Section A6.8.2.2 Multigeneration Reproduction Toxicity Study

Annex Point IIA6.8.2 6.8.2.2 Rat Three Generation Study Sodium tetraborate decahydrate.

Also presented in Boric Acid Dossier

5.1 Materials and methods	Predates modern protocols and GLP. Although this study is not to modern day protocols, there are literature data in 3 species that confirm the results seen. No further testing is necessary in the interests of animal welfare and protecting laboratory animals
5.2 Results and discussion	Rats exposed to the high dose of 518mg/kg bw of borax (corresponding to a level of 58.5 mg B/kg bw) were sterile. Microscopic examination of the atrophied testes of all males in this group showed no viable sperm. The authors also reported evidence of decreased ovulation in the majority of ovaries examined from the females exposed to 58.5 mg B/kg bw and no litters were obtained from these high dose females when mated with control male animals. There were no adverse effects on reproduction reported at exposures of 50 and 155 mg/kg bw borax (5.9 and 17.5 mg B/kg bw). The authors reported no adverse effects on fertility, lactation, litter size, progeny weight or appearance in rats exposed to either 5.9 or 17.5 mg B/kg bw. Also, no gross abnormalities were observed in the organs examined from either parents or weanlings from these dose groups. Based on these study data, the authors concluded that exposure of rats at levels up to 17.5 mg B/kg bw in the diet in a 3 generation reproduction study was without adverse effect. Data also presented with boric acid data to support the data obtained with boric acid
5.3 Conclusion	
5.3.1 LO(A)EL	1170 ppm boron in the diet, equivalent to 518 (58.5) mg borax (mg B)/kg bw based on sterility in males and females
5.3.1.1 Parent males	as above
5.3.1.2 Parent females	as above
5.3.1.3 F1 males	none
5.3.1.4 F1 females	none
5.3.1.5 F2 males	none
5.3.1.6 F2 females	none
5.3.2 NO(A)EL	Non-entry field
5.3.2.1 Parent males	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw
5.3.2.2 Parent females	350 ppm boron in the diet, equivalent to 155 (17.5) mg borax (mg B)/kg bw
5.3.2.3 F1 males	as above
5.3.2.4 F1 females	as above
5.3.2.5 F2 males	as above
5.3.2.6 F2 females	as above
5.3.3 Reliability	2
5.3.4 Deficiencies	Predates modern protocols and GLP. Although this study is not to modern day protocols, there are literature data in 3 species that confirm the results seen. No further testing is necessary in the interests of animal

Section A6.8.2.2	**Multigeneration Reproduction Toxicity Study**
Annex Point IIA6.8.2	6.8.2.2 Rat Three Generation Study Sodium tetraborate decahydrate. Also presented in Boric Acid Dossier
	welfare and protecting laboratory animals

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	11 April 2005
Materials and Methods	In contrast to what the applicant states, the sperm parameters were not assessed (3.4.5) and the testes of the high dose males were not examined microscopically (3.4.8). In the study, reference is made to a 2 year study with borax, in which histopathological examination demonstrated lack of viable sperm in the males received food containing 1.03% disodium tetraborate (borax). It should be mentioned that the control group in the present study also served as the control group for the multigeneration reproduction study with boric acid. Otherwise the version of the applicant is acceptable.
Results and discussion	The description of the results by the applicant is adopted. In addition, in the high dose group, i.e. the rats that failed to produce offspring, a 73 % reduction in relative testes weight was found. In the other 2 doses groups, neither effects on reproduction nor effects on testes weight were observed. It is noted that the quality of the study is poor. Histopathology is not performed, except for the ovaries and uterus of the high-dose females. The mating index (nr pregnancies/nr matings) in general was low. The high mortality in the pups (up to 52% in the control group) casts further doubt on the quality of the study.
Conclusion	The study does not allow the derivation of a LOAEL and NOAEL and is not acceptable for risk assessment purposes. The study does indicate that reproductive potency in males and females rats is impaired by disodium tetraborate decahydrate.
Reliability	4
Acceptability	not acceptable
Remarks	
	COMMENTS FROM ...
Date	Give date of comments submitted
Materials and Methods	Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state
Results and discussion	Discuss if deviating from view of rapporteur member state
Conclusion	Discuss if deviating from view of rapporteur member state
Reliability	Discuss if deviating from view of rapporteur member state
Acceptability	Discuss if deviating from view of rapporteur member state
Remarks	

Section A6.8.2.2 Multigeneration Reproduction Toxicity Study

Annex Point IIA6.8.2 6.8.2.2 Rat Three Generation Study Sodium tetraborate decahydrate.
Also presented in Boric Acid Dossier

Table A6_8_2-1. Table for animal assignment for mating (modify as appropriate)

		Number of animals			
		Controls	**Low Dose**	**Medium Dose**	**High Dose**
Parents	**m**	**8**	**8**	**8**	**8**
	f	**16**	**16**	**16**	**16**
F_1	**m**	**8**	**8**	**8**	-
	f	**16**	**16**	**16**	-
F2	**m**	**8**	**8**	**8**	-
	f	**16**	**16**	**16**	-

Section A6.14	**Human Case Report**	
Annex Point IIA6.14	Section IIA6.14	

		Official use only
	1 REFERENCE	
1.1 Reference	Cain William S., Alfredo A. Jalowayski, Michael Kleinman, Nam Soo Lee, Bo Ryung Lee, Byung-Hoon Ahn, Kevin Magruder, Roland Schmid[1], and B. Dwight Culver (2002). Sensory Perception of Mineral Dusts at Occupationally Relevant Concentrations: *Laboratory Department of Surgery (Otolaryngology) University of California, San).* Interim Draft Report to US Borax Inc – 1 January 2002 (Published) Cain, William S. Alfredo A. Jalowayski, *Michael Kleinman, Nam-Soo Lee, Bo-Ryung Lee,* Byung-Hoon Ahn,1 Kevin Magruder, *Roland Schmidt, Brian K. Hillen, Craig B. Warren, and B. Dwight Culver. (2004)* Sensory and Associated Reactions to Mineral Dusts: Sodium Borate, Calcium Oxide, and Calcium Sulfate Journal of Occupational and Environmental Hygiene, 1: 1–14 in press	
1.2 Data protection	Yes	
1.2.1 Data owner	[redacted]	
1.2.2 Companies with letter of access	**Curent Access** [redacted]	
1.2.3 Criteria for data protection	*Data on new a.s. for first entry to Annex I/IA*	
	2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	

Section A6.14	**Human Case Report**
Annex Point IIA6.14	Section IIA6.14

3 MATERIALS AND METHODS

3.1	**Substance**	Disodium tetraborate pentahydrate
3.2	**Persons exposed**	
3.2.1	Sex	Male
3.2.2	Age/weight	18-35 years old
3.2.3	Known Diseases	Healthy
3.2.4	Number of persons	12, 9 finished the study
3.2.5	Other information	Exposure to carbon dioxide vapour was used to set a reference scale for subjects to judge the feel of the stimulus materials. Six concentrations of carbon dioxide that varied in increments of five percentage points from 10% to 35% at 9 L/min were delivered from glass cones. A 2-sec sniff of 10% carbon dioxide produces a just noticeable feel for most persons. As concentration increases, the feel becomes sharper, with a more irritating character. The same progression of sensation holds for the eyes. During an exposure, subjects judged level of feel or irritation in the eye, nose, and throat (nasopharynx) at 5-min intervals. The subjects indicated the absence of any feel or irritation by a judgement of zero. At the intervals indicated, heart rate, oxygen saturation, minute ventilation and respiration rate were recorded as well.
3.3	**Exposure**	Inhalation
3.3.1	Reason of exposure	Occupational,
3.3.2	Frequency of exposure	14 sessions with variable exposures over 7 –12 weeks
3.3.3	Overall time period of exposure	
3.3.4	Duration of single exposure	20 mins
3.3.5	Exposure concentration/dose	Nominal concentrations 5, 10, 20, 30, and 40 mg/m^3
3.3.6	Other information	
3.4	**Examinations**	Measured parameters included nasal resistance, nasal secretion, minute ventilation, heart rate, blood oxygenation, mucociliary transport time, and chemesthetic magnitude, calibrated to pungency of carbon dioxide.
3.5	**Treatment**	No treatment needed as no intoxication
3.6	**Remarks**	

Section A6.14 **Human Case Report**

Annex Point IIA6.14 Section IIA6.14

4 RESULTS

.

4.1 Clinical Signs None

4.2 Results of examinations

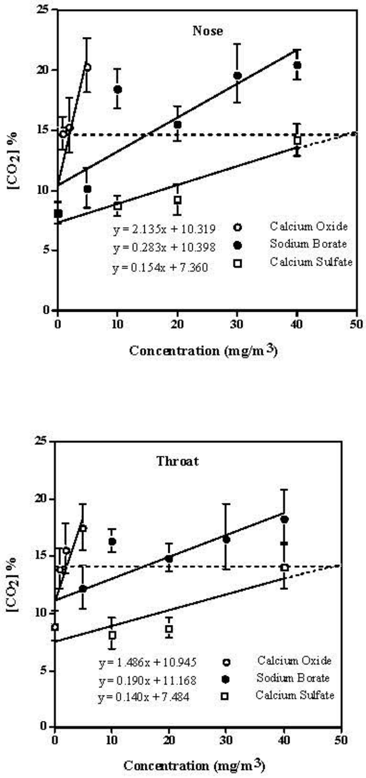

Figure 14. from Cain et al, 2002. Concentrations of carbon dioxide that matched the intensity felt in the final seconds of the exposures (t = 20 min). The horizontal dashed lines in the panels for the nose and throat show points of equal intensity, using the calculated intensity of 2 mg/m^3 calcium oxide as reference.

4.3 Effectivity of medical treatment Not relevant

4.4 Outcome *Describe outcome / manifestation of symptoms / disease*

4.5 Other *Describe any other significant observations*

5 APPLICANT'S SUMMARY AND CONCLUSION

Section A6.14	**Human Case Report**
Annex Point IIA6.14	Section IIA6.14

5.1	**Materials and methods**	This study investigated chemosensory feel, denoted chemesthesis here, to dusts of calcium oxide (1 to 5 mg/m3), sodium tetraborate pentahydrate [sodium borate] (5 to 40 mg/m3), and calcium sulphate (10 to 40 mg/m3); examined correlates of the chemesthetic sensations; and sought to illuminate the basis for potency. Twelve screened men exercised against a light load while they breathed air in a dome fed with controlled levels of dust for 20 min. Measured parameters included nasal resistance, nasal secretion, minute ventilation, heart rate, blood oxygenation, mucociliary transport time, and chemesthetic magnitude, calibrated to pungency of carbon dioxide. Subjects registered time-dependent feel from exposures in the nose, throat, and eyes.	

5.2 Results and discussion

The results show that of the three sites by which people might perceive the three mineral dusts, the nose registered the strongest sensation, followed by the throat, then the eye. The nose may not necessarily have higher intrinsic sensitivity than the eye, but may register the higher perceived magnitude because of the flow through the nasal passage.

All three minerals possessed irritant properties with calcium sulphate the least potent and calcium oxide the most. Although about equally soluble in water as is calcium oxide (0.18 g per 100 ml), calcium sulphate (0.25 g per 100 ml) required a concentration in excess of 20 mg/m^3 in air to trigger perception above that of plain air, whereas calcium oxide required a concentration of 1 mg/m^3. Sodium borate has higher water solubility (3.5 g/100 ml) than calcium oxide, and was perceived more rapidly than calcium oxide, being registered almost immediately whereas calcium oxide had registered essentially no effect at 2 minutes.

It is not possible from the data presented to indicate at which point for each chemical the sensation became irritant in nature as opposed to being just perceptible. One way of assessing the degree of irritation is to compare the effects of borate with the known irritant calcium oxide. This comparative procedure was used by the ACGIH in setting an acceptable level for calcium oxide when they compared it with sodium hydroxide (ACGIH, 1991). There is a large literature on the irritant effects of calcium oxide in industrial settings, and based on this, the occupational exposure limit for calcium oxide has been set in different countries as follows:

2mg/m^3: Australia, Sweden, UK, USA (ACGIH)

5mg/m^3: Germany, Holland.

To assess the acceptable occupational exposure limit for sodium borate, a comparison of the concentration of borate in air, which produces an equivalent sensory response to a concentration of 2 mg/m^3 calcium oxide has been made. By examination of the graphs in the results section 4.2, it can be seen that for the most sensitive tissues, nose and throat, the response to 2 mg/m^3 calcium oxide is approximately equivalent to 14% carbon dioxide vapour. The corresponding responses for sodium borate on the nose and throat are achieved at around 14 -15 mg/m^3 sodium borate.

5.3 Conclusion

The concentration of sodium borate in air, which produces a degree of sensory irritation in the nose and throat equivalent to the lowest occupational exposure level of 2 mg/m^3 for the known irritant calcium oxide, is be 14-15 mg/m^3 sodium borate. This level would also be protective for ocular irritation. This value is compatible with the previously published results of the field studies on borate workers by Wegman and colleagues. Therefore the data supports a limit of 10 mg/ m^3 (the general nuisance level) for all borates.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17 May 2005
Materials and Methods	The version of the applicant is acceptable.
Results and discussion	The present data indicate that following a 20 min exposure, sensory irritation to sodium tetraborate pentahydrate occurs at levels of approximately 14 mg/m^3.
Conclusion	The present data indicate that following a 20 min exposure, sensory irritation to sodium tetraborate pentahydrate occurs at levels of approximately 14 mg/m^3. The data from the present study are in line with data from other studies. Workers exposed occupationally to borax dust (average air concentration 4.1 mg/m3) reported eye irritation, dry mouth, nose or throat, sore throat and productive cough (Garabrant et al., 1984). In a second study by Garabrant et al. (1985) exposure ≥ 4.5 mg/m3 induced acute and chronic respiratory irritation at levels ≥ 4.5 mg/m3. Concentrations ≥ 4 mg/m3 induced eye irritation. From a prospective cohort study Wegman et al (1994) concluded that a threshold limit value (TLV) of 10 mg/m3 was protective of workers' health.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A7.1.1.1.1 **Annex Point IIA7.6.2.1**	**Hydrolysis as a function of pH and identification of breakdown products**

Official use only

5.4 Reference

1. [redacted] 2001, A study on the identification and comparison of the dissociation products of Polybor tech, Borax Manufacturing Grade and Boric Acid manufacturing Grade in Aqueous Solution using Raman spectrometry. 2001 [redacted]
2. Farmer, J. 1982. Structural Chemistry in the Borate Industry. Chem. and Ind., 6 March 1982
3. Holleman, 1995. Lehrbuch der anorganischen Chemie. 101st ed de Gruyter, Berlin
4. Kemp P H, 1956 "The Chemistry of Borates Part 1", Borax
5. Maeda, M. 1979. Raman spectra of polyborate ions in aqueous solution. J.Inorg. Nucl. Chem., Vol 41, pp 1217-1220 (1979)
6. [redacted] (2004). Boric Acid (CAS No. 10043-35-3): Statement on Hydrolysis as a function of pH and identification of breakdown products [redacted]

5.5 Data protection Yes on [redacted].

5.5.1 Data owner [redacted]

5.5.2 Companies with letter of access **Curent Access**
[redacted]
[redacted]

5.5.3 Criteria for data protection Data on new a.s. for first entry to Annex I

6 GUIDELINES AND QUALITY ASSURANCE

6.1 Guideline study No.

6.2 GLP Yes

6.3 Deviations No

7 MATERIALS AND METHODS

Section A7.1.1.1.1 Hydrolysis as a function of pH and identification of breakdown products

Annex Point IIA7.6.2.1

7.1	**Test material**	Disodium Octaborate Tetrahydrate ([redacted] Sodium Tetraborate Decahydrate (Borax, [redacted]
7.1.1	Lot/Batch number	144-99-303
7.1.2	Specification	[redacted] B_2O_3: 66.2%-69.0% Equivalent $Na_2B_8O_{13}.4H_2O$: 98.0%-102.2% Na_2O: 14.0%-15.1% Borax, [redacted] B_2O_3: 36.9-38.2% Equivalent $Na_2B_4O_7.10H_2O$ 101.0%-104.6% Na_2O 16.4%-17.0%
7.1.3	Purity	[redacted].>98% Borax [redacted] >99%
7.1.4	Further relevant properties	none
7.2	**Reference substance**	Yes Orthoboric acid (Boric Acid, [redacted])
7.2.1	Initial concentration of reference substance	0.02 mol.l^{-1}
7.3	**Test solution**	Solutions of [redacted] (Disodium octaborate tetrahydrate) tech., Borax [redacted]de and Boric Acid [redacted], with a final solution concentration of 0.02mol.l^{-1} were prepared by dissolving 0.5181g, 0.9578g and 0.6206g of the test substances in 500ml ultrapure water respectively. From these test solutions, five portions of 100ml of each substance solution were made. One portion of each test substance was not buffered, whereas the other portions were acidified or made alkaline to pH 6.0, 7.0, 8.0 and 9.0 with the aid of 2M HCl and 2M NaOH respectively. The Raman spectra of these solutions were recorded. **Note:** the final solution volumes and concentrations of the buffered solutions were similar to those of the non-buffered, since only a few drops of HCl or NaOH were required to change the pH.
7.4	**Testing procedure**	*Non-entry field*
7.4.1	Test system	The principle of the test is based upon the article of Maeda(1). Test solutions of the substances [redacted] *(*Disodium octaborate tetrahydrate*)* tech.; Borax [redacted]) and of Boric Acid, [redacted]

Section A7.1.1.1.1 Hydrolysis as a function of pH and identification of breakdown products

Annex Point IIA7.6.2.1

[redacted], are prepared under non-buffered conditions and at pH 6.0, 7.0, 8.0 and 9.0. The Raman spectrum of each solution was measured and the spectrum of the test substance compared to Raman spectra of boric acid reported in the literature (Maeda, 1979) and that of Boric Acid, [redacted], under the same circumstances. Comparison of the unique Raman bands of the products used show whether the dissociation products of [redacted] and Borax, [redacted] are comparable to those of Boric Acid, [redacted].

7.4.2	Temperature	Room temperature
7.4.3	pH	See Tables
7.4.4	Duration of the test	Because we are dealing with an inorganic system, no decomposition products are formed. The system equilibrates rapidly, therefore, test duration is not relevant in the circumstances.
7.4.5	Number of replicates	Non reported
7.4.6	Sampling	Stable system, therefore sampling interval and storage not relevant
7.4.7	Analytical methods	Raman Spectrometry

7.5 Preliminary test No

8 RESULTS

Section A7.1.1.1.1

Annex Point IIA7.6.2.1

Hydrolysis as a function of pH and identification of breakdown products

8.1	**Concentration and hydrolysis values**	*See table A7_1_1_1_1-4*
8.2	**Hydrolysis rate constant (k_h)**	Not determined. Inorganic material speciation under consideration.
8.3	**Dissipation time**	Not relevant – Inorganic Material
8.4	**Concentration – time data**	Concentration is constant in all cases (0.02M).
8.5	**Specification of the transformation products**	There are no transformation products (inorganic material). Reference Farmer, 1982
		9 APPLICANT'S SUMMARY AND CONCLUSION
9.1	**Materials and methods**	The objective of the study was to identify and compare the dissociation products of *Polybor* Technical, and Borax, Manufacturing Grade, in aqueous solution with those of Boric acid, Manufacturing Grade, using Raman spectrometry. The Raman spectra of dilute solutions of *Polybor* Technical and Borax Manufacturing Grade were measured and compared to Boric Acid, Manufacturing Grade as well as data on boric acid from open literature Maeda, 1979). The measurements were carried out under non-buffered conditions and at pH6, 7, 8 and 9. The test was performed in compliance with the OECD principles of Good Laboratory Practice.
9.2	**Results and discussion**	Solutions containing suitable low concentrations of all three boron salts were examined so as to simulate those occurring under aqueous environmental conditions. In the spectra from all three substances, a major band was found at 872 cm^{-1}, which corresponds to that reported by Maeda' 1979 for dissociated and undissociated boric acid. A few characteristic bands of boric acid that were reported in the literature were less clearly seen or were absent in the spectra due to the low concentrations of the test and reference substances. The concentrations used in this study were 75 times lower than those reported by Maeda , 1979. Most of the simple inorganic borates (for example, boric acid, boric oxide, sodium metaborates, tetraborates and octaborates) are highly water-soluble. The mode of dissolution of metal borates as well as of boric acid is complex and depends very much on the conditions (pH, temperature, and concentration). Depending on the boron concentration monomeric and, with increasing concentration of boron, polymeric species will be found (Farmer, 1982) $[B(OH)_3] < 0{,}02M$ $B(OH)_3 + H_2O \text{ --> } [B(OH)_4]^+ + H^+$ pKa = 9,15

$0{,}025M <= [B(OH)3] <= 0{,}4/0{,}6M$
$[B_3O_3(OH)_4]^-$; $[B_3O_3(OH)_5]^{2-}$ predominant

$[B(OH)_3] > 0{,}6M$
$[B_4O_5(OH)_4]$-; $[B_5O_6(OH)_4]^{2-}$ predominant

The nucleation process can be described as the interaction of boric acid with the borate anion shown in the following equation for the example of $[B_3O_3(OH)_5]^{2-}$

$$B(OH)_3 + 2\ [B(OH)_4]- \text{<--->} [B_3O_3(OH)_5]^{2-} + 3\ H_2O$$

Therefore, regardless of whether the boron source is boric acid or one of the other borates (such as boric oxide or a sodium borate), monomeric species are predominant in most biological fluids as well as under environmental conditions. Below pH 7 boric acid and borates exist as undissociated boric acid, whereas above pH 10 the metaborate ion becomes the main species. The metaborate ion will also be present in aqueous solutions at environmental temperature and pH mainly as weakly dissociated boric acid (pKa value at room temperature 9.25, Holleman, 1995). As a result, the toxicology and the ecotoxicology of all these simple borates are likely to be similar on an equivalent boric acid basis or boron basis.

Since disodium octaborate tetrahydrate is a solidsolution of boric acid and disodium tetraborate decahydrate (borax), disodium octaborate tetrahydrate in dilute aqueous solution dissociates to predominantly free boric acid plus some monoborate anions (Kemp, 1956), therefore it can be considered to exist as undissociated boric acid under physiological conditions.

The dissolution to undissociated boric acid by all the borates was confirmed in the study by de Vette et al, which identified and compared the dissociation products of sodium borates (disodium tetraborate decahydrate and disodium octaborate tetrahydrate) and boric acid in dilute aqueous solutions. The data showed through Raman spectra that the predominant species present was undissociated boric acid.

9.2.1	k_H	Not determined
9.2.2	DT_{50}	Not determined
9.2.3	r^2	Not determined

9.3 Conclusion

Conclusions are based on the fact that this is the speciation of an inorganic material.

The band at 872 cm^{-1} which appeared in every spectrum, corresponds to the literature. A relationship between intensity of the peaks and pH was found and is also reported by Maeda 1979,. It is therefore concluded that all bands correspond to bands of dissociation products of Boric Acid manufacturing Grade.

The most recent internationally accepted test guideline for a hydrolysis test is the OECD 111 guideline. Buffers with different pH values (pH 4, 7 and 9) containing the test substance is incubated at an elevated temperature for at least one week in the preliminary test. The concentration of the test substance is measured. If hydrolyzed a Tier 1 study will follow. Persistent (i.e. not biodegradable) breakdown products should also be considered

Boric acid is an inorganic compound and does not have any chemical bonds prone to hydrolysis. However, polymeric borate species occurs in significant amounts at certain pH values, temperatures and at concentrations above 0.1 molar. The most important polyborate species are tri-, tetra- and pentaborate anions. Boric acid and tetrahydroxyborate are the dominant species at low pH values and at pH values >9, respectively. These and other borate species are at equilibrium with each other; the concentration of the individual species dependent on the conditions.

Hydrolysis of boric acid is therefore not a relevant ‘degradation’ mechanism and this study by [redacted] is adequate to cover the endpoint ([redacted] 2004).

Section A7.1.1.1.1 **Annex Point IIA7.6.2.1**	**Hydrolysis as a function of pH and identification of breakdown products**

9.3.1	Reliability	1
9.3.2	Deficiencies	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	26-04-2005
Materials and Methods	Applicant's version is acceptable
Results and discussion	Applicant's version is adopted
Conclusion	The proportion of boric acid in dilute solutions with a neutral pH is > 99 %. The relative concentration of the tetrahydrate anion, $[B(OH)4]^-$, becomes dominant at pH > 9. Boric acid is an inorganic compound and does not have any chemical bonds prone to hydrolysis. Hydrolysis is thus not a relevant pathway at environmental pH.
Reliability	1
Acceptability	acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A7_1_1_1_1-1: Type and composition of buffer solutions (specify kind of water if necessary)

Test Substance*	**Natural pH**	**Buffered pH's**			
Polybor tech.	8.62	6.03	6.99	8.03	9.00
Borax Manufacturing Grade	9.18	5.99	6.99	8.03	9.02
Boric Acid Manufacturing Grade	5.10	6.02	6.99	7.99	9.00

* Solutions of [redacted]., Borax [redacted] and Boric Acid [redacted] with a final solution concentration of 0.02mol.l^{-1} were prepared by dissolving 0.5181g, 0.9578g and 0.6206g of the test substances in 500ml ultrapure water respectively. From these test solutions, five portions of 100ml of each substance solution were made. One portion of each test substance was not buffered, whereas the other portions were acidified or made alkaline to pH 6.0, 7.0, 8.0 and 9.0 with the aid of 2M HCl and 2M NaOH respectively.

Results of the comparison of the bands found **for** [redacted]. In non-buffered solution and at pH 6.0, pH 7.0 and pH 8.0 and the bands found for the polyborate solutions in the literature (1)

Raman shift (Rel. cm^{-1})	Non- buffered pH 8.62	pH 6.03	pH 6.99	pH 8.03	pH 9.00
385	-	-	-	-	-
430	-	-	-	-	-
447	-	-	-	-	-
458	-	-	-	-	-
490	+	+	+/-	+/-	+/-
524/525	+	-	-	+/-	+/-
565	+	+	+	+	+/-
609	-	-	-	+/-	-
745	+/-	-	-	+/-	-
872	+	+	+	+	+
917	-	-	-	-	-
940	-	-	-	-	-
995	-	-	-	-	-

(1) *Maeda, M. Raman spectra of polyborate ions in aqueous solution. J.Inorg. Nucl. Chem., Vol 41, pp 1217-1220 (1979)*

\+ = band in accordance with (1)

+/- = intensity of band on detection level

\- = band not found in spectrum

Results of the comparison of the bands found **Borax** [redacted]. In non-buffered solution and at pH 6.0, pH 7.0 and pH 8.0 and the bands found for the polyborate solutions in the literature (1)

Raman shift (Rel. cm^{-1})	Non- buffered pH 8.62	pH 6.03	pH 6.99	pH 8.03	pH 9.00
385	-	-	-	-	-
430	-	-	-	-	-
447	-	-	-	-	-
458	-	-	-	-	-
490	-	-	-	-	-
524/525	+	-	-	-	-
565	+/-	+	-	-	+/-
609	+/-	-	+/-	-	-
745	+	-	-	+/-	+
872	+	+	+	+	+
917	-	-	-	-	-
940	-	-	-	-	-
995	-	-	-	-	-

(1) Maeda, M. Raman spectra of polyborate ions in aqueous solution. J.Inorg. Nucl. Chem., Vol 41, pp 1217-1220 (1979)

+ = band in accordance with (1)

+/- = intensity of band on detection level

- = band not found in spectrum

Results of the comparison of the bands found **Boric Acid,** [redacted]. In non-buffered solution and at pH 6.0, pH 7.0 and pH 8.0 and the bands found for the polyborate solutions in the literature (1)

Raman shift (Rel. cm^{-1})	Non- buffered pH 8.62	pH 6.03	pH 6.99	pH 8.03	pH 9.00
385	-	-	-	-	-
430	-	-	-	-	-
447	-	-	-	-	-
458	-	-	-	-	-
490	+/-	+/-	+	+	+
524/525	+/-	-	-	-	-
565	+/-	+/-	-	-	-
609	-	-	-	-	+/-
745	-	-	-	-	+/-
872	+	+	+	+	+
917	-	-	-	-	-

940	-	-	-	-	-
995	-	-	-	-	-

(1) Maeda, M. Raman spectra of polyborate ions in aqueous solution. J.Inorg. Nucl. Chem., Vol 41, pp 1217-1220 (1979)

+ = band in accordance with (1)

+/- = intensity of band on detection level

- = band not found in spectrum

In all spectra a band is observed at 872cm^{-1}. the spectra of Borax, Manufacturing grade, contain a band at 745cm^{-1} in the natural pH and at pH 9.0. Boric acid, Manufacturing Grade, has a vibration at 490cm^{-1} at pH 7.0, pH 8.0 and pH 9.0 apart from the band at 872 cm^{-1} in all samples. The Raman spectra of *Polybor* tech. show a band at 565cm^{-1} (non-buffered, pH 6.0, pH7.0 and pH 8.0), a band at 524/525 cm^{-1} (pH = natural) and at 490cm^{-1} (pH= natural and pH=6.0).

Table A7_1_1_1_1-2: Description of test solution

Criteria	**Details**
Purity of water	Ultrapure water, per description by [redacted], where the study was conducted.
Preparation of test medium	Solutions of [redacted]., Borax [redacted] and Boric Acid [redacted], with a final solution concentration of 0.02mol.l were prepared by dissolving 0.5181g, 0.9578g and 0.6206g of the test substances in 500ml ultrapure water respectively. From these test solutions, five portions of 100ml of each substance solution were made. One portion of each test substance was not buffered, whereas the other portions were acidified or made alkaline to pH 6.0, 7.0, 8.0 and 9.0 with the aid of 2M HCl and 2M NaOH respectively. *Describe preparation in detail*
Test concentrations (mg a.i./L)	0.02M
Temperature (°C)	Ambient
Controls	Boric Acid
Identity and concentration of co-solvent	No co-solvent
Replicates	None

Table A7_1_1_1_1-3: Description of test system

Glassware	Standard chemical laboratory-ware
Other equipment	Raman spectrometer
Method of sterilization	Not necessary – inorganic speciation under investigation.

Table A6_8_2-2. Table for reproductive toxicity study (modify if appropriate)

If effects are found in one generation, the figures for the other generation(s) should be given as well (as shown as an example for mortality). Give only information on endpoints with effects, delete other endpoints.

Parameter			**control**		**low dose**		**medium dose**		**High dose**			
		Genera-tion	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**		
Mortality	incidence	**P**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**		
		F_1	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**		
		F_2	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**		
Food consumption	% of control	**not affected**										
Body weight gain	% of control		-	-	-	-	-	-	↓	↓		
Clinical Observations *specify effects*	Incidence		-	-	-	-	-	-	+	+		
Organ weights	% of control	**only effect noted was increase in absolute and relative thyroid wt. in low and mid dose groups (not thought to biologically significant)**										
Pathology												
Histopathologic examination *specify effects*	Incidence	**Evidence of testis atrophy in high dose males of P0 generation.** **Evidence in ovary of reduced ovulation in high dose females.**										
Reproductive Performance		**P0 to F1a**				**F1b to F2b**			**F2b to F3b**			
		cont	**low**	**mid**	**high**	**cont**	**low**	**mid**	**cont**	**low**	**mid**	
Mating index: (No. pregnant/No. mated)	**%**	**63**	**69**	**75**	**0**	**80**	**75**	**94**	**69**	**88**	**100**	
Fertility index: No. litters born/No. Pregnant	**%**	**100**	**100**	**100**	-	**100**	**100**	**100**	**91**	**100**	**100**	
Number of implantation sites	Mean											
Duration of pregnancy	Mean											
Birth index												
Live birth index: No.pups alive/No. born	**%**	**98**	**98**	**100**		**99**	**92**	**99**	**100**	**100**	**100**	
Gestation index												
Litter size	Mean	**12**	**12**	**13**		**12**	**15**	**12**	**12**	**12**	**12**	
Litter weight	Mean											
Pup weight at 24h (g)	Mean	**7.0**	**6.8**	**7.1**		**6.4**	**6.2**	**7.0**	**6.0**	**7.0**	**8.0**	
Sex ratio	Male/female	**6/6**	**6/6**	**6/7**		**6/6**	**8/7**	**5/7**	**6/6**	**7/5**	**6/6**	
Survival index												
Viability index												
Lactation index: Pup wt. at weaning		**55**	**55**	**51**		**56**	**58**	**53**	**48**	**52**	**52**	

Section A8
Annex Point IIA8

10 MEASURES TO BE ADOPTED TO PROTECT MAN, ANIMALS AND THE ENVIRONMENT

Section B8

Subsection		**Official use only**
8.1 Handling and Storage	No special handling precautions are required, but dry indoor storage is recommended. Good housekeeping procedures should be followed to minimise dust generation and accumulation. No specific firefighting measures are required since boric acid in not flammable, combustible or explosive. The product is itself a flame retardant.	X
8.2 Combustion Products	Fused borate glass and water	
8.3 Emergency measures in case of accident	**Inhalation:** If symptoms such as nose or throat irritation are observed, remove to fresh air. **In case of contact with Eyes:** Rinse immediately with plenty of clean water or sterile saline solution for at least 15 minutes. If appropriate, remove contact lenses after 5 minutes rinsing. If symptoms persist, seek medical attention. **Skin Contact:** No treatment necessary because non-irritating. **Ingestion:** Swallowing small quantities (one teaspoon) will cause no harm to healthy adults. If larger amounts are swallowed, give two glasses of water to drink and seek medical attention. Avoid creation of dust. Use vacuum cleaners wherever possible.	
8.4 Decontamination	a) **Air:** Borates are non-volatile. As a dust borates rapidly settle from the atmosphere. b) **Water:** Borates are naturally occurring minerals and are present in surface and underground waters. Borates are rapidly dissolved in water and will disperse with dilution. Removal at low concentrations is unnecessary. Where water containing high levels of borates can be captured precipitation with lime can be used to reduce boron levels to the 100ppm range. Treatments with boron specific ion exchange resins and activated carbon are also possible. c) **Soil:** Borates are naturally found in rocks and soil and are an essential micronutrient for all plant growth. Contaminated soil can be leached with water or acid to reduce boron levels.	
8.5 Waste Management	Small quantities can usually be disposed to landfill sites. No special disposal treatment is required, but local authorities should be consulted about any specific local requirements. Tonnage quantities of products are not considered appropriate for landfills. Such products should, if possible, be used for an appropriate application.	

8.6 Unintended side effects	Borates are essential micronutrients for all plant life but at high levels they are phytotoxic.

	Evaluation by Competent Authorities
	~~Use separate "evaluation boxes" to provide transparency as to the comments and views submitted~~
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27-May-08
Materials and methods	Section 8.1 Information on container material is given in Doc IIIA3.17
Conclusion	Adapted in doc IIC and Doc I
Reliability	-
Acceptability	acceptable
Remarks	-
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	