10 % /1000 μL/cm^2 was 0.19 % dose	1 (reliable without restriction) key study **Test material (Common name): Boric acid (CAS No. 10043-35-3), disodium tetraborate decahydrate (CAS No. 1303-96-4) and disodium octaborate tetrahydrate (CAS No. 12280-03-4)** **purity unknown**	Hartway T, Wester RC & Maibach HI (1997) Wester RC, Hui X, Hartway T, Maibach HI, Bell K, Schell MJ, Northington (1998) Wester RC, Hartway T, Maibach HI, Schell MJ, Northington DJ, Culver (1998)

surface was washed. Boric acid (enriched) was applied at 0.05 %, 0.5 % and 5 % and either an infinite dose of 1000 mL/ cm^2 or a finite dose of 2 mL/ cm^2. Changes in boron isotope ratios by IPCMS (Inductively Coupled Plasma-Mass Spectrometry) was used to measure absorption. Endpoint addressed: basic toxicokinetics Endpoint addressed: dermal absorption	absorbed. Skin surface wash recovery was 91.3 ± 25.2 % dose. Flux was 0.8 x 10^{-4} cm/h. These in vitro results from infinite dose (1000 µL) were several magnitudes higher than those obtained in vivo. The results from the finite dose (2 µL) were closer to in vivo results (also 2 µL).		
Study type: In vivo human excretion of boron, specifically examining renal clearance. Details on study design: Boron intake was from the background in the diet. In 16 second-trimester women and 15 nonpregnant age-matched referents, dietary boron provided the blood and urine boron concentrations used for calculating boron clearance. Blood for boron, creatinine and urea was collected at the start, at 2 h and 24 h. Urine was collected during the first 2 h in the Clinical Research Centre and during 22 h outside the centre for measurement of volume, boron and creatinine. Renal boron clearance measured over the initial two h, the most complete urine collection period since after that time the accuracy of urine	The pregnant and non-pregnant boron intake was 1.35 mg boron/24 h and 1.31 mg boron/24 h respectively. Renal boron clearance measured over the initial 2 h, the most complete urine collection period, was 68.30 ± 35.0 mL/min/1.73 m^2 for pregnant subjects and 54.31 ± 19.35 mL/min/1.73 m^2 for non-pregnant subjects based on surface area. Based on body weights, the renal clearances were 1.02 ± 0.55 mL/min/kg and 0.8 ± 0.31 mL/min/kg for pregnant and nonpregnant subjects respectively. For the 24 h period, where urine collection was known not to be complete, the renal clearance was 61.04 ± 36.7 mL/min/1.73 m^2 for pregnant subjects and 43.85 ± 21.59 mL/min/1.73 m^2 for nonpregnant subjects based on surface area. Based on body weights, the renal clearances were 0.92 ± 0.59 mL/min/kg and 0.64 ± 0.4 mL/min/kg for pregnant and nonpregnant subjects respectively. The baseline plasma levels of boron were 0.022 ± 0.013 and 0.023 ± 0.015 mg B/mL for nonpregnant and pregnant subjects respectively. At 2 hour and 24 hours the levels were as follows: 2 hours: 0.024 ± 0.015 and 0.018 ± 0.011 mg B/mL for non-pregnant and pregnant subjects respectively; 24 hours: 0.027 ± 0.018 and 0.013 ± 0.006 mg B/mL for non-pregnant and pregnant subjects respectively. Comparison of renal boron clearance with creatinine clearance indicated that tubular reabsorption of boron occurred in both pregnant and non-pregnant women.	1 (reliable without restriction) key study **Test material (Common name): Boron** **purity unknown**	Pahl MV & Culver BD (2000) Pahl MV, Culver BD, Strong PL, Murray FJ & Vaziri ND (2001)

collection cannot be guaranteed. Differences in the serum creatinine clearances indicated that urine collection had not been complete over the entire 24 h collection period. Endpoint addressed: basic toxicokinetics			
Study type: Daily dietary boron intake and on-the-job inspired boron were compared with blood and urine and boron concentrations in workers engaged in packaging and shipping borax (disodium tetraborate). Fourteen workers handling borax at jobs of low, medium and high dust exposures were sampled throughout full shifts for 5 consecutive days each. Details on study design: Daily dietary-boron intake and on-the-job inspired boron were compared with blood and urine and boron concentratons in workers engaged in packaging and shipping borax (disodium tetraborate). Fourteen workers handling borax at jobs of low, medium and high dust exposures were sampled throughout full shifts for 5 consecutive days each. Airborne borax (disodium tetraborate) concentrations ranged from means of 3.3 mg/m^3 to 18	End-of-shift mean urine concentrations ranged from 3.16 to 10.72 µg/mg creatinine. There was no progressive increase in end-of-shift blood- or urine-boron concentrations across the days of the week. Urine testing done at the end of the work shift gave a somewhat better estimate of borate exposure than did blood testing, was sampled more easily and was analytically less difficult to perform.	Not relevant for Epidemiology study Supporting study **Test material (Common name): Boron and borax(disodium tetraborate anhydrous (CAS No. 1330-43-4), disodium tetraborate pentahydrate (CAS No. 12179-04-3), and disodium tetraborate decahydrate (CAS No. 1303-96-4))** **purity unknown**	Culver BD, Shen PT, Taylor TH, Feldstein AL, Anton-Culver H & strong P. (1993) Culver BD, Shen PT, Taylor TH, Lee-Feldstein A, Anton- Culver H & strong P. (1994)

mg/m^3, measured gravimetrically. Creatine measures were used to adjust for differences in urine-specific gravity such that 1 mL of urine contained approximately 1 mg creatine. Endpoint addressed: basic toxicokinetics			
Study type: The boron content of plasma in 22 newborn infants was assessed following repeated daily applications of a water-emulsifying ointment containing the equivalent of 3 % boric acid to the napkin region. Details on study design: The boron content of plasma in 22 newborn infants was assessed following repeated daily applications of a water- emulsifying ointment containing the equivalent of 3 % boric acid to the napkin region. 3 g ointment administered in total to each infant, corresponding to 90 mg boric aid or 15.7 mg boron. Endpoint addressed: dermal absorption Endpoint addressed: basic toxicokinetics	The mean plasma-boron concentration fell over 5 days from a pre-treatment value of 0.49 to 0.29 mg/L, the corresponding values in ten untreated neonates being 0.62 and 0.21 mg/L, respectively.	2 (reliable with restrictions) supporting study **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Friis-Hansen B, Aggerbeck B, Aas Jensen J. (1982)
Study type: Eight young male adult volunteers were given a single dose of boric acid (562 - 611 mg) by 20 min IV infusion. The plasma concentration curves were followed for 3 days. For 3	The excretion of boric acid in the urine of the eight experimental subjects was reasonably constant except for subject 4, who showed significantly increasing excretion during the control period and was therefore excluded from subsequent results. The plasma boric acid concentrations of 6 of the 7 remaining subjects showed a reasonable constancy. One subject was	2 (reliable with restrictions) supporting study **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Jansen JA, Andersen J & Schou JS. (1984)

days prior to intravenous boric acid administration, urine was collected in 12 -h fractions and blood was sampled for estimation of the basic alimentary boric acid level and excretion of the subjects. There were no restrictions on diet during the study. Endpoint addressed: basic toxicokinetics	excluded from the calculation of pharmacokinetic parameters as neither a three- nor a two- compartment model could be fitted satisfactorily and calculations could not be performed. The 120 h urinary excretion was 98.7 ± 9.1 % of dose, Cltot 54.6 ± 8 mL/min/1.73 m^2, $t_{1/2\beta}$ 21.0 ± 4.9 h and distribution volumes V1, V2 and V3: 0.25 ± 0.099, 0.456 ± 0.067 and 0.340 ± 0.128 L/kg.		
Study type: A two-week experiment in which 10 students (average age 24 ± 1.6 years, average weight 72.6 ± 7.9) drank mineral water was carried out to clarify the position in regard the oral intake, accumulation and excretion during mineral water consumption. Details on study design: A two-week experiment in which 10 students (average age 24 ± 1.6 years, average weight 72.6 ± 7.9) drank mineral water was carried out to clarify the position in regard the oral intake, accumulation and excretion during mineral water consumption. No special dietary instructions were given. Alcoholic drinks and heavy work were forbidden. In the first week of the experiment, 5 subjects drank 0.7 L bottled spring water daily in three portions spread over the day for 4 days and another 5 subjects drank 0.7 L a day of a boron	The normal excretion of boron in the urine on the control day before the start of the first period of water drinking averaged 1.7 mg ± 30 %. The excretion of boron in the urine after daily administration of 0.7 L spring water or water with the same concentration of boron increased in exactly the same way notwithstanding the differences between the two kinds of water in chemical composition. The excretion of boron during the test periods followed the same pattern in both weeks, reaching a maximum (94.1 mg/day) on the third to fourth day of the test period. Subtraction of the normal excretion (1.7 mg/day) gives a 92.4 mg/day increase - about 91 % of the daily intake, leaving a residue of 9.6 mg that follow other pathways. Part of this is probably never absorbed, or excreted via the intestinal tract and sweat, while a further component appears to accumulate slowly.	4 (not assignable) Supporting study **Test material (Common name): Boron** **purity unknown**	Job C. (1973)

solution of the same concentration. The types of water given were switched in the second week of the experiment. The water was not drunk on the first and sixth day of each week. On these days blood samples were taken from the arm vein. The 24 h urine was tested for volume, conductivity and boron, sulphate and chloride concentrations. Blood samples were frozen and transported for determinations of boron in the whole blood. Endpoint addressed: basic toxicokinetics			
Study type: Two male subjects wore regulation navy short sleeve undershirts saturated and kept moist for an 8 h period with a 5 % aqueous solution of boric acid. Analysis of various specimens continued up to 48 h. In a second experiment boric acid ointment was applied for 6 h to the upper half of the body (neck to waist) of 2 normal male subjects. Individual voidings of urine were collected. In a third experiment, 2 subjects, after voiding, immersed their feet to the ankles in hot saturated (5 %) boric acid solution for periods of 30 and 60 minutes respectively. To avoid contamination the subject was not	Experiment 1: Repeated analysis of urine specimens up to 48 h failed to demonstrate any boric acid in the urine using the turmeric paper test which is usually sensitive to 1 part in 5000. Experiment 2: Urine was negative for boric acid using the turmeric paper test for the entire 24 h period after application. Experiment 3: Urine samples at 0.5, 1, 3 and 13 h were negative for boric acid by the turmeric paper test. These samples were alkalized and dried and were found to be almost entirely negative for boron on spectrographic analysis. Only the 30 min urine samples had faint boron lines. In the 30 min urine sample of one subject the boron line at 2497 angstroms was slightly less dense than the platinum line at 2428 angstroms. These densities were reversed in the second subject. Since the only source of platinum was the dish used to ash the urine sample, the amount of platinum and boron in the total ashed specimen can be estimated to be about 10 angstroms. This indicates that the boron in the original urine sample was in the order of 1 part of boron to 10000000 parts of urine.	2 (reliable With restrictions) supporting study **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Pfeiffer CC, Hallman LF & Gersh I. (1945)

allowed to touch the foot bath at any time. Urine samples at 0.5, 1, 3 and 13 h were collected and tested using the turmeric paper test. These samples were alkalised and dried and tested for boron. Endpoint addressed: basic toxicokinetics			
Study type: The correlation between the concentrations of the postshift urine and 24 h potential boron intake through air particles was analysed and contrasted so as to estimate their different absorption rates in different situations. Details on study design: Three groups were recruited, namely the group of boron-involved workers from boron mineral exploitation and processing groups as the boron exposure group, the second group was a nonboron workers from nonboron plants from around the boron industry area as an community group and the third group of people from the area far away from boron production as an community contrast group. All of the subjects were considered generally healthy adult males within the age group 20 – 40 years. Samples of postshift urine, both of the 8-h shift air particle intakes and 24 h diet of the subjects were	The results showed that boron exposure channels for the people that were from the non-boron industry area were mainly exposed via food and drinking water, while the boron workers were not only from food and drinking water, but also through air particles. For the boron mine workers, no significant correlation was found between their post-shift urine boron and 24 h potential boron intake, while for the workers from boric acid or borax (disodium tetraborate) production section the correlation proves significant. This study was a part of the larger Robbins et al. study, and was disregarded at the conclusion of the larger study. The Xing X et al. study has a number of internal flaws.	Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **purity unknown**	Xing X, Wu G-P, Hu W, Wang C-L, Wei F-S & Shen Y-X. (2007)

checked to measure their boron concentrations. The correlation between the concentrations of the postshift urine and 24 h potential boron intake through air particles was analysed and contrasted so as to estimate their different absorption rates in different situations. Endpoint addressed: basic toxicokinetics			
Study type: Boron was studied in detail in biological samples collected from hospital and clinics around the UK, namely whole blood, blood serum, urine, scalp hair, finger and toenails (50 samples of each); and standard reference materials. The samples were prepared by wet digestion and dry ashing techniques (depending on the nature of the sample) prior to analysis by ICP-MS. Endpoint addressed: basic toxicokinetics	Blood products, which are homeostatically regulated, were found to contain comparatively low concentrations of boron and a narrow range (upper-lower quartiles). The remaining matrices measured can all be regarded as excretory pathways; urine in the short term, hair and nails over a long time period, which may account for the wide ranges obtained. The higher concentrations found in tissues (scalp hair and nails) are largely due to a build-up over along period of time and accumulation into a solid form.	2 (reliable with restrictions) supporting study **Test material (Common name): Boron** **purity unknown**	Abou-Shakra FR, Havercroft JM & Ward NI. (1989)
Study type: ETA-AAS and ICP-AES Details on study design: Neutron activation analysis-electrothermal atomic absorption spectroscopy (ETA-AAS) and inductively coupled plasma atomic emission spectrometry (ICP-AES) were used for the determination of 46 elements in urine,	Boron was not present in the blood or serum of healthy Italian subjects. Boron was present in the urine of 119 subjects. The mean concentration ± standard deviation was 1890 ± 126 µg/L; with an experimental range of 470 – 7800 µg/L. The reference values were 9490 - 3290 µg/L and range of uncertainty was > 3290 – 7800 µg/L. The upper limit form metabolic anomalies was > 7800 µg/L.	2 (reliable with restrictions) supporting study **Test material (Common name): Boron** **purity unknown**	Minoia C, Sabbioni E, Apostoli P, Pietra R, Gallorini M, Nicolaou (1990)

blood and serum of unexposed Italian subjects living in the same region. The subjects were considered representative of five subgroups resident in urban, suburban, rural and low and high hill areas. A questionnaire supplied detailed information on age, sex, area of residence, occupation, smoking habits, body weight, alimentary habits, socioeconomic and ethnic factors as well as on the elemental composition of the drinking water from the municipal supply and mineral water used. Endpoint addressed: basic toxicokinetics			
Study type: The renal blood clearance of sodium pentaborate was observed in patients under going neutron capture therapy for intracranial malignant tumours. Details on study design: Urine collections were made on patients with an indwelling catheter which the patient required for reasons other than participation in the test. Blood concentrations were estimated by interpolation between points on a curve of analytical data, assuming a straight-line relationship between any two points in sequential time series.	The renal clearance for boron was found to average 39.1 mL/min for a man with a surface area of 1.73 m^2. The variations were not greater than would be expected from the clinical conditions of the patients concerned. It is not known whether comparable variations in urea or other clearances were occurring simultaneously.	2 (reliable with restrictions) supporting study **Test material (EC name): sodium pentaborate** **CAS No: 12007-92-0** **purity unknown**	Farr LE & Konikowski T. (1963)

Endpoint addressed: basic toxicokinetics			

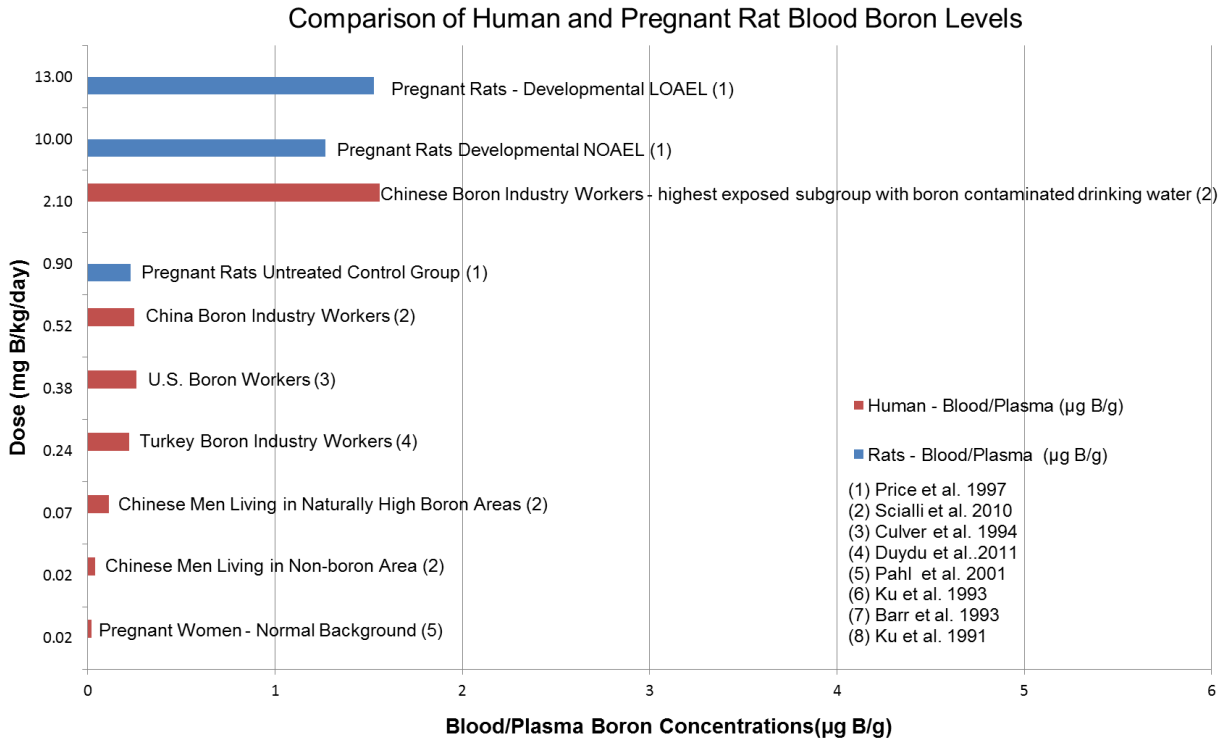
4.1.3 Summary and discussion on toxicokinetics

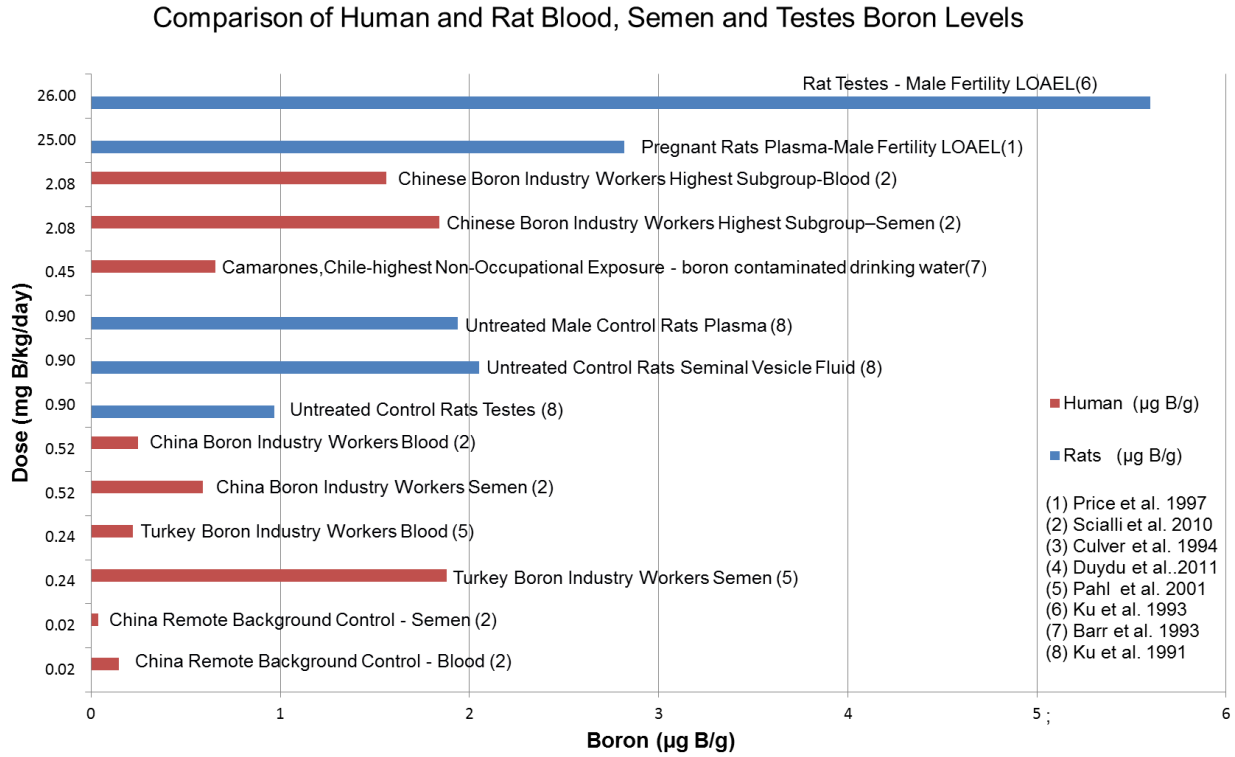
There is little difference between animals and humans in absorption, distribution, and metabolism. A difference in renal clearance (based on body mass) is the major determinant in the differences between animals and humans, with the renal clearance in rats approximately 3 times faster than in humans. (Clearance based on surface area is similar across species.)

Boric acid is not metabolised in either animals or humans, owing to the high energy level required (523 kJ/mol) to break the B - O bond (Emsley, 1989). Other inorganic borates convert to boric acid at physiological pH in the aqueous layer overlying the mucosal surfaces prior to absorption. Most of the simple inorganic borates exist predominantly as undissociated boric acid in dilute aqueous solution at physiological and environmental pH, leading to the conclusion that the main species in the plasma of mammals is un-dissociated boric acid. Since other borates dissociate to form boric acid in aqueous solutions, they too can be considered to exist as un-dissociated boric acid under the same conditions. Additional support for this derives from studies in which more than 90 % of administered doses of inorganic borates are excreted in the urine as boric acid. Absorption of borates via the oral route is nearly 100 %. For the inhalation route also 100 % absorption is assumed as worst case scenario. Dermal absorption through intact skin is very low with a percent dose absorbed of 0.226 ± 0.125 in humans. Using the % dose absorbed plus standard deviation (SD) for boric acid, a dermal absorption for borates of 0.5 % (rounded from 0.45 %) can be assumed as a worse case estimate.

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

A comparison of blood, semen and target organ boron levels in studies of laboratory animals and human studies shows that boron industry worker exposures are lower than untreated control rats. Background boron levels in standard rat chow are high (10-20 ppm), as a result control rats in toxicity studies receive 45 times more boron than background exposure in humans. Blood boron levels in female control rats is about 0.23 μg B/g, approximately equal to the blood levels in boron industry workers in China, Turkey and U.S. of 0.25, 0.22 and 0.26 μg B/g, respectively. Plasma and seminal vesicle fluid (the major component of semen) boron levels in untreated male control rats were 1.94 and 2.05 μg B/g, respectively, while boron levels in testes in rats dosed at the rat fertility LOAEL (26 mg B/kg) was 5.6 μg B/g. Values in male control rats were higher than corresponding boron levels in the highest exposed Chinese boron industry workers with blood boron levels of 1.56 μg B/g and 1.84 μg B/g in semen. Blood and semen boron levels in highly exposed Turkish boron workers were also lower than control rats with levels of 0.22 and 1.88 μg B/g, respectively. The blood level at the lowest animal LOAEL (13 mg B/kg) was 1.53 μg B/g, about 6 times greater than typical boron industry workers. Only under extreme conditions do human levels reach those of this animal LOAEL: the subgroup of Chinese boron workers who also drank contaminated water.


Comparison of Human and Pregnant Rat Blood Boron Levels
Dose (mg B/kg/day)
13.00
10.00
2.10
0.90
0.52
0.38
0.24
0.07
0.02
0.02
Pregnant Rats - Developmental LOAEL (1)
Pregnant Rats Developmental NOAEL (1)
Chinese Boron Industry Workers - highest exposed subgroup with boron contaminated drinking water (2)
Pregnant Rats Untreated Control Group (1)
China Boron Industry Workers (2)
U.S. Boron Workers (3)
Turkey Boron Industry Workers (4)
Chinese Men Living in Naturally High Boron Areas (2)
Chinese Men Living in Non-boron Area (2)
Pregnant Women - Normal Background (5)
Human - Blood/Plasma (µg B/g)
Rats - Blood/Plasma (µg B/g)
(1) Price et al. 1997
(2) Scialli et al. 2010
(3) Culver et al. 1994
(4) Duydu et al..2011
(5) Pahl et al. 2001
(6) Ku et al. 1993
(7) Barr et al. 1993
(8) Ku et al. 1991
0
1
2
3
4
5
6
Blood/Plasma Boron Concentrations(µg B/g)


Comparison of Human and Rat Blood, Semen and Testes Boron Levels
Dose (mg B/kg/day)
26.00
25.00
2.08
2.08
0.45
0.90
0.90
0.90
0.52
0.52
0.24
0.24
0.02
0.02
Rat Testes - Male Fertility LOAEL(6)
Pregnant Rats Plasma-Male Fertility LOAEL(1)
Chinese Boron Industry Workers Highest Subgroup-Blood (2)
Chinese Boron Industry Workers Highest Subgroup–Semen (2)
Camarones,Chile-highest Non-Occupational Exposure - boron contaminated drinking water(7)
Untreated Male Control Rats Plasma (8)
Untreated Control Rats Seminal Vesicle Fluid (8)
Untreated Control Rats Testes (8)
China Boron Industry Workers Blood (2)
China Boron Industry Workers Semen (2)
Turkey Boron Industry Workers Blood (5)
Turkey Boron Industry Workers Semen (5)
China Remote Background Control - Semen (2)
China Remote Background Control - Blood (2)
Human (µg B/g)
Rats (µg B/g)
(1) Price et al. 1997
(2) Scialli et al. 2010
(3) Culver et al. 1994
(4) Duydu et al..2011
(5) Pahl et al. 2001
(6) Ku et al. 1993
(7) Barr et al. 1993
(8) Ku et al. 1991
0
1
2
3
4
5
6
Boron (µg B/g)

4.2 Acute toxicity

Not evaluated in this dossier.

4.3 Specific target organ toxicity – single exposure (STOT SE)

Not evaluated in this dossier.

4.4 Irritation

Not evaluated in this dossier.

4.5 Corrosivity

Not evaluated in this dossier.

4.6 Sensitisation

Not evaluated in this dossier.

4.7 Repeated dose toxicity

Not evaluated in this dossier.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Not evaluated in this dossier.

4.9 Germ cell mutagenicity (Mutagenicity)

Not evaluated in this dossier.

4.10 Carcinogenicity

Not evaluated in this dossier.

4.11 Toxicity for reproduction

Table 14: Summary table of relevant fertility/reproductive toxicity studies

Method	Results	Remarks	Reference
rat (Sprague-Dawley) male/female three-generation study oral: feed 0, 670, 2000 or 6700 ppm boric acid (0, 117, 350 and 1,170 ppm boron) in the diet, equivalent to 0, 34 (5.9), 100 (17.5) and 336 (58.5) mg boric acid (mg B)/kg bw/day. Exposure: Groups of 8 males and 16 females were used for all generations and were exposed from beginning of the study until sacrifice of parents P0, and from weaning till sacrifice of the F1- and F2-generations. The high dose group P animals were sterile so only controls, low and mid dose groups were taken to the F2 and F3 generations. (Daily) No guideline specified, but conforms to the standard 3 generation 2 litters per generation multi-generation studies normally used at that time.	LOAEL (P): 336 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 1170 ppm In the diet. Based on sterility.) NOAEL (P): 100 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) NOAEL (F1): 100 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) NOAEL (F2): 100 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) LOAEL (P): 58.5 mg B/kg bw/day (male/female) based on: element (Based on sterility.) Testicular atrophy, reduced fertility (no offspring from high dose females mated with untreated males) NOAEL (P): 17.5 mg B/kg bw/day (male/female) based on: element NOAEL (F1): 17.5 mg B/kg bw/day (male/female) based on: element NOAEL (F2): 17.5 mg B/kg bw/day (male/female) based on: element No adverse effects in mid and low dose groups in any generation.	2 (reliable with restrictions) key study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Weir RJ (1966a) Weir RJ & Fisher RS (1972)
rat (Sprague-Dawley) male/female three-generation study oral: feed 0, 1030, 3080 or 10300 ppm disodium tetraborate decahydrate (0, 117, 350 and 1, 170 ppm boron) in the diet, equivalent to 0,	LOAEL (P): 518 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 1170 ppm boron in the diet based on sterility in males and females.) NOAEL (P): 155 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm	2 (reliable with restrictions) key study experimental result **Test material (CAS number):**	Weir RJ (1966b) Weir RJ & Fisher RS (1972)

50 (5.9), 155 (17.5) and 518 (58.5) mg disodium tetraborate decahydrate (mg B)/kg bw/day respectively (nominal in diet) Exposure: Groups of 8 males and 16 females were used for all generations. 14 weeks before mating. From beginning of the study until sacrifice of parents P0, and from weaning till sacrifice for the parents of the F1 and F2-generations. The high dose group P animals were sterile so only controls, low and mid dose groups were taken to the F2 and F3 generations. No guideline specified, but conforms to the standard 3 generation 2 litters per generation MGS normally used at that time.	boron in the diet.) NOAEL (F1): 155 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) NOAEL (F2): 155 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) LOAEL (P): 58.5 mg B/kg bw/day (male/female) based on: element (Based on sterility in males.) NOAEL (P): 17.5 mg B/kg bw/day (male/female) based on: element NOAEL (F1): 17.5 mg B/kg bw/day (male/female) based on: element NOAEL (F2): 17.5 mg B/kg bw/day (male/female) based on: element No adverse effects in mid and low dose groups in any generation.	**1303-96-4** **Common name: Borax (disodium tetraborate decahydrate CAS No. 1303-96-4))** **Purity unknown**	
rat (Sprague-Dawley) male fertility oral: feed 500, 1,000 and 2,000 ppm disodium tetraborate decahydrate, equivalent to 50, 100 and 200 mg B/kg bw (nominal in diet) Exposure: 30 or 60 days (Daily)	NOAEL (P): 50 mg/kg bw/day (nominal) (male) based on: element (30 days exposure: 1000 ppm B reduction of spermatocytes, spermatids and mature spearmatozoa. 2000 ppm B produced even greater loss of germinal elements. 60 days exposure: 1000 ppm B most germinal elements were absent. At 2000 ppm B, complete germinal aplasia was present.)	2 (reliable with restrictions) supporting study experimental result **Test material (Common name): Borax (disodium tetraborate decahydrate (CAS No. 1303-96-4))** **Purity unknown**	Lee IP, Sherins RJ & Dixon RL. (1978)
mouse (Swiss) male/female Reproductive assessment by continuous breeding oral: feed 0, 1000 ppm, 4500 ppm or 9000 ppm equivalent to 0, 152 (27), 636 (111), or 1262 (220) mg boric acid (mg B)/kg bw/d (as estimated in week 1). (nominal in diet) Exposure: 27 weeks (Daily in feed.) NTP's Reproductive Assessment by Continuous Breeding protocol.	NOAEL (F0): 27 mg B/kg bw/day (nominal) (male/female) based on:element (Fertility of the parent mice was totally eliminated at 220 mg B/kg bw.) LOAEL (F0): 27 mg B/kg bw/day (nominal) (male) based on: element (Reduced sperm motility in F0 males) LOAEL (F1): <= 27 mg B/kg bw/day (nominal) (male/female) based on: element (Significant decrease in reproductive parameters. Increased uterine weight and kidney/adrenal	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Fail PA, George JD, Seely JC, Grizzle TB & Heindel JJ. (1991) Fail PA, Chapin RE, Price CE & Heindel JJ (1998)

	weight, shortened oestrus cycle and 25 % reduction in sperm concentration (F1).) LOAEL (F2): <= 27 mg B/kg bw/day (nominal) (male/female) based on: element (Significant decrease in reproductive parameters. Reduced adjusted body weight of pups (F2).)		
rat (Albino) male oral: gavage US Federal Hazardous Substances Act	LD_{50}: > 10 g/kg bw (male) based on: test mat. (The LD50 was greater than the limit dose. No mortalities occurred at any dosage level tested.) LD_{50}: > 1500 mg B/kg bw	2 (reliable with restrictions) supporting study experimental result **Test material (EC name) Dodecaboron tetrazinc docosaoxide heptahydrate (CAS number: 138265-88-0)** **Purity unknown**	Daniels CL & Teske RH (1969)
rat (Sprague-Dawley) male/female subacute (oral: gavage) Main groups: 15, 150, 300 and 1000 mg/kg/day (actual ingested) Satelite groups: 1000 mg/kg (actual ingested) Exposure: 28 consecutive days (Daily) OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) EU Method B.7 (Repeated Dose (28 Days) Toxicity (Oral)) The Japanese Ministry of Health and Welfare Guidelines 1986 for a 28-day repeat dose oral toxicity study as required by Japanese Chemical Control Law 1973 of the Ministry of International Trade and Industry (M.I.T.I) amended 1986.	NOAEL: 150 mg/kg bw/day (actual dose received) (male/female) based on: test mat. NOEL: 15 mg/kg bw/day (actual dose received) (male/female) based on: test mat. Fertility NOAEL: 50 mg B/kg bw/day compared to 17.5 in absence of zinc	1 (reliable without restriction) key study experimental result **Test material (CAS name) Zinc borate oxide ($Zn_4(BO_3)_2O$), monohydrate (CAS number): 149749-62-2** **Purity unknown**	Wragg MS, Brooks PN & Doleman N (1996)
rat (Sprague-Dawley) male subchronic (oral: feed) 0, 7.8, 23, 78 and 230 mg/kg bw/d, equivalent to 0, 17.5, 52.5, 175 and 525 ppm boron; equivalent boron	NOAEL: > 230 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (No adverse effect were observed at any dose tested.)	2 (reliable with restrictions) supporting study experimental result **Test material (EC Name): disodium**	Weir R J (1963)

0, 0.88, 2.6, 8.8, and 26 mg B/kg bw/d. (actual ingested) Exposure: 90 Days (Daily; food ad lib)	NOAEL: 26 mg/kg bw/day (nominal) (male) based on: element	**tetraborate decahydrate** **(CAS No: 1303-96-4)** **purity unknown**	
rat (Fischer 344) male oral: feed Exposure regime: Nine weeks Doses/conc.: 3000, 4500, 6000 and 9000 ppm boric acid; 545, 788, 1050 and 1575 ppm boron (< 0.2, 26, 38, 52, 68 mg B/kg bw/day) respectively.	Inhibited spermiation could be separated from atrophy based on dose (inhibited spermiation: 3000/4500 ppm, atrophy 6000/9000 ppm) with each lesion aspect expressed at different threshold testis boron concentrations (inhibited spermiation: 5.6 µg boron /g and atrophy: 11.9 µg boron/g) with no boron accumulation during the 9-week exposure. These data suggest that separate mechanisms may be operating for these lesion aspects based on testis boron concentration and that boron dose rate was important for testicular toxicity. Inhibited spermiation was most reliably reflected by informed testicular histology with the more severe cases decreasing epipdidymal sperm count to levels that could affect fertility. After treatment, serum and testis boron levels in all dose groups rapidly fell to background levels at the earliest time points evaluated (7 days and 8 weeks post treatment respectively). The severely inhibited spermiation at 4500 ppm was resolved by 116 weeks post treatment but areas of focal atrophy were detected that did not recover post treatment. Also no signs of recovery from atrophy were observed (6000 and 9000 ppm). Atrophic tubules contained a normal complement of spermatogonia (2.6 to 2.9 germ cells/100 sertoli cells) with occasional dividing and degenerating germ cells. Elevations in serum FSH and LH levels suggested an intact hormonal response to the atrophy.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **(CAS No: 10043-35-3)** **purity unknown**	Ku WW, Chapin RE, Wine RN & Gladen BC. (1993a) Ku WW and Chapin RE (1994)

rat (Fischer 344) oral: feed Exposure regime: Up to 4 weeks Doses/conc.: 9000 ppm w/w boric acid	The first testicular lesion was noted was an inhibition of spermiation, which appeared by Day 7. Widespread exfoliation of apparently viable germ cells and pachytene cell death in stages VII and XIV appeared as exposure continued. After 28 days of dosing, extreme epithelial disorganization and germ cell loss were evident. To determine if there was a hormonal component to the boric acid-induced testicular lesions, serum levels of basal hCG- and LHRH-stimulated testosterone levels were measured. After 4 days of dosing, basal testosterone level was lower than controls and treated and control animals after wither hCG- or LHRH challenge. To determine of boron was preferentially accumulated by the testis, boron levels in testes, epididymis, liver, kidney and blood were measured. Boron levels had effectively reached steady state levels by day 4 and were not differentiated concentrated in the tissues examined. Thus, these studies characterize the testicular lesion produced by boric acid exposures and identify a decrease in basal serum testosterone levels in the absence of selective accumulation of boron in the testis.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **(CAS No: 10043-35-3)** **purity unknown**	Treinen KA & Chapin RE. (1991) Ku WW and Chapin RE (1994)
Study type: Various including plants, mammalian cells, humans Studies showing the existence of boron specific transporters and maintenance of variations in boron tissues concentrations by homeostatic mechanisms.	BOR1, BOR4, and NIP5;1 boron transport proteins in plants. NaBC1, homolog of BOR1 and BOR4, has been found in human kidney, stomach, duodenum, pancreas, brain, the anterior and posterior corneal epithelia, rena corpuscules, proximal tubules and collecting ducts in the kidney, pancreatic ducts and the choroid plexus epithelium.	4 (not assignable) supporting study experimental result **Test material (EC name): boron** **Purity unknown**	Takano J, Noguchi K, Yasumori M, Kobayashi M, Gajdos Z, Miwa K, Hayashi H, Yoneyama T, Fujiware T (2002) Takano J, Miwa K, Yuan L, von Wiren N, and Fujiwara T (2005) Takano J, Miwa K, and Fujiwara T (2008). Chen X, Schauder S, Potier N, Van

			Dorsselaer A, Pelczer I, Bassler B et al. (2002) O'Neill MA, Eberehard S, Albersheim P, and Darvill AG (2001) Kato Y, Miwa K, Takano J, Wada M & Fujiwara T (2008) Damkier HH, Nielsen S & Praetorius J (2007) Ralston NYC and Hunt CD (2001). Park M LQ, Shcheynikov N, Zeng W, Mualiem S (2004) Parker MD, Ourmozdi EP, and Tanner MJ (2001)
mouse (CD-1) male oral: feed 0 or 9000 ppm (nominal in diet) Exposure: Eight weeks (Daily)	NOAEL: < 9000 ppm (male) based on: test mat. (Serum testosterone decreased after 2 weeks of boric acid treatment and the response to human chorionic gonadotrophin was suppressed in the same boric acid treated animals one h after challenge with human chorionic gonadotrophin.)	4 (not assignable) supporting study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Sauls HR, Dennis SW, Pearce SW & Anderson SA. (1992)
Various includeing rats, mice, rabbits, dogs, humans Measurement of zinc levels in various mammalian tissues. Zinc shown to protect against testicular toxicity of chromium, cobalt and cadmium and developmental toxicity of cadmium.	Normal levels of zinc in soft tissues in humans are over 2 times greater than in comparative tissues in laboratory animals. The high zinc concentrations in humans compared to laboratory animals is also found in the target organs of boric acid including fetal tissue, epididymis, and testes.	4 (not assignable) supporting study experimental result **Test material (Common name): zinc** **CAS No. 7440-66-6** **Purity unknown**	Afonne OJ, Orisdawei OE, Ekanem IA, Akumka DD (2002) Anderson MB, Lepak K, Farinas V, George, WJ (1993) Ahokas RA, Dilts PV, Lahaye EB (1980) Daston GP (1982) Fernandez EL, Gustafson A, Andersson M, Hellman B, and Dencker L (2003)

			Hartsfield RA, Lee M, Morel JG, Hilbelink DR (1992) King JC, Shames DM and Woodhouseet LR (2000) Ranjan R, Swarup D, Patra RC (2011) Yamaguchi I, Shibata K, Takei M, Matsuda K (1996) Florianczyk B (2000) Dorea JG, Brito M, Araujo MOG (1987) Suescun MO, Campo S, Rivarola MA, Gonzalez-Echeverria F, Scorticati C, Ghirlanda J, Tezon J, Blaquier JA (1981)
Study type: cohort study (retrospective) Type of population: occupational Details on study design: METHOD OF DATA COLLECTION - Type: Interview / Questionnaire / Record review - Details: The fertility data were obtained primarily by self administered questionnaire, and a section of the group by telephone interview. A 10 % sample of questionnaires was checked against the relevant medical insurance records. The work and exposure data were provided from company records. STUDY POPULATION - Selection criteria: All male employees at the U.S. Borax mine and production facility in Southern California with more than 6 months service were invited to	There was a highly significant excess of offspring fathered by the male employees at the mine and production facility (529 observed births compared with 466.6 expected). A statistically significant excess in the standardised birth ratio (SBR) of 113, significant at $p < 0.01$. The SBR for the workers with 'low' (< 3 mg/m^3) exposures was not different from the SBR of those with 'medium' ($3 – 8$ mg/m^3) and 'high' (> 8 mg/m^3) exposures, and both exceeded 100. There was no evidence of a relation between exposure and this excess of offspring, nor were there any temporal differences during the more than 30 year period of observation. The SBR was also evaluated in 5 year periods from 1950-1990 and in every period the SBR was greater than 100. Nine percent of workers tried unsuccessfully to conceive for	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Sodium borate (CAS unknown)** **Purity unknown**	Whorton D, Haas J & Trent L (1992) Whorton D, Haas J & Trent L. (1994a) Whorton MD, Haas JL, Trent L & Wong O. (1994b)

participate in the study. - Total number of subjects participating in study: Of the 753 eligible male employees with more than 6 months service, 542 (72 %) participated. The demographic data, length of employment, age and year at hire and medical insurance records of the non-participants and the participants were compared and no significant differences were found. - Sex/age/race: Males; wide range with average duration of employment in the facility of 16 years; race not specified - Smoker/nonsmoker: Smokers and non-smokers EXPOSURE The range of exposure in one year was 2 to 35.7 mg/m^3 (sodium borates). Base in an average of 23.2 mg/m^3, Whorton et al, (1994a,b), calculated the average exposure to borate dusts to be 203 mg/day assuming a 7 hour day and a respiratory volume of 8.75 m^3 (based on 10 m^3 for 8 hours). They assumed an average or usual boron content of 14% of the dust which, for the high exposure group, is equivalent to a mean of 28.4 mg B/d or 0.4 mg B/kg/d for a 70kg worker. The average exposure for the highest exposure group was 28.4 mg B/day (approximately 0.4 mg B/kg bw/day) for two or more years. The average duration of exposure was 16 years. COMPARISON POPULATION - Type: No specific local control group was studied, but the results expressed as the Standardised Birth Ratio (SBR) were compared with the SBR for the general US population adjusted for maternal age, parity, race and calendar year. HEALTH EFFECTS STUDIED - Disease: Infertility Endpoint addressed: toxicity to reproduction / fertility	more than one year which compares with the national average of 15 % of the adult population. An excess in the percentage of female offspring (52.7 % compared with 48.8 % expected) were fathered by these male employees, this increase was not statistically significant, and was not due to a deficit of boys since 249 were observed compared with 238 expected. Thus there was an excess of 11 boys and 51 girls. There was no evidence of an exposure relationship to sodium borate exposures of the fathers and the excess of female offspring, nor were there any temporal differences. There was an inverse relationship between the increase percentage of female offspring and the sodium borate exposures of their fathers.		
Study type: cohort study (retrospective) Type of population:	Daily boron exposures were 8.214 ± 0.257 mg/day in the study group and 2.051 ± 0.257	Klimisch score Not relevant for	Korkmaz M, Sayli BS, Sayli U, Bakirdere S,

general The aim of this research was to determine the daily boron exposure of women living in the area where the water supply had boron level of 2 ppm and above, and who had been living in the area since birth. The study group consisted of 41 women with an average age of 46.20 ± 2.14. The control group included 29 women with an average age of 35.83 ± 83. The main approach to determine daily boron exposure was to study boron levels in 24 h urine collected from individuals. Urine boron level was measured by ICP-OES method.	mg/day in the control group. There was a significant difference between the study and control group. Daily boron exposures were 8.214 ± 0.257 mg/day in the study group and 2.051 ± 0.257 mg/day in the control group. There was a significant difference between the study and control group.	epidemiology study supporting study **Test material (EC name): Boron** **Purity unknown**	Atman OY, Titretirs S & Keskin S. (2006)
The aim of the study was to estimate daily boron exposure in 66 males in Turkey living in a B-rich area using water containing at least 2 mg/L boron with an average age of 38 - 55 (SE 1.66) years and an average number of years of residence in the boron rich area of 35 - 89 (SE 1.73). Another group of 57 males living in the city centres of Balikesir and Ankara were taken as controls; the average age and number of years of residence for this group were 29.44 (SE 1.43) and 10.26 (SE 1.83) years respectively. As it is assumed that boron levels in urine reflect daily boron exposure, the amount of urinary boron of both the study and control groups was analysed using an inductively coupled plasma optical emission spectrometry technique (ICP-OES).	The average daily boron exposure was calculated as 6.77 (SE 0.47) mg in the study group and 1.26 (SE 0.1) mg in the controls. None of the subjects reported any health problems which may be linked to high boron exposure.	Klimisch score Not relevant for epidemiology study supporting study **Test material (EC name): Boron** **Purity unknown**	Korkmaz M, Sayli U, Sayli BS, Bakirdere S, Titretir S, Atman OY & Keskin S. (2007)
Study type: cohort study (retrospective) Type of population: general Details on study design: HYPOTHESIS TESTED: Relationships between elevated boron intake and fertility were sought by comparing reproduction in the residents of two Turkish villages with high levels of boron in their drinking water (one with 8.5 to 29 mg B/L and the other	EXPOSURE OTHER OBSERVATIONS: In high areas average concentrations ranged from 0.7-29.0 mg B/L. In other lower boron areas 0.05- 0.45 mg B/L. Drinking water in 5 supplies from the very low control area of Camlidere had levels <0.1 mg B/L. In the high boron exposure region the infertility rate was 3.17 % in the probands and 3.0	Klimisch score Not relevant for epidemiology study supporting study **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Sayli BS, Tüccar E & Elhan AH. (1998)

with 2.05 to 2.5 mg B/L), with three nearby villages with more typical lower boron levels (0.03 to 0.45 mg B/L). The two high boron villages were designated as Region I, and the three villages with lower boron in the drinking water were designated Region II. In addition to exposure to elevated boron in drinking water, 28.3 % of the probands in Region I were employed in borate mining or processing, whereas in Region II, 11.7 % were so employed. The data on fertility from these two populations was also compared with that from an area with a very low boron concentration in drinking water and no occupational exposure, and also from data for the whole Turkish population. METHOD OF DATA COLLECTION - Type: Interview STUDY POPULATION - Total population: The group with the high boron exposures in Regions I and II comprised 927 probands and by the use of a pedigree technique covering three generations, fertility data on 5934 marriages were investigated. - Selection criteria: Relationships between elevated boron intake and fertility were sought by comparing reproduction in the residents of two Turkish villages with high levels of boron in their drinking water (one with 8.5 to 29 mg B/L and the other with 2.05 to 2.5 mg B/L), with three nearby villages with more typical lower boron levels (0.03 to 0.45 mg B/L). The two high boron villages were designated as Region I, and the three villages with lower boron in the drinking water were designated Region II. In addition to exposure to elevated boron in drinking water, 28.3 % of the probands in Region I were employed in borate mining or processing, whereas in Region II, 11.7 % were so employed. - Sex/age/race: Males and females; 40 % of the probands were 30-39	% averaged over 3 generations. In the very low exposure control area infertility was 4.48 %, and in the general Turkish population was 3.84 % . No difference in fertility was observed between 399 men with occupational exposure to boron, and 222 men with similar occupations but not exposed to boron. It was concluded that within the limits of the study, there was no evidence that boron interfered with human fertility and reproduction.		

y; 35 % 40-60 y; and 15 % < 30 y - Smoker/nonsmoker: Smokers and non-smokers COMPARISON POPULATION - Type: Other comparison group: The data on fertility from the study populations was also compared with that from an area with a very low boron concentration in drinking water and no occupational exposure, and also from data for the whole Turkish population. National population of Turkey 49,856 randomly chosen families Regional population of Camlidere (relatively boron free soils) 625 families covering three generations. HEALTH EFFECTS STUDIED - Disease(s): Relationships between elevated boron intake and fertility were sought Endpoint addressed: toxicity to reproduction / fertility			
Study type: Epidemiology study Details on study design: METHOD OF DATA COLLECTION - Type: Questionnaire - Details: Designed to determine the reproductive history of the family and its kindred; to ascertain all marriages of both the proband and their siblings, those of the proband's and spouse's parents' siblings and the children of the proband and their siblings' children. This three-generation analysis covered a substantial proportion of the population at risk. Selection of the probands was done by visiting the study areas and identifying volunteers at home, in the workplace or in the villages. The sample was not statistically randomised but was a convenience sample. The questionnaire involved age at marriage, age at first pregnancy, number and gender of offspring, miscarriages and stillbirths, congenital malformations and early infant deaths. General questions about health and lifestyle as well as demographic data about	By the pedigree technique, 5934 marriages were ascertained over three-generations from all study areas. Childless families among 916 probands were 29 in number and 3.17 % in frequency with minor variations from one area to the next, and 3.0 % averaged over the generations. Infertility rates in a boron-free community near Ankara with 625 families studied over three generations was 4.48 %, and in a larger population of 49856 families randomly investigated by us throughout the country was 3.84 %. No significant differences were observed in terms of marital status and childbearing between 222 and 399 occupationally boronunrelated and boronrelated men, respectively Nor was there any difference with respect to other aspects studied. It was concluded that within the limitations of this study, there was no evidence that boron interferes with human fertility and reproduction.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Sayli BS (1998)

their age, sex, place of birth and residence, education and occupation. The proband was then questioned about each member of their family. Unknown or doubtful information was excluded. No formal selection procedure was used to identify probands, except that they had to be or have been married. Care was taken to include only those born in the area in order to maintain homogeneity. Care was taken to avoid duplications. Boron concentrations in the Region I village of Iskele were 23 – 29 mg B/L in one drinking water supply and other. In a second Region I village (Osmanca) the concentration ranged from 2.05 to 2.50 mg B/L. The boron concentrations in drinking water in Region 2 were 0.05 and 0.45 mg B/L. Drinking water levels up to 2.05 mg B/L were measured in some villages in the county of Belikesir. In some counties east of Belikesir it was not possible to separate the boron-rich and –poor regions and drinking water here was determined as 1.13 to 9.05 mg B/L. A third province, also with widespread boron deposits had boron drinking water levels of 0.7 to 6.65 mg B/L. SETTING: The investigation was conducted in three provinces of Turkey, covering an area of 240 by 60 miles. STUDY POPULATION - Selection criteria: Selection of the probands was done by visiting the study areas and identifying volunteers at home, in the workplace or in the villages. The sample was not statistically randomised but was a convenience sample. - Total number of subjects participating in study: 927 probands COMPARISON POPULATION - Type: Control or reference groups: 51 families from an area of Turkey where there are no boron deposits Or mines with the water			

content of boron < 0.1mg B/L; and the general Turkish population over a 10 y period where 49856 families were studied throughout Turkey and estimated infertility rates used for comparison. HEALTH EFFECTS STUDIED - Disease: Infertility Endpoint addressed: toxicity to reproduction / fertility			
Study type: Epidemiology study Type of population: Both general and occupational Details on study design: METHOD OF DATA COLLECTION - Type: Interview - Details: The proband was interviewed about the male and female sibs of the proband and spouse. Sibs were grouped as follows: Those born and living in high-boron areas mainly exposed to borates environmentally via food and water; those from such areas both environmentally and occupationally at work in an ore pit or a processing plant; and those from low-boron areas and from regions distant from boron deposits, occupationally at a work related to the boron industry. Boron amounts of drinking waters from natural sources measured routinely changed from 0.05 to 29.0 ppm B. Elevated levels of boron were limited to Iskele town and its vicinity of Bigadiç county changing from 6.1 to 29.0 ppm B. SETTING: Interviewed at home, at work or in a coffeehouse. STUDY POPULATION - Total number of subjects participating in study: 2197 COMPARISON POPULATION - Type: Other comparison group - Details: Three sub-groups: A former mining county consisting of 80 probands; a rural county capital with relatively boron-poor soils consisting of 75 families; and a segment from the general	The rates of childless families of the type described were 0.0 - 3.4 % among male and 0.9 - 3.8 % among female sibs of the participant and 2.3 - 10.0 % among male and 0.0 - 5.6 % among female sibs of the spouse with averages of 2.3 % of 1589, 2.6 % of 1589, 4.0 % of 1341 and 3.3 % of 1436 instances respectively. The differences were insignificant and the rates were not different from those concerning probands themselves and that of a comparable segment of Turkish population.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Sayli BS (2001)

population consisting of 431 subjects. HEALTH EFFECTS STUDIED - Disease: Fertility Endpoint addressed: toxicity to reproduction / fertility			
Study type: Epidemiology study Details on study design: A study to assess the health effects of boron exposure was performed to assess the fertility/infertility of subjects exposed to borates environmentally and/or occupationally in a country with all the worlds largest deposits were described. The study covered all centres of borate production, an area of 350 km long and 150 km wide. Drinking water piped out from springs and wells had boron concentrations 0.2 to 29 ppm (mg B/kg or mg B/L). Dust amount at work sites was below the permissible level of 10 mg/m^3. The work, questionnaire based, was realized in field as an observational one. Residents were visited at home and in coffeehouses in villages and public buildings in towns, and workers at facilities and ore pits without any selection. The inquiry was mainly concerned with marital state and childbearing properties of probands and other members in the kindred. Endpoint addressed: toxicity to reproduction / fertility	Infertility of the primary type among 2529 probands as a convenient sample was 3.1 % changing from 0.0 % to 6.5 % regarding subpopulations from 12 centres, differences being statistically insignificant. No differences with respect to birthplace and professional state were revealed. Pedigree data showed the rate was 3.2 % covering 14320 marriages over 3 generations. No appreciable concentration of infertiles either in subgroups or in so-called "borate families" in borate towns was observed. Approached as an independent test, marriages of male and female sibs of proband and his (her) spouse ranged from 2.4 % to 4.2 %. None of these was so far higher than found in different sets of controls and of general population over 50000 families. Childlessness was found in 1.7 % among workers vs 4.3 % among employees from all facilities, the difference attributable to soci-cultural grounds.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Sayli BS, Cöl M, Elhan AH & Genc Y (2004)
Study type: Epidemiology study Type of population: occupational Details on study design: METHOD OF DATA COLLECTION - Type: Questionnaire - Details First phase: The questionnaire covered marital status and childbearing properties of the proband, and included the age at marriage, its duration, the period of first conception, the number of pregnancies, births,	At the first phase of the investigation, 191 workers were interviewed. Among these there were six infertiles of the primary type with a rate of 3.1 %. Boron-unrelated infertile couples among sibs were found to be 2.6 - 3.6 % and 3.2 % for three-generation marriages - none being higher than those revealed in different sets of controls. In the second stage of work, computerised files of all workers of the facility and all employees of the general management sharing the same location were checked without an interview.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Borates** **Purity unknown**	Sayli BS (2003)

foetal losses and congenital malformations, and the number and sex of children both alive and deceased. No physical examination was conducted but medical records if available were recorded. Second phase: Computerised individual files of all workers as well as all general management people were checked without interview. Studies were divided into three: Those places up to 2 ppm (mg B/L); those up to 10 ppm B and those with higher levels. The highest cocnentration was consistently found in Iskele-Osmanca belt, where 6.7 - 9.7 ppm B was found in one street fountain and 18.5 - 29.0 in the other, both of which were still in use. Amounts as high as 60 – 90 ppm B were reported in one well no longer in use. In recent years, freshwater from a remotes pring with as little as 1.7 ppm B is pumped to houses. Boron amounts ranged from 0.1 to 2.8 ppm B/L in other places, none were due to contamination. Higher levels up to 9.05 ppm B were reported in Emet- Hisarcik belt. In Kirka the concentration was 0.30 - 2.35 ppm B. SETTING: Borates plant, prior to or immediately after an 8 h shift. STUDY POPULATION - Total number of subjects participating in study: Phase 1: 191 Phase 2: 712 HEALTH EFFECTS STUDIED - Disease: Infertility Endpoint addressed: toxicity to reproduction / fertility	Twenty-four subjects (3.4 %) out of 712 workers were childless versus 2.7 % among 108 employees and 2.2 % among 91 workers of a distantly located sulfuric acid plant of the same complex. The differences were not significant. 94.2 % of probands had at least 1 living child at the time of inquiry, including one widow and one separated. 307 children were born to proband families of which 50.1 % were males and 49.9 % females, all alive at the time of the investigation, with a sex ratio of 1.0. Nine males and 6 female infants were described as deceased early in life. There were 1.7 alive and 0.1 deceased offspring per family. Of 119 interviewed, 32.5 % had 1 child, 56.6 % had 2 children and 8.8 % had 3 children. The remaining 2.3 % had 4 - 7 children. No discussion of foetal losses or congenital malformations were included		
Study type: Epidemiology study Type of population: occupational Details on study design: METHOD OF DATA COLLECTION - Type: Interview	Infertility rates were 1.2 % among 328 borate workers from Region 1, 1.1 % among 298 workers from Region 2 and 4.1 % among 173 workers from Region 3. Total infertility rate was 1.8 % for all of the workers. These rates were similar to the	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron**	Cöl M, Sayli BS, Genc Y, Ercevik E, Elhan AH & Keklik A.. (2000)

STUDY POPULATION - Selection criteria: Married male workers - Total number of subjects participating in study: 799 in total, 642 production workers and 157 office workers. The boron levels in drinking water ranged from 1.7 to 9.4 ppm for Region I, from 2.79 to 5.94 in Region II and from 0.36 to 0.62 in Region III according ot measurements taken. In production departments, dust concentrations varied from 1.11 to 2.96 mg/m^3 in Region I, 0.69 to 9.25 mg/m^3 in Region II and 0.39 to 9.47 mg/m^3 in Region III. HEALTH EFFECTS STUDIED - Disease: Infertility OTHER DESCRIPTIVE INFORMATION ABOUT STUDY: Definition of primary infertility was - no visible evidence of conceptus in a non-parous, monogamous, pre-menopausal person who maintained conjugal relationship for at least 9 months prior and after neither partner used any type of birth control method for the preceding 12 months. Definition of secondary infertility was - no visible evidence of conceptus in a parous, monogamous, premenopausal person who maintained conjugal relationship for at least 9 months prior and after neither partner used any type of birth control method for the preceding 12 months. Endpoint addressed: toxicity to reproduction / fertility	results of studies made in the same region and in other parts of Turkey. Total male/female ratio was found to be 1.12 , so no increase in the number of female offspring could be found when compared with previously reported data. No significant influence was observed in parameters used to define possible developmental effects. Stillbirths, abortions, prematurities or having low birth weights and early deaths of offspring were not more than the ones found in any part of the country. There were no differences in infertility rate, sex ratios and possible developmental effects between the production workers and office workers.	**Purity unknown**	
Study type: Epidemiology study Endpoint addressed: repeated dose toxicity: oral A regional scale geographical study in Northern France was conducted. Assessment of boron levels in a group of 180 healthy individuals and correlation with boron content in drinking water were followed by an assessment of	After necessary adjustments, men living in municipalities with more than 0.30 mg/L of boron in drinking water had elevated but not significant boron blood levels compared with those living in municipalities with boron water levels of less than 0.30 mg/L (159.1 vs 123.0 ng/g; $p > 0.05$). The standardised birth ratio	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Yazbeck C, Kloppmann W, Cottier R, Sahuquillo J, Debotte G & Huel G. (2005)

health indicators such as birth rates, mortality rates, and sex ratios in zones of different boron content in drinking water.	adjusted for the reference geographic zone and calendar time period was 1.07 and 1.28 in the low and high (> 0/3 mg/L) boron content municipalities, respectively. The birth rate in municipalities with high boron content in drinking water was higher than that of the reference geographic zone and of the French general population (p < 10E-4). The standardised mortality ratio adjusted for the reference geographic zone and calendar time period was 0.94 and 0.92 in low and high boron content municipalities, respectively. The mortality rate in municipalities with high boron content in drinking water was less than that of the reference geographic zone and of the French general population (p < 10E-03). No statistical difference was noted in the male-female sex ratios between the different municipality zones (p = 0.45). The results of the study do not support the idea of a deleterious effect of boron on human health, at the boron water level contents found in this specific region. In fact, there was a tendency towards a beneficial effect with low-dose environmental exposure (less than 1 mg/L of boron) in drinking water.		
Study type: Epidemiology study Endpoint addressed: repeated dose toxicity: oral A study was carried out in a population of newborns exposed to general environmental boron concentrations.	A negative association between blood delta-aminolevulinic acid dehydratase activity and placental boron was discovered and a potential boron threshold for this association was estimated.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Yazbeck C & Huel G. (2006)
Study type: Epidemiology study Type of population: occupational Details on study design: The sperm Y:X ratio in men exposed to a range of environmental and workplace boron was assayed. Participents included 63 workers in the boron industry; 39 men living in an area of high	Total exposure was correlated with internal dose (Pearson correlation for total exposure and boron in blood = 0.63, P < 0.0001; semen = 0.80, P < 0.001; and urine = 0.79, P < 0.0001). Linear regression of logged boron in biologic fluids on Y:X ratio was significant for blood P = 0.2, semen P = 0.0003	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Robbins WA, Wei F, Elashoff DA, Wu G, Xun L & Jia J (2008)

environmental boron but not employed in the boron industry and 44 controls living in an area of low environmental boron. Total daily boron exposure was calculated as the sum of boron in 24-h duplicate food and fluid intakes plus personal air sampling for workplace inhalable dust. Sperm were analysed by fluorescence in situ hybridisation for Y-versus X-bearing cells. Potential confounders were identified using a questionaire. Boron exposure assessment: A composite of total daily exposure was generated by collecting 24-h duplicate food portions and 24-h duplicate fluid intakes plus full work shift breathing zone air samples using Institute of Medicine (IOM) lapel filter cassettes and personal air monitoring pumps. Daily boron exposure in boron workers from dust, food and fluid intake was 41.2 ± 37.4 mg (mean ± SD); in the high boron community comparison in was 4.3 ± 3.1; and in the low boron control is was 2.3 ± 3.0. Endpoint addressed: toxicity to reproduction / fertility	and urine P = 0.005. Additionally when subjects were categorized by exposure groups, decreased Y:X sperm ratio was found for boron workers compared with men in a high boron environment and controls (P,0.0001). Exogenous environmental or workplace boron exposures were associated with decreases in Y-versus Xbearing sperm. However, the Y:X ratio did not correlate with the boron concentration in blood within exposure groups.		
Study type: various These reviews summarises the progress made in establishing essential roles for boron in human and animal physiology and assesses that progress in view of criteria of elements. Supporting studies report on beneficial effects of boron.	Adult Americans consume slightly less than 1.0 mg/day on average and can increase that average by increasing consumption of fruits and vegetables. Humans and animals may use boron to support normal biological functions but the biochemical mechanisms responsible are poorly understood.	Klimisch score Not relevant supporting study **Test material (Common name): Boron** **Purity unknown**	Hunt CD (1994, 1996, 1998, 2007, 2012) Mertz (1993) Devirian and Volpe (2003) Nielsen FH (1994, 1996, 1998) Penland (1994, 1998) Hunt CD, Herbel JL, and Nielsen FH (1997) Nielsen and Penland (1999) Hunt and Idso (1999) WHO (1996) FNB (2001)

			EGVM (2003) EFSA (2004) Gorustovich AA, Steimetz T, Nielsen FH, (2008) Barranco WT and Eckhert CD (2004) Barranco WT and Eckhert CD (2006) Barranco WT, Hudak PF, Eckhert CD (2007) Gallardo-Williams MT, Maronpot RR, Wine RN, Brunssen SH, Chapin RE (2003) Gallardo-Williams MT, Chapin RE, King PE, et al (2004). Korkmaz M, Sayli BS, Sayli U, Bakirdere S, Atman OY, Titretirs S & Keskin S (2006) Mahabir S, Spitz MR, Barrera SL, Dong YQ, Eastham C, and Forman MR (2008) Armstrong TA, Spears JW, Crenshaw TD and Nielsen FH (2000) Armstrong TA, Spears JW and Lloyd KE (2001) Armstrong TA, and Spears JW (2003)

Study type: Epidemiology study Type of population: non-occupational Studies comparing boron exposures in drinking water and lower incidences of some cancers.	Epidemilogical studies show boron in drinking water associated with lower incidences of prostate, lung, cervical and esophageal cancer.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Zhang Z-F, Winton JI, Rainey C, Eckhert CD (2001) Cui Y, Winton MI, Zhang Z, Rainey C, Marshall J, De Kernion JE and Eckhert CD (2004) Barranco WT, Hudak PF, Eckhert CD (2007) Barranco WT and Eckhert CD (2004) Barranco WT and Eckhert CD (2006) Henderson K, Stella SL, Jr, Kobylewski S, and Eckhert CD, (2009a, b) Barranco WT Kim DH, Stella SL Jr., and Eckhert CD (2009) Mahabir S, Spitz MR, Barrera SL, Dong YQ, Eastham C, and Forman MR (2008) Kibblewhite MG, Van Rensburg SJ, Laker MC, Rose EF (1984) Korkmaz M, Sayli U, Sayli BS, Bakirdere S, Titretir S, Atman OY & Keskin S (2007)
Study type: Epidemiology study Details on study design: This article described the lifestyle patterns of boron mining and processing workers (N = 936) and a comparison group (N = 251) in	34 % of boron workers reported eating in the contaminated work areas. Nearly all boron workers (99 %) showered or bathed after work although approximately 10 % redressed in their contaminated clothes.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name):**	Chang BL, Robbins WA, Wei F, Xun L, Wu G & Elasoff DA. (2006)

Northeast China, and explores relationships between boron exposure and reproductive health. An English version of an interview guide addressing areas of work and lifestyle relevant to boron exposure and metabolism was developed by an occupational health research team, translated to Chinese, and translated back, for clarity. Modifications incorporated suggestions from local community advisory board and boron industry workers; the translation-back translation process was reapplied and cultural settings and semantic equivalence was attained. The environmental boron exposure for the boron works (mean) and the comparison group (mean) were 2.6 - 3.8 mg/L for boron workers and 0.005 - 0.67 mg/L for the comparison group in surface water; 1.2 - 25.1 mg/L in boron workers well water and 0.002 - 0.67 mg/L for the comparison group's well water. The study was a cross-sectional, descriptive design based on interviews with participants who had occupational exposure to boron and a comparison group selected from an environment without significant exposure to boron. Endpoint addressed: toxicity to reproduction / fertility	Reproductive health outcomes were explored, including delayed pregnancy, multiple births, spontaneous miscarriages, induced abortions, stillbirths and unusual male:female offspring. On average boron workers fathered nearly 2.0 pregnancies compared with 2.1 pregnancies in the control group (P = 0.6). Of the self-reported pregnancies fathered by boron workers, an average of 1.3 resulted in livebirths, compared to an average of 1.4 for the comparison group (P = 0.3). A significant difference existed between groups in delay in pregnancy, defined as the inability to conceive within 1 year of desiring a child, with boron workers experiencing greater delays. However in logistic regression models adjusting for age, education, race, tobacco, alcohol and soybean consumption the difference was no longer statistically significant (P = 0.11) with an odds ratio of 1.7 for boron workers compared to the control group (95 % confidence interval, 0.09 to 3.5).	**Boron** **Purity unknown**	
Study type: cohort study (retrospective) Details on study design: The study population was divided into three sub-groups. The individuals that were interviewed in each subgroup served as probands for the study. The first subgroup of probands was identified in Region 1 which covers and area near on boron-rich territories. Dwellings of Region 1 were located close to borate pits and a processing plant. Region 2 probands were from villages far from boron deposits, but were within the same zone. Region 3 probands were born and live in areas with a mixed group some near to and some far from deposits and pits. In Region 1 drinking	The infant death rate in Region 2 (low boron area) was higher than those of other regions (significantly different). Although it is difficult to recognise spontaneous abortions and stillbirths in a retrospective study depending on the description only the probands (mostly females) these were considered separately, but no differences were found. The observed number of congenital malformation was not sufficient within the study groups to perform statistical tests. There was no evidence that B affects human developemnt adversely.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Tüccar E, Elhan AH, Yavus Y & Sayli BS. (1998)

waters forming from (natural) springs ad wells contain as much as 29 ppm boron, but in Region 2 the concentration was between 0.3 and 0.50 ppm. In the third region no measurements were regularly made but boron content was not known to be too high. In all three areas there were active and former borate workers. From Region 1, 226 families over three generations with respect to probands (that of the proband being the second) and from Region 2, 164 families were included. There were 177 families from Region 3 and 80 from Kirka. Criteria for selection was the presence of legal marriage regardless of whether one member was dead or whether there had been a divorce. The study was carried out by home visits. Workers and other related individuals were contacted at borate plants and pits. Questionnaires were arranged in order to obtain the number of pregnancies, early infant deaths, congenital malformations, stillbirths and spontaneous abortions. Findings were compared with $\chi 2$ test. Endpoint addressed: toxicity to reproduction / fertility			
Study type: Epidemiology study Type of population: occupational Details on study design: Cöl et al. (2000) investigated infertility rates, gender ratio, stillbirths and spontaneous abortions, premature births or low birth weights, and infant mortality rates among the families of 799 workers (642 production workers, 157 office workers) at three production facilities in Turkey. Data were collected by personal interviews of workers at their work place in 1998. Endpoint addressed: developmental toxicity / teratogenicity	The boron level in drinking water ranges from 1.7 to 9.4 ppm for Region I, from 2.79 to 5.94 in Region II and from 0.36 to 0.62 in Region III. Dust concentrations in production departments varied from 1.11 to 2.96 mg/m^3 in Region I, 0.69 to 9.25 mg/m^3 in Region II and 0.39 to 9.47 mg/m^3 in Region III. No boron exposure measurements were available for the spouses of the workers during their pregnancies, however their exposures were likely lower than the male workers who would also exposed to boron at the production facilities. No significant adverse effects were found among production workers with high boron exposures compared to national	supporting study **Test material (Common name): Boron** **Purity unknown**	Cöl M, Sayli BS, Genc Y, Ercevik E, Elhan AH & Keklik A. (2000)

	or regional rates or to office workers with low boron exposure. Infertility rates among the workers averaged 1.8% compared to the Turkish national rate of 1.49–3.8 %. When comparing the production workers to office workers, the only significant differences were that average pregnancies and live births among production workers exceeded those of office workers. There is no increase of premature births or low birth weights for these study regions when compared to national rates. Stillbirths per 100 pregnancies were 1.64 for Region I, 1.68 for Region III, but 3.09 for Region II, compared to 1.5 per 100 pregnancies in the Turkish demographic and health survey. The number of premature births or low birth weight per couple was 0.14, 0.12 and 0.11 for Region I, Region II and Region III, respectively compared to 0.26 in Ankara. Spontaneous abortion rates per 100 pregnancies were 6.75, 7.31 and 8.97 for the three regions, similar to the national rate of 8.7 per 100 pregnancies. The infant mortality rate per 1000 live births for Region I was 67.7, 91.8 for Region II and 66.3 for Region III, compared to an infant mortality rate of 63 per 1000 live births in Ankara, and 43 per 1000 live births for Turkey. Region II had the highest mortality rate but did not have the highest exposure to boron. The differences between the regions were likely due to social and cultural issues. Cöl et al. concluded that exposure to boron did not to adversely influence the infertility ratio, the male to female ratio at birth, the number of stillbirths, the number of spontaneous abortions, the number of premature births with low birth weight and the infant mortality rate for the workers from three boron plants. Primary		

	infertility, secondary infertility, sex ratio, stillbirth, prematurity/low birth weight, spontaneous abortions and infant mortality did not show any relation with work assignment.		
Study type: cohort study (retrospective) Type of population: occupational Details on study design: HYPOTHESIS TESTED: The null hypothesis for each biologic fluid was that the means of the respective four groups are equal. METHOD OF DATA COLLECTION - Type: Questionnaire, Atmosphere measurement, boron level determination in of blood, semen and urine, determinetion of semen and sperm parameters. - Details: Questionnaire: demographic, exposure, reproductive and general health information, drinking and eating habits. Atmosphere measurement: - Personal sampling: exposed group only, personal air sampler (SKC, AirCheck 2000), flow rate 2 L/min, sampling time 8 hours; low-ash PVC filters (SKC, 5 37 mm, preweighed) and SureSeal cassettes (SKC, 37 mm) Analysis of dust collected in cassettes by gravimetric and instrumental methods (Selin B (2010) Boron Determination in Body Fluids by Inductively Coupled Plasma Optical Emission Spectrometry and Inductively Coupled Plasma Mass Spectrometry. Dissertation, Middle East Technical University, Ankara, Turkey. & OSHA (2009) Chemical Sampling Information, Boric Acid, www.osha.gov .) - Area air sampling: control group only: same devices and parameters were used as for the personal sampling but the devices were not carried by	The high boron contamination (9.47± 0.18 mg B/L) of water sources for cafeteria and infirmary was not anticipated in the planning phase of the study. This "background" exposure lead to relatively high exposure of the "control" group. Total average exposure of occupationally exposure exposed workers: 12.08 ± 6.18 mg boron/day) Total average exposure of control workers: 5.83 ±1.71 mg boron/day The average daily boron exposure (DBE, in mg B/d) calculated for the reclassified groups are: Control 4.68 ± 1.63 Low exposure 7.39 ± 3.97 Medium 11.02 ± 4.61 High 14.45 ± 6.57 • Mean calculated daily boron exposure levels (DBE): ignificantly higher in exposure groups than in the new control group. Exposure to boron: • Restricted to the tap water in the infirmary and the cafeteria of the company (oral) and to the atmosphere in the boron production sites (inhalation). • The mean levels of inhaled boron (mg/8 h) 0.23 ± 0.79, 1.15 ± 3.14, 1.47 ± 2.69, and 2.58 ± 4.96 in control, low, medium and high exposure groups respectively. Medium and high exposure group significantly higher than in the control group - Boron levels in biological fluids: • Mean urine boron levels: 2.59 ± 1.32, 5.01 ± 2.07, 7.03 ± 2.37, and 9.83 ± 5.13 mg/g creat. in	Klimisch score Not relevant for epidemiology study supporting study **Test material: Boric acid (CAS No. 10043-35-3), disodium tetraborate decahydrate (CAS No. 1303-96-4)** **Purity unknown**	Duydu Y, Başaran N, Ustündağ A, Aydın S, Undeğer U, Ataman OY, Aydos K, Düker Y, Ickstadt K, Waltrup BS, Golka K, Bolt HM. (2011) Başaran N, Duydu Y, Bolt HM (2012)

individuals, but used statically, to determine an average value for the control workers. Biological sampling: taken at the end of a work shift; no samples taken on the first working day of the week or shift period; workers were informed of the importance to avoid a possible contamination (sampling after showering and changing of clothes) STUDY PERIOD: not described in detail exposure periods (years employed, boron blood level based groups): Control 15.30 + 8.63 Low exposure 16.85 + 7.06 Medium 17.21 + 6.77 High 13.96 + 8.04 STUDY POPULATION - Total population (Total no. of persons in cohort from which the subjects were drawn): exposed: 428 workers, 102 participated: boric acid production workers (n=57), borax (disodium tetraborate decahydrate) production workers (n=31), sodium perborate production unit workers (n=5), boric acid plus borax (disodium tetraborate decahydrate) production workers (n=5), laboratory workers (n=2), a storage worker (n=1), a mechanic technician (n=1) controls: 432 workers, sulfuric acid production plant workers (n=28), steam power plant workers (n=17), demineralized water production (DWP) unit workers (n=2), energy suppliers (n=11), mechanical workshop workers (n=19), garage workers (n=14), steelyard workers (n=2), construction service workers (n=3), laboratory technicians (n=3), and office workers (n=3). - Selection criteria: original groups: exposed: all married workers of the plants described above, wishing to participate, were	control, low, median and high exposure groups. Significantly higher in exposure groups than in the new control group. • Mean blood boron (ng/g) levels: < 48.5, 72.94 ± 15.43, 121.68 ± 15.62, and 223.89 ± 69.49 in control, low, med and high exposure groups, respectively. • Calculated DBE levels: positively correlated with the blood boron concentrations of the workers (Pearson corr. coeff.: 0.635). • Urine boron concentrations: positively correlated with the blood boron concentrations of the workers (Pearson corr. coeff: 0.633). • Semen boron concentrations (ng/g): 807.92 ± 1625.58, 1422.07 ± 1939.03, 1482.19 ± 1410.71 and 1875.68.2255.07 ± 2255.07 in control, low, med and high exposure groups. • Semen boron concentrations in exposure groups vs. new control group significantly different; the dose response trend was not significant, variations within groups were great. • Correlation between semen boron concentration and blood boron concentration: very low (Pearson corr. coeff.: 0.222). - Hormone levels: • no significant differences between grooups except for LH, mid dose vs. high dose • Very weak correlation between blood boron concentration and hormone levels (FSH: Pearson corr. coeff: 0.143; LH: Pearson corr. coeff: 0.164; total testosterone level: -0.053). • No statistical significant difference in testosterone levels between new control group and exposure groups. - Semen and sperm parameters (including morphology and DNA integrity testes): • No significant difference in		

enrolled. controls: probably matched for age and years of employment (and possibly additional parameters), not described in detail boron blood level based groups: Exposure groups n (204) Re-classification (ng boron/g blood) New control group 49 <LOQ (48.5) Low exposure group 72 >LOQ–100 Medium exposure group 44 >100–150 High-exposure group 39 >150 Significant background exposure to boron via the diet prepared in the same cafeteria for both groups made a regrouping necessary which was based on the blood boron levels. All participating workers were re-classifed both according to their calculated daily boron exposure levels and to the blood boron levels. For the re-classification of dose groups blood boron levels published in recent epidemiological studies were taken into account. Workers with a blood boron concentration below the LOQ were combined to form the new control group. - Total number of subjects participating in study: 204 - Sex/age/race: males original groups: exposed: 42.62 ± 4.76 (range: 28 — 50) years, caucasian controls: 41.75 ± 6.29 (range: 23 — 53) years, caucasian - Smoker/nonsmoker: not reported - Total number of subjects at end of study: 204 - Matching criteria: not reported, probably age and years of employment (and possibly additional parameters) COMPARISON POPULATION - Type: Control group - Details: The control group was defined as the group which had	any parameter tested between the exposure groups and the new control group. • Correspondingly only a weak correlation between the percentages of the normal morphology and blood boron levels. • Only weak correlation between inhaled boron (mg/8 h) and blood boron (0.279), inhaled boron– semen boron (0.185), and inhaled boron–urine boron (0.106) levels • Boron unfavorable effects on semen parameters, reproductive hormone levels, or DNA integrity in sperm cells is absent. No significant dosedepentent relationship between reproductive toxicity biomarkers and blood boron concentration. The relatively extreme boron exposure conditions did not result in blood boron concentrations above considered safe. - The PSA level was not statistically significantly different when groups are compared. Conclusions: - Due to the background exposure via drinking water no clear realation could be found between inhalation exposure and boron levels in biological fluids. - Blood and urine boron levels increased steadily with rising DBE, while semen boron levels failed to follow a steady trend. - Variation in semen boron levels was high. - Boron is accumulated in semen and the concentration factor is highest at the lowest exposure. - Adverse effects in hormone levels were absent when exposure groups are compared to the new control group. - For any of the semen parameters a statistically significant difference was not seen between the new control		

blood boron levels below the LOQ (level of quantification). HEALTH EFFECTS STUDIED DBE and blood boron concentrations effects on: Sperm concentration parameters, motility parameters of sperm cells, sperm morphology parameters, DNA integrity with COMET assay, hormone levels (FSH, LH, total testosterone) and total PSA. OTHER DESCRIPTIVE INFORMATION ABOUT STUDY: Endpoint addressed: toxicity to reproduction/fertility	group and exposure groups. Together with the affore mentioned fact this indicates that boron does not have an adverse effect on the male reproductive system at typical exposure conditions.		
Study type: cohort study (retrospective) Type of population: occupational Details on study design: HYPOTHESIS TESTED: The null hypothesis for each biologic fluid was that the means of the four groups are equal. Workers were grouped based on semen and urine boron concentrations. Semen boron concentrations: <LOQ (48,5), >LOQ – 500, >500 – 1500 and >1500 ng/g for the control, low, medium and high exposure groups respectively. Urine boron concentrations: 0 - 3, >3 - 5, >5 - 7, >7 mg boron/g creatinine for the control, low, medium and high exposure groups, respectively. METHOD OF DATA COLLECTION As described above under Duydu et al. 2011. STUDY POPULATION As described above under Duydu et al. 2011. HEALTH EFFECTS STUDIED Semen and urine boron concentrations effects on: Sperm concentration parameters, motility parameters of sperm cells, sperm morphology parameters, hormone	EXPOSURE Daily boron exposure (DBE), urine, blood and semen boron concentrations same as reported above under Duydu et al. 2011. FINDINGS **Re-consititued groups from Duydu et al. 2011 according to semen boron levels:** • Hardly any evidence is seen that higher semen boron levels are correlated with adverse effects. • For Neck/mid-piece defects (%) a statistical significant difference in the percentage was seen in the pairwise comparison of the low dose with the high dose and the mid dose with the high dose but not the control with the high dose. No clear dose response is seen, also reflected by the weak correlation coefficient of 0.228. **Re-consititued groups from Duydu et al. 2011 according to urine boron levels:** • Hardly any evidence is seen that higher urine boron levels are correlated with adverse effects. • For FSH (follicle stimulating hormone) the global null hypothesis that all group means are equal is rejected. The significant pair wise differences are between Control-Medium	Klimisch score Not relevant for epidemiology study supporting study **Test material: Boric acid (CAS No. 10043-35-3)** **Purity unknown**	Duydu Y (2011)

levels (FSH, LH, total testosterone) and total PSA. OTHER DESCRIPTIVE INFORMATION ABOUT STUDY: Endpoint addressed: toxicity to reproduction/fertility	and Medium-High. No clear dose response is seen, also reflected by the absence of a significant correlation. • A significant correlation was seen between urine boron concentrations and LH (lutenising hormone) levels. Nevertheless this correlation is quite weak (correlation factor = 0.244) • It has to be stated that for several parameters the scattering of values within the respective groups are large resulting often in standard deviations that have almost the same magnitude as the average value. In these cases the relative low number of volunteers per group complicates the determination of correlations. • The seen weak effects are not indicative for a reproductive toxicity potential of boric acid. This strengthens the position made in the publication that boron does not have an adverse effect on the male reproductive system at high human exposure conditions.		
Study type: Epidemiological Type of population: occupational Details on study design: In one study over 7 years, categories of exposure to boron-containing dust were arbitrarily assigned as "high" (> 8 mg/m3), "medium" (3 to 8 mg/ m3), and "low" (< 3 mg/m3) since dust measurements were not available until the late 1970s. Spirometry (peak expiratory flow rates (PEF) results were compared to a previous pulmonary function study performed 7 years previously. In a second study, the acute effects of exposure were assessed in 79 exposed workers and 27 unexposed workers (Wegman et al, 1994, 1991; and Hu et al, 1992). Exposed workers were all those with a known pattern of exposure to borate dust, and the non-exposed workers were non-office workers without regular exposure. Data were collected on pre-existing conditions such as	Exposed workers reported more frequent irritations than unexposed workers for a number of symptoms (nose, eye, throat irritation and breathlessness), but not for cough. These findings persisted when account was taken of smoking, age and presence of the common cold. The average 6 hour time weighted average exposure to sodium borate dust in the exposed group was 5.7 mg/m3 (range 0.01 to 115 mg/m3) or IOM equivalent of 14.25 mg/m3 (range 0.025 to 287.5 mg/m3). The majority of exposures were between 1 and 10 mg/m3 (IOM 2.5-25 mg/m3) as sodium borate. Analysis indicated that short-term peak exposures to dust were primarily responsible for the excess of symptoms reported. There was a clear dose-response demonstrated by an increasing incidence of clinical effects with increasing	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Sodium borate (CAS unknown)** **Purity unknown**	Wegman DH, Eisen EA & Smith RG (1991)

cold, allergy and smoking at a pre-study exposure interview. Each subject was investigated on 4 consecutive days. Exposures were monitored continuously with a personal aerosol monitor and at the shift end by weighing deposits on air filters. As eye, nose and throat irritation may result from exposure to dusts of a "non-respirable" particle size, the aerosol monitor used was validated as capable of use as a total dust sampler (Woskie et al, 1993). The clinical symptoms of respiratory and eye irritation were assessed hourly using a questionnaire, and peak expiratory flow was measured at this time. These methods allowed exposure and clinical data to be resolved into 15 minute periods, as well as to provide the 6 hour daily average. Analysis of the data was by logistic regression. Endpoint addressed: respiratory irritation Endpoint addressed: eye irritation	measured exposure levels, which was more marked using the 15 minute period compared to the 6 hour period. Individual nasal or respiratory symptoms were reported to a far greater extent than eye irritation. Symptoms were graded for severity, and most reported irritant signs were mild. There was no difference in the irritation recorded following exposure to borate dusts of different degrees of hydration.		

4.11.1 Effects on fertility

4.11.1.1 Non-human information

Effects on male fertility have been investigated in detail. A dose related effect on the testis was observed in rats, mice and deer mice, with confirmation from limited studies in dogs. Effects in rats start with reversible inhibition of spermiation after 14 days (at 39 mg B/kg bw/day) and 28 days (at 26 mg B/kg bw/day, Weir 1963). At doses equal to and above 26 mg B/kg bw/day testicular atrophy, degeneration of seminiferous tubules and reduced sperm counts were observed. Male fertility was further investigated in two serial mating studies of treated male rats with untreated female rats. Infertility of treated males correlated well with germinal aplasia. Similar effects on male fertility were described in deer mice (*Peromyscus maniculatus*) after treatment with boric acid. Fertility studies in rats (two three-generation studies with boric acid and disodium tetraborate decahydrate, Weir 1966 a,b) and mice (a continuous breeding study with boric acid (Fail et al. 1991) further support effects on testes as the underlying cause for reduced male fertility. First indications that boric acid treatment has effects on LH and FSH were noted by Lee (1978). Fail et al. (1991), Treinen & Chapin (1991) described that boron exposure might lead to serum testosterone decrease, which might be the cause for reduced testis weights found by Fail et al. 1991 at 111.3 mg B/kg bw/day. Ku et al. (1993b) analysed the effect of boric acid exposure in cell culture systems and found effects on DNA synthesis in mitotic and meiotic germ cells and on energy metabolism of Sertoli cells at concentrations that were comparable to those responsible for testis atrophy and a decrease of the ratio of early germ cells/Sertoli cells that was seen prior to the atrophy *in vivo*. Despite this extensive research the mechanism behind the inhibition of spermiation still remains unclear.

A NOAEL of 17.5 mg B/kg bw/day for effects on female fertility was derived in the Transitional Annex XV dossier (European Chemicals Agency 2008) based on Weir (1966a,b) and Fail et al.1991. However, the Transitional Annex XV dossier failed to adequately distinguish between effects on female fertility and effects on development. Fertility is generally defined in males as the ability to produce sperm which are capable of producing fertilisation of an ovum leading to conception. In females, it is defined as the ability to produce and release ova which can be fertilised leading to conception and implantation. To test fertility in animals males and females are pretreated to cover the period of development of the sperm and eggs, then mate and treat until the time of implantation, around Day 6 following mating, and then stop treatment in the females. To test for effects on development pregnant females are treated from Day 6 till the end of pregnancy. Neither the Weir and Fisher (1972) multigeneration study nor the Fail (1991) Reproductive toxicity of boric acid in Swiss (CD-1) mice: Assessment using the continuous breeding protocol (RACB) studies were performed with this division of treatments. They both treated animals continuously before and during pregnancy and also after delivery.

In a three generation study in rats groups of 8 males and 16 females were treated with boric acid or disodium tetraborate decahydrate equivalent to 0, 5.9, 17.5 and 58.8 mg B/kg bw/day (Weir 1966c,d). An attempt was made to study the fertility of the P1 females at the top dose level by mating them with untreated males but only one litter of 16 pairs was produced. This highest dose level was clearly clinically toxic to the females after 2-3 weeks of dosing, with rough fur, scaly tails, inflamed eyelids and staining of the fur on the face and abdomen. The mating procedure to test the fertility of the females was not a satisfactory one. To avoid treatment of the males used for pairing, food was withdrawn from the cages of the females for 8 hours per day during the pairing process, and this is known to be very stressful to laboratory rats. There was no evidence on whether mating actually occurred for any of the rats, and no vaginal examinations for the presence of sperm were carried out. The females of the top dose P1 generation were sacrificed after 45 weeks of treatment and histopathological examination of the ovaries and uterus carried out. In the ovaries the presence of corpora lutea was regarded as a major indication of cyclic function, and these were found in 7 of 15 females, with reduced or absent function in the remaining 8 animals. The changes in the ovaries were not clearly different from those of controls. No treatment related changes were found in the uterus. No changes were found that could account for the reduced litter production, and no conclusions could be drawn about fertility in the top dose females. Comparable results were found in the Weir and Fisher (1972) multigeneration study on borax (disodium tetraborate decahydrate), with clear testicular atrophy at the top dose levels in males, and no clear explanation of the reduced number of litters in the top dose females, using the same unsatisfactory mating technique. The authors of the study concluded that testis atrophy was clearly produced in males at the top dose level, but that the evidence of the decreased ovulation in females did not account for the reduced number of litters in the cross mating study in females. Thus the Weir and Fisher studies produced clear evidence of adverse effects on male fertility, but did not produce clear evidence for an adverse effect on female fertility.

In a continuous breeding study of boric acid in Swiss mice (Fail et al., 1991, 1998), the three administered doses were 1000 ppm (26,6 mg B/kg bw/day), 4500 ppm (111,3 mg B/kg bw/day) and 9000 ppm (220,9 mg B/kg bw/day). A dose-related effect on the testis (testicular atrophy and effects on sperm motility, morphology and concentration) was noted; fertility was partially reduced at 111 mg B/kg bw/day, and absent at 221 mg B/kg bw/day.

For cross over mating only the mid dose group (111.3 mg B/kg bw/day) could be mated with control animals, since the high dose produced no litter. Indices of fertility for mid dose males 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. The latter finding has also been observed in the developmental toxicity study by Price et al. (1996, see chapter 4.11.2).

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. A crossover mating study of controls and 4500 ppm groups confirmed the males as the affected sex. Necropsy at 27 weeks confirmed reduced testes weight, seminiferous tubule degeneration, decreased sperm count and motility and increase in abnormal sperm. In females at 27 weeks, 4500 ppm boric acid was toxic with decreased liver, kidney and adrenal weights, but no effect on oestrous cycles, mating, number of litters and number of pups. 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 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.

The authors concluded that the male is the most sensitive sex and that the testis is the primary target organ for boron. The NOAEL for testicular pathology in the present mouse study is probably 1000 ppm (26 mg B/kg bodyweight). While males are more sensitive to boron induced toxicity, data also suggest an effect of boron on the female reproductive system. A reduced number of pups per litter and number of pups born alive at high dose levels are in agreement with earlier reports and could result from an effect of boron to alter implantation or to disrupt cell division in the embryo. This is supported by results of developmental toxicity studies in rats and mice in which higher dose levels can reduce the number of implants (see chapter 4.11.2). Although F1 females had significantly increased kidney/adrenal and uterus weights and the oestrus cycle was significantly shorter compared to control female, similar effects were not observed in the 4500 ppm dose group, therefore the NOAEL in females was the dose level in diet of 4500 ppm, 846 mg/kg bw of boric acid or equivalent to 148 mg B/kg bodyweight.

In conclusion, the effects described in the Fail study on fertility show that 4500 ppm (111.3 mgB/kg bw) is a NOAEL for the females, and that other small effects in females are the result of developmental toxicity for which a NOAEL of <1000ppm (26.6mg B/kg bw) may be valid.

No further studies on the effects of boron on female fertility were reported by the National Toxicology Program team who published several other studies on the mechanism of action of boron on male fertility and on spermatogenesis. No effects on steroidogenic function were found in Leydig cells (Sauls 1992, see chapter 4.12.3), and no clear mechanism of action to cause testis atrophy and inhibited spermiation was identified by Ku and Chapin (1994).

Boron has been shown to be essential for reproduction in the frog, Xenopus laevis (Fort et al 1998, 1999a,b, 2002a,b). Ovaries and testes of adult frogs cultured in low boron environments were atrophied, had decreased testis weight and sperm count.

4.11.1.2 Human information

Although boron has been shown to adversely affect male reproduction in laboratory animals, male reproductive effects attributable to boron have not been demonstrated in studies of highly exposed workers.

The potential reproductive effects of inorganic borate exposure to a population of workers at a large mining and production facility was assessed using the Standardised Birth Ratio (SBR), a measure of the ratio of observed to expected births. The average exposure for the highest exposure group was 28.4 mg B/day (approximately 0.4 mg B/kg bw/day) for two or more years. The average duration of exposure was 16 years. The number of offspring indicated no adverse effects on reproduction in these workers (Whorton et al., 1994a,b). Exposure data used in this study was the same as reported by Wegman et al. 1991, and was collected using the total dust sampler. The IOM equivalent exposure would be 71 mg B/day.

In a study of a highly exposed population in Turkey, where exposure comes mainly from naturally high levels of B in drinking water (up to 29 mg B/L) as well as from mining and production, no adverse effect has been reported on fertility over three generations (Sayli, 1998; 2001).

Boron treatment of rats, mice and dogs has been associated with testicular toxicity, characterised by inhibited spermiation at low dose levels and a reduction in epididymal sperm count at high dose levels. Studies in human workers and populations have not identified adverse effects of boron exposure on fertility or on sperm analysis which is the most sensitive indicator of testicular toxicity in humans (Robbins et al. 2010, Scialli et al. 2010; Duydu et al. 2011).

Chinese boron workers were studied by a research team from the Beijing University of Science and Technology and the China National Environmental Monitoring Centre in collaboration with University of California at Los Angeles (Robbins et al. 2010). Boron exposure/dose measures in workplace inhalable dust, dietary food/fluids, blood semen and urine were collected from boron workers and two comparison worker groups (n = 192) over three months and correlations examined between boron and semen parameters. The boron worker group exposure averaged 42 mg B/day (SD 58 mg B/day). Parameters for total sperm count, sperm concentration, motility and morphology were not significantly different across the three boron exposure comparison groups. Continuous measures of boron in workers' postwork shift urine and blood were inversely correlated with percent normal morphology but this did not remain statistically significant after controlling for age, abstinence interval, smoking, alcohol intake, pesticide exposure and boron blood levels. No other significant correlations between boron levels and conventional semen parameters were found. DNA strand breakage and percent apoptotic cells were similar cross the exposure groups and not correlated with boron levels in post-work shift urine or blood ($p > 0.05$). Sperm aneuploidy and diploidy did not differ by exposure group or boron levels (Robbins et al. 2010).

Scialli et al (2010) reviewed and summarized the papers of the study of Chinese workers that described the reproductive effects of boron exposure, particularly in North Eastern China. This study was reported in a series of publications, some of which were in Chinese and some in English. Boron workers (n = 75) had a mean daily boron intake of 31.3 mg B/day, and a subset of 16 of these men, employed at a plant where there was heavy boron contamination of the water supply, had an estimated mean daily boron intake of 125 mg B/day. Estimates of mean daily boron intake in local community and remote background controls were 4.25 mg B/day and 1.40 mg/day, respectively. Three categories of endpoints were identified: Semen analysis, reproductive outcome and sperm X: Y ratio. There were no statistically significant differences in semen characteristics between exposure groups including in the highly exposed subset, except that sperm X: Y ratio was reduced in boron workers. Within exposure groups the X: Y ratio did not correlate with the boron

concentration in blood, semen and urine. While boron has been shown to adversely affect male reproduction in laboratory animals, there was no clear evidence of male reproductive effects attributable to boron in studies of highly exposed workers (Scialli et al. 2010).

Limitations of this research include:

1) The number of workers in the study cohort is limited given the large variation in most semen characteristics.

2) Recruitment procedures of workers for the various study groups are not entirely clear raising a concern with respect to possible selection bias.

3) It is uncertain if results obtained in the Chinese population fully apply to people in other regions of the world.

4) One semen study (presented in several papers) is insufficient to provide strong evidence that a given exposure is not representing a human hazard at the given exposure levels.

5) The highest exposed workers were exposed to about 5 mg B/Kg/day, which is more than 100 times greater than the average daily exposure of the general population. It is nevertheless only about one third to one quarter of the NOAEL for testis effects in rodents. However, this shows that humans are not significantly more sensitive to this type of toxic effect than rodents.

A recent study by Duydu et al. (2011) was conducted to investigate the reproductive effects of boron exposure in workers employed in boric acid production plant in Turkey. In order to characterize the external and internal boron exposures, boron was determined in biological samples (blood, urine, semen), in workplace air, in food, and in water sources. Unfavorable effects of boron exposure on the reproductive toxicity indicators (concentration, motility, morphology of the sperm cells and blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone) were not observed. The mean calculated daily boron exposure of the highly exposed group was 14.45 ± 6.57 (3.32–35.62) mg B/day. Consistent with the Chinese study, an accumulation of boron in human semen over blood levels was observed in Turkish workers.

Başaran et al. (2012) study did not demonstrate boron-mediated unfavorable effects on semen parameters, reproductive hormone levels, or DNA integrity in sperm cells. That is, it was not found unfavorable dosedependent relationships between reproductive toxicity biomarkers and blood boron concentrations in a range of boron intakes common to boron production plant workers.

The Chinese and Turkish semen studies in highly exposed workers are a major source of information as to human reproductive toxicity. Not only are these the most exposed workers with exposures measured directly from food, drink and inhalation, but the Chinese and Turkish workers studies are the most sensitive studies that have been carried out as semen analysis was performed, a very sensitive detection system for testicular damage.

4.11.2 Developmental toxicity

Table 15: Summary table of relevant developmental toxicity studies

Method	Results	Remarks	Reference
rat (Crl: CD VAF/Plus (Sprague Dawley))	LOAEL (maternal toxicity): 143 mg/kg bw/day based on: test mat. (Based on relative kidney	1 (reliable without restriction)	Price CJ, Marr MC & Myers CB

oral: feed 0, 0.025, 0.050, 0.075, 0.1 or 0.2% (0, 250, 500, 750, 1000, 2000 ppm) equivalent to 19 (3.3), 36 (6.3), 55(9.6), 76 (13.3) and 143 (25) mg boric acid (mg B)/kg bw (nominal in diet) Exposure: Days 0 - 20 post mating (phase I) Days 0 - 20 post mating then on normal diet until termination on day 21 postpartum (phase II) Groups of 28-32 females were used for both phase I and phase II. In phase I the dams were killed on Day 20 for detailed fetal examination. In phase II the dams were allowed to deliver and the pups reared to weaning and then killed for full visceral and skeletal examination as for phase I. OECD Guideline 414 (Prenatal Developmental Toxicity Study)	weights.) NOAEL (maternal toxicity): 76 mg/kg bw/day based on: test mat. LOAEL (developmental toxicity): 76 mg/kg bw/day based on: test mat. (Developmental effects were found in fetuses from animals exposed to 76 mg/kg bw boric acid (13.3 mg B/kg bw) and above (Phase I) associated with a reduction in the mean foetal bodyweight per litter (6 % compared to controls) at 13.3 mg B/kg bw. Skeletal changes were observed (increase in incidence of wavy ribs and short rib XIII, decreased incidence of rudimentary extra rib on lumbar 1). At the high dose for Phase I these changes were more pronounced. The animals from the Phase II group which were killed on postnatal day 21 showed no reduction in pup bodyweight in any group at any time point compared to controls, which indicates full recovery in the offspring already by postnatal Day 0 from treatment-related bodyweight effects. The rib variations observed in the foetuses from Phase I were not observed in any dose group in Phase II. Only at the highest dose in Phase II (25.3 mg B/kg bw) was an increased incidence of short rib XIII observed.) NOAEL (developmental toxicity): 55 mg/kg bw/day based on: test mat. LOAEL (maternal toxicity): 25 mg/kg bw/day based on: element (Based on relative kidney weights.) NOAEL (maternal toxicity): 13.3 mg/kg bw/day based on: element LOAEL (developmental toxicity): 13.3 mg/kg bw/day based on: element (Based on reduced foetal body weight and increased incidence of short rib XIII.) NOAEL (developmental toxicity): 9.6 mg/kg bw/day	key study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	(1994) Price CJ, Strong PL, Marr MC, Myers CB, & Murray FJ (1996a)

	based on: element		
rabbit (New Zealand White) oral: gavage 0, 62.5, 125 or 250 mg/kg bw boric acid equivalent to 0, 10.9, 21.8 and 43.5 mg B/kg bw Exposure: Groups of 30 rabbits were used treated on Day 6 - 19 post-mating equivalent or similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study)	LOAEL (maternal toxicity): 250 mg/kg bw/day based on: test mat. (Based on reduced food intake, reduced body weight gain and abortions.) NOAEL (maternal toxicity): 125 mg/kg bw/day based on: test mat. LOAEL (developmental toxicity): 250 mg/kg bw/day based on: test mat. (Based on increased resorptions and CVS malformations in surviving foetuses.) NOAEL (developmental toxicity): 125 mg/kg bw/day based on: test mat. LOAEL (maternal toxicity): 43.5 mg/kg bw/day based on: element (Based on reduced food intake, reduced body weight gain and abortions.) NOAEL (maternal toxicity): 21.8 mg/kg bw/day based on: element LOAEL (developmental toxicity): 43.5 mg/kg bw/day based on: element (Based on increased resorptions and CVS malformations in surviving foetuses.) NOAEL (developmental toxicity): 21.8 mg/kg bw/day based on: element	1 (reliable without restriction) key study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Price CJ, Marr MC, Myers CB, Heindel JJ & Schwetz BA (1991) Price CJ, Marr MC, Myeos CB, Seely JC, Heindel JJ, & Schwetz BA (1996b)
rat (Sprague-Dawley) male/female three-generation study oral: feed 0, 670, 2000 or 6700 ppm boric acid (0, 117, 350 and 1,170 ppm boron) in the diet, equivalent to 0, 34 (5.9), 100 (17.5) and 336 (58.5) mg boric acid (mg B)/kg bw/day. Exposure: Groups of 8 males and 16 females were used for all generations and were exposed from beginning of the study until sacrifice of parents P0, and from weaning till sacrifice of the F1- and F2-generations. The high dose group P animals were sterile so only controls, low	LOAEL (P): 336 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 1170 ppm In the diet. Based on sterility.) NOAEL (P): 100 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) NOAEL (F1): 100 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) NOAEL (F2): 100 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) LOAEL (P): 58.5 mg B/kg	2 (reliable with restrictions) key study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Weir RJ (1966a) Weir RJ & Fisher RS (1972)

and mid dose groups were taken to the F2 and F3 generations. (Daily) No guideline specified, but conforms to the standard 3 generation 2 litters per generation multi-generation studies normally used at that time.	bw/day (male/female) based on: element (Based on sterility.) Testicular atrophy, reduced fertility (no offspring from high dose females mated with untreated males) NOAEL (P): 17.5 mg B/kg bw/day (male/female) based on: element NOAEL (F1): 17.5 mg B/kg bw/day (male/female) based on: element NOAEL (F2): 17.5 mg B/kg bw/day (male/female) based on: element No adverse effects in mid and low dose groups in any generation.		
rat (Sprague-Dawley) male/female three-generation study oral: feed 0, 1030, 3080 or 10300 ppm disodium tetraborate decahydrate (0, 117, 350 and 1, 170 ppm boron) in the diet, equivalent to 0, 50 (5.9), 155 (17.5) and 518 (58.5) mg disodium tetraborate decahydrate (mg B)/kg bw/day respectively (nominal in diet) Exposure: Groups of 8 males and 16 females were used for all generations. 14 weeks before mating. From beginning of the study until sacrifice of parents P0, and from weaning till sacrifice for the parents of the F1 and F2-generations. The high dose group P animals were sterile so only controls, low and mid dose groups were taken to the F2 and F3 generations. No guideline specified, but conforms to the standard 3 generation 2 litters per generation MGS normally used at that time.	LOAEL (P): 518 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 1170 ppm boron in the diet based on sterility in males and females.) NOAEL (P): 155 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) NOAEL (F1): 155 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) NOAEL (F2): 155 mg/kg bw/day (male/female) based on: test mat. (Equivalent to 350 ppm boron in the diet.) LOAEL (P): 58.5 mg B/kg bw/day (male/female) based on: element (Based on sterility in males.) NOAEL (P): 17.5 mg B/kg bw/day (male/female) based on: element NOAEL (F1): 17.5 mg B/kg bw/day (male/female) based on: element NOAEL (F2): 17.5 mg B/kg bw/day (male/female) based on: element No adverse effects in mid and low dose groups in any generation.	2 (reliable with restrictions) key study experimental result **Test material (EC name) disodium tetraborate decahydrate (CAS No. 1303-96-4)** **Purity unknown**	Weir RJ (1966b) Weir RJ & Fisher RS (1972)

rat (Sprague-Dawley) female oral: feed 0.025%, 0.050%, 0.075%, 0.100%, 0.200% (analytical conc.) 0, 19, 36, 55, 76, 143 mg Boric acid/kg BW/day (actual ingested) Equivalent to 0, 3, 6, 10, 13, 25 mg Boron/kg BW/day (actual ingested) Exposure: Gestation day 0 to 20 (In feed, ad libitum) Timed-mated Sprague-Dawley rats were exposed to boric acid in the diet from Gestational day 0 to 20. Dietary concentrations of Boric acid yielded average daily intakes equivalent to 0, 3, 6, 10, 13 and 25 mg/kg/d. At termination on Gestational day 20, maternal whole blood was collected in heparinized vacutainer tubes, stored frozen (- 20°C) and subsequently prepared by a high-temperature alkaline ashing procedure for analysis of boron by inductively coupled plasma optical emission spectrometry.		2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Price CJ, Strong PL, Murray FJ and Goldber MM (1997)
rat (Sprague-Dawley) oral: feed 0.1 %, 0.2 %, 0.4 % and 0.8 %; equivalent to 78, 163, 330 and 539 mg/kg/Day (actual ingested) Exposure: Gestational days 0 to 20. (Daily)	NOAEL (maternal toxicity): 0.1 % based on: test mat. LOAEL (developmental toxicity): 0.1 % based on: test mat. (Increase in the incidence of malformations. Decreased foetal body weight, skeletal malformations (short rib XIII). No NOAEL was established for developmental toxicity due to fetal weight reduction at the lowest dose level.) LOAEL (maternal toxicity): 0.2 based on: test mat. (Increased relative liver weight and increased food intake)	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Price CJ, Field EA, Marr MC & Myers CB. (1990)
rat (Sprague-Dawley) oral: feed Exposure: 20 days. Developmental toxicity risk assessment has typically relied on the estimation of reference doses or reference concentrations based on the use of NOAELs divided by uncertainty factors. The benchmark dose	BMD: (developmental toxicity): 59 mg/kg bw/day based on: test mat. (Decreased foetal body weight provided the best basis for BMD calculations. The benchmark dose is defined as the 95 % lower bound on the dose corresponding to a 5 % decrease in the mean fetal weight (BMDL05). Results are	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)**	Allen BC, Strong PL, Price CJ, Hubbard SA & Daston GP. (1996)

(BMD) approach has been proposed as an alternative basis for reference value calculations. In this analysis of the developmental toxicity observed in rats exposed to boric acid in their diet, BMD analyses have been conducted using two existing studies. By considering various endpoints and modelling approaches for those endpoints, the best approach for incorporating all of the information available from the studies could be determined. In this case, the approach involved combining data from two studies which were similarly designed and were conducted in the same laboratory to calculate BMDs that were more accurate and more precise than from either study alone	based on the studies of Heindel et al. (1992), Price, Marr & Myers (1994) and Price et al. (1996).) BMD: (developmental toxicity): 10.3 mg/kg bw/day based on: element	**Purity unknown**	
mouse (CD-1) oral: feed Groups of around 30 mice were used. 0, 0.1, 0.2 or 0.4 %. Equivalent to 0, 248 (43), 452 (79), or 1,003 (175) mg boric acid (mg B)/kg bw/day (nominal in diet) Exposure: Throughout gestation period (Day 0-17) (Daily: Food available ad libitum.)	NOAEL (maternal toxicity): < 248 mg/kg bw/day based on: test mat. NOAEL (development al toxicity): 248 mg/kg bw/day based on: test mat. NOAEL (developmental toxicity): 43 mg/kg bw/day based on: element Reduced body weight; skeletal malformations including short rib XIII.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Field EA, Price CJ, Marr MC, Myres CB, Morrissey RE & Schwetz BA. (1989) Heindel JJ, Price CJ, Field EA, Marr MC, Myers CB, Morrissey RE & Schwetz BA. (1992)
Frogs, Xenopus laevis Low Dietary and Environmental Boron Exposures In two separate 120-d depletion studies conducted previously, adult frogs *(Xenopus laevis)* fed a low boron diet (-B; 62 ug B/kg feed) for either 28 d or 12 d.	Boron deficiency produced a greater proportion of necrotic eggs and fertilized embryos that abnormally gastrulated at a greater rate and were substantially less viable at 96 h of development when compared to embryos from adults administered a diet supplemented with boron (+B; 1850 ug B/kg feed).	2 (reliable with restrictions) supporting study experimental result **Test material (Common name): Boric acid (CAS No. 10043-35-3)** **Purity unknown**	Fort DJ, Propst TL, Stover EL, Murray FJ, Strong PL (1999a) Fort et al. DJ (1998) Fort et al. DJ (1999b) Fort DJ (2002a,b)
Trout and Zebrafish Low Dietary and Environmental Boron Exposures	Boron deficiency produced developmental and retinal effects.	2 (reliable with restrictions) supporting study experimental result **Test material (Common name): Boron**	Eckhart CD (1998) Rowe RI et al. (1998) Eckhert CD and Rowe RI (1999).

		Purity unknown	
Rat and Mouse Fed boron deficient diet Study tested the effects of low (0.04 11gB/g) and adequate (2.00 11gB/g) dietary B on the in vitro development of mouse reirnplantation embryos. Two-cell embryos obtained from the dams were cultured in vitro for 72 h. To investigate the influence of maternal boron status on early embryonic development. mice were fed a low boron (0.04 ug B/g, LOW), or a suppplemented boron (2.05 ug B/g, SUPP) purified diet, or a high boron (11.8 IJ.g B/g, STOCK) commercial stock diet. ln Study 2A.two-cell embryos were collected after the females had been fed the diets for 10. 12, or 16 weeks. Embryos were cultured in B+ medium. In Study 2b, two-cell embryos were collected after the females had been fed the diets for 16 weeks. and the embryos were cultured in B- medium. In	Early embryonic development impaired in rodents fed boron deficient diet. Dams fed the low B diet had a significantly reduced number of implantation sites compared to darns fed the B-adequate diet. Maternal exposure to the low B diet for 10, 12, and 16 wk was associated with a reduction in blastocyst formation, a reduction in blastocyst cell number, and an increased number of degenerates. The in vitro development of two-cell embryos collected from mice fed either one of the boron purified diets was not severely impaired when they were cultured in B+ medium. However, two-cell embryos from the LOW diet had a lower frequency of blastocyst formation (83.5%, LOW vs. 90.1 %, SUPP), and an increased frequency of degenerate embryos (13.0%, LOW vs. 8.0%, SUPP) after 72 h of culture compared to embryos from the SUPP diet. Low dietary boron combined with low boron in the medium resulted in the highest percentage of degenerate embryos (57.0%	2 (reliable with restrictions) supporting study experimental result **Test material (Common name): Boron** **Purity unknown**	Lanoue L. et al. (1998) Lanoue L, Strong PL, and Keen CL (1999)
rat (CD-1) intraperitoneal 1000 mg/kg boric acid (Actual dose injected.) Exposure: Single injection on Day 8 of gestation. (Single injection)	NOAEL (developmental toxicity): 1000 mg/kg single injection based on: test mat. (Mice were deliberately given a teratogenic dose.)	4 (not assignable) supporting study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Di Renzo F, Cappellett G, Broccia ML, Giavini E & Menegola E (2007)
Rat (Sprague-Dawley) Gavage 500 mg/kg boric acid twice daily Exposure: rats were dosed with BA on GD 9;	NOAEL (developmental toxicity): 1000 mg/kg based on: test mat. (Rats were deliberately given a teratogenic dose.)	4 (not assignable) supporting study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)**	Wery N, Narotsky MG, Pacico N, Kavlock RJ, Picard JJ, and Gofflot F (2003)

		Purity unknown	
Rat (Sprague-Dawley) Gavage 500 mg/kg boric acid twice daily Exposure: rats were dosed with BA on GD 6, 7, 8, or 9; In the second block, rats were dosed on GD 9, 10, or 11	NOAEL (developmental toxicity): 1000 mg/kg based on: test mat. (Rats were deliberately given a teratogenic dose.)	4 (not assignable) supporting study experimental result **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Narotsky MG, Wery N, Hamby BT, Best DS, Pacico N, Picard JJ, Gofflot F, and Kavlock J (2004).
Study type: cohort study (retrospective) Type of population: general The aim of this research was to determine the daily boron exposure of women living in the area where the water supply had boron level of 2 ppm and above, and who had been living in the area since birth. The study group consisted of 41 women with an average age of 46.20 ± 2.14. The control group included 29 women with an average age of 35.83 ± 83. The main approach to determine daily boron exposure was to study boron levels in 24 h urine collected from individuals. Urine boron level was measured by ICP-OES method.	Daily boron exposures were 8.214 ± 0.257 mg/day in the study group and 2.051 ± 0.257 mg/day in the control group. There was a significant difference between the study and control group. Daily boron exposures were 8.214 ± 0.257 mg/day in the study group and 2.051 ± 0.257 mg/day in the control group. There was a significant difference between the study and control group.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Korkmaz M, Sayli BS, Sayli U, Bakirdere S, Atman OY, Titretirs S & Keskin S. (2006)
Study type: Epidemiology study Type of population: occupational Details on study design: METHOD OF DATA COLLECTION - Type: Questionnaire - Details First phase: The questionnaire covered marital status and childbearing properties of the proband, and included the age at marriage, its duration, the period of first conception, the number of pregnancies, births, foetal losses and congenital malformations, and the number and sex of children both alive and deceased. No physical examination was conducted but medical records if available were recorded.	At the first phase of the investigation, 191 workers were interviewed. Among these there were six infertiles of the primary type with a rate of 3.1 %. Boron-unrelated infertile couples among sibs were found to be 2.6 - 3.6 % and 3.2 % for three-generation marriages - none being higher than those revealed in different sets of controls. In the second stage of work, computerised files of all workers of the facility and all employees of the general management sharing the same location were checked without an interview. Twenty-four subjects (3.4 %) out of 712 workers were childless versus 2.7 % among 108 employees and 2.2 % among 91 workers of a distantly located sulfuric acid plant of the	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Borates** **Purity unknown**	Sayli BS (2003)

Second phase: Computerised individual files of all workers as well as all general management people were checked without interview. Studies were divided into three: Those places up to 2 ppm (mg B/L); those up to 10 ppm B and those with higher levels. The highest cocnentration was consistently found in Iskele-Osmanca belt, where 6.7 - 9.7 ppm B was found in one street fountain and 18.5 - 29.0 in the other, both of which were still in use. Amounts as high as 60 – 90 ppm B were reported in one well no longer in use. In recent years, freshwater from a remotes pring with as little as 1.7 ppm B is pumped to houses. Boron amounts ranged from 0.1 to 2.8 ppm B/L in other places, none were due to contamination. Higher levels up to 9.05 ppm B were reported in Emet- Hisarcik belt. In Kirka the concentration was 0.30 - 2.35 ppm B. SETTING: Borates plant, prior to or immediately after an 8 h shift. STUDY POPULATION - Total number of subjects participating in study: Phase 1: 191 Phase 2: 712 HEALTH EFFECTS STUDIED - Disease: Infertility Endpoint addressed: toxicity to reproduction / fertility	same complex. The differences were not significant. 94.2 % of probands had at least 1 living child at the time of inquiry, including one widow and one separated. 307 children were born to proband families of which 50.1 % were males and 49.9 % females, all alive at the time of the investigation, with a sex ratio of 1.0. Nine males and 6 female infants were described as deceased early in life. There were 1.7 alive and 0.1 deceased offspring per family. Of 119 interviewed, 32.5 % had 1 child, 56.6 % had 2 children and 8.8 % had 3 children. The remaining 2.3 % had 4 - 7 children. No discussion of foetal losses or congenital malformations were included		
Study type: Epidemiology study Type of population: occupational Details on study design: METHOD OF DATA COLLECTION - Type: Interview STUDY POPULATION - Selection criteria: Married male workers - Total number of subjects participating in study: 799 in total, 642 production workers and 157	Infertility rates were 1.2 % among 328 borate workers from Region 1, 1.1 % among 298 workers from Region 2 and 4.1 % among 173 workers from Region 3. Total infertility rate was 1.8 % for all of the workers. These rates were similar to the results of studies made in the same region and in other parts of Turkey. Total male/female ratio was found to be 1.12 , so no increase in the number of female offspring could be found when compared with previously	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Cöl M, Sayli BS, Genc Y, Ercevik E, Elhan AH & Keklik A.. (2000)

office workers. The boron levels in drinking water ranged from 1.7 to 9.4 ppm for Region I, from 2.79 to 5.94 in Region II and from 0.36 to 0.62 in Region III according ot measurements taken. In production departments, dust concentrations varied from 1.11 to 2.96 mg/m^3 in Region I, 0.69 to 9.25 mg/m^3 in Region II and 0.39 to 9.47 mg/m^3 in Region III. HEALTH EFFECTS STUDIED - Disease: Infertility OTHER DESCRIPTIVE INFORMATION ABOUT STUDY: Definition of primary infertility was - no visible evidence of conceptus in a non-parous, monogamous, pre-menopausal person who maintained conjugal relationship for at least 9 months prior and after neither partner used any type of birth control method for the preceding 12 months. Definition of secondary infertility was - no visible evidence of conceptus in a parous, monogamous, premenopausal person who maintained conjugal relationship for at least 9 months prior and after neither partner used any type of birth control method for the preceding 12 months. Endpoint addressed: toxicity to reproduction / fertility	reported data. No significant influence was observed in parameters used to define possible developmental effects. Stillbirths, abortions, prematurities or having low birth weights and early deaths of offspring were not more than the ones found in any part of the country. There were no differences in infertility rate, sex ratios and possible developmental effects between the production workers and office workers.		
Study type: Epidemiology study Endpoint addressed: repeated dose toxicity: oral A regional scale geographical study in Northern France was conducted. Assessment of boron levels in a group of 180 healthy individuals and correlation with boron content in drinking water were followed by an assessment of health indicators such as birth rates, mortality rates, and sex ratios in zones of different boron content in drinking water.	After necessary adjustments, men living in municipalities with more than 0.30 mg/L of boron in drinking water had elevated but not significant boron blood levels compared with those living in municipalities with boron water levels of less than 0.30 mg/L (159.1 vs 123.0 ng/g; $p > 0.05$). The standardised birth ratio adjusted for the reference geographic zone and calendar time period was 1.07 and 1.28 in the low and high (> 0/3 mg/L) boron content municipalities, respectively. The birth rate in municipalities with high boron	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Yazbeck C, Kloppmann W, Cottier R, Sahuquillo J, Debotte G & Huel G. (2005)

	content in drinking water was higher than that of the reference geographic zone and of the French general population ($p < 10E-4$). The standardised mortality ratio adjusted for the reference geographic zone and calendar time period was 0.94 and 0.92 in low and high boron content municipalities, respectively. The mortality rate in municipalities with high boron content in drinking water was less than that of the reference geographic zone and of the French general population ($p < 10E-03$). No statistical difference was noted in the male-female sex ratios between the different municipality zones ($p = 0.45$). The results of the study do not support the idea of a deleterious effect of boron on human health, at the boron water level contents found in this specific region. In fact, there was a tendency towards a beneficial effect with low-dose environmental exposure (less than 1 mg/L of boron) in drinking water.		
Study type: Epidemiology study Endpoint addressed: repeated dose toxicity: oral A study was carried out in a population of newborns exposed to general environmental boron concentrations.	A negative association between blood delta-aminolevulinic acid dehydratase activity and plactental boron was discovered and a potential boron threshold for this association was estimated.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Yazbeck C & Huel G. (2006)
Study type: Epidemiology study Details on study design: This article described the lifestyle patterns of boron mining and processing workers (N = 936) and a comparison group (N = 251) in Northeast China, and explores relationships between boron exposure and reproductive health. An English version of an interview guide addressing areas of work and lifestyle relevant to boron exposure and metabolism was developed by an occupational health research team, translated to Chinese, and translated back, for	34 % of boron workers reported eating in the contaminated work areas. Nearly all boron workers (99 %) showered or bathed after work although approximately 10 % redressed in their contaminated clothes. Reproductive health outcomes were explored, including delayed pregnancy, multiple births, spontaneous miscarriages, induced abortions, stillbirths and unusual male:female offspring. On average boron workers fathered nearly 2.0 pregnancies	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Chang BL, Robbins WA, Wei F, Xun L, Wu G & Elasoff DA. (2006)

clarity. Modifications incorporated suggestions from local community advisory board and boron industry workers; the translation-back translation process was reapplied and cultural settings and semantic equivalence was attained. The environmental boron exposure for the boron works (mean) and the comparison group (mean) were 2.6 - 3.8 mg/L for boron workers and 0.005 - 0.67 mg/L for the comparison group in surface water; 1.2 - 25.1 mg/L in boron workers well water and 0.002 - 0.67 mg/L for the comparison group's well water. The study was a cross-sectional, descriptive design based on interviews with participants who had occupational exposure to boron and a comparison group selected from an environment without significant exposure to boron. Endpoint addressed: toxicity to reproduction / fertility	compared with 2.1 pregnancies in the control group (P = 0.6). Of the self-reported pregnancies fathered by boron workers, an average of 1.3 resulted in livebirths, compared to an average of 1.4 for the comparison group (P = 0.3). A significant difference existed between groups in delay in pregnancy, defined as the inability to conceive within 1 year of desiring a child, with boron workers experiencing greater delays. However in logistic regression models adjusting for age, education, race, tobacco, alcohol and soybean consumption the difference was no longer statistically significant (P = 0.11) with an odds ratio of 1.7 for boron workers compared to the control group (95 % confidence interval, 0.09 to 3.5).		
Study type: cohort study (retrospective) Details on study design: The study population was divided into three sub-groups. The individuals that were interviewed in each subgroup served as probands for the study. The first subgroup of probands was identified in Region 1 which covers and area near on boron-rich territories. Dwellings of Region 1 were located close to borate pits and a processing plant. Region 2 probands were from villages far from boron deposits, but were within the same zone. Region 3 probands were born and live in areas with a mixed group some near to and some far from deposits and pits. In Region 1 drinking waters forming from (natural) springs ad wells contain as much as 29 ppm boron, but in Region 2 the concentration was between 0.3 and 0.50 ppm. In the third region no measurements were regularly made but boron content was not known to be too high. In all three areas there were active and former borate workers.	The infant death rate in Region 2 (low boron area) was higher than those of other regions (significantly different). Although it is difficult to recognise spontaneous abortions and stillbirths in a retrospective study depending on the description only the probands (mostly females) these were considered separately, but no differences were found. The observed number of congenital malformation was not sufficient within the study groups to perform statistical tests. There was no evidence that B affects human developemnt adversely.	Klimisch score Not relevant for epidemiology study supporting study **Test material (Common name): Boron** **Purity unknown**	Tüccar E, Elhan AH, Yavus Y & Sayli BS. (1998)

From Region 1, 226 families over three generations with respect to probands (that of the proband being the second) and from Region 2, 164 families were included. There were 177 families from Region 3 and 80 from Kirka. Criteria for selection was the presence of legal marriage regardless of whether one member was dead or whether there had been a divorce. The study was carried out by home visits. Workers and other related individuals were contacted at borate plants and pits. Questionnaires were arranged in order to obtain the number of pregnancies, early infant deaths, congenital malformations, stillbirths and spontaneous abortions. Findings were compared with $\chi 2$ test. Endpoint addressed: toxicity to reproduction / fertility			
Study type: case control study (retrospective) Endpoint addressed: developmental toxicity / teratogenicity The effects of the use of boric acid vaginal tablets for treatment of infectious diseases of the genital organs were evaluated in a Hungarian Case Control Surveillance of Congenital Abnormalities (HCCSCA) study. In most cases, treatment consisted of two vaginal tablets of 30 mg each daily for 7 days.	For the 22843 infants born with congenital abnormalities in the study group, 43 mothers (0.19 %) had received boric acid treatment and for the 38151 controls 52 mothers (0.14 %) had received boric acid treatment. There were no significant differences between the groups in maternal sociodemographic characteristics, occurrence of acute and chronic diseases and frequently used drugs. The extremely high prevalence of acute infectious diseases of the genital organs (85.8 % in the study group and 91.9 % among controls) explains the use of the boric acid. Cases of congenital abnormalities affecting the skeletal system only occurred in the offspring of others who were treated with boric acid during their entire pregnancy. In this study there was a higher risk of neural tube defects when boric acid was used during the second and third months of pregnancy, but this finding was based on only two cases. It is suggested that topical exposure to boric acid is unlikely to induce developmental toxicity	Klimisch score Not relevant for epidemiology study supporting study **Test material (EC name): boric acid (CAS No. 10043-35-3)** **Purity unknown**	Acs N, Bánhidy F, Puhó E & Czeizel AE. (2006)

	because unless the skin or vaginal epithelium is severely damaged, boric acid absorption is limited.		
Study type: cohort study (retrospective) Details on study design: Tüccar et al. (1998) investigated the effects of boron on reproductive and developmental effects in three generations of families living in boron rich regions of Turkey. This study was part of a larger study of the health effects of boron in residents living in boron rich territories of Turkey (Sayli 2001; Sayli et al. 1998; Sayli 1998; Sayli 2003). The study population was divided into three subgroups based on levels of environmental boron exposure. Region I included residents living in boron rich territories, located close to borate pits and a processing plant. Questionnaires were administered by home visits, and workers were contacted at the borate plants and pits. The questionnaires obtained information on number of pregnancies, early infant deaths, congenital malformations, stillbirths and spontaneous abortions. Endpoint addressed: developmental toxicity / teratogenicity	Drinking water in Region I come from natural springs and wells that contain as much as 29 ppm B. Region II residents lived far away from borate deposits. The concentration of boron in drinking water serving residents of Region II was between 0.30 and 0.50 ppm. Region III residents were born and live within the study region with some residents close to and some far from deposits and pits. Daily exposures of 6.77 mg/day for males living in the boron-rich region and 1.26 mg/day for controls was later estimated for residents of these regions by Korkmaz et al. (2007). However, no exposure estimates of women during their pregnancies were available. A total of 226 families over three generations from Region I, 164 families from Region II and 177 families from Region III were included in the study. The infant death rate was higher in Region II, the region with the low boron levels, compared to the other regions. No other significant differences in developmental effects were observed between high boron exposed populations compared to low boron exposed populations. The observed number of congenital malformations was not sufficient in the study groups to allow for statistical evaluation.	supporting study **Test material (Common name): Boron** **Purity unknown**	Tüccar E, Elhan AH, Yavus Y & Sayli BS. (1998) Sayli BS, Tuccar E & Elhan AH. (1998) Sayli BS (1998) Sayli BS (2001) Sayli BS (2003)
Study type: Epidemiology study Type of population: occupational Details on study design: Cöl et al. (2000) investigated infertility rates, gender ratio, stillbirths and spontaneous abortions, premature births or low birth weights, and infant mortality rates among the families of 799 workers (642 production workers, 157 office workers) at three production facilities in Turkey. Data were	The boron level in drinking water ranges from 1.7 to 9.4 ppm for Region I, from 2.79 to 5.94 in Region II and from 0.36 to 0.62 in Region III. Dust concentrations in production departments varied from 1.11 to 2.96 mg/m^3 in Region I, 0.69 to 9.25 mg/m^3 in Region II and 0.39 to 9.47 mg/m^3 in Region III. No boron exposure measurements were available for the spouses of the workers	supporting study **Test material (Common name): Boron** **Purity unknown**	Cöl M, Sayli BS, Genc Y, Ercevik E, Elhan AH & Keklik A. (2000)

collected by personal interviews of workers at their work place in 1998. Endpoint addressed: developmental toxicity / teratogenicity	during their pregnancies, however their exposures were likely lower than the male workers who would also exposed to boron at the production facilities. No significant adverse effects were found among production workers with high boron exposures compared to national or regional rates or to office workers with low boron exposure. Infertility rates among the workers averaged 1.8% compared to the Turkish national rate of 1.49–3.8 %. When comparing the production workers to office workers, the only significant differences were that average pregnancies and live births among production workers exceeded those of office workers. There is no increase of premature births or low birth weights for these study regions when compared to national rates. Stillbirths per 100 pregnancies were 1.64 for Region I, 1.68 for Region III, but 3.09 for Region II, compared to 1.5 per 100 pregnancies in the Turkish demographic and health survey. The number of premature births or low birth weight per couple was 0.14, 0.12 and 0.11 for Region I, Region II and Region III, respectively compared to 0.26 in Ankara. Spontaneous abortion rates per 100 pregnancies were 6.75, 7.31 and 8.97 for the three regions, similar to the national rate of 8.7 per 100 pregnancies. The infant mortality rate per 1000 live births for Region I was 67.7, 91.8 for Region II and 66.3 for Region III, compared to an infant mortality rate of 63 per 1000 live births in Ankara, and 43 per 1000 live births for Turkey. Region II had the highest mortality rate but did not have the highest exposure to boron. The differences between the regions were likely due to social and cultural issues. Cöl et al. concluded that		

	exposure to boron did not to adversely influence the infertility ratio, the male to female ratio at birth, the number of stillbirths, the number of spontaneous abortions, the number of premature births with low birth weight and the infant mortality rate for the workers from three boron plants. Primary infertility, secondary infertility, sex ratio, stillbirth, prematurity/low birth weight, spontaneous abortions and infant mortality did not show any relation with work assignment.		
Study type: Epidemiology study Details on study design: Chang et al. (2006) evaluated reproductive health in a cohort of boron mining and processing male workers (N=936) and a comparison group of males (N=251) in northeast China. The comparison group was selected from a community 30 miles away from the boron mines and processing plants with a known low background of environmental boron. This study was based on interview data from a larger study of workplace exposure to boron-containing compounds and adverse male reproductive effects. The reproductive effects data were obtained by self-report of delays in pregnancy, pregnancy outcomes, total number of children, and gender of children. Endpoint addressed: developmental toxicity / teratogenicity	Exposure estimates for the boron workers was 31.3 mg boron/day and 1.40 mg B/day for the comparison group (Scialli et al. 2010). No exposure measurements were available for the wives of the workers whose boron exposure would be through environmental sources such as food and water. However, concentrations of boron in the surface water, well water, soil, legumes and potatoes of the boron workers group were greater than in the comparison group. Well water in the boron group ranged from 37 to 600 times the comparison group, and the mean boron concentrations in legumes and potatoes from the boron group was approximately double those found in the comparison group. Reproductive health parameters evaluated included: delay in pregnancy, multiple births, spontaneous miscarriage, induced abortion, stillbirth, tubal or ectopic pregnancy, and boy/girl ratio. No statistically significant differences were observed between the boron workers and the comparison group after adjustment for age, educational level, race, smoking, ethanol use, and soybean intake.	supporting study **Test material (Common name): Boron** **Purity unknown**	Chang BL, Robbins WA, Wei F, Xun L, Wu G & Elasoff DA. (2006)

4.11.2.1 Non-human information

Developmental effects have been observed in three species, rats, mice and rabbits. The most sensitive species being the rat with a NOAEL of 9.6 mg B/kg bw/day (Price et al. 1994). This is based on a reduction in mean foetal body weight/litter, increase in wavy ribs and an increased incidence in short rib XIII at 13.3 mg B/kg bw/day. The reduction in foetal body weight and skeletal malformations had reversed, with the exception of short rib XIII, by 21 days postnatally. At maternally toxic doses, visceral malformations observed included enlarged lateral cerebral ventricles and cardiovascular effects.

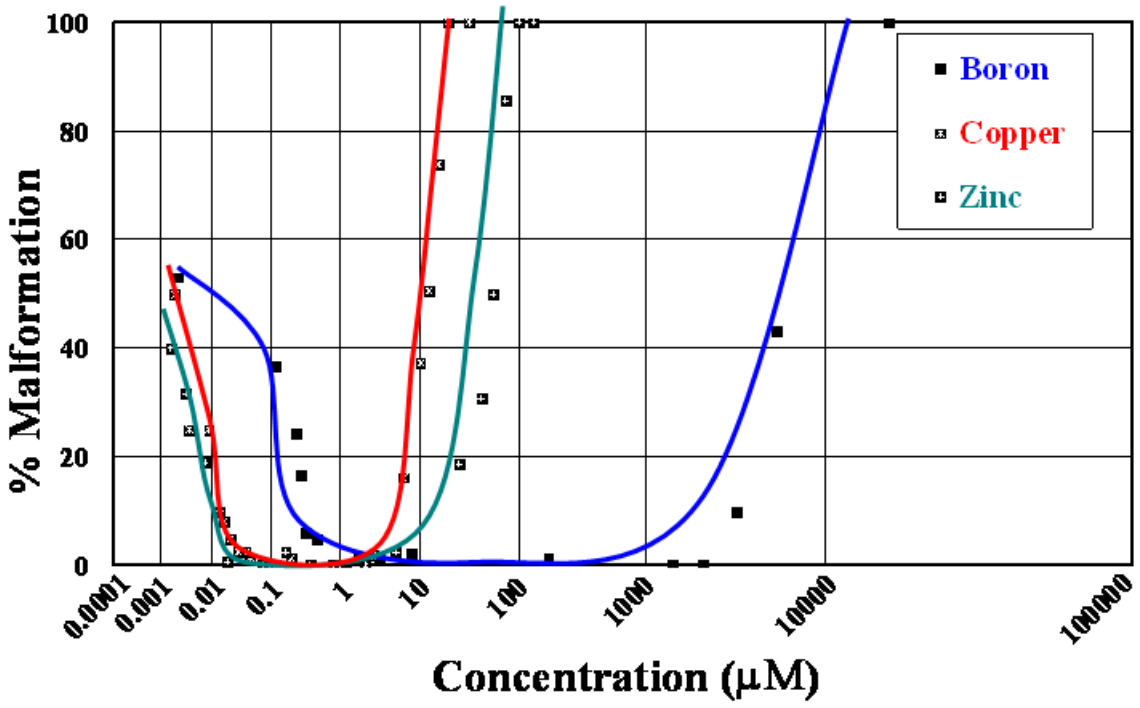
The NOAEL for this endpoint is 9.6 mg B/kg bw/day corresponding to 55 mg boric acid/kg bw/day; 85 mg disodium tetraborate decahydrate/kg, 65 mg disodium tetraborate pentahydrate/kg and 44.7 mg disodium tetraborate anhydrous/kg.

The critical effect is considered to be decreased fetal body weight in rats, for which the NOAEL was 9.6 mg/kg body weight per day. A benchmark dose developed by Allen et al. (1996) was based on the studies of Heindel et al. (1992), Price et al. (1994) and Price et al. (1996). The benchmark dose is defined as the 95 % lower bound on the dose corresponding to a 5 % decrease in the mean fetal weight ($BMDL_{05}$). The $BMDL_{05}$of 10.3 mg/kg body weight per day as boron is close to the Price et al. (1996) NOAEL of 9.6 mg/kg body weight per day.

Boron has been shown to be essential for development in the frog, Xenopus laevis (Fort et al 1998, 1999a,b, 2002a,b). Embryos from frogs cultured in low boron environments showed increased necrosis and poor viability. Boron generates a broader concentration-response curve for teratogensis than copper or zinc in Xenopus. Comparative dose-response curves for boron, copper and zinc are presented in Figure 1. The broad dose-response curve indicates a wider margin of safety for boron between nutritionally deficient levels and the higher levels. When the boron curve is compared to the dose response curves for copper and zinc, the curve for boron is shifted to the right, showing that adverse effects from boron deficiency occur at a higher level than for copper or zinc. Further, this also shows that boron is not as developmentally toxic in Xenopus as copper or zinc (Fort et al. 1999a).

Development and retinal health effects were observed in trout and zebrafish in a low boron environment (Eckhart 1998; Rowe et al. 1998; Eckhert and Rowe 1999). Early embryonic development was impaired in rodents fed boron deficient diet (Lanoue et al 1998, 1999).

Figure 1. Comparison of concentration-response relationships for boron, copper and zinc in *Xenopus* based on 4-day embryo-larval malformations (Fort et al. 1999a).



4.11.2.2 Human information

In addition to the absence of effects on male fertility in humans, there is no evidence of developmental effects in humans attributable to boron in studies of populations with high exposures to boron. Epidemiological studies of human developmental effects have shown an absence of effects in exposed borate workers and populations living in areas with high environmental levels of boron. Although these studies have methodological deficiencies, collectively these studies consistently show an absence of effects in highly exposed populations.

Tuccar et al. (1998) investigated the effects of boron on reproductive and developmental effects in three generations of families living in boron rich regions of Turkey. A total of 567 families over three generations across 3 regions were studied. No significant differences in the number of pregnancies, congenital malformations, stillbirths and spontaneous abortions were observed between high boron exposed populations compared to low boron exposed populations. Tuccar et al. (1998) investigated the effects of boron on reproductive and developmental effects in three generations of families living in boron rich regions of Turkey. This study was part of a larger study of the health effects of boron in residents living in boron rich territories of Turkey (Sayli 2001; Sayli et al. 1998; Sayli 1998; Sayli 2003). The study population was divided into three subgroups based on levels of environmental boron exposure. Region I included residents living in boron rich territories, located close to borate pits and a processing plant. Drinking water in Region I come from natural springs and wells that contain as much as 29 ppm B. Region II residents lived far away from borate deposits. The concentration of boron in drinking water serving residents of Region II was between 0.30 and 0.50 ppm. Region III residents were born and live within the study region with some residents close to and some far from deposits and pits. Daily exposures of 6.77 mg/day for males living in the boron-rich region and 1.26 mg/day for controls was later estimated for residents of these regions by Korkmaz et al. (2007). However, no exposure estimates of women during their pregnancies were available. A total of 226 families over three generations from Region I, 164 families from Region II and 177 families from Region III were included in the study. Questionnaires were administered by home visits, and workers were contacted at the borate plants

and pits. The questionnaires obtained information on number of pregnancies, early infant deaths, congenital malformations, stillbirths and spontaneous abortions. The infant death rate was higher in Region II, the region with the low boron levels, compared to the other regions. No other significant differences in developmental effects were observed between high boron exposed populations compared to low boron exposed populations. The observed number of congenital malformations was not sufficient in the study groups to allow for statistical evaluation.

Cöl et al. (2000) investigated infertility rates, gender ratio, stillbirths and spontaneous abortions,premature births or low birth weights, and infant mortality rates among the families of 799 workers (642 production workers, 157 office workers) at three production facilities in Turkey. Data was collected by personal interviews of workers at their work place in 1998. The boron level in drinking water ranges from 1.7 to 9.4 ppm for Region I, from 2.79 to 5.94 in Region II and from 0.36 to 0.62 in Region III. Dust concentrations in production departments varied from 1.11 to 2.96 mg/m3 in Region I, 0.69 to 9.25 mg/m3 in Region II and 0.39 to 9.47 mg/m3 in Region III. No boron exposure measurements were available for the spouses of the workers during their pregnancies, however their exposures were likely lower than the male workers who were also exposed to boron at the production facilities. No significant adverse effects were found among production workers with high boron exposures compared to national or regional rates or to office workers with low boron exposure. Infertility rates among the workers averaged 1.8 % compared to the Turkish national rate of 1.49–3.8 %. When comparing the production workers to office workers, the only significant differences were that average pregnancies and live births among production workers exceeded those of office workers. There is no increase of premature births or low birth weights for these study regions when compared to national rates. Stillbirths per 100 pregnancies were 1.64 for Region I, 1.68 for Region III, but 3.09 for Region II, compared to 1.5 per 100 pregnancies in the Turkish demographic and health survey. The number of premature births or low birth weight per couple was 0.14, 0.12 and 0.11 for Region I, Region II and Region III, respectively compared to 0.26 in Ankara. Spontaneous abortion rates per 100 pregnancies were 6.75, 7.31 and 8.97 for the three regions, similar to the national rate of 8.7 per 100 pregnancies. The infant mortality rate per 1000 live births for Region I was 67.7, 91.8 for Region II and 66.3 for Region III, compared to an infant mortality rate of 63 per 1000 live births in Ankara, and 43 per 1000 live births for Turkey. Region II had the highest mortality rate but did not have the highest exposure to boron. The differences between the regions were likely due to social and cultural issues. Cöl et al. (2000) concluded that exposure to boron did not adversely affect the number of stillbirths, the number of spontaneous abortions, the number of premature births with low birth weight or the infant mortality rate for the wives of workers from three boron plants. Primary infertility, secondary infertility, sex ratio, stillbirth, prematurity/low birth weight, spontaneous abortions and infant mortality did not show any relation with work assignment among the families of 799 workers at 3 production facilities in Turkey.

Chang et al. (2006) evaluated developmental effects in families of a cohort of boron mining andprocessing workers and a comparison group in northeast China. Well water in the boron group ranged from 37 to 600 times the comparison group, and the mean boron concentrations in legumes and potatoes from the boron group was approximately double those found in the comparison group. No statistically significant differences were observed between the boron workers and the comparison group in delay in pregnancy, multiple births, spontaneous miscarriage, induced abortion, stillbirth, tubal or ectopic pregnancy, and boy/girl ratio. Chang et al. (2006) evaluated reproductive health in a cohort of boron mining and processing male workers (N=936) and a comparison group of males (N=251) in northeast China. The comparison group was selected from a community 30 miles away from the boron mines and processing plants with a known low background of environmental boron. This study was based on interview data from a larger study of

workplace exposure to boron-containing compounds and adverse male reproductive effects. The reproductive effects data was obtained by self-report of delays in pregnancy, pregnancy outcomes, total number of children, and gender of children. Exposure estimates for the boron workers was 31.3 mg boron/day and 1.40 mg B/day for the comparison group (Scialli et al. 2010). No exposure measurements were available for the wives of the workers whose boron exposure would be through environmental sources such as food and water. However, concentrations of boron in the surface water, well water, soil, legumes and potatoes of the boron workers group were greater than in the comparison group. Well water in the boron group ranged from 37 to 600 times the comparison group, and the mean boron concentrations in legumes and potatoes from the boron group was approximately double those found in the comparison group. Reproductive health parameters evaluated included: delay in pregnancy, multiple births, spontaneous miscarriage, induced abortion, stillbirth, tubal or ectopic pregnancy, and boy/girl ratio. No statistically significant differences were observed between the boron workers and the comparison group after adjustment for age, educational level, race, smoking, ethanol use, and soybean intake.

4.11.3 Other relevant information

Table 16: Summary table of other relevant information

Method	Results	Remarks	Reference
rat (Sprague-Dawley) female oral: feed 0.025%, 0.050%, 0.075%, 0.100%, 0.200% (analytical conc.) 0, 19, 36, 55, 76, 143 mg Boric acid/kg BW/day (actual ingested) Equivalent to 0, 3, 6, 10, 13, 25 mg Boron/kg BW/day (actual ingested) Exposure: Gestation day 0 to 20 (In feed, ad libitum) Timed-mated Sprague-Dawley rats were exposed to boric acid in the diet from Gestational day 0 to 20. Dietary concentrations of Boric acid yielded average daily intakes equivalent to 0, 3, 6, 10, 13 and 25 mg/kg/d. At termination on Gestational day 20, maternal whole blood was collected in heparinized vacutainer tubes, stored frozen (- 20°C) and subsequently prepared by a high-temperature alkaline ashing procedure for analysis of boron by inductively coupled plasma optical emission spectrometry.		2 (reliable with restrictions) supporting study experimental result Test material (EC name): boric acid	Price CJ, Strong PL, Murray FJ and Goldberg MM (1997)
Study type: Epidemiology study review	Semen analysis: The data do not indicate that	Not relevant for epidemiology study	Scialli AR, Bonde JP, Brüske-

Details on study design: A review panel reviewed and summarized papers of studies of highly exposed Chinese workers in China. Male workers at one boron mine and four boron processing plants in northeast China were studied. The 5 workplaces were selected based on the location, number of employees and the presence and cooperation of an industrial hygienist at the site. 957 men between 18 and 40 years of age agreed to an interview to provide demographic, exposure, reproductive and general health information. Of the interviews, 945 were considered eligible. Potential subjects were 25 - 35 years of age, married without a history of contact with a number of substances and disorders. In addition to general physical examination, men were evaluated for hair distribution breast tissue size; the size, firmness and location of testes, epididymides and ductus deferens and the presence of variocele of hydrocele. A comparison group of 251 men were recruited from an area 30 miles away with low background boron exposure levels. Later in the course of the studies, another comparison group was added, consisting of 63 workers without occupational exposure to boron but drawn from the same community as the boron workers and was termed the local community control group. Boron content of environmental and biological samples was measured. The detection limits and relative standard deviation for boron in different media were: Airborne particulates 0.01 µg/g ± 5.01 %; food 0.0063 µg/g ± 0.63 %; drinking water and urine by ICP-AES 0.0072 ng/mL ± 0.6 %; drinking water and urine by ICP-MS 0.057 µg/mL ± 1.25 %. Personal measurements were performed in borate processing areas using IOM inhalable dust sampler. Total airborne dust concentrations ranged from 0.3 to 33 mg/m^3. The boron concentration in the dust ranged	boron exposure under the conditions described impairs testicular function with respect to sperm concentration, motility morphology or chromatin denaturability. The methods used to assess these endpoints were standard methods reliably performed. Reproductive success: Evaluation of sex ratio did not show a significant effect of boron exposure. Sperm X:Y ratio There were differences in Y:X ratio across the three groups defined by boron exposure. Y:X ratio appeared to be more related to group membership than boron exposure. The within- subject variability of Y:X ratio and possible determinants of Y:X ratio are unknown, except for possible miniscule effects of age, calendar time and race. Y:X ratio is not known to be associated with impaired semen quality, reproductive success or offspring health. There is no clear evidence of male reproductive effects attributable to boron in studies of highly exposed workers.	key study **Test material (Common name): Boric acid and borax**	Hohlfeld, Culver DB, Li Y & Sullivan FM. (2010)

from 1.5 to 4.2 %. Ingestion was measured from the sum of boron intake from food and drink several times using a duplicate plate method. Boron workers were calculated to ingest a mean of 31.3 mg B/day, with a subset of 16 workers exposed mean boron intake of 125 mg B/day, while the community comparison group's boron intake was 4.25 mg B/day and remote background controls of 1.40 mg B/day. Endpoint addressed: toxicity to reproduction / fertility/semen analyses			
Study type: Daily dietary boron intake and on-the-job inspired boron were compared with blood and urine and boron concentrations in workers engaged in packaging and shipping borax. Fourteen workers handling borax at jobs of low, medium and high dust exposures were sampled throughout full shifts for 5 consecutive days each. Details on study design: Daily dietary-boron intake and on-the-job inspired boron were compared with blood and urine and boron concentratons in workers engaged in packaging and shipping borax. Fourteen workers handling borax at jobs of low, medium and high dust exposures were sampled throughout full shifts for 5 consecutive days each. Airborne borax concentrations ranged from means of 3.3 mg/m^3 to 18 mg/m^3, measured gravimetrically. Creatine measures were used to adjust for differences in urine-specific gravity such that 1 mL of urine contained approximately 1 mg creatine. Endpoint addressed: basic toxicokinetics	End-of-shift mean urine concentrations ranged from 3.16 to 10.72 µg/mg creatinine. There was no progressive increase in end-of-shift blood- or urine-boron concentrations across the days of the week. Urine testing done at the end of the work shift gave a somewhat better estimate of borate exposure than did blood testing, was sampled more easily and was analytically less difficult to perform.	Not relevant for Epidemiology study Supporting study **Test material (Common name): Boron and borax** **purity unknown**	Culver BD, Shen PT, Taylor TH, Feldstein AL, Anton-Culver H & strong P. (1993) Culver BD, Shen PT, Taylor TH, Lee-Feldstein A, Anton- Culver H & strong P. (1994) A, Anton- Culver H & strong P. (1994)
Study type: cohort study (retrospective) Type of population: occupational Details on study design: HYPOTHESIS TESTED:	EXPOSURE Daily boron exposure (DBE), urine, blood and semen boron concentrations same as reported above under Duydu et al. 2011.	Not relevant for epidemiology study supporting study **Test material: Boric acid**	Duydu Y (2011)

The null hypothesis for each biologic fluid was that the means of the four groups are equal. Workers were grouped based on semen and urine boron concentrations. Semen boron concentrations: <LOQ (48,5), >LOQ – 500, >500 – 1500 and >1500 ng/g for the control, low, medium and high exposure groups respectively. Urine boron concentrations: 0 - 3, >3 - 5, >5 - 7, >7 mg boron/g creatinine for the control, low, medium and high exposure groups, respectively. METHOD OF DATA COLLECTION As described above under Duydu et al. 2011. STUDY POPULATION As described above under Duydu et al. 2011. HEALTH EFFECTS STUDIED Semen and urine boron concentrations effects on: Sperm concentration parameters, motility parameters of sperm cells, sperm morphology parameters, hormone levels (FSH, LH, total testosterone) and total PSA. OTHER DESCRIPTIVE INFORMATION ABOUT STUDY: Endpoint addressed: toxicity to reproduction/fertility	FINDINGS **Re-consititued groups from Duydu et al. 2011 according to semen boron levels:** • Hardly any evidence is seen that higher semen boron levels are correlated with adverse effects. • For Neck/mid-piece defects (%) a statistical significant difference in the percentage was seen in the pairwise comparison of the low dose with the high dose and the mid dose with the high dose but not the control with the high dose. No clear dose response is seen, also reflected by the weak correlation coefficient of 0.228. **Re-consititued groups from Duydu et al. 2011 according to urine boron levels:** • Hardly any evidence is seen that higher urine boron levels are correlated with adverse effects. • For FSH (follicle stimulating hormone) the global null hypothesis that all group means are equal is rejected. The significant pair wise differences are between Control-Medium and Medium-High. No clear dose response is seen, also reflected by the absence of a significant correlation. • A significant correlation was seen between urine boron concentrations and LH (lutenising hormone) levels. Nevertheless this correlation is quite weak (correlation factor = 0.244) • It has to be stated that for several parameters the scattering of values within the respective groups are large resulting often in standard deviations that have almost the same magnitude as the average value. In these cases the relative low number of volunteers per group complicates the determination of correlations. • The seen weak effects are not indicative for a reproductive		

	toxicity potential of boric acid. This strengthens the position made in the publication that boron does not have an adverse effect on the male reproductive system at high human exposure conditions.		
rat (Fischer 344) male oral: feed Exposure regime: Daily for 7 days Doses/conc.: 0 and 9000 ppm (1575 ppm boron); 93 – 96 mg B/kg bw/day.	Main ADME results: absorption: Boric acid is readily and completely absorbed in rats given borates orally. distribution: All tissues examined, except bone and adipose tissue, appeared to reach steady state boron levels by three to four days. distribution: Bone achieved the highest concentration of boron (2 to 3 times plasma levels), and bone boron levels continued to increase throughout seven days of dietary administration. Toxicokinetic parameters: Half-life 1st: A half-life of < 12 hours can be estimated assuming first order kinetics. Metabolites identified: no Details on metabolites: Boric acid is not metabolised.	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Ku WW, Chapin RE, Moseman RF, Brink RE, Pierce KD & Adams KY. (1991)
rat (Fischer 344) male oral: feed Exposure regime: Nine weeks Doses/conc.: 3000, 4500, 6000 and 9000 ppm boric acid; 545, 788, 1050 and 1575 ppm boron (< 0.2, 26, 38, 52, 68 mg B/kg bw/day) respectively.	Inhibited spermiation could be separated from atrophy based on dose (inhibited spermiation: 3000/4500 ppm, atrophy 6000/9000 ppm) with each lesion aspect expressed at different threshold testis boron concentrations (inhibited spermiation: 5.6 µg boron /g and atrophy: 11.9 µg boron/g) with no boron accumulation during the 9-week exposure. These data suggest that separate mechanisms may be operating for these lesion aspects based on testis boron concentration and that boron dose rate was important for testicular toxicity. Inhibited spermiation was most reliably reflected by informed testicular histology with the more severe cases decreasing	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **CAS No: 10043-35-3** **purity unknown**	Ku WW, Chapin RE, Wine RN & Gladen BC. (1993)

	epipdidymal sperm count to levels that could affect fertility. After treatment, serum and testis boron levels in all dose groups rapidly fell to background levels at the earliest time points evaluated (7 days and 8 weeks post treatment respectively). The severely inhibited spermiation at 4500 ppm was resolved by 116 weeks post treatment but areas of focal atrophy were detected that did not recover post treatment. Also no signs of recovery from atrophy were observed (6000 and 9000 ppm). Atrophic tubules contained a normal complement of spermatogonia (2.6 to 2.9 germ cells/100 sertoli cells) with occasional dividing and degenerating germ cells. Elevations in serum FSH and LH levels suggested an intact hormonal response to the atrophy.		
Boron-induced changes in human prostate cancer cell lines were assessed. Human prostate cancer cell lines were cultured with boric acid supplemented media. Following incubation, cells were trypsinised and prepared for flow cytometry. β-galactosidase assays, western blots, fluorescent probe detection of actin and acidic compartments and cell attachment, migration and invasion assays were also performed.	Pharmacologically relevent levels of boric acid induce the following morphological changes in cells: Increases in granularity and intracellular vesicle content, enhanced cell spreading and decreased cell volume. Increases in β-galactosidase activity were also noted. Boric acid also caused a dose-dependent reduction in cyclines A-E as well as MAPK proteins. Treated cells displayed reduced adhesion, migration and invasion potential, along with F-actin changes indicative of reduced metastatic potential. Media acidosis in treated cells corrleated with an accumulation of lysosome-associated membrane protein type 2 (LAMP-2)-negative acid compartments	2 (reliable with restrictions) supporting study experimental result **Test material (EC name): boric acid** **purity unknown**	Barranco WT, & Eckert CD (2006)
rat (CD-1) intraperitoneal 1000 mg/kg boric acid (Actual dose injected.) Exposure: Single injection on Day	NOAEL (developmental toxicity): 1000 mg/kg single injection based on: test mat. (Mice were deliberately given a teratogenic dose.)	4 (not assignable) supporting study experimental result **Test material (EC name): boric acid**	Di Renzo F, Cappellett G, Broccia ML, Giavini E & Menegola E (2007)

8 of gestation. (Single injection)			

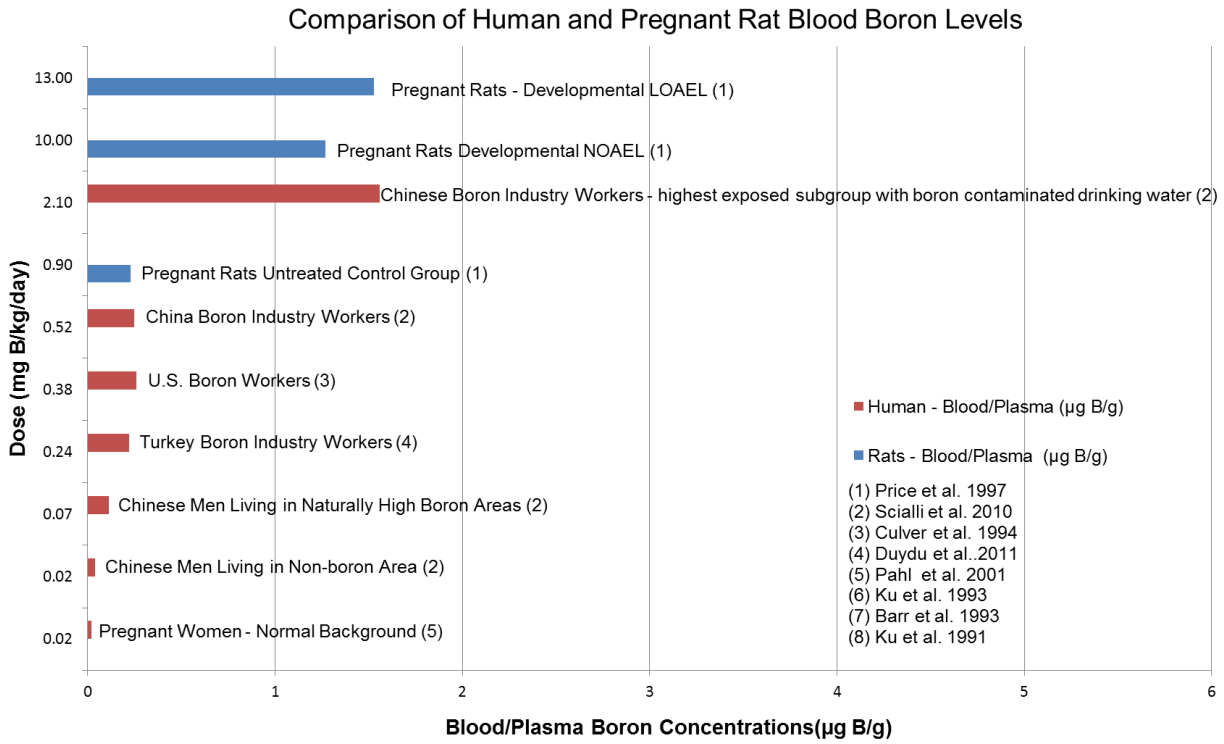
Comparison of Blood, Semen and Testes Boron Levels in Human and Rat

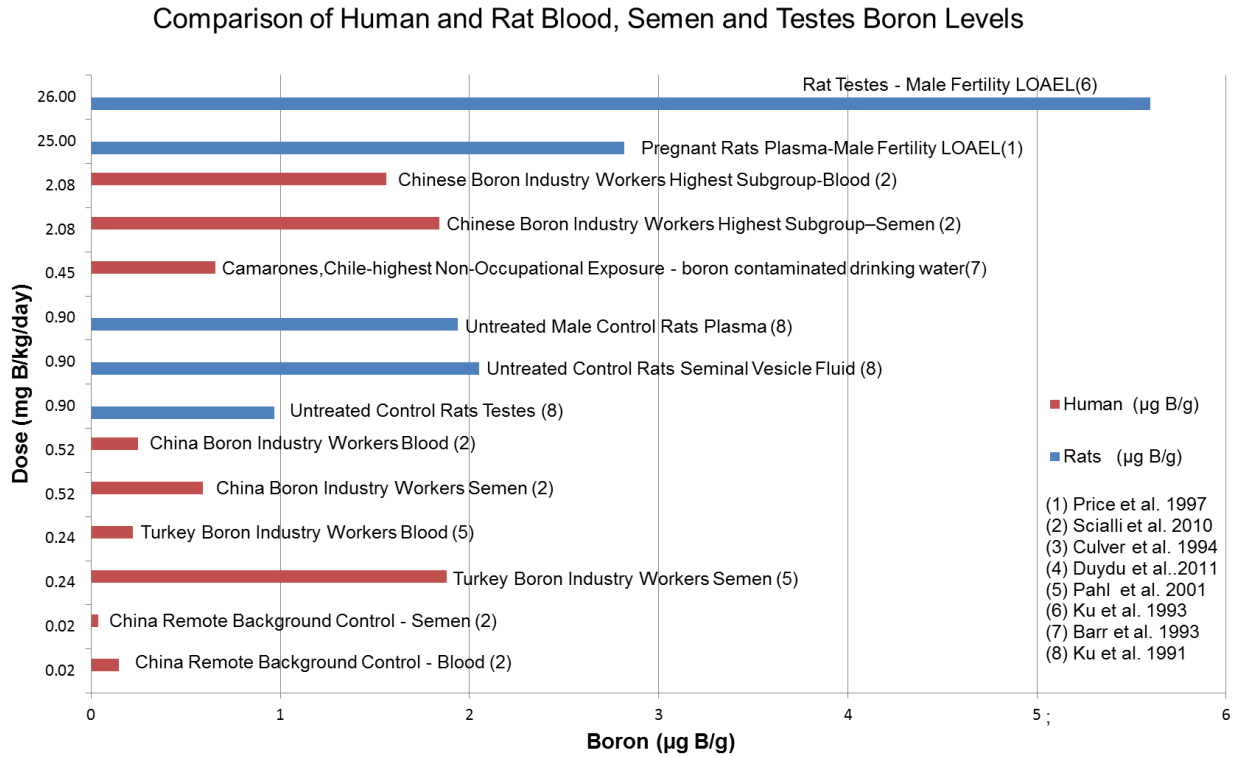
A comparison of blood, semen and target organ boron levels in studies of laboratory animals and human studies shows that boron industry worker exposures are lower than untreated control rats. Background boron levels in standard rat chow are high (10-20 ppm), as a result control rats in toxicity studies receive 45 times more boron than background exposure in humans. Blood boron levels in female control rats is about 0.23 μg B/g (Price et al. 1997), approximately equal to the blood levels in boron industry workers in China, Turkey and U.S. of 0.25, 0.22 and 0.26 μg B/g, respectively (Scialli et al. 2010; Culver et al. 1994; Duydu et al. 2011). Plasma and seminal vesicle fluid (the major component of semen) boron levels in untreated male control rats were 1.94 and 2.05 μg B/g, respectively, while boron levels in testes in rats dosed at the rat fertility LOAEL (26 mg B/kg) was 5.6 μg B/g (Ku et al. 1991,1993a). Values in male control rats were higher than corresponding boron levels in the highest exposed Chinese boron industry workers with blood boron levels of 1.56 μg B/g and 1.84 μg B/g in semen (Scialli et al. 2010). Blood and semen boron levels in highly exposed Turkish boron workers were also lower than control rats with levels of 0.22 and 1.88 μg B/g, respectively (Duydu et al. 2011). Boron levels in testes of rats dosed at the rat fertility LOAEL was over 3x the blood boron levels in highest exposure group of Chinese boron industry workers. The blood level at the lowest animal LOAEL (13 mg B/kg) was 1.53 μg B/g, about 6 times greater than typical boron industry workers (Price et al. 1997). No adverse effects on sperm were seen in Turkish boron industry workers or in the most highly exposed subgroup of Chinese boron industry workers drinking boron contaminated water (mean blood level 1.52 μg B/g, the human NOAEL). Only under extreme conditions do human levels reach those of this animal LOAEL: the subgroup of Chinese boron workers who also drank contaminated water. Since no boron accumulation occurs in soft tissues (testes) over plasma levels biological monitoring in humans provide direct comparison to test animal target organ boron levels.

Workers in boron mining and processing industries represent the maximum possible human exposure however their blood and semen boron levels are less than levels in untreated control rats. This provides an explanation why studies of highly exposed boron industry workers have shown no adverse effects and demonstrates that maximal possible exposures in humans are insufficient to cause reproductive toxicity effects. Graphs comparing the rodent and human exposure, blood, semen and tissue boron levels are presented below. The human exposure data do not support classification of boric acid as Category 1(B) reproductive toxicant.

Extensive evaluations of sperm parameters in highly exposed workers have demonstrated no effects on male fertility. While no developmental effects have been seen in highly exposed populations, epidemiological studies of developmental effects are not as robust as the fertility studies. Reproductive effects data for the developmental epidemiological studies were obtained by self-reported data collected by personal interviews of workers and questionnaires, small sample sizes, and lack of actual exposure measurements during pregnancy limit the conclusions that can be made from the developmental studies in humans.

Therefore, based on a total weight of evidence, Category 2 H361d: suspected human reproductive toxicant, suspected of damaging the unborn child is considered the appropriate classification. Extensive evaluations of sperm parameters in highly exposed workers have demonstrated no effects on male fertility. While no developmental effects have been seen in highly exposed populations, epidemiological studies of developmental effects are not as robust as the fertility studies, warranting the Category 2 H361d.


Comparison of Human and Pregnant Rat Blood Boron Levels
Dose (mg B/kg/day)
13.00
10.00
2.10
0.90
0.52
0.38
0.24
0.07
0.02
0.02
Pregnant Rats - Developmental LOAEL (1)
Pregnant Rats Developmental NOAEL (1)
Chinese Boron Industry Workers - highest exposed subgroup with boron contaminated drinking water (2)
Pregnant Rats Untreated Control Group (1)
China Boron Industry Workers (2)
U.S. Boron Workers (3)
Turkey Boron Industry Workers (4)
Chinese Men Living in Naturally High Boron Areas (2)
Chinese Men Living in Non-boron Area (2)
Pregnant Women - Normal Background (5)
Human - Blood/Plasma (µg B/g)
Rats - Blood/Plasma (µg B/g)
(1) Price et al. 1997
(2) Scialli et al. 2010
(3) Culver et al. 1994
(4) Duydu et al..2011
(5) Pahl et al. 2001
(6) Ku et al. 1993
(7) Barr et al. 1993
(8) Ku et al. 1991
0
1
2
3
4
5
6
Blood/Plasma Boron Concentrations(µg B/g)


Comparison of Human and Rat Blood, Semen and Testes Boron Levels
Dose (mg B/kg/day)
26.00
25.00
2.08
2.08
0.45
0.90
0.90
0.90
0.52
0.52
0.24
0.24
0.02
0.02
Rat Testes - Male Fertility LOAEL(6)
Pregnant Rats Plasma-Male Fertility LOAEL(1)
Chinese Boron Industry Workers Highest Subgroup-Blood (2)
Chinese Boron Industry Workers Highest Subgroup–Semen (2)
Camarones,Chile-highest Non-Occupational Exposure - boron contaminated drinking water(7)
Untreated Male Control Rats Plasma (8)
Untreated Control Rats Seminal Vesicle Fluid (8)
Untreated Control Rats Testes (8)
China Boron Industry Workers Blood (2)
China Boron Industry Workers Semen (2)
Turkey Boron Industry Workers Blood (5)
Turkey Boron Industry Workers Semen (5)
China Remote Background Control - Semen (2)
China Remote Background Control - Blood (2)
Human (µg B/g)
Rats (µg B/g)
(1) Price et al. 1997
(2) Scialli et al. 2010
(3) Culver et al. 1994
(4) Duydu et al..2011
(5) Pahl et al. 2001
(6) Ku et al. 1993
(7) Barr et al. 1993
(8) Ku et al. 1991
0
1
2
3
4
5
6
Boron (µg B/g)

Mechanisms

Recent studies provide possible mechanisms of boric acid related developmental effects in laboratory animals, including histone deacetylase inhibition (HDACi) and effects of boric acid on expression of Hox genes. A major difference between laboratory animals and humans is the large zinc stores in bone and soft tissues in humans compared to laboratory animals. Zinc has been shown to be protective against the acute toxicity and male fertility effects of boron in addition to protective effects against testicular and developmental toxicity of cadmium, chromium and cobalt. Each of these mechanisms is discussed in greater detail below.

Histone Deacetylase Inhibitors (HDACi)

The ability of some histone deacetylase inhibitors (HDACi) including valproic acid (VPA), trichostatin A (TSA), apicidin (API), entinostat, and sodium butyrate (BUT) to induce hyperacetylation on mouse embryo tissues has been correlated to teratogenic property in mice. Hyperacetylation of target organs, such as the embryonic axial structures (somites), has been directly related to axial skeletal malformations (fusions of vertebrae and/or ribs, duplication of axial segments, homeotic transformations) in mice. The targets of HDACi in embryos are the histone core proteins of somites. Somites are transient embryonic structures giving rise to dermal, muscular, and skeletal structures of the trunk (Di Renzo et al. 2007).

Recent studies by Di Renzo et al. (2007) provide evidence for HDAC inhibition by boric acid that suggests a molecular mechanism for the induction of boric acid related malformations in laboratory animals. The data indicate that boric acid is able to induce hyperacetylation in specific embryonic target tissues (somites), associated with direct interference with HDAC enzyme activity. No effects were recorded at the level of other embryonic tissues and at the level of other proteins. HDAC inhibition could be the mechanism for hyperacetylation of somites and consequently for axial malformations observed at term of gestation in laboratory animals (Di Renzo et al. 2007). Since the critical period for the effects of boric acid on development of the axial skeleton in laboratory animals is very narrow, particularly relative to the length of gestation, and also requires a high dose during that period, the likelihood of similar effects in humans is low due to the long gestational period in humans.

Using immunohistochemical analysis, the hyperacetylation was detected specifically at the level of somites, the embryonic structures involved in the axial morphogenesis. Comparison between the stained histological sections of VPA, TSA and boric acid embryos showed that for all groups the localization of positive nuclei was mainly at the level of the dorsal epithelium of somites and of the internal core of the ventral somitic mesenchyme. The amount of stained nuclei was similar for both boric acid and TSA. VPA showed a higher immunostaining at the level of somitic dorsal epithelium, while the reaction of somitic mesenchyme was comparable to those observed in boric acid and TSA groups. A distinguishing difference between boric acid and the other HDACi is that in contrast with results observed in studies on TSA and VPA (Menegola et al., 2005), in which hyperacetylation was also observed at the caudal neural tube level, immunostaining for boric acid group was restricted to somites. This difference could explain how VPA and TSA are also able to induce neural tube defects while neural tube defects are not the typical malformation after boric acid exposure (Di Renzo et al. 2007).

Boric Acid Effects on Hox Gene Expression

Boric acid related axial abnormalities in rodents have also been attributed to a shift in Hox gene expressions (Wery et al., 2003). During embryonic development, positional information determining the craniocaudal identity of the somites, the precursors to the vertebrae, is thought to be conferred by the hox genes. Hox expression in the paraxial mesoderm begins during gastrulation before the formation of the somites. Hox genes have overlapping domains of expression in the somites and prevertebrae (PV) that extend from the caudal end of the embryo to a precise cranial limit that is correlated to the linear order of the genes within a given cluster. This expression pattern along the craniocaudal axis of the embryo suggests a combinatorial code according to which the expression of a given combination of hox genes will specify the identity of a vertebral segment (Narotsky et al. 2004).

Studies by Wery et al. (2003) and Narotsky et al. (2004) suggest an impact of boric acid on the basic control mechanisms that define the positional identity of the somites and, consequently, the vertebrae. Homeotic genes that are known to confer positional information in the cervical and the cranial most thoracic regions include hoxd4, a4, a5, c5, c6, and a6. Narotsky et al. (2004) hypothesized that hox expression may be affected by GD-9 exposure to boric acid. Comparison of expression patterns between boric acid exposed embryos and controls revealed a shift in the expression domain of two genes, hoxc6 and hoxa6 on GD 13.5. These shifts are likely to result in posterior transformation of cervical vertebrae later in development, without altering the total number of vertebrae. This is consistent with the observed morphological defects at GD 21 after boric acid exposure, suggesting that these hox gene alterations are part of the dysmorphogenic cascade resulting from boric acid exposure (Narotsky 2004). Studies by Wery et al. (2003) and Narotsky et al. (2004) show that the effect on the hox gene occurs at a high dose and during a very narrow window of gestation. Because of the longer period of organogenesis and gestation in humans compared to rodents, these effects are unlikely to occur in humans.

Protective Effects of Zinc against Boric Acid Reproductive and Developmental Toxicity

The protective effect of the large zinc stores in the human body against boric acid associated toxicity explains in part the absence of effects in humans exposed to high levels of boron. Zinc has been shown to protect against testicular toxicity of chromium, cobalt and cadmium (Afonne et al. 2002; Anderson et al. 1993), and developmental toxicity of cadmium (Ahokas et al. 1980; Daston 1982; Fernandez et al. 2003; Hartsfield et al. 1992). A similar interaction with boron may well explain the absence of fertility and developmental effects in humans.

Normal levels of zinc in soft tissues in humans are over two times greater than in comparative tissues in laboratory animals (King et al. 2000; Ranjan et al. 2011; Yamaguchi et al. 1996; Florianczyk 2000). These excess zinc stores compared to laboratory animals provide added protection against the toxic effects of high levels of boric acid not available in laboratory animals. The high zinc concentrations in humans compared to laboratory animals is also found in the target organs of boric acid, including fetal tissue, epididymis, and testes (Ahokas et al. 1980; Dorea et al. 1987; Suescun et al. 1981).

The protective effect of zinc against boric acid toxicity is demonstrated by the low acute toxicity of zinc borate (ZB) compared to disodium tetraborate pentahydrate, both with equivalent boron concentrations. No mortality occurred in an acute toxicity study of zinc borate in rats administered 10 g/kg-bw, equivalent to 1492 mg B/kg bw (Daniels 1969) compared to disodium tetraborate pentahydrate with a LD50 value of 3.3 g/kg-bw, equivalent to 488 mg B/kg bw. No mortality was observed at a boron dose three times the boron dose shown to produce 50% mortality in the absence of zinc.

Furthermore, no toxic effects were observed in the testes of males administered 1000 mg ZB415/kg/day in a 28-day repeated dose oral gavage toxicity study, an equivalent dose of 50 mg B/kg bw (Wragg et al. 1996). The LOAEL for testicular effects is 26 mg B/kg body weight. This shows that Zn interacts with boric acid in the body reducing the toxicity of boric acid.

To determine if the low toxicity of zinc borate was due to reduced bioavailability of boric acid a toxicokinetic study in rats of zinc borate was conducted. Following a single oral dose (1000 mg/kg) of zinc borate 2335, zinc and boron appeared in rat plasma and tissue samples, indicating the hydrolysis of zinc borate 2335 in the gastrointestinal tract, and subsequent systemic absorption of zinc and boron (Muzzio et al. 2010).

Beneficial Effects

The essentiality of dietary boron in humans is suspected but has not been directly proven (Mertz 1993; Devirian and Volpe 2003). A recent review of evidence for the essentiality of dietary boron shows that boron meets the criteria for essentiality in humans (Hunt 2007, 2012): 1) it reacts with biological material or forms chelates; 2) it is present in healthy tissues of different animals at comparable concentrations; 3) toxicity results only at relatively high intakes; 4) tissue concentrations during short term variations in intake are maintained by homeostatic mechanisms; 5) depletion prevents growth and completion of the life cycle; 6) depletion consistently results in reduction of a physiologically important function; and 7) when an integral part of an organic structure, depletion causes reduction in performance of a vital function.

A nutritional role for boron has been demonstrated in humans and animals (Nielsen 1994, 1996, 1998; Hunt 1994, 1996, 1998; Penland 1994, 1998; Hunt et al 1997; Nielsen and Penland 1999; Hunt and Idso 1999). A World Health Organization (WHO) expert committee concluded that boron is “probably essential” (WHO1996). Although the data are not sufficient to confirm essentiality in humans, the U.S. Food and Nutrition Board in 2001 (FNB 2001) published a Tolerable Upper Intake Level (UL) for boron of 20 mg/day. Also, the UK Expert Group on Vitamins and Minerals (EGVM 2003) and the European Food Safety Authority (EFSA 2004) also regarded boron as nutritionally important and determined an acceptable daily intake for boron (0.16 mg /kg bw/day).

Beneficial effects of boron have been reported for bone health (Hunt 1996; Nielsen 1998; Gorustovich et al 2008), cell membrane function (Nielsen 1994, 1996), psychomotor skills and cognitive processes of attention and memory (Penland 1994, 1998), response to estrogen therapy (Nielsen 1994, 1996), control of inflammatory disease (Hunt 1996, Penland 1998, Hunt and Idso 1999), enzyme regulation (Nielsen 1996, Hunt 1998), energy metabolism (Hunt 1996), macroscale mineral metabolism (Hunt 1994, Nielsen 1996, Hunt et al 1997, Nielsen 1998), and potential anticarcinogenic properties (Barranco et al 2004, 2006, 2007; Gallardo-Williams et al 2003, 2004; Korkmaz et al 2007; Mahabir et al 2008). Boron deficiency has been shown to affect bone healing by reduction in osteogenesis (Gorustovich et al 2008). Boron supplementation in pig diets (5 mg-B/kg-diet) decreased the inflammatory response to an intradermal injection of phytohemagglutinin in pigs, altered plasma lipid metabolites, and tended to increase the production of cytokines following a stress (Armstrong et al 2000, 2001, 2003).

Epidemiological studies indicate that boron exposure in drinking water is associated with lower incidences of some types of cancer including prostate, lung, cervical and esophageal cancer. Epidemiological studies have shown a correlation of reduced risk of prostate cancer incidence and mortality with increased boron intake and groundwater boron concentrations (Zhang et al., 2001,

Cui et al. 2004; Barranco, Hudak, Eckhert 2007) suggesting that higher boron intake has a beneficial effect on prevention of prostate cancer. Mechanisms for the role of boron in the inhibition of human prostate cancer cell proliferation are beginning to be revealed (Barranco and Eckhert, 2004; Barranco and Eckhert, 2006; Barranco, Hudak, Eckhert 2007; Eckhert et al. 2007; Gallardo-Williams et al. 2004; Gallardo-Williams et al. 2003; Barranco and Eckhert 2004; Henderson et al. 2009a, b; Barranco et al. 2009). One potential mechanism is the inhibition by boric acid of stored Ca^{2+} release imparing Ca^{2+} signaling, and inhibition of NAD^{+} and $NADP^{+}$ in prostate cancer cells (Henderson et al. 2009a, b; Barranco et al 2009). A recent study examining the association between boron intake and the joint effects of boron intake and hormone replacement therapy (HRT) on lung cancer risk in women found increased lung cancer risk among the women with low dietary boron intake but no HRT compared with high boron intake plus HRT use (Mahabir et al. 2008). The incidence of esophageal cancer has been reported to be significantly higher in a low boron region, compared to an area with boron exposure in the Butterworth district of Transkei, Southern Africa (Kibblewhite et al, 1984).

Two epidemiological studies have associated increased boron intake in drinking water with decreased incidences of prostate cancer. Cui et al. (2004) used the cross-sectional data from the NHANES III study, conducted from 1988 to 1994, which contained health and diet information for the non-institutionalized U.S. population. These investigators reported that men with mean intakes of ≥1.54 mg boron/day had significantly less risk of developing prostate cancer than men ingesting ≤0.52 mg/day. A second study (Barranco et al. 2007) on a Texas population correlated increased boron in groundwater with reduced prostate cancer incidence rates.

Korkmaz et al. (2007) studied 1,059 rural Turkish women and associated higher boron intake (as evidenced by approximately 8-fold higher urinary boron concentration) with lower incidences of cervical cytopathology (0 findings in the high-boron group, 15 cases in the lowboron group).

The physiological importance for boron can be demonstrated by the existence of boron specific transporters and by the maintenance of variations in boron tissue concentrations by homeostatic mechanisms. A boron transporter membrane protein, BOR1, has been identified in plant roots of Arabidopsis thaliana (Takano et al 2002; Takano et al 2005, 2008). The discovery of a "quorum sensing" cell-cell communication auto inducer molecule containing a borate-sugar diester suggests a role in bacteria (Chen et al 2002). In plants it is a component of the rhamnogalacturonan-ll dimer and is required for cell elongation, flowering, and seed formation. It is regulated using the boratetransport proteins BOR1, BOR4, and NIP5;1 (O'Neill, 2001; Kato et al., 2008; Takano et al., 2008). A homolog of the BOR1 and BOR4 transport proteins in plants, NaBC1, has been found in human kidney, stomach, duodenum, pancreas, brain, the anterior and posterior corneal epithelia, renal corpuscules, proximal tubules and collecting ducts in the kidney, pancreatic ducts, and the choroid plexus epithelium (Damkier et al., 2007). The wide spread expression of a transporter may indicate its role in maintaining boron levels in human cells and underscores an apparent physiological importance for boron.

The retention of intracellular boron against a concentration gradient in cultures of mammalian cell lines of either RAW 264.7 cells (mouse leukemic monocyte macrophatge cell line) or HL60 cells (human promyleocytic leukemia cells) indicate the presence of intracellular boron binding species or the existence of boron specific transporters on the plasma membrane (Ralston and Hunt 2001). The demonstration of the concentration of boron against a gradient indicates the existence of boron specific transporters. This line of evidence for the homeostatic control of boron is enhanced further by the discovery of a specific mammalian borate transporter, NaBC1, expressed in the basolateral membranes of epithelial cells (Park et al. 2004). The recent identification of the boron transporter, BOR1 (AtBor1), in the flowering plant Arabidopsis tha1iana (Takano et. al. 2005; Takano et al. 2002) and its mammalian homolog, BTRl, a newly discovered bicarbonate transporter superfamily

member (Parker et al. 2001), provides further evidence for the homeostatic control of boron in humans and mammals.

4.11.4 Summary and discussion of reproductive toxicity

Fertility:

A wealth on information on the detrimental effect of boron to the male reproductive system in laboratory animals is available. Effects on fertility include reversible inhibition of spermiation, testicular atrophy, degeneration of seminiferous tubules and reduced sperm counts and increased morphological aberrations in sperm cells, seen in rats, mice and dogs. Despite extensive research (Ku, Chapin, Fail and co-workers) *in vivo* and *in vivo,* the modes latter effects on DNA synthesis in mitotic and meiotic germ cells and on energy metabolism of Sertoli cells might play a role. A NOAEL of 17.5 mg B/kg bw/day for effects on fertility was derived in the Transitional Annex XV dossier (European Chemicals Agency 2008) based on Weir 1966a,b and Fail et al.1991.

In humans effects on fertility were studied in several highly exposed populations. At U.S. Borax mine and production facility in Southern California no adverse effects on reproduction were seen in workers exposed up to an average of 28.4 mg B/day (ca. 0.4 mg B/kg bw/day). In a population living in a boron rich region of Turkey (up to 29 mg/L well water) no effects on fertility were seen over three generations (Sayli 1998 and 2001). Robbins et al (2010) has analysed a population of 192 boron workers in China with two comparison worker groups. The boron worker group numbered 66 and their average exposure was 42 mg B/day (SD 58). Sperm count, sperm concentration, motility, morphology, percentage of DNA strand breakage and sperm aneuploidy and diploidy were not significantly different across the three boron exposure comparison groups. In a review paper (Scialli et al. 2010) reproductive data from 75 boron workers were analysed (average boron intake = 31.3 mg B/day, background: for local community 4.25 mg B/day, 1.40 mg B/day for remote community). Semen analysis and reproductive outcome did not show positive effects. The X:Y ratio was reduced in exposed workers, but no dose response correlation was seen.

A recent study by Duydu et al. (2011) was conducted to investigate the reproductive effects of boron exposure in workers employed in boric acid production plant in Turkey. In order to characterize the external and internal boron exposures, boron was determined in biological samples (blood, urine, semen), in workplace air, in food, and in water sources. Unfavorable effects of boron exposure on the reproductive toxicity indicators (concentration, motility, morphology of the sperm cells and blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone) were not observed. The mean calculated daily boron exposure of the highly exposed group was 14.45 ± 6.57 (3.32–35.62) mg B/day.

It was not found unfavorable dosedependent relationships between reproductive toxicity biomarkers and blood boron concentrations in a range of boron intakes common to boron production plant workers. In addition, the relatively extreme boron exposure conditions examined in this and other studies did not result in blood boron concentrations above those considered safe. In this context, the findings suggest that exposure to boric acid and sodium borates under normal handling and use conditions are not toxic for reproduction in men (Başaran et al. 2012).

In conclusion it can be stated that in animals boron has been shown to have clear effects on fertility. In humans on the contrary even in highly exposed populations a detrimental effect of boric acid exposure could not be validated. Notably, boron is an essential element in plants and a nutritionally important substance in animals and humans. Boron deprivation has also been shown to have clear

detrimental effects on fertility in animals, indicating that boron plays an essential role in normal reproduction in animals; however, an essential role of boron on reproduction has not been validated in humans.

Developmental toxicity:

As for fertility a number of studies were carried out analysing the developmental toxicity of boron in animals. The most sensitive species is the rat (Price et al. 1994, treatment on GD 0 - 20) with a NOAEL of 9.6 mg B/kg bw/day based on a reduction in mean foetal body weight/litter and an increase in wavy ribs (plus an increased incidence in short rib XIII at 13.3 mg B/kg bw/day). A comparable BMDL05 of 10.3 mg B/kg bw/day was determined by Allen et al. (1996) based on the studies by Heindel et al. (1992), Price et al. (1994) and Price et al. (1996); developmental toxicity studies carried out with Sprague-Dawley rats comparable to OECD Test Guideline 414.

Comparable to fertility developmental toxicity of boric acid could not be verified in humans. Tüccar et al. (1998) analysed in total 567 families from three different regions boron contents in drinking water of 29 – 50 ppm, resulting in an average exposure of 6.77 mg B/day for males. No significant differences in pregnancies, abortions, congenital malformations stillbirths or spontaneous abortions were seen between high and low exposure populations. Only the infant death rate was higher in the low exposure region as compared to the other regions, which would be an inverse dose response. Cöl et al. (2000) investigated infertility rates, gender ratio, stillbirths and spontaneous abortions, premature births or low birth weights, and infant mortality rates among the families of 799 workers (642 production workers, 157 office workers) at three production facilities in Turkey with the following exposures: Region I: drinking water ranges from 1.7 to 9.4 ppm, dust concentrations in production departments from 1.11 to 2.96 mg/m³; Region II: water: from 2.79 to 5.94 ppm, dust: 0.69 to 9.25 mg/m³; Region III: water: from 0.36 to 0.62 ppm, dust: 0.39 to 9.47 mg/m³. All parameter compared favourably with other populations from Turkey except for the prevalences of stillbirths and infant mortality in Region II. The latter is regarded by the authors to be due to cultural and social issues and the living conditions. In a comparison of boron exposed workers (n = 936) and non exposed workers (n = 251) from northeast China (exposure 31.3 mg boron/day and 1.40 mg B/day, respectively), Chang et al. (2006) analysed delays in pregnancy, pregnancy outcomes, total number of children, and gender of children. Due to the background exposure also the spouses of the exposed workers have a higher boron intake as compared to the control group, though this was not quantified. No significant differences were found in the following parameters after adjustment for age, educational level, race, smoking, ethanol use, and soybean intake: delay in pregnancy, multiple births, spontaneous miscarriage, induced abortion, stillbirth, tubal or ectopic pregnancy, and boy/girl ratio.

In conclusion it can be stated that in animals boron has been shown to have a developmental toxicity potential. In humans on the contrary even in highly exposed populations a detrimental effect of boric acid exposure could not be validated. Furthermore, boron is an essential element in plants and a nutritionally important substance in animals and humans. Boron deprivation has also been shown to produce clear detrimental effects to embryo and fetus, including malformations, indicating that boron is essential for normal prenatal development in animals; however, an essential role for boron on prenatal development has not been validated in humans.

The studies from Turkey have been criticised for their sampling techniques and lack of strict epidemiological study design and quantitative exposure assessment. Epidemiological studies of developmental effects were not as robust as the fertility studies. Reproductive effects data for the developmental epidemiological studies were obtained by self-reported data collected by personal interviews of workers and questionnaires, small sample sizes, and lack of actual exposure

measurements during pregnancy limit the conclusions that can be made from the developmental studies in humans.

Nevertheless exposures in China and Turkey were very high and describe the upper end of exposures to be expected in to date production processes of boron containing products.

4.11.5 Comparison with criteria

The following passages describing the basis for classification of reproductive toxicity are extracted from REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008:

"Category 1:

Known or presumed human reproductive toxicant

Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, **to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans.** The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B)."

"Category 1B:

Presumed human reproductive toxicant

The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. **However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate**."

"Category 2:

Suspected human reproductive toxicant

Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects."

"Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the total weight of evidence (see 1.1.1). Classification as a reproductive toxicant is intended to be used for substances which have an intrinsic, specific property to produce an adverse effect on reproduction and substances shall not be so classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects."

1.1.1.3 "The role and application of expert judgement and weight of evidence determination. A weight of evidence determination means that all available information bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), (Q)SAR results, human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well documented case reports and observations. The quality and consistency of the data shall be given appropriate weight. Information on substances or mixtures related to the substance or mixture being classified shall be considered as appropriate, as well as site of action and mechanism or mode of action study results. Both positive and negative results shall be assembled together in a single weight of evidence determination."

According to 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, boric acid (Index No. 005-007-00-2) is currently classified as Repr. 1B; H360FD: C ≥ 5.5 %, H360FD: May damage fertility. May damage the unborn child.

However, it is of relevance to the classification of borates that recital 2 of the 30th ATP to Directive 67/548/EEC as published in the EU Official Journal, 15 September 2008 stated that "*The classification and labelling of the substances listed in this Directive should be reviewed if new scientific knowledge becomes available. In this respect, considering recent preliminary, partial and not peer-reviewed information submitted by industry, special attention should be paid to further results of epidemiological studies on the Borates concerned by this Directive including the ongoing study conducted in China…*" The Chinese and Turkish semen studies in highly exposed workers are a major source of information as to human reproductive toxicity and the detailed results of these studies were not available at the time of the 30th ATP. Extensive evaluations of sperm parameters in highly exposed workers have demonstrated no effects on male fertility. Not only are these the most exposed workers so far studied, but the Chinese and Turkish worker studies are the most sensitive studies that has been carried out as semen analysis was performed, a very sensitive detection system for testicular damage.

While boron has been shown to adversely affect male reproduction in laboratory animals, there is no evidence of male reproductive effects attributable to boron in studies of highly exposed workers (Whorton et al. 1994a,b; Sayli 1998, 2001; Robbins et al. 2010; Scialli et al. 2010; Duydu et al. 2011).

Boric acid clearly shows adverse effects on fertility as well as developmental toxicity in laboratory animals. Therefore a classification as reproductive toxicant is needed. Nevertheless for classification in category 1 the available data must allow "a strong presumption that the substance has the capacity to interfere with reproduction in humans." The discrepancy between the results obtained in animals and humans raises doubts that the database is robust enough at the moment to clearly place boric acid in category 1.

Further it is described that "when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate".

The low ToxPi score, the fact that boric acid is not mutagenic and is not carcinogenic in either mice or rats support the conclusion that boric acid is not an endocrine active substance. The lack of an endocrine-related mechanism for the fertility and developmental effects in animals, the numerous studies showing the physiological importance for boron, evidence for the homeostatic control of boron in humans and mammals, and that boron meets the criteria of essentiality; demonstrate a low intrinsic hazard of boron in humans.

Based on the contradicting results from animal and human data, the definition for category 2 is the most appropriate:

"Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1."

A recent review of evidence for the essentiality of dietary boron shows that boron meets the criteria for essentiality in humans (Hunt 2007). The U.S. Food and Nutrition Board in 2001 (FNB 2001) published a Tolerable Upper Intake Level (UL) for boron of 20 mg/day. Also, the UK Expert Group on Vitamins and Minerals (EGVM 2003) and the European Food Safety Authority (EFSA 2004) also regarded boron as nutritionally important and determined an acceptable daily intake for boron (0.16 mg /kg/day). A U-shaped correlation between boron intake and health can therefore be expected.

Occupational exposures in the studies in Chinese, Turkish and USA workers were lower than laboratory exposures of animals, but the highest of these likely describe the upper limits of exposures in production of boron-containing products. The Chinese exposures were higher than would be expected from production processes because as Chang et al. (2006) reported, 34 % of workers reported eating in contaminated areas. It is unlikely that in the future workplace exposures will be as high. It is also unlikely that non-occupational exposures will approach the 42 mg B/day found in the Chinese workers. The highest non-occupational exposure found were among populations in Northern Chile studied by Barr et al. (1993) in which estimated intake of boron was 27 ± 8 mg B/day in the village of Camarones and 21 ± 7 mg B/day in Molinos. These appeared associated with drinking local river waters containing 15.2 and ll.7 mg B/L, respectively.

No significant effects on reproductive parameters were seen in these studies. In addition in the current classification the relevance of the level of exposure for reproductive toxicity is already implemented.

Based on a total weight of evidence, Repr. Category 2 H361d: suspected of damaging the unborn child is considered the appropriate classification. Extensive evaluations of sperm parameters in highly exposed workers have demonstrated no effects on male fertility. While no developmental effects have been seen in highly exposed populations, epidemiological studies of developmental effects are not as robust as the fertility studies, warranting the Category 2 H361d.

Concluding the arguments presented above, classification of boric acid as suspected human reproductive toxicant, category 2 (H361d: Suspected of damaging the unborn child) is regarded appropriate. This classification accommodates for both the positive findings in laboratory animals and the absence of significant effects in humans.

4.11.6 Conclusions on classification and labelling

Based on the argumentation above the following classification is deemed applicable for boric acid regarding reproductive toxicity:

- Category 3; R63: Possible risk of harm to the unborn child according to Council Directive 2001/59/EC (28th ATP of Directive 67/548/EEC, Dangerous Substance Directive)

- Category 2 (H361d: Suspected of damaging the unborn child) according to CLP (REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL) as implementation of UN GHS in the EU.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The Dossier Submitter (DS) proposed to revise the current harmonised Repr. 1B classification of boric acid (H360FD; index number 005-007-00-2 in Annex VI to CLP[1]). The proposal was to remove the classification for fertility effects and to downgrade the classification for developmental effects from category 1B to 2 (Repr. 2, H361d).

According to the DS, extensive evaluations of sperm parameters in highly exposed workers demonstrated no effects on male fertility, justifying no classification. While no developmental effects were seen in highly exposed populations, the epidemiological studies of developmental effects were not considered to be as robust as the fertility studies, and would therefore warrant classification in reproductive toxicity category 2 (H361d).

The DS concluded that based on adverse developmental effects of boron in rats and rabbits, boric acid should be classified with Repr. 2, H361d 'Suspected of damaging the unborn child' according to CLP. According to Directive 67/548/EEC (DSD), the DS proposed to classify boric acid with reproductive toxicity category 3 and assign the risk phrase R63 'Possible risk of harm to the unborn child'. While not proposed for discussion by RAC, the specific concentration limit (SCL) for these effects inserted in the CLH report by the DS is in line with the current SCL for boric acid already included in Annex VI.

Comments received during public consultation

A total of 141 comments were received during the public consultation (PC) on boric acid. None of the 8 member states competent authorities (MSCAs) who commented during the PC supported the revision of the classification for toxicity to reproduction of boric acid. By contrast, the European Borates Association (EBA) and other companies or industry associations supported the proposal from the Polish MSCA.

The comments received during PC covered a number of aspects including:

- the results obtained in epidemiological studies that may or may not be used to overrule positive results from animal studies with respect to reproductive and developmental toxicity
- the concept of exposure and risk in the context of classification and labelling which may or may not be taken into consideration
- the mechanistic or Mode of Action (MoA) studies that may or may not be relevant for humans
- the hypothesis that zinc stores in the human body may or may not protect against testicular toxicity of boric acid. Several studies on zinc borate were announced and/or submitted by EBA during or after public consultation of boric acid. The full study reports and non-confidential executive summaries received on 15 January 2014 were made available through CIRCA BC to the RAC (Hofman-Huther, 2013, Durand, 2013, Kirkpatrick, 2013a, Kirkpatrick, 2013b, Edwards, 2013 and Edwards, 2014).

A detailed response to these comments from the Polish MSCA is available in the RCOM.

Assessment and comparison with the classification criteria

Studies of reproductive toxicity and repeated dose toxicity studies in mice, rats and dogs clearly indicate that boron (B) impairs fertility through an effect on the testes. The effects

observed in the different species are similar in nature. Based on data from the 2 years feeding study with boric acid in rats (Weir, 1996), the overall NOAEL for fertility is therefore 100 mg/kg bw/day, equal to 17.5 mg B/kg bw/day. This conclusion is supported by the study with disodium tetraborate decahydrate (Weir, 1996). There are no indications that the impaired fertility is secondary to other toxic effects.

Developmental toxicity (malformations) was clearly observed in studies in rats and rabbits, the rat being the most sensitive species, with an overall NOAEL of 9.6 mg B/kg bw/day. There were no indications that the developmental effects were secondary to other toxic effects. In addition, the teratogenicity was possibly caused by an altered hox gene expression, caused by inhibition of histone deacetylases, a mechanism that is likely to be also relevant for humans (see below).

There are a number of cross sectional epidemiological studies available on cohorts of workers studies available from China, Turkey and the US on the potential effects of boron exposure on parameters mainly related to fertility among workers occupationally exposed to B. The average daily boron exposure for the high exposure groups in these studies were estimated to be 1.8 mg B/kg/day (n=16), 0.2 mg B/kg/day (n=39) and 0.4 mg B/kg/day (n=109) (Scialli *et al.,* 2010, Duydu *et al.,* 2011, and Whorton *et al.,* 1994, respectively). Average daily exposure values in these workers were one to two orders of magnitude below the lowest observed adverse effect levels (LOAEL) for fertility in mice (Fail *et al*., 1991, 1998), and for developmental toxicity in rats (Price *et al.*, 1994, 1996).

The Chinese studies (reviewed in Scialli *et al*., 2010) showed the highest B exposure levels, with a small subset (n= 16) of the highly exposed group having an average intake of 1.8 mg B/kg bw/day. The analysis was also conducted on a larger group having an average exposure of 0.45 mg B/kg bw/day (n= 75). Parameters included semen analysis, reproductive outcomes and sperm X:Y ratio: no statistically significant effects were observed in either group compared to controls. It is noted that most study groups contained a rather low number of participants, as illustrated by a local and a regional control group of 15 and 23 persons, respectively, thus decreasing the power of the studies. Some of the parameters showed a large variation (e.g. the total sperm count (±S.D.) in controls was 218±124 million), making it difficult to identify potential effects. Furthermore, the selection of participants in the Chinese study was unclear, as it was not explained how 75 workers were selected out of the 957 interviewed workers. Also, it was not explained why 21 out of 60 workers from a pilot study were selected to participate in the full study, but not the other workers. Overall, it is acknowledged that no effects were found, but it is considered that the power of the studies could have been higher and that there are questions regarding the selection of participants (Scialli *et al*., 2010).

The Turkish studies (Duydu *et al.*, 2011, 2012; Başaran *et al.*, 2012) were initially set up based on the assumption that different occupational categories would give groups with quantitatively different exposure to B. However, high B concentrations in drinking water resulted in high exposure also in the controls (without occupational exposure), and a very poor correlation between occupational air exposure and blood concentrations of B was observed. Therefore, participants were grouped according to blood concentrations of B rather than based on occupational exposure. It is not clear how well these new groups were matched. Also, the participation rate was very low (about 24%). The estimated average daily B exposure for the high exposure group was 14.45 mg B/day, which can be calculated into an external daily dose of 0.2 mg B/kg bw/day based on an assumed body weight of 70 kg. No adverse effects of B exposure on sperm analysis parameters were found, but the group size (n=39 in the high exposure group) was limited, leading to low statistical power. The B exposure level was still approximately two orders of magnitude lower compared to the rat NOAEL for reproductive and developmental effects; moreover the difference in exposure level between the groups was relatively low.

No epidemiological studies on possible adverse pregnancy outcomes in female workers are available.

In addition to the non-occupational exposure data presented in the Boric Acid CLH Report (Page 110), the highest non-occupational exposures were found in communities from Northern Chile in which the estimated intake of boron was 21 to 27 mg B/day, which correlated to naturally high B concentrations in local rivers (Barr *et al*. 1993). In a recent study of populations in Chile, exposure levels of B in drinking water and urine was measured from volunteers in Arica, an area in the North of Chile with high levels of naturally occurring B (Cortes *et al*. 2011). The concentration of boron in urine varied between 0.45 and 17.4 mg/l, with a median of 4.28 mg/l and was found to be correlated with tap water sampled from the homes of the volunteers (r=0.64). Espinoza-Navaro *et al*. (2010) analysed sperm for total sperm count, sperm concentration, volume, vitality, pH, morphology, overall motility and grade A for motility in a sample of 102 healthy young males aged 18 to 30 years residing in Arica, Chile. The volunteers also completed a questionnaire about fertility, habits and andrologic diseases. Males sampled in Arica had normal sperm values in comparison with international reports (Espinoza-Navarro *et al*. 2010). No analysis was apparently performed on potential developmental effects of high environmental B exposure.

The overall negative epidemiological studies on male fertility effects of B should be considered as additional information, due to several limitations in design as pointed out by Scialli *et al*. (2010). The available human studies show no clear evidence of adverse effects on male fertility at these exposure levels, which is quite different than showing no evidence for such effects. In contrast experimental studies in animals showed clear and significant reproductive toxicity in four different species. For effects on fertility, the lowest effect level (LOAEL) was 27 mg B/kg/day in mice (Fail *et al.*, 1991, 1998), and for developmental toxicity 13.3 mg B/kg/day in rats (Price *et al.,* 1994, 1996). The highest occupational exposure levels in the two occupational cohorts and in the environmental exposed cohort were, thus, 15-135 times lower than the animal LOAEL for fertility effects and 7-66 times lower than the animal LOAEL for developmental toxicity. Assuming a similar sensitivity of humans as in the four laboratory species studied, it would have been unlikely to observe any adverse effects on human male fertility at those exposure levels. Also, effects on female fertility and prenatal development were not investigated in the epidemiological studies, which anyway had human exposure levels far below the animal LOAELs for these effects. In line with CLP, Annex 1, Section 1.1.1.4, RAC concluded that human data showing no clear evidence do not contradict the animal data.

Several studies on zinc borate were announced and/or submitted by EBA during or after public consultation on boric acid. Non-confidential executive summaries were submitted by EBA for Hofman-Huther, 2013; Durand, 2013; Kirkpatrick, 2013a; Kirkpatrick, 2013b; Edwards, 2013 and Edwards, 2014). It is stated by EBA (European Borate Association; see RCOM) that zinc interacts with boric acid in the body, reducing the toxicity of boric acid. A reason for this assumption is that zinc borate is less toxic than other borates in experimental studies. EBA further proposed that higher zinc stores in humans than in the experimental animals will provide some protection in humans against the toxic effects of boron, and that this species difference raises doubt about the human relevance of the reproductive toxicity seen in animals.

The RAC acknowledged that zinc borate *in vivo* in rats appears to have a higher LOAEL than other borates, but did not find the argumentation for the protective nature of zinc convincing. Firstly, there is no proposed mechanism for this zinc/borate interaction. Secondly, the unpublished *in vitro* study by Durand (2013), referred to in the RCOM and submitted after public consultation as evidence for a protective effect of zinc, suffers from not showing any negative effects of boric acid that zinc can protect against. Thirdly, if tissue levels of zinc affect the toxicity of borates, it is difficult to explain rather similar LOAELs in the experimental animals (in the range of 13-79 mg B/kg/day in mice, rats, rabbits and dogs) despite e.g. perhaps 40-fold higher zinc concentrations in dog liver than in mouse liver (see RCOM). It is also noted that the lethal dose of boric acid is much lower in humans than in rats, so apparently humans are more sensitive than rats to acute exposure despite the alleged protection from zinc in humans. A specific protective action

of zinc against reproductive/developmental effects might not be ruled out, but the evidence is still limited. It is possible that zinc quantitatively affects the toxicity of borates at some conditions, as well as boron might impair the physiological functions of zinc, an essential trace element involved in fertility and development in both animals and humans. These statements bring about a certain scientific interest but there is at present not sufficient evidence to generally support them; most importantly, there is no reason to challenge the relevance for humans of the toxicity of borates observed in experimental animals.

EBA stated that the mechanism of action (MoA) for developmental toxicity of borates involves histone deacetylase inhibition (HDACi) and affected expression of the Hox genes, and that these effects are high dose phenomena in animals making the likelihood of similar effects in humans low. The evidence comes from studies with single exposure of pregnant mice to 1000 mg/kg boric acid on gestation day 8, causing a high incidence of malformations and showing evidence of inhibition of histone deacetylase and a shifted expression of Hoxc6 and Hoxa6. The RAC noted that this MoA might be plausible, but there is no proof that the altered histone deacetylase is only a high dose effect. On the other hand, if these effects only occur at high exposure levels, they may not represent the most sensitive and relevant MoA for the developmental toxicity of borates. Lower exposure levels were not tested so it is unclear to what extent these effects are relevant MoAs for the borates. Even if these effects are indeed the relevant MoA, it is not clear why they would not be relevant for humans. Finally, it is noted that this MoA is proposed for developmental toxicity, but not for adverse effects on fertility.

The EBA also highlighted that B is likely to be an essential mineral in mammals, and that homeostatic control of B concentrations in the cells will decrease the risk of toxic effects. The RAC noted that in its opinion on the upper tolerable intake level of B, the European Food Safety Authority concluded that, although it may have a beneficial effect on bone calcification and maintenance, B has not been established to be an essential nutrient for humans and no specific biochemical function has been identified in higher animals or man (EFSA, 2004). Therefore, the statement on the essentiality of B appears unsupported. In the unlikely situation that essentiality at very low intake levels will be demonstrated, the RAC further notes that B is still toxic to reproduction and development in experimental animals above certain exposure levels, and cannot see how the essentiality will affect the inherent toxicological properties of B.

It is stated in the EBA comments that the studied workers (in B mining and processing industries) represent the maximum possible human exposure, and that the data show that it is improbable that borates will cause effects on fertility or development in humans. The RAC had no possibility to assess the exposure potential for the different B substances in different uses, but noted that the classification criteria do not consider exposure assessments. Rather, it is the inherent toxicological properties of the substances that lead to classification. Finally, the available epidemiological investigations dealt with male fertility only, with several methodological limitations; they did not cover developmental effects at all.

Based on the total weight of evidence, toxicity data from four different species (mice, rats, rabbits and dogs) provide clear evidence of an adverse effect on sexual function, fertility, and development in the absence of other toxic effects. No evidence of reproductive toxicity was observed in the epidemiological studies but they were designed to cover only male fertility effects and had methodological limitations. Therefore, the epidemiological studies do not lead to doubt as to the relevance of the animal toxicity data to humans at similar dose levels as causing toxicity in experimental animals. In line with CLP, Annex 1, Section 1.1.1.4, it was concluded overall that the negative human data do not contradict the animal data. Therefore, there is no evidence that the effects observed in animals are not relevant to humans.

The SCL for boric acid was not addressed in detail by the RAC as it was not proposed by the DS. However, the RAC noted that the current SCL of 5.5% (w/w) in Annex VI to CLP

for reproductive toxicity is calculated based on the German method (BAuA, 1998) and not according to the new guidance for the setting of specific concentration limits proposed by an EU expert group (version 4.0 - November 2013). The SCLs for boric acid and other borates were derived from the overall NOAEL for embryotoxic/teratogenic effects of 9.6 mg B/kg bw/day, based on a reduction in mean fetal body weight/litter and an increased incidence in short rib XIII at 76 mg/kg bw/day (13.3 mg B/kg bw/day) (Price at al., 1996).

The fetal incidence of short rib XIII malformation was 1.2 and 1.5% at the LOAEL (13.3 mg B/kg bw/day) and the highest dose tested (25 mg B/kg bw/day) respectively (Price et al., 1996). As the incidences are low, it is not possible to derive an ED_{10}. In this instance the LOAEL should be used for setting the SCL, according to the guidance. Correcting for the percentage of boron (w/w), the LOAEL of 13.3 mg B/kg bw/day corresponds to a LOAEL of 76.1 mg/kg bw/day (17.48% B in boric acid). Boric acid thus belongs to the medium potency group (4 mg/kg bw/day < ED_{10} (LOAEL) < 400 mg/kg bw/day). None of the modifying factors apply. As borates are classified in category 1B, an SCL of 0.3% applies. This SCL is therefore equivalent to the generic concentration limits (GCL) for reproductive toxicants classified in category 1B (see Table 3.7.2 of CLP). For the sake of maintaining consistency for the SCLs listed for other borates in Annex VI to CLP, the revised SCL is not part of this opinion. RAC noted that the preparation of a CLH dossier proposing the update of the SCLs using the new method for all boron compounds with a harmonised classification would ensure consistency in the future.

Conclusion

In conclusion, based on the adverse developmental and fertility effects of boric acid in different species, RAC does not support the proposal from the DS to revise the current harmonised classification of boric acid (index number 005-007-00-2 in Annex VI to the CLP Regulation (EC) No 1272/2008). Boric acid should be classified with Repr. 1B, H360FD 'May damage fertility. May damagethe unborn child.' according to Regulation (EC) No 1272/2008. The RAC has reassessed the current SCL according to the new Guidance on the application of the CLP criteria (version 4.0 – November 2013) but the current RAC opinion does not include a proposal to change the SCL as this was not proposed for discussion by the DS. Thus, for the sake of maintaining consistency for the SCLs listed for other borates in Annex VI to CLP, the revised SCL is not part of this opinion. It is nevertheless noted by RAC that it would result in a value of 0.3%, thus identical to the GCL according to the new Guidance.

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4.12 Other effects

Not evaluated in this dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated in this dossier.

6 OTHER INFORMATION

A joint REACH registration dossier was available for boric acid when this CLH proposal was prepared. ECHA's dissemination website suggests two joint registration dossiers are available, but this is misleading and is a function of how information is extracted from dossiers for dissemination. The information from the joint REACH registration dossier was considered during preparation of the CLH proposal for boric acid.

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