EUROPEAN BORATES ASSOCIATION

COMMENTS ON ANNEX XV DOSSIERS

GENERAL COMMENTS

European Borates Association (EBA) members are deeply concerned over the proposal to identify disodium tetraborates and boric acid as candidates for authorisation. We do not believe that adding these substances to the candidate list is appropriate. Central to our position is the notion that disodium tetraborates and boric acid are relatively benign substances whose classification as reproductive toxicants was (and continues to be) controversial and contested. This is a point that should be taken into account at this point of the process as it appears from ECHA's consultation notice that this consultation specifically focuses on hazard properties.
With a view to safeguarding public health, the environment and good governance, it is EBA's view that of all substances meeting the Art 57 criteria, boric acid and disodium tetraborates are of lower concern. The system for putting substances on the candidate list should be subject to a more critical qualitative selection procedure than the approach that is currently used.

The dossiers contain many factual errors, are incomplete and confusing in many sections and lack consistency throughout. EBA feels strongly that these deficiencies should be addressed and corrected before they are presented for consideration by the Member States Committee and later on by ECHA.

The EBA has elaborated the below list of arguments to support the position that disodium tetraborates and boric acid should not be added to the candidate list for potential future authorisation:

1. Boron is one of seven micronutrients essential to plant nutrition and so healthy diets associated with fruits and vegetables will contain relatively high levels of boron.

2. Borates have been used safely for generations and people's greatest exposure to borates is through a healthy diet. Recent research has demonstrated several benefits associated with boron exposure in humans including bone health, cell membrane function, psychomotor skills and cognitive processes, control of inflammatory disease, enzyme regulation, energy metabolism, and potential anticarcinogenic properties. A more detailed discussion of this research is presented in the comments on the Annex (hazard section).

3. Boric acid and disodium tetraborates are relatively benign, which is a fact that was recognised when the Member States experts decided on a high concentration limit and high safety threshold as part of the decision to classify these substances. EFSA (2004) was asked by the European Parliament to provide an opinion on boron in its review of vitamins and minerals under Article 4 of the Food Supplements Directive (2002/46/EC). EFSA stated that boron might have a beneficial effect on bone calcification and maintenance and derived a tolerable upper intake level (UL) of 10 mg boron/day for adults. Based on this opinion, boron was added to Annex I (and boric acid and sodium borate were added to Annex II) in November 2009. This followed consideration of the reproductive toxicology of boric acid and the publication in September 2009 of the 1st ATP of the CLP regulation classifying these substances as 1B reproductive toxicants. The approval by EFSA of boron as a food supplement, even after publication of the 1st ATP of the CLP regulation, provides further support that including boric acid and disodium tetraborates on the candidate list is not warranted.

4. The classification decision itself was the result of a controversial, extremely lengthy and unsatisfactory decision-making process. It was a decision that was opposed by seven EU Member States (Poland, UK, Italy, Ireland, Belgium, Slovenia, Latvia), which specifically and uniquely signed a declaration that stated that they were in favour of a less rigorous classification category for boric acid and disodium tetraborates. In fact a majority of Member States experts had recommended earlier (in the context of the 29th ATP to the Dangerous Substances Directive) that boric acid and disodium tetraborates should be classified as a Category 3 under the previous Directive (note: when Member States eventually voted for a Category 2, this was done on the basis of the same evidence and arguments). Numerous European user industries have written to the European Commission to argue that borates have been used for centuries and have never raised safety issues for its workers. At different times in the process, European Commission officials and departments themselves were divided on the appropriate level of classification for borates. And finally, as part of the WTO TBT process, several non-EU countries (including Turkey, Argentina, Chile, Canada, the U.S., China and Malaysia) expressed concern over the Category 2 classification of boric acid and disodium tetraborates and some stated that this was more trade disruptive than necessary.

5. The main source of disagreement over the appropriate level of classification of boric acid and disodium tetraborates is related to the way effects found in animal studies were extrapolated to humans. Industry acknowledges that there is a reproductive effect from borates in animals that have been force-fed large quantities of boric acid or disodium tetraborates on a daily basis for a long period of time. However, industry has always argued that the Member States and the European Commission have not demonstrated that the classified borate substances have intrinsic properties which give rise to a risk of reproductive toxicity in humans during normal handling and use, as required by law (Annex VI of the Dangerous Substances Directive).

6. Moreover, multiple existing studies on humans have found no reproductive effects. Recital (2) of the 30th ATP which added certain borates to the Dangerous Substances Directive as a Category 2 toxicant and which was inserted by the European Commission, states that "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.". This study among workers in a borates mine has now been completed and peer-reviewed and confirms that there is no reproductive effect in men, which indicates even at very high exposures the effect in humans is different than the effect on laboratory animals. In the light of this Recital and since the Chinese study has not yet been evaluated by ECHA or Member States experts, adding boric acid and disodium tetraborates to the candidate list now simply does not make sense.

7. The Commission's decision to classify certain borates (including boric acid or disodium tetraborates) is subject to two court cases that are currently before the European Court of Justice and the General Court. An annulment of classification would remove the basis for the inclusion of borates under REACH authorisation as well as the legal basis for including them in the authorisation process. In the light of this uncertainty, it is not appropriate to include boric acid or disodium tetraborates on the candidate list.

8. Including disodium tetraborates and boric acid at this point does not make sense as producers and importers are developing a REACH registration dossier, which will be submitted by the December 2010 deadline. The current Annex XV dossiers are based on fragmented and incomplete information largely based on modelling data from the transition dossiers of both substances. The transition dossiers concluded however that "*There is a need for better information on occupational exposure for producing/importing processing sites, downstream user and consumer applications to adequately characterize the risks to*

workers and consumers from boron exposure via boric acid and sodium tetraborates". Industry is following-up on these recommendations. The REACH registration dossiers will contain the necessary information to identify whether there are risks for workers and consumers requiring further measures.

9. Boric acid and disodium tetraborates are already subject to strict regulation under a range of downstream EU legislation, intended to protect workers and consumers which is another argument against adding disodium tetraborates and boric acid to the candidate list for authorisation. This legislation includes:

    1. Eco-Label Award Scheme Regulation (1980/2000/EC)
    2. Directive on the safety of toys (2009/48/EC)
    3. Regulation on Cosmetic Products (RECAST) (1223/2009)
    4. Food Supplements Directive;
    5. Medicinal Products Directive
    6. Waste Framework Directive (2006/12/EC)
    7. Detergents Regulation (648/2004/EC)
    8. Regulation on the export and import of dangerous chemicals (689/2008)
    9. Biocidal Products Directive (98/8/EC)
    10. Water Framework Directive (2000/60/EC)
    11. Directive on integrated pollution prevention and control (2008/1/EC)
    12. ADR and RID Framework Directive (Transport of Dangerous Goods) (2000/61/EC)
    13. Chemical Agents Directive (2007/30/EC)
    14. Pregnant and Breastfeeding Workers Directive (92/85/EEC)
    15. Young Workers Directive (94/33/EC)
    16. Signs at Work Directive (92/58/EEC)
    17. Personal Work Equipment Directive (2007/30/EC)

10. Similarly, consumer protection from exposure to boric acid and disodium tetraborates will be addressed through Annex XVII-restrictions of CMR substances for consumer use. At the direction of the Commission RPA (2008) reviewed the uses and risks associated with borates for consumers not currently regulated by some of the legislation noted above, and concluded that risks associated with these other uses are unlikely to be of serious concern.

11. Adding disodium tetraborates and boric acid to the candidate list would have immediate negative consequences without generating public health benefits. Producers of these substances would have the obligation to communicate this listing to customers and (if requested) consumers and this involves an increase in cost and may have economic consequences, particularly with respect to the viability of any possible future applications. It is our understanding that ECHA, the Commission and the EU Member States are considering a more elaborate and balanced system for prioritising substances on the candidate list for authorisation. It is the view of the EBA that the system for putting substances on the candidate list should also be subject to a more qualitative selection procedure than the approach that is currently used.

Specific comments on the - "Proposal for Identification of a Substance as a CMR Cat 1 or 2, vPvB or a Substance of an Equivalent Level of Concern - Disodium tetraborate, anhydrous," submitted by Denmark, February 2010.

Specific comments on the justification:

2. Harmonised Classification and Labelling (p. 14)

It should be noted that
Recital (2) of the Commission directive 2008/58/EC (30th ATP) which added certain borates including disodium tetraborates to the Dangerous Substances Directive as a Category 2 toxicant, states that "*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*.".

This study among workers in a borates mine has now been completed and peer-reviewed and confirms that there is no reproductive effect in men, which indicates even at very high exposures the effect in humans is different than the effect on laboratory animals.

Specific comments on use, exposure, alternatives and risks - Disodium tetraborates

General comments

This section contains numerous inaccuracies and confusing data and tables, such as:

- The names of the substances have been mixed up in several places;
- It is unclear in several sections which tonnages are being referred to;
- The actual tonnages of disodium tetraborates in Europe have been over-estimated;
- References to older data including draft versions of tables listing the different uses of disodium tertraborates;
- The dossier contains uncertain exposure estimates which will be replaced by actual monitoring data in the registration dossiers.
- The use of disodium tetraborates in consumer uses will be restricted through Annex XVII, it does not seem relevant to include the consumer exposure estimates in this dossier.

Specific instances of such inaccuracies are listed below.

1.1 Manufacturing sites (p. 17, 1st paragraph)

While the scope of the Annex XV dossier is disodium tetraborates, the first paragraph refers to borates and boric acid production. This is confusing and not relevant for this dossier. Only the first sentence of this section is correct and should be retained.

1.2 Manufacturing volumes (p. 17-18)

1st para: According the original reference (USGS, 2008), "boron" should be replaced by "boron minerals and compounds".
The scope of this section should be limited to manufacturing volumes for <u>disodium tetraborates</u> because using general numbers leads to a significant over-estimation of the actual tonnages of disodium tetraborates.

1.3 Import and export volumes (p18)

EBA believes that the scope of this section should be limited to import and export volumes for disodium tetraborates as they are only a certain percentage of the numbers presented (Table 1 covers a range of borates different than disodium tetraborates). This should be corrected because using these general numbers, leads to an over-estimation of the actual tonnages of disodium tetraborates.

2.1 Uses
Table 2, 4 and 5 are representing the same kind of information (applications) but were created at different moments. In fact Table 2 is an outdated draft version made for the preparation of the REACH registration dossier. To prevent confusion, the most up to date information on the applications and tonnages of disodium tetraborates should be used, which is the data presented in table 5.

2.1.2 Glass and glass fibres (p. 23, 3rd paragraph)
The 3rd paragraph on p. 23 describes the tonnage used in glass, referring to the RPA study. EBA would like to underline that this data is confusing because it includes tonnage from non-disodium tetraborates, it is not clear how the quantities are expressed (substance, B2O3 or boron) and this is not the most recent data. Therefore, EBA suggests using the most recent data listed in Table 5, where it is also clear how the tonnages are expressed (as actual substance).

2.1.4 Detergents (p. 23, 2nd paragraph)
On page 23, 2nd paragraph, old data are used including not only disodium tetraborates but also boric acid.
EBA suggests focusing on disodium tetraborates and using the most recent data listed in Table 5.

2.1.5 Personal care products (p. 23)
EBA underlines that the use of disodium tetraborates in these products is largely regulated by the EU Cosmetic Products Regulation (1223/2009). Some of the uses are also regulated under the Medicinal Products Directive (RPA 2008).

2.1.9 Flame retardants (p. 24, 2nd paragraph)
On page 24, the 2nd paragraph refers to boric acid and is therefore not relevant for this dossier. This should be included in the Annex XV dossier for boric acid.

2.1.10 Biocides (p. 24)
The use of boric acid and disodium tetraborates as wood preservatives is regulated by the EU Biocidal Products Directive (98/8/EC).

2.1.12 Other uses (p.24, 2nd paragraph)
On page 24th, the 2nd paragraph refers to use of “Borates”. This should be disodium tetraborates specific.

2.2 Estimated trends in uses (p. 25)
EBA notes that this entire section refers to borates in general, which is confusing. “Borates” includes borates other than disodium tetraborates.
Consistency and accuracy is needed in the use of the terminology to identify substances and their tonnage.

2.3 Exposure
2.3.1 Occupational exposure (p. 27)
EBA considers that the occupational exposure predictions were made with the EASE model, which contains highly uncertain values. Actual occupational monitoring data is being collected within the industry, which will be presented in the registration dossier of disodium tetraborates.

2.3.2 Consumer exposure (p. 28-29)
EBA questions the relevancy of including the consumer exposure estimates in this dossier as the use of disodium tetraborates in consumer uses would be restricted by Annex XVII of CMR substances.

Furthermore, while disodium tetraborates are used in the production of consumer products, the substance disodium tetraborate is no longer present in several of the final products (eg glass and glass fibres, ceramics).

2.3.2.1 Glass and glass fibres (p. 28)
The substance disodium tetraborate is an intermediate to manufacture the substance glass. Therefore it is no longer present in the final product glass or glass fibres
The boron present in ceramics and glass-ware is physically/chemically bound into the product, therefore in these cases, the potential for the consumers to be directly exposed to the borates present is minimal (RPA 2008).

2.3.2.5 Flame retardants (p. 29)
In this section, exposure estimates are combined for both boric acid and disodium tetraborates. As boric acid is not within the scope of this dossier, EBA suggests correcting the value for disodium tetraborate decahydrate and to remove the estimates for boric acid and to simply refer to the Annex XV dossier for boric acid.

2.3.2.7 Other uses (p. 29)
This entire section refers to borates in general. Consistency is needed in terminology and this should be made disodium tetraborates specific.

2.3.3 Human exposure via the environment (p. 30)
Maximum exposures are calculated using the maximum value reported in mineral water. This value of 4,35 mgB/L exceeds however the EU drinking water limit of 1 mg B/L.
A realistic worst case scenario should rather assume concentrations equivalent to the drinking water limit. This approach was also followed by Austria (2008).

Table 8 (p. 32)
Regarding food, the typical and RWC reported by Austria (2008) should be added for completeness (as has been done for other sources).

Specific comments on the "Proposal for Identification of a Substance as Substance of Very High Concern (SVHC) – Boric acid," submitted by Germany/Slovenia, February 2010.

Specific comments on the justification:

Summary (p. 3)
EBA notes that on page 3 of the Annex XV dossier on boric acid in the following paragraph:
"Therefore, this classification of the substance in Commission Regulation (EC) No 790/2009 shows that the substance meets the criteria for classification as carcinogen in accordance with Article 57 (c) of REACH."
The term "carcinogen" should be replaced by "reproductive toxicant".

3. Classification and Labelling (p. 7)
It should be noted that
Recital (2) of the Commission directive 2008/58/EC (30th ATP) which added certain borates including boric acid to the Dangerous Substances Directive as a Category 2 toxicant, states that "*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*.".

This study among workers in a borates mine has now been completed and peer-reviewed and confirms that there is no reproductive effect in men, which indicates even at very high exposures the effect in humans is different than the effect on laboratory animals.

Specific comments on use, exposure, alternatives and risks– Boric Acid

Overall, EBA would like to comment that

- The information on tonnage, import and export is missing in this dossier.
- The substance naming is not accurate.
- The use of boric acid in consumer uses will be restricted through Annex XVII, it does not seem relevant to include the consumer exposure estimates in this dossier..
- The exposure estimations that are included in the dossier are incomplete and several of the realistic worst case (RWC) assumptions are not realistic. Examples of this are:
  - The maximum reported value of borates in mineral water is used as the exposure scenario even though the drinking water limit is 4 times lower.
  - The potential exposure from supplements was determined from a 16 year old personal communication from the United States reporting on body builder's use of supplements. The daily intake being proposed would be considered abusive.

1.1.3.3 Toys (p. 13, 1st paragraph)
On page 13, 1st paragraph, no source has been quoted regarding the *concentration of up to 8% in silly put*ty. It would be useful for stakeholders to know where this reference comes from. Furthermore, the RWC scenario assumes accidental swallowing of the entire package (17g), however, assuming that this happens daily is not realistic to serve as a reference point.
According the RIVM factsheet reasonable worst case conditions include an ingestion frequency of 1/week and ingestion of 1g of product each time.
Using these conditions, the weekly ingestion rate is 0,23 mgB/kgBW/week.
Further, use of boric acid in toys is expected to be restricted according to directive 2009/48/EC on the safety of toys, due to its classification as Reprotoxic 1 B by Commission Regulation (EC) No 790/2009.

Last, on page 13, 3rd paragraph, EBA considers that the data should be corrected: the RWC exposure of 0.025 mg boric acid corresponds to 0,0044 mg B/kg BW/day and not 0,036 mg B/kg BW/day as stated.

1.1.3.5 Cellulose Insulation (p. 14)
On page 14, line 6: "…with respirable particle concentrations of 2,75 mg/m3…" should be "…with inhalable particle concentrations of 2,75 mg/m3…" according to the reference (BTU, 2000).
In addition, exposure estimates for disodium tetraborate are included, which is not relevant for this dossier.

1.1.3.6 Glass Wool Insulation (p. 14)
The substance boric acid is an intermediate to manufacture the substance glass. Therefore it is no longer present in the final product.
The boron present in ceramics and glass-ware is physically/chemically bound into the product, therefore in these cases, the potential for the consumers to be directly exposed to the borates present is minimal (RPA 2008).

1.1.4.2 Food contact material (p. 15)
The substance boric acid is an intermediate to manufacture the substances glass and ceramic frits. Therefore it is no longer present in the final products.
The boron present in ceramics and glass-ware is physically/chemically bound into the product, therefore in these cases, the potential for the consumers to be directly exposed to the borates present is minimal (RPA 2008).

1.1.4.4 Mineral water (p. 16)
Maximum exposures are calculated using the maximum value reported in mineral water. This value of 4,35 mgB/L exceeds however the EU drinking water limit of 1 mg B/L.
A realistic worst case scenario should rather assume concentrations equivalent to the drinking water limit. This approach was also followed by ECHA (2008).

1.1.4.5 Food supplements (p. 16)
It is stated that "Food supplements for bodybuilders may possibly lead to maximum boron intakes of up to 30 mg/day (0.5 mg/kg bw/day) for a 60 kg person, BfR 2006a". The original source of this statement (Loscutoff S. Personal Communication (Memorandum)) cannot be verified nor is it a peer-reviewed or official publication. Therefore this value is not credible nor relevant. Further, consumption amounts of this nature as supplements would clearly be considered serious abuse by deliberate ingestion of extreme amounts and therefore is not relevant for this assessment.

Human Health Hazard Assessment

Beneficial Effects of Boron

These proposals for identification of boric acid and disodium tetraborates as SVHCs disregards the beneficial health effects of boron demonstrated in recent research. Research conducted at the US Department of Agriculture Human Nutrition Research Center in North Dakota has indicated a nutritional role for boron in humans and animals (Hunt and Nielsen 1981; Hunt 1989; Hunt et al. 1994; Nielsen 1991; Nielsen 1994; Hunt 1994; Penland 1994; Hunt 1996; Nielsen 1996; Hunt et al. 1997; Hunt 1998; Penland 1998; Nielsen 1998; Nielsen and Penland 1999; hunt and Idso 1999; NRC 1989; Metz 1993; Devirian and Volpe 2003). The essentiality of dietary boron in humans is suspected and a recent review of evidence for the essentiality of dietary boron shows that boron meets the criteria for essentiality in humans (Hunt 2007).

A World Health Organization (WHO) expert committee has concluded that boron is "probably essential" (WHO 1996). Although to date insufficient data is available to confirm the essentiality in humans, the U.S. Food and Nutrition Board in 2001 (USFNB 2001) published a Tolerable Upper Intake Level (UL) for boron of 20 mg/day. Also, the UK Expert Group on Vitamins and Minerals (UK 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 /kgBW/day or 10 mg/day).

Beneficial effects of boron have been reported for bone health (Hunt 1994; Hunt 1996; Nielsen 1998; Gorustovich et al. 2008), cell membrane function (Nielsen 1991; Nielsen 1996), psychomotor skills and cognitive processes of attention and memory (Penland 1994; Nielsen and Penland 1999), response to estrogen therapy (Nielsen 1991; Nielsen 1996), control of inflammatory disease (Hunt 1996; Hunt 1998; Hunt and Idso 1999), enzyme regulation (Nielsen 1996; Hunt 1998), energy metabolism (Hunt 1996), macroscale mineral metabolism (Nielsen 1994; Nielsen 1996; Hunt 1997; Nielsen 1998), and potential anticarcinogenic properties (Barranco and Eckhert 2004; Barranco and Eckhert 2006; Barranco et al. 2007; Gallardo-Williams et al. 2003; Gallardo-Williams et al. 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 may be associated with lower incidences of some types of cancer, including prostate, lung, cervical and esophageal cancer. Also, 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 et al. 2007) suggesting that higher boron intake might have a beneficial role on prevention of prostate cancer. Mechanisms for the role of boron in the inhibition of human prostate cancer cell proliferation are beginning to be explored (Barranco and Eckhert 2004; Barranco and Eckhert 2006; Barranco et al. 2007; Gallardo-Williams et al. 2003; Gallardo-Williams et al. 2004; Barranco et al. 2007; Barranco and Eckhert 2004; Eckhert et al. 2007; Henderson et al. 2009; Henderson et al. 2009; Barranco et al. 2009). In a study of women from boron-rich and boron-poor regions in Turkey, the boron-rich regions had no cytopathological indications of cervical cancer, while there were cytopathological findings in women from the boron-poor areas suggesting that ingestion of boron in the drinking water decreases the incidence of cervical cancer-related histopathological findings (Korkmaz et al. 2007). A recent study (Mahabir et al. 2008) examined 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. Also, lung cancer risk was independently increased among women with decreasing dietary boron intake. The incidence of esophageal cancer has been reported to be significantly higher in a low boron region, compared to an area with high boron exposure in the Butterworth district of Transkei, Southern Africa (Kibblewhite et al. 1984).

Borate Risk Assessments

Since 1995, 11 risk assessments have evaluated boron, using safety factors ranging from 25 to 100, and tolerable daily intake (TDI) values (mg B/kg/day) ranging from 0.1 (6 mg B/day) to 0.4 (24 mg B/day). The differences in the TDI are related to the calculated total uncertainty factors (IEHR 1995; ECETOC 1995; IPCS 1998; NAS FNB 2000; WHO 2004; UK EFSA 2004; US EPA 2004, 2006; ATSDR 2007; EU Biocides 2009; ECHA 2009). RPA (2008) reviewed several of the risk assessments for DG Enterprise and Industry and noted a considerable degree of consensus among the assessments. The RPA report stated "*In summary, the NOAEL value is of the order of 10 mg B/kg/day, which when combined with an uncertainty factor of 60 gives a 'safe' limit value of the order 0.16 mg B/kg/day or, more simply, 10 mg B/day (for an adult). For simplicity, the (daily) tolerable upper intake level (UL) values recommended by EFSA will be used when considering the degree of risk associated with exposure to borates*" (RPA 2008). Use of an uncertainty factor of 60, below the default value of 100, indicates a low level of risk related to boron exposure.

Male reproductive effects have been observed in studies in animal bioassays of boric acid and disodium tetraborate decahydrate at high doses. Developmental toxicity was reported in studies of boric acid at high doses in rats, mice, and rabbits. Reproductive and developmental toxicity in animal studies has been used as the critical endpoint in many recent risk assessments (IPCS 1998; WHO 2008; ECETOC 1995; Moore 1997; Murray 1995; USEPA 1993; Murray and Schlekat 2004; USEPA 2005; ATSDR 2007; USEPA 2008). Generally, these risk assessments indicate a minimal risk of reproductive or developmental toxicity in humans.

The high boron levels normally present in animal feeds, such as rat chow are not taken into account in the risk assessments of boron. For example, Purina Rat Chow contains 10-11 ppm boron, therefore control rats received approximately 0.9 mg B/kg/day or 45X higher dose than background exposure in humans. Humans do not reach the dose level of the control rats fed these animal chow diets. As reported by Pahl et al. 2001 and Price et al. 1997, background dose found in pregnant women was 0.02 mg B/kg/day (1.2 mg B/day) with blood/plasma B levels of 0.02 ± 0.02 μg/B/g; compared to control pregnant rats receiving background levels of B in regular rat chow of 0.9 mg B/kg/day (equivalent to 54 mg B/day in a 60 kg woman) with blood/plasma boron levels of 0.23 ± 0.14 μg/B/g.

Human Data - FERTILITY

This proposal for identification of boric acid as SVHC disregards the absence of adverse effects in multiple new studies of highly exposed workers in the borate industry.

Because of concern that boron could cause infertility and developmental effects in humans as seen in rats, mice, rabbits, and dogs, there have been several attempts to find sufficiently highly exposed human populations. One study evaluated the reproductive performance of workers exposed to borates in a borate ore processing plant over several years. Reproductive performance of workers was measured in terms of live births to the wives of workers subsequent to specific occupational exposures to disodium borates and boric acid (Whorton et al. 1984). The results were calculated as a "standardized birth ratio" (SBR). Participating male workers, (542 men or 72% of the 753 eligible workers) responded to a questionnaire with information on marital status, marital history, wife's date of birth, and number, sex, and dates of birth of offspring from each marriage. Personal air sampler data were available for most jobs beginning in 1981, and it was assumed that exposures on jobs prior to that time were equal to or greater than those measured since. Categories of exposure to boron containing dust were arbitrarily assigned as "high" (>8 mg/m3), "medium" (3–8 mg/m3), and "low" (<3 mg/m3). There was no relationship between exposure category and the standardized birth ratio

(SBR). For the total cohort the SBR was 113 (529 observed births compared with 466.6 births expected), based on national fertility tables published for successive birth cohorts of women in the United States. The high exposure group with ≥2 years of consecutive high exposures had mean exposures per year of 19.7 mg/m3 (~2.9 mg B/m3). During the time period they worked in high exposure jobs (adjusted for gestation time and allowing for one to three spermatogenic cycles), the SBRs ranged from 121 to 125. Thus, from this retrospective fertility study, it was concluded that work involving high sodium borate exposure did not decrease fertility.
The maximum-likelihood absorbed dose allowing for total respiratory retention and absorption and a 10-m3 inhaled volume per 8-h workshift for a 70-kg man would be only 0.4 mg B/kg per day (28 mg B/day).

In Turkey, a country with extensive borate ore deposits and the world's largest mining and borate production facilities, Şayli and colleagues (Sayli et al. 1998; Sayli 2001; Sayli 2003; Sayli et al. 2003) and Tüccar et al. (1998) conducted extensive studies of fertility rates in the villages in borate regions and among the employees of the Turkish borate mines and plants and found the rates to be as high as in other parts of the country. A three-generation analysis of reproductive performance of workers at a borate processing facility in Turkey was made by means of individual pedigree charts. The differences between groups compared to the general population were found statistically insignificant (Sayli 2003; Sayli et al. 2003).

Çöl et al. (2000) evaluated infertility rates, gender ratio at birth, numbers of stillbirths and spontaneous abortions, premature births, and infant mortality rates among the families of 799 boron-exposed workers in Turkey. Patterns were compared with national or regional values, and production workers were compared with office workers. No significant adverse effects were found. Infertility rates among the workers were at the low end of the Turkish national rate. The ratio of boys to girls (1.12) was higher than the national average. Average pregnancies and live births to production workers exceeded those to office workers. Çöl et al. therefore concluded that boron exposure to workers did not adversely affect any of the indicators of fertility.

The health impact of boron in drinking water was evaluated in populations served by public regional water supplies in Northern France. Birth rates, mortality rates, and sex ratios were evaluated in municipalities with varying levels of boron in the drinking water. No adverse health effects were found in municipalities with high boron content in the drinking water compared to the reference zone or French general population. No statistical difference were found in the male-female sex ratios between the different municipality zones in Northern France with different boron content in drinking water (Yazbeck et al. 2005).

Relationships between boron exposure and male reproductive health were investigated in northeast China in boron mining and processing workers. A large number of publications resulted, although many are in Chinese. These were reviewed by Scialli et al. (2010) including translations of the Chinese-language articles. The study populations included men working in boron mining and processing in Liaoning province, men living in the same area (which has naturally high boron levels in the soil) but not working in the boron industry, and men living in a remote area (Chang et al. 2006). In addition to monitoring boron exposure, the researchers evaluated reproductive outcomes, sperm and semen quality, and Y:X chromosome ratios.

Chang et al. (2006) found no significant differences between the boron workers and the local control group in multiple births, spontaneous miscarriage, stillbirths, more-boys-than-girls, or mean number of pregnancies fathered altogether. After adjusting for various confounders (age, education, race, tobacco, alcohol and soybean consumption) no significant difference was found in delay in pregnancy. Chang et al. reported a slightly lower mean total number of live births among boron workers, but this may have reflected the boron workers' younger age, lower marriage rate, and less education.

Liu et al. (2006) found no significant differences in any of the measurements of sperm quantity, motility, speed of the motile cells and departure from straight path in comparing the boron workers with both the local and remote comparison communities. Consumption of dried fruit and legumes was found to have significant effects on semen quality, although these were not related to boron exposure.

Robbins et al. (2008) also compared the ratios of sperm containing the Y chromosome and sperm containing the X chromosome in men exposed occupationally and environmentally in the same Chinese cohort. Significant differences were reported in sperm Y:X ratios when subjects were categorized by exposure group: the ratio among boron workers was 93%±3%, compared with 96%±4% for men in the local community and 99%±3% for men in the remote community. However no correlation was found between daily boron absorption and Y:X ratios among the subjects, even with a wide range of boron exposures. The biological significance of the differences in Y:X sperm ratios among exposure groups is unclear. Robbins et al. (2008) state that there were significant differences in men with "more boys than girls" between the groups as evidence that the Y:X sperm ratios have biological significance. However, the values reported for this do not follow the patterns for boron exposure or the Y:X ratio. The boron worker group (highest exposure) had a ratio of "more boys than girls" of 58%, while the local community group (intermediate exposure) had a ratio of 42% and the remote community group (lowest exposure) had a ratio of 77%.

A review by Scialli et al. (2010) found that the methods used to describe exposure may have under-estimated boron exposure. Mean daily exposures for the highly-exposed groups were 30 to 40 mg B/day. They agreed that the findings regarding testicular function were based upon standard methods used to evaluate semen quality and had reasonable statistical power. They also concluded that the methods used to evaluate reproductive success may not have been adequate and that the assessment of sex ratio in China is unlikely to be reliable. Scialli et al suggested that differences in Y:X ratios appeared to be more related to group membership than to boron exposure itself. Scialli et al. observed that Y:X ratio is not known to be associated with impaired semen quality, reproductive success or offspring health. Scialli et al. state: "In conclusion, while boron has been shown to adversely affect male reproduction in laboratory animals, there is no clear evidence of male reproductive effects attributable to boron in studies of highly exposed workers."

In a follow-up study of Robbins et al. 2008, Robbins et al (2010) examined correlations between B exposure and semen parameters (total sperm count, sperm concentration, motility, morphology, DNA strand breaks, apoptosis and aneuploidy) in B workers and in men residing in high exposure areas and low exposure areas. B concentration in blood, semen and post-shift urine were the highest in B workers compared to men from the community comparison group (high exposure area) and low environmental B area. DNA strand breaks were similar across the exposure groups and did not correlate with B levels in blood or post-shift urine samples. Sperm aneuploidy and diploidy of chromosomes Y, X and 18 did not differ by exposure groups or B levels in post-shift urine or blood, which is consistent with the lack of genotoxicity of B. Regression modeling did not predict any semen parameters as affected by B exposure before or after controlling for age, abstinence interval, alcohol intake, smoking status and pesticide exposure. Robbins et al (2010) noted that the ratio of Y:X bearing sperm was not significantly correlated with any other sperm parameters, nor did it correlate significantly with the biological measure of B exposure.

Prof Dr. Nursen Basaran from Hacettepe University, Ankara and Prof Dr. Yalcim Duydu Ankara University, Ankara are currently conducting a study identifying the effect of boron exposure on reproductive parameters in male workers from the Bandmna Boric Acid production area in Turkey. The investigators recently released an Interim Report on the project entitled "Reproductive effects of boron exposure in humans". The study population consists of 102 workers from a boric acid production plant and 102 workers from other workplaces. Boron concentrations were determined in blood, urine, and semen samples collected from the workers. FSH, LH, total testosterone and PSA were also determined in blood samples of the workers. Sperm concentration sperm motility, sperm morphology and DNA damage in sperm cells are among the most important parameters in identifying the unfavorable reproductive effects of a chemical exposure. Accordingly these parameters were also determined. Ambient air sampling and personal air monitoring was performed in order to estimate the inhalational boron exposure. Water and food samples were sampled in order to estimate the oral boron exposure. The authors concluded that according to their preliminary results boron exposure have no negative effect on the reproductive toxicity endpoints.

Human Data – DEVELOPMENTAL EFFECTS

While developmental effects of boron have been observed in rodent bioassays that include fetal body weight reduction and minor skeletal variations, similar effects have not been observed in humans. Three epidemiological studies evaluating high environmental exposures to boron and developmental effects in humans have been conducted. Epidemiological studies of human developmental effects have shown an absence of effects in exposed borate workers and populations living in areas with some of the highest environmental levels of boron worldwide.

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. Tuccar et al. concluded that no adverse effects were found among these human populations.

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 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.

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.

In conclusion, among populations known to have the highest boron exposures worldwide, no adverse fertility or developmental effects have been observed, further supporting that boric acid or disodium borates do not warrant listing as a SVHC and should not be placed on the “Candidate List”.

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