Technical Report

No 63

Reproductive and General Toxicology of some Inorganic Borates and Risk Assessment for Human Beings

February 1995

ISSN-0773-8072-63

Technical Report No. 63

Reproductive and General Toxicology of some Inorganic Borates and Risks Assessment for Human Beings

February 1995

ISSN-0773-8072-63

Brussels, February 1995

ECETOC Technical Report No. 63

TOXICOLOGY OF INORGANIC BORATES

CONTENTS

SUMMARY AND CONCLUSIONS

A review of the toxicology of some inorganic borates is provided together with a risk assessment for man. The toxicology data base is largest for boric acid (H_3BO_3) and borax ($Na_2B_4O_7.10H_2O$). Limited data are available for sodium perborate (mono and tetrahydrate) and boric oxide and even less is available (acute data only) for borax pentahydrate and anhydrous borax.

The toxicological end-points of concern identified for both boric acid and borax from animal studies were fertility and developmental toxicity. Generally, these effects were observed in more than one species. Data were available on fertility from dog and rat studies on both borax and boric acid. In addition, mouse data were available on boric acid.

For both boric acid and borax, the lowest NOAEL for fertility in male and females rats was determined to be 17 mg boron/kg bw. Effects seen at the LOAEL included testicular toxicity, reduced spermiation in males and decreased ovulation in females. At higher dose levels testicular atrophy was observed. A lower NOAEL was available from a dog study (8.8 mg boron/kg bw) but the data were considered unsuitable for risk assessment purposes. For female mice, the NOAEL for fertility was around 27 mg boron/kg bw. Effects included reduced ovulation and decreased pup weights in the second generation offspring.

For developmental toxicity, only data on boric acid were available from rat, mouse and rabbit studies. The rat was confirmed as the most sensitive species with a NOAEL of 9.6 mg boron/kg bw, based on reduced foetal body weight and skeletal effects observed at the LOAEL.

Taking NOAELs for fertility and developmental toxicity, an uncertainty factor (UF) was applied to derive a tolerable daily intake for a 60 kg human. Justification for an uncertainty factor of 30 is presented, taking into account the nature of the hazard, adequacy of the data base and detailed knowledge of how borates are absorbed, distributed and excreted without liver metabolism. Limited human data were also available for consideration. A tolerable daily intake of borates for a 60 kg person was calculated to be 34 mg boron/day and 19.2 mg boron/day which could be ingested without the risk of fertility (testicular) or developmental effects respectively.

Based on the tolerable daily intake of 19.2 mg boron and taking into consideration the maximum boron intake from diet is 7 mg/d from food, mineral waters and other beverages including wine, up to 12 mg boron could be obtained from other sources including drinking water without exceeding the total daily intake. With a drinking water standard at the current EC Guide Level of 1 mg boron/l, the total boron intake from food and water is well below the calculated total daily intake. Therefore, the current drinking water Guide Level of 1 mg boron/l is considered to be sufficiently conservative and there is no need for it to be reduced even further to 0.3 mg boron/l as recently recommended by WHO (1993).

The overall conclusion is that, at high doses, boric acid and borax cause adverse effects on fertility and developmental toxicity in animals models. Preliminary investigations have been carried out to try to identify the mechanism concerning the testicular effects observed, but very little relevant work has yet been done to establish the cause of developmental toxicity effects. The precise mechanism of action is unclear but it is known that borates are not metabolised, neither do they accumulate in the body except for low deposits in bone. At borate concentrations found in the environment either as a food constituent or when present in fresh waters and in some drinking waters, the risk assessment has demonstrated that exposure is not likely to cause any undue health risk to human beings.

SECTION 1. INTRODUCTION

The element boron (B) is widely distributed in nature in low concentrations. Because of its high affinity for oxygen, boron always occurs in nature bound to oxygen in the form of inorganic borates. Apart from their occurrence in a few commercially exploitable deposits (mainly as sodium or calcium borate minerals), the borates are present everywhere at low concentrations in rocks (< 100 mg B/kg), soils (<10-20 mg B/kg), fresh waters (< 1 mg B/l) and sea water (5 mg B/l).

Throughout this review the term "borate" is used as an abbreviation for the boron-oxygen substance under consideration. The term "boron" is used to express data as the equivalent boron (B) content of a borate, and is not intended to mean elemental boron. The term is also used to compare the effect of an equivalent B content of one borate with another when discussing doses applied in animal studies (details for conversion are given in section 2.4). Except for sodium perborate the toxicological effects are likely to result from the ultimate chemical species in aqueous solution, namely undissociated boric acid (see section 2.1).

Borates are in extensive commercial use. The nature of the product or end use will determine the extent of exposure to consumers and the environment. In some of the larger applications such as glass wool (insulation), enamels, ceramics and borosilicate glass, the borate becomes fixed into a water-insoluble matrix with little or no environmental impact. Applications where slow leaching into the environment will occur include adhesives, flame retardants and timber preservatives. The borates enter the aqueous environment most readily when used or discharged directly in the form of water-soluble inorganic borates. These include perborate-containing detergents, boronated fertilisers, additives to corrosion inhibitors in anti-freeze formulations, biocides for cutting fluids, insecticides and as buffers/preservatives for cosmetic and pharmaceutical preparations.

This last mentioned application has been used for more than 100 years, until superseded by other products considered medically more effective. During this period there have been occasionally problems associated with the misuse of borates, resulting in poisoning in adults, children and babies. Currently boric acid is permitted in a range of cosmetic products in the European Union (EU) at the following levels; talcum powder (5%), oral hygiene products (0.5%) and other products (3%).

Borates are taken up naturally in all life forms and are found especially in fruit, vegetables, nuts and wine. Although borates are essential plant micronutrients, their essentiality for animals is not proven, but it does appear that borates may be nutritionally important for animals and man. During the past 5 years, largely through US Department of Agriculture dietary studies on animals and human beings, there has been renewed interest in the nutritional importance of boron. For example, it is suggested (Nielsen, 1992) that inadequate dietary boron (≤ 0.2 mg B/d) may be one factor that contributes to susceptibility to bone loss or osteoporosis. Further work is still required to establish whether there is an essential requirement for boron in man.

The concentration of borates in fresh waters is under scrutiny because of the widespread use of perborates in laundry detergents, since borate is not removed during the sewage treatment process. The EC is currently revising its guideline values of drinking water, which for boron is at present set at 1 mg B/l. The WHO (1993) has recently published a new guideline value for boron in drinking water of 0.3 mg B/l, following a risk assessment based on a 1972 study investigating the reproductive effects of borates in dogs (Weir and Fisher, 1972). In the light of more recent data, this guideline will be subject to further review and WHO have indicated that boron will be given top priority for re-evaluation at the first opportunity.

The objective of this Task Force is to present a comprehensive review of the toxicology of inorganic borates and to focus mainly on the reproductive toxicity of borates including recently published data. Because similar effects have not been observed in man, extrapolation of animal data will be required and a risk assessment will be presented based on estimated human exposures to borates from a variety of sources. Finally, a suitable safe level of borate in drinking water will be recommended. A companion ECETOC document will consider the ecotoxicological properties of the borates to provide similar guideline values for environmental parameters.

SECTION 2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, PRODUCTION AND USES

2.1 IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES

Borax, the principal naturally occurring commercial source of the element boron, with the formula $Na_2B_4O_7.10H_2O$, can be considered as the basis of inorganic borates. Borates are odourless white crystalline granules or powders. Identity and physical/chemical properties of the seven major inorganic borates discussed in this report are summarised in Table 1.

Of particular interest in a toxicology review is an understanding of what species of chemical interacts with biological tissue and the consequences of any such interaction. Because boric acid is stable and a very weak acid (pKa 9.15), the undissociated acid (H_3BO_3) is the predominant species in aqueous solution at physiological pH. This applies also to boric oxide and sodium borates. As a consequence, the toxicology of all these substances is likely to be similar on an equivalent boric acid basis (as boron). Furthermore, it is known that boric acid can form complexes with carbohydrates and proteins (Kliegel, 1980). For the series of boron-containing compounds identified in Table 1 (except sodium perborate), it is assumed that the final species in question will either be the undissociated boric acid or a complex of boric acid with a carbohydrate or protein.

Different considerations of toxicology apply to sodium perborate, a peroxygen compound, that readily generates hydrogen peroxide in addition to sodium borate in biological systems. Thus, sodium perborate will provide a local environment with a pH of around 10, which may be partially responsible for some of the acute inflammatory and tissue reactions described in this review.

2.2 PRODUCTION

Limited published data are available on production statistics of the inorganic borates, as follows:

- the estimated total world production of boron minerals and compounds in 1991 was almost 3 million tonnes (Lyday, 1992);
- the world's annual capacity (expressed in tonnes per annum B_2O_3) to make the major boron chemicals in 1989 (CEH, 1993) was

  USA, 750,000 of sodium borates and 195,000 of boric acid,

  Western Europe, 30,000 of sodium borate, 56,000 of boric acid.

Table 1 Identity, Physical and Chemical Properties

Physical/Chemical Properties	Boric Acid[a]	Borax[a]	Borax Pentahydrate[a]	Anhydrous Borax[a]	Boric Oxide[a]	Sodium Perborate Tetrahydrate[b]	Sodium Perborate Monohydrate[c]
Chemical Formula	H_3BO_3	$Na_2B_4O_7.10H_2O$	$Na_2B_4O_7.5H_2O$	$Na_2B_4O_7$	B_2O_3	$NaBO_3.4H_2O$	$NaBO_3.H_2O$
Chemical Name	Orthoboric acid	Disodium tetraborate decahydrate	Disodium tetraborate pentahydrate	Disodium tetraborate	Diboron trioxide	Sodium perborate tetrahydrate	Sodium perborate monohydrate
Synonyms	Boracic acid	Borax decahydrate, Borax 10 Mol	Borax 5 Mol, Sodium tetraborate pentahydrate	Sodium tetraborate, Borax Glass	Boron trioxide, Anhydrous boric acid	PBS4, PBST	PBS1, PBSM
CAS Reg. No.	10043-35-3	1303-96-4	12179-04-3	1330-43-4	1303-86-2	10486-00-7	10332-33-9
EINECS No.	233-139-2	215-540-4	215-540-4	215-540-4	215-125-8	234-390-0	234-390-0
Physical Form	White crystalline granules or powder	White crystalline granules or powder	White crystalline granules or powder	White vitreous granules	White vitreous granules	White crystalline powder	White crystalline powder
Molecular Weight	61.83	381.37	291.35	201.27	69.62	153.9	99.8
Specific Gravity (20°C)	1.51	1.73	1.81	2.37	1.83		
Bulk Density (kg m^{-3})	880	935	1,000-1,150	1,075-1,380	975-1,090	700-900	500-650
Melting Point Closed Space (°C) Anhydrous Form (°C)	 171 450 (crystal)	 > 62 742 (crystal)	 < 200 742 (crystal)	 742 (crystal)	 450 (crystal)	 Decomp.	 Decomp.
Boron Content (%)	17.48	11.34	14.85	21.49	31.06	7.03	10.8
Available Oxygen (%wt)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	10.0	15
Water Solubility (%w/w)	4.72 (20°C) 27.53 (100°C)	4.71 (20°C) 65.63 (100°C)	3.6 (20°C) - 50.15 (100°C)	2.48 (20°C) - 34.5 (100°C)	Rapidly hydrates to boric acid	23 g/l (20°C) - 37 g/l (30°C)	15g/l (20°C) - 24g/l (30°C)
pH of Aqueous Solution (20°C)	6.1 at 0.1% 3.7 at 4.7%	9.24 (constant)	9.24 (constant)	9.24 (constant)	Rapidly hydrates to boric acid	10 at 1.5%	10 at 1.5%
pK_a (pK_1) (20°C)	9.15[d]						
Pow (25°C)	0.175[e]	Not applicable (dissociates)	Not applicable (dissociates)	Not applicable (dissociates)	Not applicable (Rapidly hydrates to boric acid)	Not applicable (decomposition)	Not applicable (decomposition)

References

a Borax Consolidated (1992)
b Interox Chemicals (1982a)
c Interox Chemicals (1982b)
d Dawber and Matusin (1982)
e Barrès (1967)

The European consumption of sodium perborate tetrahydrate in 1993 was 620,000 tonnes (CEFIC, 1994).

2.3 USES

Borates are in widespread use in industrial, agricultural and consumer products. The specific end uses of each substance are outlined below.

2.3.1 Boric Acid

Boric acid is an important source of soda-free boric oxide (B_2O_3) in vitreous systems such as glass, enamels and ceramic glazes. It is a flame retardant with effective anti-smoulder characteristics. The high-purity form is used in the production of capacitors, and for the control and emergency shutdown of nuclear reactors (absorption of neutrons by ^{10}B isotope). Boric acid is also used as a preservative in some cosmetic and pharmaceutical preparations. In admixture with borax it is a useful buffer in eye lotions.

2.3.2 Borax

Borax is generally the sodium borate selected for applications in aqueous solutions, e.g., anti-corrosion additive in vehicle cooling systems or in cutting fluids. Borax is also used for cosmetic/pharmaceutical applications.

2.3.3 Borax Pentahydrate

Borax pentahydrate is the major borate raw material for the glass, ceramics and enamel industries. It is used as the feedstock for the production of sodium perborate bleach.

2.3.4 Anhydrous Borax

Anhydrous borax is borax from which the water of crystallisation has been removed by fusion. The resultant molten glass is cooled and crushed to form a granular product, but the glassy nature of the particles can still be discerned. The finished product has a higher bulk density than either borax or borax pentahydrate and is preferred to these materials in the glass, ceramic and enamel industries if furnace capacity and/or storage capacity is at a premium.

2.3.5 Boric Oxide

Boric oxide is prepared by the dehydration of boric acid. As in the case of anhydrous borax, the water is removed by fusion and the glassy product is crushed to form a coarse granular or a powder product. The glassy nature of the material can be discerned in the coarse form.

Boric oxide is used in the manufacture of ferroboron and other master alloys. It is used for heat treatment in the metallurgical industries.

Boric oxide is hygroscopic, absorbing moisture from the atmosphere to form boric acid.

2.3.6 Sodium Perborate Tetrahydrate

Sodium perborate tetrahydrate is used primarily as a bleaching agent in detergent powders and in bleaching powders. It is used to a smaller extent as a mild disinfectant and deodorant in cosmetic and pharmaceutical preparations (Martindale, 1977).

2.3.7 Sodium Perborate Monohydrate

Sodium perborate monohydrate is used primarily as a bleaching agent in detergent powders.

2.4 CONVERSION FACTORS TO BORON EQUIVALENT

Studies reported in the literature have been conducted with different boron compounds. The boron content of each compound is determined by its chemical composition. Conversion factors have to be applied in order to compare the real doses of boron. Therefore the equivalent of boron (B) to the doses used in the studies are given throughout this report. The calculations were based on following data:

1 part boric acid, H_3BO_3, contains 0.175 parts of boron, B.
1 part borax, $Na_2B_4O_7.10H_2O$, contains 0.113 parts of boron, B.
1 part sodium perborate tetrahydrate, $NaBO_3.4H_2O$, contains 0.070 parts of boron, B.
1 part sodium perborate monohydrate, $NaBO_3.H_2O$, contains 0.108 parts of boron, B.

2.5 ANALYTICAL METHODS

A variety of techniques is available for the analysis of borates, as boron, including absorption and emission spectrophometry and both atomic and mass spectrometry. Before carrying out the appropriate analytical procedure on biological materials, it is generally necessary to prepare the sample by extracting the borate from unwanted components, that may interfere with the colorimetric or other instrumental methods of analysis. A detailed review of these methods is available in the companion ECETOC report on the ecotoxicity of borates (ECETOC, 1995).

The British Standards Institution (1979) has published a Standard in 29 parts (BSI, 1979) for the analysis of the commercial inorganic borates and perborates, which is also recognised by the International Organisation for Standardisation.

SECTION 3. TOXICOKINETICS IN ANIMALS AND MAN

This section reviews the relevant data on absorption, distribution, metabolism and excretion of borate. Although absorption describes the processes involved in the transfer of a substance from the site of administration to the systemic blood circulation, it is possible, particularly for substances administered by the oral route, to use urinary levels of the substance as an indicator of absorption. This may be helpful in the absence of specific blood/plasma values.

A representative set of blood and urine concentrations in animals are summarised in Tables 2 and 3. Normal blood boron concentrations in man are generally within a fairly narrow range and these concentrations are usually lower than those seen in untreated animals. Urinary boron output reflected boron intakes. In view of the large amount of available data, not all the studies referred to in the Tables will be discussed in the text. Salient features of the toxicology will be discussed by reference to appropriate studies.

3.1 ABSORPTION

3.1.1 Animal Studies

3.1.1.1 Oral

Ingested borate is readily absorbed by various species. For example, eighteen 45kg sheep were fed supplemental boron as sodium borate to provide total doses, equivalent to 1.7 or 4.4 mg B/kg bw/d for 11 days during which time faecal boron and urinary boron estimations were made. Total daily boron intakes including diet were 30mg for the control group and 75 or 200mg for the supplement group. Urinary boron excretion was proportional to exposure and accounted for 72 and 85% respectively of the total boron excreted (faecal and urine) over the observation period in the supplement groups (Brown *et al*, 1989).

Owen (1944) measured absorption in two cows receiving 18-23 g/d of borax in their feed, equivalent to 5.6-7.3 mg B/kg bw/d, for 42 days. Boron was excreted in urine, faeces and milk with no adverse findings reported. Weeth *et al* (1981) conducted similar studies for 10 days and confirmed these findings on heifers receiving water containing borax at 15, 30, 60 or 120mg B/l, equivalent to 2.8, 4.6, 7.7 and 13.8 mg B/kg bw/d. In this study boron plasma levels were also measured, and these were shown to increase with exposure in a curvilinear fashion, as were urinary boron levels.

Table 2 Concentration as Boron in Blood

Species	Route	Dose	Blood*	References
Human being	Inhalation	untreated	0.04 - 0.40 µg B/g	Imbus *et al*, 1963
	Inhalation (Preceeding 10 d) Pre-shift Post-shift	untreated untreated 0.38 mg B/kg bw/d (5d)	0.02 µg B/g 0.072 µg B/g 0.239 µg B/g	Culver *et al*, 1994a
	Oral	control 1.41 mg B/kg bw/d (14 d)	1.4 µg B/ml 2.9 µg B/ml	Job, 1973
	Dermal	control 0.9 mg B/kg bw (single dose)	0.06 µg B/ml 0.19 µg B/ml	Stüttgen *et al*, 1982
	i.v.	control 1.50 mg B/kg bw (single dose)	0.04 µg B/ml (plasma) 0.4 µg B/ml (steady state, plasma) 3.5 µg B/ml (peak, plasma)	Jansen *et al*, 1984b
	Diet	untreated	0.0 - 0.35 µg B/ml (serum)	Linden *et al*, 1986
	Diet	untreated untreated	0.097 µg B/g 0.022 µg B/g	Clarke *et al*, 1987a Clarke *et al*, 1987b
	Diet	untreated	0.022-0.66 µg B/g	Barr *et al*, 1993
	Diet	untreated	0.031 µg B/g	Woittiez and Iyengar, 1988
	Diet	untreated	0.14 - 0.74 µg B/ml	Ward, 1987
	Diet	untreated	0.057 µg B/ml	Abou-Shakra *et al*, 1989
Dog	Oral	control 8.8 mg B/kg bw/d (2 y)	2.1 µg B/ml 4.8 µg B/ml	Weir and Fisher, 1972
Rat	Oral	control 94 mg B/kg bw/d (7 d)	1.94 µg B/g (plasma) 16 µg B/g (plasma)	Ku *et al*, 1991
	Oral	control 61 mg B/kg bw/d (28 d)	0.16 µg B/g (plasma) 11.7 µg B/g (plasma)	Treinen and Chapin, 1991
	Oral	control 68 mg B/kg bw/d (7 d)	< 4 µg B/ml 17.3 µg B/ml	Ku *et al*, 1993a

* Whole blood unless stated otherwise