Compound	Route	duration of study	Species Strain	Results	NOAEL (mg B/kg bw/d)	LOAEL (mg B/kg bw/d)	Reference
							Report Series No. 324, 1987
Boric acid	Oral in diet	2 year	Mouse, B6C3F1	Testicular atrophy, loss of spermatogenia. and various stages of spermatogenesis of the seminiferous tubules	48	96	National Toxicology Program (NTP) Technical Report Series No. 324, 1987
Boric acid	Oral in diet	2 year, interim kills at 6 and 12 months	Rat Sprague Dawley	testicular atrophy	17.5	58.5	Weir, 1966a
Borax	Oral in diet	2 year, interim kills at 6 and 12 months	Rat Sprague Dawley	testicular atrophy	17.5	58.5	Weir, 1966b
Boric acid	Oral in diet	90 days	Dog Beagle	reduction in testes weight, histopathological changes	0.46	4.2	Paynter, 1963a
Borax	Oral in diet	90 days	Dog Beagle	reduction in testes weight, histopathological changes	0.39	4.7	Paynter, 1963b

The lowest NOAELs for effects on the testes were observed in two concurrent 90-day dietary studies in the dog, performed with boric acid and borax (O. E. Paynter, 1963a,b). Group size was 5 dogs per dose group. In these studies, at a dose of about 4 mg Boron/kg bw/day, reductions in relative testes weight were observed. In the study with boric acid a statistically significant 25% reduction in relative testis weight was observed at a dose level of 24 mg boric acid/kg bw/day, equal to 4.2 mg/B/kg bw/day. In the study with borax a 15% reduction (not statistically significant) in relative testis weight was observed at a dose level of 42 mg borax/kg bw/day, equal to 4.7 mg B/kg bw/day. Furthermore, at these doses of both boric acid and borax, in the testes of the males histological changes, described as 'artifactual distortion of the tubules in the outer one-third of the glands' were observed. Although these changes are described as artifactual, it is striking that they were found in all males at this dose, but not in males of the control or the low dose groups. Therefore these histological changes observed at the mid-dose are considered by the present evaluators to be a consequences of a boron-related alteration of the structure of the testes. Since at this dose also the testes weights were reduced, the histological changes are considered to be toxicologically relevant. The NOAELs, expressed as boron equivalents, in the boric acid and borax studies were 0.46 and 0.39 mg B/kg bw/day, respectively. Based on these two studies the overall NOAEL for this effect is considered to be 0.46 mg/kg bw/day. The original study reports of these two 90-day studies in the dog were provided by the notifier.

It was noted that in the two 90-day dog studies it was not mentioned which statistical tests were used to determine whether changes in testicular weight were significant, which could be a reason for criticism on the study. We therefore subjected the individual animal data (boron consumption, testes weight and testes/body weight ratio) to a dose-response modeling, in order to provide a Bench Mark type approach using all the individual data in this study (see Appendix). For this a program developed by RIVM (PROAST) was used. PROAST is a

widely accepted dose-response modeling program used also in international evaluations (e.g. within the WHO/FAO JECFA committee and EMEA/CVMP). Our analysis indicates that no statistical difference could be found between the studies with boric acid and borax. Therefore, the data are allowed to be pooled providing a control group of n=5 and a treatment group with n=9-10/dose. This analysis indicated that the critical effect dose for a 5 or 10% change in testicular weight (critical effect size) was 1.2 (90% confidence interval (CI) = 0.59 - 3.01) mg B/kg bw/day or 2.6 (90% CI =1.27 - 6.39) mg B/kg bw/day respectively. These values of the critical effect doses are in between the NOAEL and LOAEL determined from the boric acid study, with the lower confidence limits close to the NOAEL of 0.46 mg/kg bw/day. This dose response analysis strongly supports the choice of the NOAEL being 0.46 mg/kg bw/day. At present, there is no general agreement on the choice for a CES for changes in testicular weight. Therefore, the NOAEL of 0.46 mg B/kg bw/day is used as a Point of Departure for setting the AOEL.

In addition, for the present evaluation two 2-year dietary studies in the dog with boric acid and disodium tetraborate decahydrate were available (Weir, 1966c,d; 1967a,b). In these studies the testes were identified as a major targer organ. However, since these studies had a number of deficiencies, they were considered by the present evaluators not acceptable for use in risk assessment.
Also two multigeneration reproduction toxicity studies in the rat with boric acid (Weir, 1966c) and disodium tetraborate decahydrate (Weir, 1966d) were available. In these studies again the testes were identified as a major target organ. However, since these studies had a number of deficiencies, they were considered by the present evaluators not acceptable for use in risk assessment.

Weir and Fisher, Toxicol. Appl. Pharmacol 23 (1972)pp 351-364.
It appears that a number of evaluations performed within other frameworks are partly based on a description of the dog studies in an article in published literature by Weir and Fisher. In this article a very concise, and not completely accurate description of the 90-day and 2-year dog studies was presented. With respect to the 90-day dog study, the Weir and Fisher article reports that the mid dose (25.1 mg/kg bw/day) boric acid induced a reduction in testes/body weight ratio, but no histological change in the testes. No further information on the mid-dose groups of dogs treated with boric acid or borax is presented. The article further reports that in the 90-day study both boric acid and borax induced a significant reduction in testes/body weight ratio, and testicular atrophy at the high dose. For the high-dose groups data on testes weight and testes/body weight ratio are presented.
With respect to the 2-year dog study, it is reported that boric acid and borax did not cause any effects up to dose levels 62.4 and 84.7 mg/kg bw/day respectively, and that a 38 weeks exposure to boric acid or borax at levels of 233 and 338 mg/kg bw/day respectively causes decreased testes weight, testicular atrophy and spermatogenic arrest. However, the authors fail to discussion some serious flaws in the 2-year study, e.g. that conclusion are drawn upon data from 1-2 animals/dose group and that testicular atrophy was observed in some control dogs. Since for the present evaluation of borates within the framework of biocides, the original study reports were available, we based our assessment on these study reports rather than on the publication of Weir and Fisher.

Discrepancy with evaluations within other frameworks

The toxicology of simple borates has also been evaluated within other frameworks. We noticed that in these other evaluation in general the overall NOAEL was based on

developmental effects observed in a developmental toxicity study in the rat (Price et al., 1994). In this study the NOAEL was 55 mg boric acid/kg bw/day (equal to 9.7 mg B/kg bw/day) based on reduced fetal bodyweight and increased incidence of short rib XIII at 76 mg boric acid/kg bw/day (equal to 13.3 mg B/kg bw/day).

In order to explain the reason for the apparent discrepancy in the choice of the critical endpoint between our evaluation for biocides and the other evaluations, we looked into the data base of the other evaluatons upon which the overall NOAEL was based, and to the justification for choosing the developmental effects in the rat rather than the testis effects in the dog as the critical endpoint.

Below, a number of toxicological evaluations of borates are discussed.

Environmental Health Criteria 204 (IPCS, WHO, 1998)
The evaluation of the WHO task group on Environmental Health Criteria for Boron appears to be based upon data from published literature.
The 90-day dog studies, as described by Weir and Fisher (1972) are mentioned in the EHC204 document. On page 75 it is mentioned that indeed in the 90-day study with boric acid in the dog a statistically significant reduction of 25 and 40% in testes weight was observed in the mid and high-dose group. However, the information concerning the reduction in testes weight in the mid-dose animals is not presented in the summarising table on page 79. In addition the data from the 2-year dietary studies in the dogs, also as described by Weir and Fisher (1972) were discussed. On the basis of the deficiencies in the 2-year dog studies, EHC204 concluded that these 2-year studies were considered not suitable for inclusion into the risk assessment.
No further mention of the 90-day dog studies was made, probably since the Weir and Fisher article presents only limited data on these studies. But it was not stated that this particular experiment neither the species used (dogs) would be irrelevant. In the EHC204 document the study on the developmental effects in the rat is considered the provide the overall NOAEL of 9.6 mg B/kg bw/day.

US-EPA. Toxicological review of boron and compounds, June 2004
US-EPA describes the 90-day dog studies with boric acid and borax. In addition to the testicular effects in the high dose groups, it is stated that "decreased testes:body weight ratio was also observed in one dog from the mid-dose boric acid group". It is not clear why the US-EPA came to the latter conclusion (in fact 4 out of 5 dogs of the mid-dose group have a testes/body weight ratio outside the range of the control group). The 2-year studies in the dog were considered not to be adequate for establishment of a defensible NOAEL. It is not clear whether the original studies were available for the US-EPA evaluation, or whether it is based on the Weir and Fisher publication of 1972, although the remark about just one dog from the mid-dose group having a decreased testes: body weight ratio may suggest that the original study report was available to the US-EPA.
The study on the developmental effects in the rat is considered the provide the overall NOAEL of 9.6 mg B/kg bw/day.

ECETOC Technical report No. 63 (1995)
The reproductive and general toxicology of borates has been evaluated by an expert group on behalf of ECETOC. In the bibliography of the ECETOC Technical report reference is made to *"Weir and Fisher, 1961-1967. Full toxicologic study reports on borax and boric acid. Volume 1-8, prepared for US Borax."* It is not clear whether the 90-day dog studies are described in

the Weir and Fisher 1961-1967 report. Furthermore, for the ECETOC report the Weir and Fisher article (1972) was also available. Nevertheless, in the ECETOC report the 90-day dog studies are not mentioned at all. The 2-year studies in dogs as described by Weir and Fisher, are discussed. Due to their deficiencies these studies ECETOC considers the 2-year studies not suitable for use in Risk Assessment
In the ECETOC document the study on the developmental effects in the rat is considered the provide the overall NOAEL of 9.6 mg B/kg bw/day.

EFSA: Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Boron (Sodium Borate and Boric Acid). Request No EFSA-Q-2003-018 (July 2004)
The evaluation of the EFSA Scientific panel is based upon information from published literature. Again it is mentioned that in the 90-day dog study (as described by Weir and Fisher, 1972) at the mid- and high dose significantly lower testes weights were observed. The 90-day studies are however not further mentioned in the document. So no reason was provided for neglecting the study or the animal species. The 2-year dog studies were considered equivocal. The study on the developmental effects in the rat is considered the provide the overall NOAEL of 9.6 mg B/kg bw/day.

WHO guideline for drinking-water quality. Addendum to Volume 1. WHO 1998
Evaluation based upon EHC204 (1998). The testes are recognized as a target in mice, rats and dogs. The drinking water limit is based upon the NOAEL of 9.6 mg/kg bw/day from the developmental toxicity study in the rat. Apart from the developmental study no individual studies are described at all.

US-Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile: Boron
The ATSDR mentions that in animals, boron affects gonads in dogs, rats and mice. It is stated that the data suggest that dogs are more sensitive than rats or mice. The evaluation is only based on data from published literature (among others Weir and Fisher, 1972). In the summarizing table 2-2, 'Levels of significant exposure to Boron and compounds-oral' composed by ATSDR, the NOAEL and LOAEL for the testes effects in the dog are set at 4.4 and 44 mg Boron/kg bw/day, respectively. In view of the lack of information on the testes effects at 4.4 mg Boron/kg bw/day, provided in the Weir and Fisher article it is easy to understand why ATSDR concluded this was the NOAEL.

Commission Working Group of Specialized Experts in the fields of Reprotoxicity. Summary record 1.a: Boric acid and Borates. ECBI/132/04 Rev2, 2004
The reproduction and developmental effects of boric acid and the borates were discussed by the Working Group of Specialized Experts. A representative from the industry maintained that reprotoxic properties were not disputed, but did not merit classification. Among others, the representative referred to a dog study of very poor quality. The Expert Working Group concluded that boric acid and borates have an adverse effect on fertility in rat, mouse and dog, and development in rat, mouse and rabbit. The experts recommend to classify boric acid and the borates with Repr. Cat. 2; R60-61.
Remark: The original 90-day dog studies were not discussed. The reference of the representative from the industry to the dog study of poor quality presumably concerns the 2-year study in the dog. It should be noted that the Expert Working Group identifies the hazards of the substance and does not determine overall NOAELs, ADIs, AOELs etcetera.

Discussion

The toxicology of borates has been evaluated within many frameworks. Although it is recognized that the testes is a target organ in mice, rats and dogs, and that in this respect the dog may be more sensitive than rats and mice, the dog data are not used to set the NOAEL. However, many, if not all of these evaluations appear to be based upon data from published literature. In published literature (i.e. Weir and Fisher, 1972) the description of the dog data is not completely adequate and very concise. In particular the description of the 90-day studies in the dog is very limited. Since the 2-year studies in the dog, also described in the same publication, have serious deficiencies, these studies are generally discarded as being inadequate to include in risk assessment. None of these evaluations discarded the dog as an irrelevant or hypersensitive species (compared to humans). None of these evaluations provided specific reasons for not including the 90-day dog studies. Apparently, the limited description of the 90-day studies by Weir and Fisher and the poor quality of the 2-year studies, led to the exclusion of these data in the risk assessment.
The original study reports from the 90-days studies in the dog were available for the present evaluation. Although the studies are old, not according to GLP, and have limitations, they were considered by the present evaluators to be acceptable for use in risk assessment. The effects of boron on the testes of the dogs are in line with findings in other species and are marked (relative testes weight reduction: 25 and 40% for boric acid mid- and high-dose groups, 15 and 50% for borax mid- and high-dose groups). Dose response modelling supports the choice of the NOAEL.
The discrepancy in the choice of the overall NOAEL between the present evaluation and evaluations performed within other frameworks may be caused by the different data sets available for the evaluations.

Justification of the used assessment factors

For the present evaluation the default assessment factor of 100 was used. With respect to toxicodynamics of borates, no data on human intraspecies variability or relative sensitivity of humans compared to other species are available. With respect to toxicokinetics of borates, little information is present. The available data do indicate however that substantial differences in toxicokinetic exist (e.g. elimination half-lives of 1h in the mouse, 3h in the rat and 21h in humans are reported). In view of this, we considered that there was insufficient evidence to deviated from the default assessment factors.

EHC 204
EHC 204 (1998) considered it not appropiate to deviate from the inter- and intraspecies factor of 2.5 and 3.2 for toxicodynamics. With respect to toxicokinetics EHC204 considered that an interspecies factor of 1.25 (default =4) was appropriate since it was argued that no marked interspecies were observed in the extent of oral absorption, metabolism, distribution and excretion. With respect to intra-human variability in toxicokinetics it was argued that a reduction of the default value of 3.2 to 2.5 was justified in view of the lack of boron metabolism.

Based on the reasons given above, EHC204 considered a total assessment factor of 2.5 x 3.2 x 1.25x 2.5= 25

WHO Guidelines for drinking water quality
The evaluation of The Working group on Chemical Substances in Drinking Water was based on the EHC204 (1998). The Working group took note of the lower uncertainty factor

proposed in EHC204 by decided to use a more conservative uncertainty factor. The Working group considered it not appropiate to deviate from the default inter- and intraspecies assessment factors for toxicodynamics, and the interspecies default assessment factor for toxicokinetics. With respect to intraspecies variability it was noted that an increased glomerular filtration rate (GFR) is a recognized physiological adaptation in pregnancy. Accordingly it can be assumed that renal clearance of boron is increased in pregnant women. Based on data on human mean GFR in pregnancy and intraspecies variation of this factor it was concluded that the standard intraspecies factor of 3.2 could be reduced to 1.8, resulting in a total uncertainty factor of 60. This was considered appropriate since the Working Group considered that developmental toxicity in the rat was the critical endpoint for borates. A detailed description can be found in Dourson et al., Biological Trace Element Research, V66 (1998) pp. 453 - 463.

Discussion

The general view within different frameworks appears to be that there are no data available to justify a deviation from the default assessment factor for toxicodynamics. Both EHC204 and the WHO Working Group for Drinking Water considered it appropriate to decrease the assessment factor for toxicokinetics. We recognize that borates are simple compound that, in the body, will be predominantly be present as boric acid, which will not under go further metabolism. Accordingly, the default assessment factor for toxicokinetics of borates may be conservative. However, we consider to have no actual data to justify a reduction of the standard assessment factor.
Should the developmental toxicity in rats be considered as the critical endpoint for borates, then the increased glomerular filtration rate during pregnancy could be used as an argument to reduce the intraspecies assessmentfactor for toxicokinetics. However, since we considered the testes effects to be the critical endpoint, the increased renal clearance during pregnancy does not justify a reduction of the standard assessment factor.

Discussion of the risk assessment of naturally occurring substances

The toxicological data base reveals that a major target for toxicity of borates is the testes. Based on the testes effects in the 90 days feeding studies with boric acid and borax in dogs an overall NOAEL of 0.46 mg B/kg bw/day was established.
For the general population the average daily intake of boron through food is about 1.2 mg per day (WHO, 1998). Drinking water on average contains 0.1 - 0.3 mg boron per liter (WHO, 1998), although in some regions much higher concentrations (up to 29 mg/L) have been reported (Sayli, 1998). Based on the intake of boron through food and drinking water, the average daily exposure for the general population will be 1.4 - 1.8 mg, equal to 0.023 - 0.03 mg B/kg bw/day for a person weighing 60 kg. In subpopulations with relatively high food and water intake, such as children, or in populations living in regions with high boron levels in the drinking water exposure may be considerably higher. In view of the LOAEL of 4.2 mg B/kg bw/day and the NOAEL of 0.46 mg B/kg bw/day in the 90-day dog study it can be concluded that the margin between the daily exposure level to boron and the levels at which toxic effects are observed in experimental animals is small.
A small margin between background exposure levels and levels at which toxicity occurs is not uncommon for substances from natural sources (e.g. copper, selenium). It appears that the traditional methodology for risk assessment, based on application of assessment factors to data from animal toxicity studies may be not adequate to perform risk assessment for these naturally occurring substances.

References

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[redacted]

1963a.

[redacted]

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[redacted]

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[redacted]

1966a.

[redacted]

1966b.

[redacted]

1966c

[redacted]

1966b.

[redacted]

1967d.

[redacted]

1967b.

[redacted]

1966c.

[redacted]

1966d.

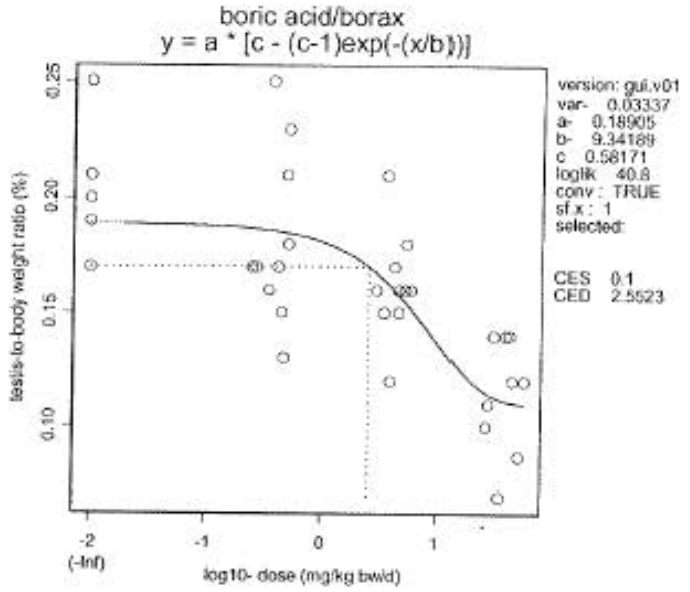
WHO. Guidelines for drinking-water quality, Addendum to Volume 1, 1998.

Appendix a

group	# dog	substance (mg/kg bw/d)	Boron (mg/kg bw/d)	testes weight	rel. testes weight	av. rel. testes weight.
1	4521	0	0	18,6	0,2	
1	4912	0	0	20	0,19	
1	4932	0	0	20	0,21	
1	4939	0	0	14,6	0,25	
1	4970	0	0	12,8	0,17	0,204
2	4595	3	0,53	22	0,25	
2	4800	2,7	0,47	18,5	0,23	
2	4917	2,4	0,42	17,5	0,18	
2	4921	2,1	0,37	21	0,21	
2	4972	2,9	0,51	15	0,17	0,208
		2,62	0,46			
2	4922	20	3,5	17	0,15	
2	4925	30	5,3	14	0,16	
2	4928	31	5,4	17	0,18	
2	4935	23	4	13	0,12	
2	4937	17	3	10,5	0,16	0,154
		24,2	4,24			
2	4798	172	30	13	0,14	
2	4927	153	27	9,5	0,11	
2	4933	150	26	9	0,1	
2	4967	312	55	10,5	0,12	
2	4983	216	38	10,5	0,14	0,122
		200,6	35,2			
3	4879	4,2	0,47	10	0,13	
3	4882	3,1	0,35	14	0,16	
3	4904	3,7	0,42	18	0,17	
3	4920	2,4	0,27	17,5	0,17	
3	4968	4	0,45	12,5	0,15	0,156
		3,48	0,392			
3	4914	33	3,7	24,5	0,21	
3	4936	38	4,3	14	0,17	
3	4971	42	4,7	12	0,15	
3	4973	53	6	14	0,16	
3	4984	42	4,7	14,5	0,16	0,17
		41,6	4,68			
3	4875	302	34	6	0,07	
3	4918	360	41	14	0,14	
3	4977	390	44	10	0,12	
3	4979	443	50	8,4	0,087	0,10425
		373,75	42,25			

Individual animal data from the 90-day dog studies
groups: 1 = control, 2= boric acid, 3= borax

Dose-response modeling (PROAST) of data from 90-day studies with boric acid and borax in the dog



Critical Effect Size (CES)	Critical Effect Dose (CED) (90% Confidence Interval) in mg Boron/kg bw/d
-5%	1.189 (0.593 – 3.013)
-10%	2.552 (1.269 – 6.388)

Section 6.4 Annex Point IIA 6.4	Sub-Chronic Toxicity Section: 6.4.2 Dermal; 6.4.3 Inhalation	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [x] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [ ]	
Detailed justification:	▪ **Dermal 6.4.2** A dermal repeated dose study is not necessary. TNGs P 39 states that a subchronic dermal study should not be required for substances with low dermal toxicity, e.g. substances which have shown no toxic effects in the 28 day study at limit-dose. However, TNsG P39 also states that Repeated dose toxicity (dermal) is required 'where potential dermal exposure is significant and route-to-route extrapolation is not possible'. From dermal absorption studies (see Doc IIIA A_6.2 Percutaneous Boric acid.doc; Doc IIIA A_6.2 Percutaneous BO read across.doc; DOC IIIA A_6.2 Percutaneous DOT.doc; Doc IIIA A_6.2 Percutaneous Tetraborates.doc) no significant absorption occurs for any borate. In addition, due to the simple toxicokinetics of borates extrapolation from route to route is possible. Therefore the borates are likely to be of low dermal toxicity and no further animal testing is warranted. ▪ **Inhalation 6.4.3** An inhalation repeated dose study is not necessary TNGs P 39 states that a subchronic inhalation toxicity test is required for volatile substances and gases (vapour pressure >1x 10- Pa) and also where inhalation exposure is significant an inhalation study is required instead of the oral'. Since the vapour pressure of all borates is low and also and 100% absorption by inhalation can be assumed therefore extrapolations can be made, then no inhalation test is required. Therefore no further animal testing is warranted.	
Undertaking of intended data submission [ ]	In the interests of animal welfare and protecting Laboratory animals no further testing is deemed necessary	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	24 March 2005
Evaluation of applicant's justification	The justification of the applicant for the non submission of studies with repeated dermal or inhalation administration is acceptable.
Conclusion	The justification of the applicant is 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	

Section 6.5 **Chronic toxicity**

Annex Point IIA6.3 / 6.4 / 6.5

Section 6.5; Oral; Rat Boric Acid

Official use only

2 REFERENCE

Reference

[redacted] 1966). Two-year dietary feeding study - albino rats. Boric acid [redacted]

Electronic File

Data protection

Yes

Data owner

[redacted]

Companies with letter of access

Curent Access

[redacted]

Criteria for data protection

Data on new a.s for first entry to Annex I/IA

GUIDELINES AND QUALITY ASSURANCE

Guideline study

No

Predates Guidelines, there is another (see 6.7) 2 year study in mice carried out by the US NTP. In addition there are a number of other old studies and literature studies that support the results and NOAELS observed. Therefore in the interests of animal welfare and protecting Laboratory animals no further testing is deemed necessary.

GLP

No

Although this is an old, pre GLP study, there is another 2 year study in mice carried out by the US NTP. In addition there are a number of other old studies and literature studies that support the results and NOAELS observed. Therefore in the interests of animal welfare and protecting Laboratory animals no further testing is deemed necessary.

Deviations

MATERIALS AND METHODS

Test material	Boric Acid
Lot/Batch number	not available
Specification	As given in section 2 of boric acid and Sodium Tetraborate
2.1.1.1 Description	Fine white powder with no odour
2.1.1.2 Purity	> 99%
2.1.1.3 Stability	Stable
Test Animals	Non-entry field
Species	Rat
Strain	Sprague Dawley
Source	not specified
Sex	male and female
Age/weight at study initiation	Age not specified; Weight males 93-129g ; females 86-128g
Number of animals per group	35 per sex per group for treated and 70 per sex per group for controls
Control animals	Yes
Administration/ Exposure	Oral (fill in respective route in the following, delete other routes)
Duration of treatment	2 years (5 per sex per group were killed at 6 and 12 months)
Frequency of exposure	Daily
Postexposure period	None
Oral	
2.1.1.4 Type	in food

2.1.1.5 Concentration	0; 670 (117); 2000 (350); 6690 (1170) ppm boric acid (ppm as boron equivalents) equivalent to 0, 33 (5.9), 100 (17.5), 334 (58.5) mg boric acid (B)/kg bw per day ad libitum
2.1.1.6 Vehicle	Dry mix with feed
2.1.1.7 Controls	plain diet
Examinations	
Observations	
2.1.1.8 Clinical signs	yes: recorded weekly for first 52 weeks then 4 weekly.
2.1.1.9 Mortality	yes: recorded daily
Body weight	yes: recorded weekly for first 52 weeks then 4 weekly.
Food consumption	yes: recorded weekly for first 52 weeks then 4 weekly.
Water consumption	no: given ad libitum
Ophthalmoscopic examination	no
Haematology	yes at 1, 2, 3, 6, 12, 18 and end of study on 5 per sex per group. Parameters: Haematocrit, haemoglobin concentration, erythrocyte count, total and differential leukocyte count.
Clinical Chemisty	yes: At interim sacrifice at 6, 18 and 24 months blood pH, sodium, potassium, chloride, carbon dioxide combining power on 2 rats per sex per group. At 6, 12 and 24 months SGPT and SGOT were determined in 5 rats per sex in the control and high dose group.

Urinalysis	yes: at 6 months on individual samples from 2 rats per sex per group for 5 days; also at 18 and 24 months on pooled samples from 5 per sex per group Parameters: appearance, volume, osmolality, specific gravity, pH, protein, glucose, blood, acetone, bilirubin and microscopy.
Sacrifice and pathology	
Organ Weights	yes organs: liver, kidneys, adrenals, testes, thyroid, spleen, brain.
Gross and histopathology	yes: At 6 and 12 months 5 rats per sex per group, all interim deaths and at termination in 10 per sex per group in controls and high dose surviving animals. organs: brain, pituitary, thyroid, stomach, small and large intestines, liver, pancreas, kidneys, adrenals, spleen, heart, lungs, gonads, urinary bladder, sternum, rib junction and all unusual lesions. In addition, 10 rats per sex per group from the mid and low dose groups had gonads examined histologically.
Other examinations	samples of blood, brain, liver and kidney were taken at 6, 12 and 24 months and frozen for boron analysis.
Statistics	yes as appropriate.
Further remarks	

RESULTS AND DISCUSSION

See Tables A6_3-1 and A6_3-2

Observations	
Clinical signs	No signs in the low and mid dose groups. Coarse hair coats, hunched position, swollen pads and inflamed bleeding eyes were observed in animals receiving the highest dose of boric acid
Mortality	Survival at 6, 12 and 24 months was comparable in all groups including controls.
Body weight gain	No difference from controls in the low and mid dose group. Retarded body weight gain in animals receiving the highest dose of boric acid.
Food consumption and compound intake	No difference from controls in the low and mid dose group. Reduced food intake in the highest dose group during weeks 1-13 sin males, and in weeks 1-13 and 42-52 in females.
Ophthalmoscopic examination	Not done

Blood analysis

Haematology

No difference from controls in the low and mid dose groups. Significantly decreased red cell volume and haemoglobin were observed in the high dose group males at 3, 6, 12, 18 and 24 months. Results shown in Table A6_3-2.

Results quoted from the Study: 'Hemoglobin values for the males in the high level test group were consistently below the normal range for adult male rats. Cell volume values for this group were, at most periods of determination, also below normal or within low normal range. The total leukocyte counts for the high level males were lower than those for the male controls at each determination but generally within normal limits. The hematological values determined during the first year for the low and intermediate level males and the females at all three test levels were generally within normal limits and comparable with the control values.

Clinical chemistry

no significant differences between groups.

Urinalysis

no significant differences between groups.

Sacrifice and pathology

Organ weights

The testes weights and the testes/bodyweight ratios were significantly lower in the high dose group than those of control animals. The brain- and thyroid-to-bodyweight ratios in the high dose females were significantly higher than those of controls. This was thought to relate to the reduced bodyweight of the animals.

Gross and histopathology

Atrophic testes were found in all males exposed to the high dose (334 (58.5) mg boric acid (B)/kg bw) of boric acid at 6, 12 and 24 months. Microscopic examination of the tissue revealed atrophied seminiferous epithelium and decreased tubular size in the testes. Cysts in the eyelids, probably in the Meiobomian glands were observed in 4 high dose females, probably related to treatment. There was no treatment related increase in tissue masses.

Other

none

APPLICANT'S SUMMARY AND CONCLUSION

Materials and methods

Non guideline 2 year dietary feeding study in Sprague Dawley rats, 35 per sex per treated group and 70 controls per sex with interim kills of 5/sex/group at 6 and 12 months

Results and discussion

Testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months at the highest dose level only. No treatment related effects were observed in the mid and low dose groups.

Conclusion

LO(A)EL

In males 334 (58.5) mg boric acid (B)/kg bw caused testicular atrophy. In females 334 (58.5) mg boric acid (B)/kg caused reduced bodyweight.

NO(A)EL

In males and females 100 (17.5)mg boric acid(B)/kg bw.

Other

Reliability

2

Deficiencies

Although an old study, data are clear and acceptable.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	14 February 2005
Materials and Methods	The version of the applicant is acceptable.
Results and discussion	In addition to the description of clinical signs by the applicant, in the high dose group desquamation of the skin of the tail and the pads of the paws and marked respiratory involvement, were observed. In all males of the high dose group the scrotum appeared shrunken. As compared to the control group, in the high-dose group marked reductions in body weight were observed (19 and 32% in males and females respectively). These reductions may be the result of a reduced food consumption in these animals. At the high dose the testes weights and the testes/bodyweight ratios were significantly lower than those of control animals. The reduction was already observed at 26 weeks and the extent of the reduction did not increase over the course of the treatment period. No effect on relative testes weight were observed at the other dose groups at 26, 52 or 104 weeks. Haematology: Hemoglobine levels and red cell volume were consistently reduced in males of the high dose groups throughout the study. Occasionally, significant reductions in these parameters were found in males of the low- and mid-dose groups. Significant reductions in white blood cell counts were observed in males of the high dose group at 30 days and 24 months. Since only 5 animals per group were sampled the statistical power is low. In general, the number of animals per dose group, and the number of animals used for clinical chemistry, haematology, urinalysis gross and histopathology were low.
Conclusion	LO(A)EL: 6690 ppm, equivalent to boric acid doses of 334 mg/kg bw/day (equal to 58.5 mg B/kg bw/day), based on testicular atrophy and haematological effects in the males. NO(A)EL: 2000 ppm, equivalent to boric acid doses of 100 mg/kg bw/day (equal to 17.5 mg B/kg bw/day.
Reliability	3
Acceptability	acceptable
Remarks	The study doesn't comply with present requirements for a chronic rat study. Since haematology, clinical chemistry and urinalysis was performed on samples of only 5 animals/sex/dose the statistical power of the study is low. However, the data can be used for the purpose of risk assessment.
	COMMENTS FROM ... *(specify)*
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 A6_3-1. Results Chronic Rat Study

Parameter	Control		low dose		medium dose		high dose		dose-response +/-	
	m[a]	f[a]	m[a]	f[a]	m[a]	f[a]	m[a]	f[a]	m	f
number of animals examined	70	70	35	35	35	35	35	35		
Mortality at 104 weeks	25/60	20/60	12/25	8/25	9/25	7/25	6/25	8/25		
clinical signs*										
bodyweight gain 0-104 weeks (g)	557	405	533	334	563	349	429	264		
food consumption at week 52 (g/kg/day)	33.3	43.7	34.7	44.6	34.9	45.7	40.2	51.4		
clinical chemistry*	no differences									
haematology*	see separate table									
urinalysis*	no differences									
Organ x testes weight*(g) at 26 weeks	3.76±0.29		3.71±0.20		3.52±0.42		1.00±0.08 (sig low)			
testes weight (g) at 104 weeks	3.65±0.84		2.84±0.95 (Sig low)		3.43±0.47		0.92±0.22 (Sig low)			
microscopic pathology*Testis atrophy at 24 months	3/10		4/10		2/10		10/10			

** specify effects; for different organs give special findings in the order organ weight, gross pathology and microscopic pathology if there are effects*

[a] *give number of animals affected/total number of animals, percentage, or just ↑or ↓for increased or decreased*

Table A6_3-2. Summary of Haematological Haematological Data from 2 Year Rat Study Boric Acid

Months	Cell Volume (%)				Hb Value (g/100ml)				WBC Count (x10^3/cm^2)				RBC Count (x10^6/cm^2)			
	Male				Male				Male				Male			
	Control	0.067%	0.2%	0.67%	Control	0.067%	0.2%	0.67%	Control	0.067%	0.2%	0.67%	Control	0.067%	0.2%	0.67%
	0	5.9 mg B/kg	17.5 mg B/kg	58.5 mg B/kg	0	5.9 mg B/kg	17.5 mg B/kg	58.5 mg B/kg	0	5.9 mg B/kg	17.5 mg B/kg	58.5 mg B/kg	0	5.9 mg B/kg	17.5 mg B/kg	58.5 mg B/kg
1	42.6	45.3	42.7	39.0	14.5	14.2	14.2	12.6*	18.1	13.6	15.3	8.0*				
2	44.1	44.9	45.5	40.8*	14.7	14.1	14.4	13.2	19.3	18.4	16.8	14.7	8.2	7.68	7.98	7.00*
3	45.9	46.7	45.7	39.7*	15.7	15.2	14.9	13.3*	20.9	23.4	19.4	16.7	7.14	6.72	7.47	6.47
6	45.4	45.9	46.5	44.6	15.4	15.0	14.2	13.7*	19.4	15.6	14.3	15.3				
12	47.3	45.5	44.8	41.4*	14.1	13.2	13.4	12.6*	10.9	10.9	10.9	10.5				
18	47.8	43.2*	42.8*	39.2*	15.6	14.9	13.8*	12.7*	23.4	22.9	19.5	18.4	5.16	5.46	5.55	4.92
24	46.4	36.4*	43.8	41.68	14.7	11.9	13.6*	12.8*	19.8	18.1	14.3	13.2*	7.09	5.72	7.35	7.90
	Female				Female				Female				Female			
1	42.1	44.5	42.4	43.3	14.6	15.3	14.3	14.0	19.8	20.9	17.3	14.7				
2	41.7	43.7	43.0	40.8	14.9	15.2	14.4	14.7	16.6	28.9	17.1	17.4	7.36	7.44	7.46	7.57
3	44.2	47.2	45.1	42.0	14.9	15.7	14.0	14.2	26.6	19.0	18.6	21.1	5.64	7.03	6.47	6.52
6	43.3	44.7	Data missing		14.5	14.8	Data missing		14.6	14.1	Data missing					
12	42.8	43.9	41.8	40.6	12.9	13.2	13.2	12.6	9.5	13.5	7.3	11.4				
18	43.0	43.0	42.8	39.3*	14.8	13.9	14.6	13.6	10.9	11.5	16.4	11.6	6.58	6.11	5.69	5.73
24	46.2	45.6	44.4	41.6	14.4	13.2*	13.0*	12.5*	17.6	12.8	11.3	10.5	6.22	6.24	6.22	5.92.

* Significantly different from controls

Missing data not thought to be significant according to the summary of the study

Section 6.5 **Annex Point IIA 6.5**	**Chronic Toxicity Second Study**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [x] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [ ]**	
Detailed justification:	▪ *Two Year Carcinogen Study – see Section 6.7*	
Undertaking of intended data submission [ ]	*In the interests of animal welfare and protecting Laboratory animals no further testing is deemed necessary*	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	14 Feb 2005	
Evaluation of applicant's justification	see data waiver second carcinogenicity study.	
Conclusion	The justification of the applicant is 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		

Section A6.6.1/6.6.2/ 6.6.3

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

Genotoxicity in vitro

A6.6.1 Bacteria In vitro

Official use only

3 REFERENCE

Reference

[redacted] 1991, Salmonella/microsome plate incorporation assay of boric acid. [redacted]

Electronic File

Data protection

Yes

Data owner

[redacted]

Companies with letter of access

Current Access

[redacted]

Criteria for data protection

Data on new a.s. for first entry to Annex I/IA / authorisation

GUIDELINES AND QUALITY ASSURANCE

Guideline study

Yes

US EPA 40 CRF Part 158; FIFRA, Section 158.340, Guideline 84-2. Comparable to OECD 471

GLP

Yes

Deviations

This study generally complies with OECD 471. However there is a failure to justify the maximum concentration of 2500 ug/plate

MATERIALS AND METHODS

In some fields the values indicated in the EC or OECD test guidelines are given as default values. Adopt, change or delete these default values as appropriate

Test material

As given in section 2

Lot/Batch number

As given in section 2

Specification

Boric acid, Granular Technical Grade >99.7%. [redacted]

3.1.1.1 Description

3.1.1.2 Purity

>99%.

3.1.1.3 Stability

Stable

Study Type

Select / delete as appropriate:
Bacterial reverse mutation test

Organism/cell type

Select / delete as appropriate:
S. typhimurium:
TA 1535, TA 1537, TA 97, TA 98, TA 100, TA 1538

Deficiencies / Proficiencies

Metabolic activation system

S9 mix
Aroclor 1254 induced Rat liver S9 at 4% and 10%

Positive control

Sodium azide; 9-Aminoacridinne hydrochloride;2-Notrofluorene;2-Anthramine

Administration / Exposure; Application of test substance

Non-entry field

Concentrations

10; 50; 100; 1000; 2500 µg/plate

Way of application

In water

Pre-incubation time

None

Other modifications

Examinations

Number of cells evaluated

4 RESULTS AND DISCUSSION

.

Non-entry field

Genotoxicity

No

without metabolic activation

No

with metabolic activation

No

Cytotoxicity

APPLICANT'S SUMMARY AND CONCLUSION

Materials and methods

US EPA 40 CRF Part 158; FIFRA, Section 158.340, Guideline 84-2. This study generally complies with OECD 471.

Results and discussion

Negative with and with out metabolic activation.

Conclusion

Negative

Reliability

1

Deficiencies

Yes

This study generally complies with OECD 471. However there is a failure to justify the maximum concentration of 2500 µg/plate. Although this study only complies generally to OECD 471 and therefore EU protocols, there are at least 3 other bacterial assays (one carried out by NTP and others in the literature) that confirm the data. – see IUCLID

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	15 February 2005
Materials and Methods	The applicants version is acceptable.
Results and discussion	The version of the applicant is adopted.
Conclusion	The version of the applicant is adopted.
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	

Section A6.6.2	**Genotoxicity in vitro**
Annex Point IIA 6.6.2	**A6.6.2 Chromosome Abberations**

Official use only

5 REFERENCE

Reference

National Toxicology Program (NTP) Technical Report Series No. 324.1987. Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F1 Mice (feed studies), US Department of Health and Human Services.

Electronic file

Data protection

No

No data protection claimed

Criteria for data protection

GUIDELINES AND QUALITY ASSURANCE

Guideline study

Yes

1985; NTP protocol Although this was carried out to an internal NTP protocol, it generally complies with OECD guidelines. Other literature data confirm the results. Also based on Galloway et al., 1985.

GLP

Yes

Deviations

No

MATERIALS AND METHODS

Test material

As given in section 2

Lot/Batch number

Specification

As given in section 2

5.1.1.1 Description

>99.7%

5.1.1.2 Purity

Stable

5.1.1.3 Stability

Study Type

In vitro mammalian cell gene mutation test

Organism/cell type	Chinese hamster Ovary (CHO)
Deficiencies / Proficiencies	
Metabolic activation system	S9 mix Aroclor 1254 induced rat (Sprague-Dawley)liver S9 fraction
Positive control	Mitomycin; Cyclophosphamide
Administration / Exposure; Application of test substance	Non-entry field
Concentrations	With S9: 1000;1600;2000; 2500 µg/ml Without S9: ; 500; 1500; 2000 µg/ml
Way of application	In water
Pre-incubation time	
Other modifications	
Examinations	
Number of cells evaluated	Not given

6 RESULTS AND DISCUSSION

Genotoxicity	Non-entry field
without metabolic activation	No
with metabolic activation	No
Cytotoxicity	No

APPLICANT'S SUMMARY AND CONCLUSION

Materials and methods	NTP protocol Although this was carried out to an internal NTP protocol, it generally complies with OECD guidelines. Other literature data confirm the results. Also based on Galloway et al., 1985.
Results and discussion	Negative
Conclusion	Non genotoxic
Reliability	2
Deficiencies	*No*

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16 February 2005
Materials and Methods	Under section 3.2: Study type, the authors incorrectly classify the study as an in vitro mammalian cell gene mutation test. In fact the study is an in vitro mammalian chromosome aberration test. Otherwise the version of the applicant is acceptable.
Results and discussion	The version of the applicant is adopted.
Conclusion	The version of the applicant is adopted.
Reliability	2
Acceptability	acceptable
Remarks	In the NTP document only a table with the results and a very concise description of the test is presented.
	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 A6.6.3 — **Genotoxicity in vitro**

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3 — *A6.6.3 In vitro Gene Mutation*

Official use only

7 REFERENCE

Reference

[redacted] 1991, SRI International, Mouse Lymphoma Cell Mutagenesis Assay of Boric Acid [redacted]

Electronic File

Data protection

Yes

Data owner

[redacted]

Companies with letter of access

Current Access

[redacted]

Criteria for data protection

Data on new a.s. for first entry to Annex I/IA

GUIDELINES AND QUALITY ASSURANCE

Guideline study

Yes

40 CFR Part 158 US-EPA-FIFRA, Section 156.340; Complies with OECD 476.

GLP

Yes

Deviations

no

MATERIALS AND METHODS

As given in section 2

Test material

Lot/Batch number

As given in section 2

Specification

Boric acid, Granular Technical Grade >99%. Supplied by US Borax Inc

7.1.1.1 Description

Boric acid, Granular Technical Grade >99%.

7.1.1.2 Purity

Stable

7.1.1.3 Stability

Study Type

In vitro mammalian cell gene mutation test

Organism/cell type

Mouse lymphoma L5178Y cells

Deficiencies / Proficiencies

Metabolic activation system

S9 mix or other

Aroclor 1254 induced rat (Fischer 344) liver S9 fraction used at 1%

Positive control

Hycanthone methylsulphonate; 3-methylcholnathrene

Administration / Exposure; Application of test substance

Non-entry field

Concentrations

0, 1.2, 1.7, 2.45, 3.5, and 5.0 mg/ml boric acid

Way of application

R_{OP} plus 5% heat treated horse serum

Pre-incubation time

Other modifications

Examinations

Number of cells evaluated

Approx 600/dose

8 RESULTS AND DISCUSSION

Describe findings. If appropriate, include table. Sample tables are given below.

Non-entry field

Genotoxicity

Negative

without metabolic activation

Negativer

with metabolic activation

Yes

Cytotoxicity

Concentration related cytoxicity (60% reduction over controls at 5 mg/m)l

APPLICANT'S SUMMARY AND CONCLUSION

Materials and methods

Gene mutation assay in L5178Y mouse lymphoma cells at the tk locus with and without metabolic activation

Results and discussion

Negative

Conclusion

Negative

Reliability

1

Deficiencies

No

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	16 February 2005
Materials and Methods	The applicants version is acceptable.
Results and discussion	The version of the applicant is adopted.
Conclusion	The version of the applicant is adopted.
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 A6_6_1-1. Table for Gene Mutation Assay (modify if necessary)

Concentration mg/ml	Number of mutant cells Per 10^6 Cell ± SD				Comments *give information on cytotoxicity or other*
	Exp 1	**Exp 2**	**Exp 1**	**Exp 2**	
	-S9	**-S9**	**+ S9**	**+S9**	
0	54± 10	42±1	29±10	36 ±7	
1.2	46±28	38±15	34±0	36±7	
1.7	39±17	31±9	41±7	49±4	
2.45	27±3	32±9	40±16	36±6	Minor Cytoxicity seen
3.5	31±18	46±1	41±13	41±6	Cytoxicity seen
5	50±22	41±5	53±2	47±3	Cytoxicity seen. Increase +S9 in first study not reproducible

Section A6.6.4 — **Genotoxicity in vivo**

Annex Point IIA6.6.4 — *Section A6.6.4*

APPLICANT'S SUMMARY AND CONCLUSION

Materials and methods

Results and discussion

Not necessary since all in vitro data is negative however, there is negative in vivo study given in IUCLID

Conclusion

Reliability

Deficiencies

	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 Feb 2005
Materials and Methods	Not applicable
Results and discussion	The version of the applicant is adopted
Conclusion	Not applicable
Reliability	Not applicable
Acceptability	0
Remarks	In the IUCLID chemical data sheet on boric acid (ECB homepage) an in vivo MN assay is described: [redacted]: Bone marrow erythrocytes micronucleus assay of boric acid in Swiss Webster mice. [redacted] 1991. [redacted]". In the EPA toxicological review (2004) the results are summarized as "no chromosomal or mitotic spindle abnormalities in bone marrow erythrocytes in the micronucleus assay in Swiss-Webster mice were found".

Section A6.7 **Carcinogenicity**
Annex Point IIA6.7 6.7 Mouse Oral Carcinogenicity Study

Official use only

9 REFERENCE

Reference

National Toxicology Program (NTP) Technical Report Series No. 324 1986. . Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F1 Mice (feed studies), October 1987, US Department of Health and Human Services.).

Electronic file

Data protection

None

GUIDELINES AND QUALITY ASSURANCE

Guideline study

Not cited but conforms to OECD Guide-line 451 although the full report is not published by the NTP. Sufficient detail is available to make an assessment of chronic toxicity and carcinogenesis although limited details are available and all individual animal data are not available.

GLP

Yes

Deviations

No

MATERIALS AND METHODS

Test material

As given in section 2 – Boric Acid

Lot/Batch number

As given in section 2

Specification

99.7%

9.1.1.1 Purity

Stable

9.1.1.2 Stability

Non-entry field

Test Animals

Mouse

Species

B6C3F1

Strain

Frederick Cancer Research Center, Frederick MD, USA

Source

male and female

Sex

Age/weight at study initiation	7 weeks; mean weights per group:males 21.6-21.8g, females 17.1-17.7g.
Number of animals per group	50 per sex per group
9.1.1.3 at interim sacrifice	none
9.1.1.4 at terminal sacrifice	41, 32 and 22 males, and 33, 33 and 37 females in the control, low and high dose groups respectively
Control animals	Yes
Administration/ Exposure	Oral
Duration of treatment	103 weeks
Interim sacrifice(s)	none
Final sacrifice	103 weeks
Freqency of exposure	daily
Postexposure period	none
	Oral
Type	in food
Concentration	in food 0, 2500, 5000 ppm equivalent to 0, 446 and 1150 mg/kg bw/d food consumption per day ad libitum
Vehicle	none, dry powdered diet
Concentration in vehicle	not relevant
Total volume applied	not relevant
Controls	plain diet

Examinations

Body weight	Yes
Food consumption	Yes
Water consumption	No
Clinical signs	Yes
Makroskopic investigations	Palpable masses, skin tumours
Ophthalmoscopic examination	No
Haematology	No
	Number of animals: Time points: Parameters:
Clinical Chemistry	No
	Number of animals: Time points: Parameters: Other
Urinalysis	No
	Number of animals: Time points: Parameters: Other
Pathology	Yes/No

9.1.1.5 Organ Weights

	No
	from: Organs:

Histopathology	Yes	
	from:	all dose groups and control
	from:	all animals unless excessively autolysed or cannibalised
	Organs:	at terminal sacrifice From all control and high dose groups and low dose animals dying before end: Brain, pituitary, thyroid, parathyroid, thymus, oesophagus, salivary glands, stomach, small and large intestines, liver, pancreas, kidneys, adrenals, spleen, heart, trachea, lungs, aorta, gonads, uterus, mammary gland, prostate, seminal vesicles, urinary bladder, gall bladder, vertebrae, mandibular and mesenteric lymph nodes, bone marrow, skin, eyes, tissue masses, abnormal regional lymph nodes, costochondral junction, From low dose group at end: lung, liver, stomach, kidney, salivary glands, testis, pancreas, and brain from males, and lung, liver, ovary and brain from females.
9.1.2 Other examinations	none	

Statistics

Further remarks

10 RESULTS AND DISCUSSION

See Table A6_7-1

Body weight

Bodyweight gain reduced during first year; mean final bodyweights were 7% and 13% below control values for exposed males and 7% and 20% below control values for females.

Food consumption

average daily consumption in low and high dose males was118% and 160% of controls, and in low and high dose females was118% and 136% of controls. These were thought to be probably related to spillage caused by reduced palatability.

Water consumption

not measured

Clinical signs

No treatment related signs observed

Macroscopic investigations

Survival in high dose males was significantly lower than controls after week 63, and in the low dose males after week 84 except for week 101. No significant differences in females. There was a dose related reduction in bodyweight gain after week 30 in both males and females.

Ophthalmoscopic examination

Not done

Haematology

Not done

Clinical Chemistry

Not done

Urinalysis

Not done

Pathology

No effects reported.

Organ Weights

Not done

Histopathology

An increase of testicular atrophy was seen at the high dose (3/49 control, 6/50 low dose and 27/47 high dose) and interstitial cell hyperplasia (0/49, 0/50, 7/47) in male mice. There was variable loss of spermatogenia, and various stages of spermatogenesis from the seminiferous tubules. No evidence of carcinogenicity was found.

Other examinations

No effects reported

Time to tumours

No treatment related tumours reported.

Other

None

APPLICANT'S SUMMARY AND CONCLUSION

Materials and methods

An OECD 451 study in B6C3F1 mice, 50 per sex per group treated in diet for 103 weeks with 0, 2500 or 5000 ppm boric acid.

Results and discussion

No treatment related increase in tumours observed. Dose related testicular atrophy and loss of spermatogonia and other spermatogenic cell types observed at termination.

Conclusion	No evidence of carcinogenicity (NTP classification meaning no chemically related increase in benign or malignant neoplasms).
Reliability	*2*
Deficiencies	Yes Not cited but conforms to OECD Guide-line 451 Although the full report is not published by the NTP, sufficient detail is available to make an assessment of carcinogenesis and histopathology.

	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 February 2005
Materials and Methods	dose: see results and discussion
Results and discussion	Dose conversion from ppm to mg/kg bw/day: It is likely that the higher level of food intake in the treatment groups is due to feed spillage. Therefore, the 2500 and 5000 ppm doses are considered to be equivalent to 275 and 550 mg/kg bw/day respectively, as described by the NTP study authors. In the males an increased incidence of extramedullary haematopoiesis in the spleen was observed at both doses.
Conclusion	The version of the applicant is adopted.
Reliability	2
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 A6_7-1. Results of Carcinogenicity study

Parameter	control data				low dose		medium dose		high dose		dose-response + /	
	historical		study									
	m	f	m	f	m	f	m	f	m	f	m	f
	If differing numbers of animals are examined, give number affected/number of animals examined for each individual finding.											
Number of animals examined			50	50	50	50	-	-	50	50		
Mortality			9	18	20	17			28	13	Y	N
clinical signs			0	0	0	0			0	0		
body weight gain			20.3g	27.2g	17.5g	24.1g			14.7g	18.8g	Y	Y
food consumption			na	na	na	na			na	na		
clinical chemistry			Not done									
haematology			not done									
urinalysis			not done									
Overall tumour incidence:			31	25	37	27			23	26	N	N
No. of animals with neoplasms			31	25	37	27			23	26	N	N
No. of animals with benign neoplasms			23	8	22	11			16	14	N	N
No. of animals with malignant neoplasms			13	20	23	15			11	17	N	N
No. of animals with > 1 neoplasm												

Section x.y **Annex Point x.y**	**(Sub)heading** *(specify where appropriate)*	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA *As outlined in the TNsG on data requirements, the applicant must always be able to justify the suggested exemptions from the data requirements. The justifications are to be included in the respective location (section) of the dossier.* *If one of the following reasons is marked, detailed justification has to be given below. General arguments are not acceptable*	Official use only
Other existing data [x] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [x]**	
Detailed justification:	A second carcinogenicity study is not specifically submitted for the following reasons 1. A chronic study in rats for boric acid and disodium tetraborate decahydrate has been submitted – see Doc IIIA A_6.5 Chronic rat Boric acid.doc and Doc IIIA A_6.5 Chronic Rat Tetraborates BA Entry.doc. The data requirements are "one rodent and one other mammalian species should be tested" and therefore there are 2 long term studies albeit both in rodents. Please note that the TNsG specifically mentions that for subchronic toxicity 'one rodent and one non-rodent' are required. A non-rodent study is not specifically mentioned for carcinogenicity therefore 2 rodent studies should suffice. 2. There is no genotoxicity potential for humans as indicated by both in vivo and in vitro genotoxicity tests 3. There are no structural alerts for carcinogenicity 4. The chronic study in rats and the carcinogenicity (chronic study) in mice indicate not concern for carcinogenicity, and identify the target organ as being the testis with no concerns for a carcinogenic response. 5. Sub chronic studies in rodents and non-rodents also indicate that the target organ is the testis with no indication of concern for a carcinogenic response. In addition the data in two year dogs, while being of limited value indicate that the dog is no more sensitive to the effects of borates than rats. 6. Various regulatory authorities have accepted that there is no concern of carcinogenicity such as EPA and WHO. In the interests of animal welfare and protecting Laboratory animals no further testing is deemed necessary	
Undertaking of intended data submission [ ]		

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	14 Feb 2005
Evaluation of applicant's justification	The applicant provides valid arguments for not submitting additional data on the carcinogenic potency of borates. It should be noted that, although the chronic studies in rats do not indicate that borates have a carcinogenic potency, in these studies only 10 animals per groups were macroscopically and histologically examined.
Conclusion	The justification of the applicant is 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	

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rabbit Developmental Toxicity Study**

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11 REFERENCE

Reference

Price CJ, Marr MC, Myers CB, Heindel JJ and Schwetz BA. 1991
Final Report on the Developmental Toxicity of Boric Acid (CAS No 10043-35-3) in New Zealand White Rabbits", National Toxicology Program, National Institute of Environmental Health Sciences (TER 90-003; NTIS Accession No PB92-129550) November 1991.
Laboratory Supplement (NTIS Accession No PB92-129568). December 1991
Plus Addendum March 1994 (Published)
Electronic file

Data protection

No

GUIDELINES AND QUALITY ASSURANCE

Section A6.8.1 **Annex Point IIA6.8.1**	**Teratogenicity Study** **Section A6.8.1 Rabbit Developmental Toxicity Study**
Guideline study	Yes NTP protocol; but conforms to OECD 414.
GLP	Yes
Deviations	
	MATERIALS AND METHODS
Test material	As given in section 2
Lot/Batch number	Fisher Scientific Co. lot No. 872703
Specification	As given in section 2
11.1.1.1 Description	no reported
11.1.1.2 Purity	>99.7%
11.1.1.3 Stability	Stable
Test Animals	Non-entry field
Species	rabbit,
Strain	New Zealand White
Source	Hazleton Research Products Inc., Denver, PA, USA
Sex	female
Age/weight at study initiation	5 months of age, weight 2690-4380g
Number of animals per group	30 per group
Control animals	Yes
Mating period	Artificial insemination; designated Day 0
Administration/ Exposure	Oral gavage

Section A6.8.1 Annex Point IIA6.8.1	Teratogenicity Study Section A6.8.1 Rabbit Developmental Toxicity Study
Duration of exposure	rabbit: day 6-19 post mating
Postexposure period	11 days to day 30 of gestation
	Oral
Type	Gavage
Concentration	Gavage 0, 62.5, 125 or 250 mg/kg bw boric acid equivalent to 0, 10.9, 21.8 and 43.5 mg B/kg bw
Vehicle	distilled/deionised water
Concentration in vehicle	maximum 55mg/ml boric acid
Total volume applied	5ml/kg bw.
Controls	Vehicle
Examinations	
Body weight	Yes
Food consumption	Yes
Clinical signs	Yes; maternal liver and kidneys were weighed at termination and kidney histology examined.
Examination of uterine content	Gravid uterine weight Number of corpora lutea Number of implantations Uteri stained with ammonium sulphide if no implantations visible.

Section A6.8.1	**Teratogenicity Study**
Annex Point IIA6.8.1	**Section A6.8.1 Rabbit Developmental Toxicity Study**
Examination of foetuses	No entry field
11.1.1.4 General	Litter Size; Nr. of dead foetuses; foetal weight; external examination including for cleft palate; after dissection half were decapitated and fixed in Bouin for Wilson slicing
11.1.1.5 Skelet	Yes all fetuses skinned and cleared and stained with alcian blue/alizarin red S
11.1.1.6 Soft tissue	Yes by dissection (Staples) and sex determined
Further remarks	

12 RESULTS AND DISCUSSION

Maternal toxic Effects	Pregnant does exhibited no overt symptoms attributable to boric acid toxicity except thatin the high dose group a decreased food intake (30% reduction vs. controls during exposure period) and decreased maternal bodyweight were observed, and vaginal bleeding was noted at 43.5 mg B/kg bw between gestational days 19 - 30. All high-dose animals with vaginal bleeding had no live foetuses at sacrifice. At mid dose, increased body weight gain not clearly adverse. The authors considered 43.5 mg B/kg bw as the LOAEL for pregnant does and 21.8 mg B/kg bw as the NOAEL for maternal toxicity.
Teratogenic / embryo-toxic effects	At the highest dose in this study of 250 mg/kg bw boric acid (43.5 mg B/kg bw/day), 90% of implants/litter were resorbed compared to 6% for controls, and 73% had complete litter loss (0% in controls). In the mid and low dose groups, no difference in percentage resorptions per litter was seen, compared to controls. Average foetal bodyweight per litter was 92% of the controls at the high dose (43.5-mg B/kg bw) but even at this exposure, it did not reach statistical significance possibly due to the low number of pups surviving (14 fetuses from 6 litters). An increased incidence of malformed live foetuses/litter was observed at 43.5 mg B/kg bw, primarily due to cardiovascular defects (72% for major defects of heart and/or great vessel in the high-dose group vs. 3% in controls). In the mid and low dose groups, there was no increase in malformations per litter or total malformations. There were no variations between any groups concerning the incidence of skeletal malformations. The only skeletal variations of interest was a dose related reduction in the incidence of extra ribs on Lumbar I which the authors did not consider to be toxicologically important. Since no definitive developmental effects were observed in animals exposed to either 62.5 or 125 mg/kg bw boric acid (10.9 or 21.8 mg B/kg bw/day), the authors concluded that125 mg/kg boric acid per day (21.8 mg B/kg bw/day) was the NOAEL for developmental toxicity.
Other effects	None

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rabbit Developmental Toxicity Study**

APPLICANT'S SUMMARY AND CONCLUSION

Materials and methods

Conforms to OECD 414. Pregnant NZW rabbits given boric acid 0, 62.5, 125 or 250 mg/kg bw (equivalent to 0, 10.9, 21.8 or 43.5 mg B/kg bw) by gavage from days 6-19 of gestation and killed on day 30 with full foetal examination.

Results and discussion

The highest dose level was very toxic to the dams and 90% of implants were resorbed at the highest dose level, and 72% of surviving foetuses had cardiac or great vessel malformations. No treatment related malformations or increase in resorptions were reported in the mid and low dose groups.

Conclusion

LO(A)EL maternal toxic effects

250 mg/kg bw per day boric acid (43.5 mg B/kg bw) based on reduced food intake and reduced bodyweight gain and abortions

NO(A)EL maternal toxic effects

125 mg/kg bw per day boric acid (21.8 mg B/kg bw)

LO(A)EL embryotoxic / teratogenic effects

250 mg/kg bw per day boric acid (43.5 mg B/kg bw) based on increased resorptions and CVS malformations in surviving foetuses.

NO(A)EL embryotoxic / teratogenic effects

125 mg/kg bw per day boric acid (21.8 mg B/kg bw)

Reliability

1

Deficiencies

No

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rabbit Developmental Toxicity Study**

	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 February 2005
Materials and Methods	The version of the applicant is accepted.
Results and discussion	The version of the applicant is adopted.
Conclusion	The version of the applicant is adopted.
Reliability	1
Acceptability	acceptable
Remarks	It is noted that there is a remarkable small difference (only two-fold) between the NOAEL and the LOAEL, considering the severity of the effects observed at the LOAEL, i.e. 90% mortality/litter and 81% of the surviving fetuses have malformations.
	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 A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rabbit Developmental Toxicity Study**

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
Number of dams examined		**30**	**30**	**30**	**30**	
Clinical findings during application of test substance					**reduced food and bodyweight**	
Mortality of dams *state %*		**0**	**1**	**1**	**0**	
Abortions		**0**	**0**	**0**	**3**	
Body weight gain *day 0-x, day 0-y,n* **day 6-19**		**93**	**132**	**97**	**-137***	
day 0-30,		**357**	**493**	**543**	**226**	
Food consumption g/kg/day day 0-6		**48.1**	**48.0**	**48.9**	**46.4**	
day 6-19		**38.8**	**40.0**	**38.7**	**26.6***	
day 19-25		**36.9**	**37.0**	**40.0**	**44.9**	
Water consumption *if test substance is applied with drinking water*		-	-	-	-	
Pregnancies % pregnant at sacrifice		**75**	**89**	**87**	**96**	
Necropsy findings in dams dead before end of test			**gavage error lungs**	**stomach damage**		

*** P<0.05**

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rabbit Developmental Toxicity Study**

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter		control data		low dose	medium dose	high dose	dose-response + / -
		historical	study				
Corpora lutea *mean No. per dam*	**number ±SEM**		**12.2** **0.7**	**10.7** **0.5**	**11.5** **0.4**	**10.0*** **0.7**	
Implantations sites per litter *state total/number of dams*	**number ±SEM**		**9.5** **0.8**	**8.4** **0.6**	**8.3** **0.5**	**8.6** **0.7**	
Resorptions % per litter *state total/number of dams*	**% ±SEM**		**6.3** **2.4**	**5.9** **1.9**	**7.7** **2.1**	**89.9** **5.0**	
total number of fetuses			**159**	**175**	**153**	**14**	
pre-implantation loss *state %*		**not reported**					
post-implantation loss *state %*		**not reported**					
total number of litters			**18**	**23**	**20**	**6**	
fetuses / litter		**not reported**					
live fetuses / litter *state ratio*	**number ±SEM**		**8.8** **0.8**	**7.6** **0.6**	**7.7** **0.5**	**2.3*** **0.8**	
dead fetuses / litter *state ratio*	**%**		**0**	**2.8**	**0.4**	**0**	
fetus weight (mean)	**weight (g) ±SEM**		**44.8** **1.5**	**46.5** **1.4**	**45.7** **1.2**	**41.1** **2.7**	
placenta weight (mean) *[g]*		**not reported**					
crown-rump length (mean) *[mm]*		**not reported**					
Fetal sex ratio	**% male per litter ±SEM**		**50** **5**	**51** **4**	**55** **4**	**69** **10**	

*** P<0.05**

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rabbit Developmental Toxicity Study**

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
External malformations*		0.8	1.4	1.0	11.1*	
% fetuses per litter ±SEM		0.8	1.0	1.0	8.2	
External malformations No. of fetuses		1	2	1	2	
Skeletal malformations*		19.9	19.9	24.3	38.9	
% fetuses per litter ±SEM		5.4	4.0	6.4	20.0	
Skeletal malformations No. of fetuses		30	39	44	4	
Visceral malformations*		7.3	5.9	7.4	80.6*	
% fetuses per litter ±SEM		1.9	2.0	2.0	16.3	
Visceral malformations No. of fetuses		13	11	12	11	
% fetuses with cardiovascular		2.7	3.1	4.2	72.2*	
% malformations						
±SEM		1.6	1.5	1.3	16.5	

*** P<0.05**

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rat Developmental Toxicity Study**

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13 REFERENCE

Reference

[redacted] 1994). Determination of the no-observable-adverse-effect-level (NOAEL) for developmental toxicity in Sprague-Dawley (CD) rats exposed to boric acid in feed on gestational days 0-20, and evaluation of postnatal recovery through postnatal day 21.

[redacted]

Electronic File

Data protection

Yes

Data owner

[redacted]

Companies with letter of access

Current Access

[redacted]

Criteria for data protection

Data on new a.s. for first entry to Annex I/IA

GUIDELINES AND QUALITY ASSURANCE

Guideline study

Yes : OECD 414

The objective was to determine a NOAEL for pre-natal effects and to evaluate post-natal recovery after exposure to boric acid during foetal development for risk assessment purposes. In a previous study, which conformed to OECD 414, an NOAEL was not identified (see IUCLID summary). Data in other studies and species confirm the results. In the interests of animal welfare testing to recognisd protocols is not necessary.

GLP

Yes

Although this is not necessarily to a recognised protocol it was carried out in a reputable laboratory and was designed specifically to look for a NOAEL.

Deviations

Yes

This is essentially an OECD 414 study with an additional postnatal survival phase to day 21 pp

MATERIALS AND METHODS

In some fields the values indicated in the EC or OECD test guidelines are given as default values. Adopt, change or delete these default values as appropriate.

Section A6.8.1 **Annex Point IIA6.8.1**	**Teratogenicity Study** **Section A6.8.1 Rat Developmental Toxicity Study**
Test material	As given in section 2
Lot/Batch number	Fisher Scientific Co Lot No. 872703
Specification	As given in section 2
13.1.1.1 Description	
13.1.1.2 Purity	>99%
13.1.1.3 Stability	Stable
Test Animals	Non-entry field
Species	rat
Strain	Crl:CD VAF/Plus (Sprague Dawley)
Source	Charles River Laboratories Inc., Raleigh, USA
Sex	female
Age/weight at study initiation	9 weeks of age. Weight on day of mating 219-296g
Number of animals per group	28-32 per group for teratology phase (Phase I) and 28-32 per group for postnatal phase (Phase II).
Control animals	Yes
Mating period	Time-mated
Administration/ Exposure	Oral Fill in respective route in the following, delete other routes
Duration of exposure	rat: day 0-20 post mating (Phase I) day 0-20 post mating then on normal diet until termination on day 21 postpartum (Phase II)

Section A6.8.1 Annex Point IIA6.8.1	Teratogenicity Study Section A6.8.1 Rat Developmental Toxicity Study
Postexposure period	none
	Oral
Type	in food
Concentration	added in food 0, 0.025, 0.050, 0.075, 0.1 or 0.2% (0, 250, 500, 750, 1000, 2000ppm), equivalent to 19 (3.3), 36 (6.3), 55(9.6), 76 (13.3) and 143 (25) mg boric acid (mg B)/kg bw food consumption per day ..... ad libitum
Vehicle	In powdered diet
Concentration in vehicle	As above
Total volume applied	NA
Controls	plain diet (The intake of naturally occurring boron from the diet was <0.4 mg B/kg bw per day.
Examinations	
Body weight	Yes
Food consumption	Yes and water consumption over generally 3 day periods throughout
Clinical signs	Yes: daily
Examination of uterine content	In Phase I, animals killed on day 20. Gravid uterine weight Number of corpora lutea Number of implantations live and resorptions, and fetuses live and dead. Empty uteri were stained with ammonium sulphide to look for implantation sites.

Section A6.8.1	**Teratogenicity Study**
Annex Point IIA6.8.1	**Section A6.8.1 Rat Developmental Toxicity Study**

	No entry field
Examination of foetuses	
13.1.1.4 General	All fetuses were delivered and examined externally including for cleft palate and weighed. Half of the fetuses were selected for visceral examination by dissection (Staples) and sexed. These fetuses were then decapitated and the heads fixed in Bouins and sliced for examination (Wilson). The remaining fetuses were then eviscerated and all the fetuses werecleared and stained with alcian blue/alizarin red S for skeletal examination.
13.1.1.5 Skelet	Yes
13.1.1.6 Soft tissue	Yes
Further remarks	In Phase II, dams were transferred to control diet on day 20 of gestation, the mothers were allowed to litter naturally and the pups were delivered and reared to day 21 pp. As well as all the maternal examinations described above during gestation, maternal bodyweight, food and water consumption were measured postpartum to day 21pp. The pups were examined daily and weighed at intervals until day 21 when they were killed and examined for visceral and skeletal development exactly as in Phase I.

14 RESULTS AND DISCUSSION

See Table A6_8-1.

Maternal toxic Effects	No clinical effects or effects on bodyweight. There was an increase in relative kidney weight in the highest dose group in phase I of the study but not in Phase II. The authors concluded that there was little evidence of maternal toxicity at any of the doses tested (Phase I or 11).
Teratogenic / embryo-toxic effects	Developmental effects were found in foetuses from animals exposed to 76mg/kg bw boric acid (13.3 mg B/kg bw) and above (Phase I) which are mainly associated with foetotoxic activity. Specifically, a reduction in the mean foetal bodyweight per litter (6% compared to controls) was observed in Phase I foetuses at 13.3 mg B/kg bw. At this dose, skeletal changes which included an increased incidence of short rib XIII (considered a malformation by authors of this study but a variation by most workers) and an increased incidence of wavy rib (considered a variation) were also observed. At the high dose for Phase I animals of 143mg/kg bw boric acid (25 mg B/kg bw), the bodyweight reductions and skeletal changes were more pronounced. The reduction in incidence in extra rib on Lumbar I (a variation) which was noted in the previous rat study was not statistically significant here due to the low incidence in control animals (3.2% in controls in this study compared to 14% in the study from Heindel et al, 1992). There was no evidence of any increase in external or visceral malformations in any treatment group.

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rat Developmental Toxicity Study**

The authors concluded that the NOAELs for the prenatal and postnatal study phases (Phase I and Phase II) were 9.6 and 12.9 mg B/kg low/d, respectively.

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rat Developmental Toxicity Study**

Other effects

The animals from the Phase II group which were killed on postnatal day 21 showed no reduction in pup bodyweight in any group at any time point compared to controls, which indicates full recovery in the offspring already by postnatal day 0 from treatment-related bodyweight effects. The rib variations observed in the foetuses (wavy rib) from Phase I were not observed in any dose group in Phase II. Only at the highest dose in Phase II (25.3 mg B/kg bw), was an increased incidence of short rib XIII observed.

APPLICANT'S SUMMARY AND CONCLUSION

Materials and methods

The objective was to determine a NOAEL in pregnant rats for pre-natal effects and to evaluate post-natal recovery after exposure to boric acid during foetal development for risk assessment purposes. In a previous study, which conformed to OECD 414, an NOAEL was not identified (see IUCLID summary). In the first phase (Phase I), time-mated Sprague-Dawley rats (approximately 30 females/group) were exposed to boric acid at 0, 0.025, 0.050, 0.075, 0.1 or 0.2% in the diet for the entire period of gestation (days 0 - 20). Average daily doses reported were 19, 36, 55, 76 and 143 mg boric acid/kg bw bodyweight which were calculated to be 3.3, 6.3, 9.6, 13.3 and 25 mg B/kg bw, respectively. Phase I animals were killed on day 20 for full fetal examination for visceral and skeletal defects. For postnatal evaluation (Phase II), additional dams (approximately 30/group) were exposed to the same levels of boric acid in the diet also for the entire period of gestation up to day 20 and then transferred to control diet till day 21 postpartum. The calculated daily doses for Phase II animals were 3.2, 6.5, 9.7, 12.9 and 25.3 mg B/kg bw. These animals were allowed to deliver and rear their litters until they were killed on postnatal day 21. The average intake from the control diet was less than 0.4 mg B/kg bw for control animals. In both phases, offspring were evaluated for post-implantation mortality, bodyweight and morphology (external, visceral and skeletal).

Results and discussion

Fetotoxicity was observed as a reduction in the mean foetal bodyweight per litter (6% compared to controls) was observed in Phase I foetuses at 76 mg boric acid/kg bw(13.3 mg B/kg bw) per day. At this dose, skeletal changes which included an increased incidence of short rib XIII (considered a malformation by authors of this study) and an increased incidence of wavy rib (considered a variation) were also observed. At the high dose for Phase I animals of 143mg boric acid/kg bw (25mg B/kg bw), the bodyweight reductions and skeletal changes were more pronounced. When the fetuses were allowed to be delivered and raised to day 21p.p.in Phase II of the study, the pups showed no reduction in bodyweight on any day from Day 0 onwards in any group compared to controls, which indicates full recovery in the offspring already by postnatal day 0 from treatment-related bodyweight effects during gestation. The rib variations observed in the foetuses (wavy rib) from Phase I were not observed in any dose group in Phase II. At the highest dose in Phase II (25.3 mg B/kg bw), an increased incidence of short rib XIII was observed.

Conclusion

There was no evidence of developmental toxicity in offspring of rats fed boric acid in diet throughout gestation up to 0.075% (55 mg/kg bw boric acid).

Section A6.8.1 Annex Point IIA6.8.1	Teratogenicity Study Section A6.8.1 Rat Developmental Toxicity Study
	At 0.100% boric acid (76 mg/kg bw boric acid) there was reduced fetal bodyweight, short and wavy ribs, and these effects disappeared during the postnatal period. Similar but more marked effects were observed at the highest dose of 0.200% (143 mg/kg bw boric acid) and apart from the short 13th rib, they also disappeared during the postnatal period..
LO(A)EL maternal toxic effects	143mg boric acid/kg bw (25mg B/kg bw) per day based on relative kidney weight
NO(A)EL maternal toxic effects	76 mg boric acid/kg bw (13.3 mg B/kg bw) per day
LO(A)EL embryotoxic / teratogenic effects	76 mg boric acid/kg bw (13.3 mg B/kg bw) per day based on reduced fetal bodyweight and increased incidence of short rib XIII
NO(A)EL embryotoxic / teratogenic effects	55 mg boric acid/kg bw (9.7mg B/kg bw) per day.
Reliability	1
Deficiencies	The objective was to determine a NOAEL for pre-natal effects and to evaluate post-natal recovery after exposure to boric acid during foetal development for risk assessment purposes. In a previous study, which conformed to OECD 414, an NOAEL was not identified (see IUCLID summary). Data in other studies and species confirm the results. In the interests of animal welfare testing to recognised protocols is not necessary

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rat Developmental Toxicity Study**

	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 February 2005
Materials and Methods	The version of the applicant is adopted.
Results and discussion	The version of the applicant is adopted (with one exception for the NOAEL for maternal toxicity).
Conclusion	It is not considered appropriate to base the NOAEL solely on the slight increase in relative maternal kidney weight. Therefore, the NOAEL for maternal toxicity in this study is 143 mg/kg bw/day, i.e. the highest dose tested. LOAEL embryotoxicity/fetotoxicity: 76 mg boric acid/kg bw (13.3 mg B/kg bw) per day based on reduced fetal bodyweight and increased incidence of short rib XIII. NOAEL embryotoxicity/fetotoxicity: 55 mg boric acid/kg bw (9.6mg B/kg bw) per day.
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	

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rat Developmental Toxicity Study**

Table A6_8-1. Table for Teratogenic effects

Maternal effects Phase I and II

Modify if necessary and give historical data if available

Parameter	Control	0.025 dose	0.05 dose	0.075 dose	0.10 dose	0.20 dose
Number of dams examined	60	60	60	60	60	60
Clinical findings during application of test substance	none significant in any group					
Mortality of dams *state %*	0	0	0	0	0	0
Abortions	0	0	0	0	0	0
Body weight gain *day 0-x, day 0-y, day x-y, day 0-end of test,*	no sig differences					
Food consumption	no sig differences					
Water consumption *if test substance is applied with drinking water*	no sig differences					
Pregnancies *pregnancy rate or %*	56/60	56/60	55/60	58/60	55/60	55/60
Necropsy findings in dams dead before end of test	none					

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rat Developmental Toxicity Study**

Table A6_8-2. **Table for Teratogenic effects (separate data for all dosage groups)**

Litter response (Caesarean section data) Phase 1

Modify if necessary and give historical data if available

Parameter		Control	0.025 dose	0.05 dose	0.075 dose	0.10 dose	0.20 dose
Number of pregnancies		27	29	27	29	30	27
Corpora lutea	n	19.4	19.3	19.4	17.9	19.0	19.0
No. per dam	±SEM	0.7	0.3	0.7	0.6	0.6	0.7
Implantations	n	16.4	16.5	16.6	15.8	16.4	16.0
No. per dam	± SEM	0.7	0.6	0.7	0.7	0.7	0.7
Resorptions	% per litter	9.5	3.3	2.6	3.9	6.7	4.8
	±SEM	3.6	1.0	0.8	0.8	3.4	1.1
total number of live fetuses		417	461	437	437	471	411
pre-implantation loss	%	13.8	13.5	13.2	12.8	11.5	14.1
state %	±SEM	4.1	2.7	3.5	3.7	4.0	4.1
post-implantation loss	%	9.5	3.3	2.6	4.7	6.7	4.8
state %	±SEM	3.6	1.0	0.8	1.0	3.4	1.1
total number of litters		26	29	27	29	29	27
fetuses / litter							
live fetuses / litter	n	16.0	15.9	16.2	15.1	16.2	15.2
state ratio	±SEM	0.4	0.6	0.7	0.7	0.6	0.7
Litters with one or more late fetal deaths		0	0	0	7	0	0
fetus weight (mean)	male	3.71	3.64	3.62	3.60	3.48	3.23
	female	3.52	3.47	3.45	3.38	3.27	3.04
	average	3.61	3.56	3.54	3.50	3.38	3.16
placenta weight (mean) *[g]*		not recorded					
crown-rump length (mean) *[mm]*		not recorded					
Fetal sex ratio *[state ratio m/f]*		not reported					

Section A6.8.1 **Teratogenicity Study**

Annex Point IIA6.8.1 **Section A6.8.1 Rat Developmental Toxicity Study**

Table A6_8-3. **Table for Teratogenic effects (separate data for all dosage groups)**

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	Control	0.025 dose	0.05 dose	0.075 dose	0.10 dose	0.20 dose
External malformations	0.4	0.0	0.4	0.4	0.0	3.7
mean						
% offspring per litter ±SEM	0.3	0.0	0.4	0.3	0.0	3.7
External variations	0.2	0.0	0.0	0.5	0.0	0.0
mean						
% offspring per litter ±SEM	0.2	0.0	0.0	0.3	0.0	0.0
Skeletal malformations	2.0	0.9	1.6	2.5	3.5	4.3
mean						
% offspring per litter ±SEM	0.7	0.6	0.6	0.7	1.2	1.5
Skeletal variations	10.0	3.4	6.5	5.3	7.4	12.1
mean						
% offspring per litter ±SEM	2.0	1.0	1.8	1.4	2.1	3.0
Visceral malformations	39.9	40.6	44.3	42.9	45.4	46.4
mean						
% offspring per litter ±SEM	7.0	6.3	6.5	6.6	6.9	6.5
Visceral variations	1.4	2.1	2.9	0.0	1.3	0.5
mean						
% offspring per litter ±SEM	0.8	1.2	1.5	0.0	0.7	0.5

Section A6.8.2.1	**Multigeneration Reproduction Toxicity Study**
Annex Point IIA6.8.2	6.8.2.1 Rat Three Generation Study – Boric Acid

Official use only

7 REFERENCE

Reference [redacted] (1966). Three-generation reproductive study - rats. Boric acid [redacted]

Electronic File

Data protection Yes

Data owner [redacted]

Companies with letter of access **Current Access** [redacted]

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

GUIDELINES AND QUALITY ASSURANCE

Guideline study No but conforms to the standard 3 generation 2 litters per generation MGS normally used at that time.

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

GLP No

Although these studies predate modern protocols and GLP, other data available support the results. Further testing is not warranted in the interests of animal welfare.

Deviations

MATERIALS AND METHODS

Test material As given in section 2

Boric acid

Lot/Batch number Not available

Specification As given in section 2

14.1.1.1 Description Fine white powder without odour.

14.1.1.2 Purity >99%

14.1.1.3 Stability Stable

Test Animals Non-entry field

Species Rat

Strain Crl:CD Sprague Dawley

Source Charles River Laboratories, USA

Section A6.8.2.1	**Multigeneration Reproduction Toxicity Study**
Annex Point IIA6.8.2	6.8.2.1 Rat Three Generation Study – Boric Acid
Sex	male and female
Age/weight at study initiation	Weight males 121-150g; females 110-147g.
Number of animals per group	8 males and 16 females per group
Mating	See table below
Duration of mating	21 days on each occasion, 1 male and 2 females per cage.
Deviations from standard protocol	This is a three generation multigeneration study with two matings (two litters) per generation. The F1a, F2a and F3a litters were sacrificed at weaning, and the F1b and F2b litters raised and used for breeding, and the F3b killed at weaning.
Control animals	Yes
Administration/ Exposure	Oral
	Fill in respective route in the following, delete other routes
Animal assignment to dosage groups	By stratified randomisation
Duration of exposure before mating	14 weeks
Duration of exposure in general P, F1, F2 males, females	From beginning of the study until sacrifice of parents P0 , and from weaning till sacrifice for the parents of the F1 and F2-generations. The high dose group P animals were sterile so only controls, low and mid dose groups were taken to the F2 and F3 generations.
	Oral
Type	in food
Concentration	food: 0, 670, 2000 or 6700 ppm boric acid (0, 117, 350 and 1,170 ppm boron) in the diet, equivalent to 0, 34 (5.9), 100 (17.5) and 336 (58.5) mg boric acid (mg B)/kg bw food consumption per day ..... ad libitum
Vehicle	dry powdered food
Concentration in vehicle	as above
Total volume applied	food ad libitum
Controls	plain diet
Examinations	
Clinical signs	Yes weekly
Body weight	yes weekly
Food/water consumption	yes weekly for food; water ad libitum not recorded.
Oestrus cycle	not done
Sperm parameters	not done except in the high dose group in which histology of testes was performed.

Section A6.8.2.1	Multigeneration Reproduction Toxicity Study
Annex Point IIA6.8.2	6.8.2.1 Rat Three Generation Study – Boric Acid
Offspring	number and sex of pups stillbirths live births presence of gross anomalies weight gain physical or behavioural abnormalities culled to 8 per litter at 24 hours after delivery
Organ weights P only	Uterus ovaries testes brain liver kidneys spleen thyroid adrenals
Histopathology P.F1,F2 parents	All parental animals were necropsied and a range of tissues preserved in formalin but not examined histologically except for testes, ovaries and uterus of the high dose group only.
Histopathology F1 not selected for mating, F2	5 of each sex from all groups of the F3b litters were necropsied and a range of tissues fixed in formalin but not examined histologically.
Further remarks	

15 RESULTS AND DISCUSSION

See Table A6_8_2-1 and Table A6_8_2-2.

Effects

Parent males	Rats of the P0 generation exposed to the high dose of 336 mg/kg bw boric acid (corresponding to a level of 58.5 mg B/kg bw) had reduced bodyweights though food intake was not affected and they were sterile. Microscopic examination of the atrophied testes of all males in this group showed no viable sperm. There were no adverse effects on reproduction reported at exposures of 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 from these dose groups.
Parent females	The high dose groups of the Po generation had reduced bodyweight without any effect on food intake. Evidence of decreased ovulation in about half of the ovaries examined from the females exposed to 58.5 mg B/kg bw and only one of 16 females produced a litter when mated with control male animals. There were no adverse effects on reproduction and no gross abnormalities were observed in the organs at exposures of 5.9 and 17.5 mg B/kg bw.
F1 males	There were no adverse effects on reproduction and no gross abnormalities were observed in the organs at exposures of 5.9 and 17.5 mg B/kg bw.

Section A6.8.2.1	**Multigeneration Reproduction Toxicity Study**
Annex Point IIA6.8.2	6.8.2.1 Rat Three Generation Study – Boric Acid
F1 females	There were no adverse effects on reproduction and no gross abnormalities were observed in the organs at exposures of 5.9 and 17.5 mg B/kg bw.
F2 males	There were no adverse effects on reproduction and no gross abnormalities were observed in the organs at exposures of 5.9 and 17.5 mg B/kg bw.
F2 females	There were no adverse effects on reproduction and no gross abnormalities were observed in the organs at exposures of 5.9 and 17.5 mg B/kg bw.
Other	The high dose group (58.5 mgB/kg bw)males and females showed clinical signs of toxicity with rough fur, scaly tails, respiratory distress and inflamed eyelids.
	APPLICANT'S SUMMARY AND CONCLUSION

Section A6.8.2.1	**Multigeneration Reproduction Toxicity Study**
Annex Point IIA6.8.2	6.8.2.1 Rat Three Generation Study – Boric Acid
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*
Results and discussion	*Rats exposed to the high dose of 336 mg/kg bw boric acid (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 about half of the ovaries examined from the females exposed to 58.5 mg B/kg bw and only 1/16 matings produced a litter from these high dose females when mated with control male animals. There were no adverse effects on reproduction reported at exposures of 34 and 100 mg/kg bw boric acid (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.*
Conclusion	
LO(A)EL	*1170 ppm boron in the diet, equivalent to 336 (58.5) mg boric acid (mg B)/kg bw based on sterility in males and females*
15.1.1.1 Parent males	*as above*
15.1.1.2 Parent females	*as above*
15.1.1.3 F1 males	*none*
15.1.1.4 F1 females	*none*
15.1.1.5 F2 males	*none*
15.1.1.6 F2 females	*none*
NO(A)EL	Non-entry field
15.1.1.7 Parent males	*350 ppm boron in the diet, equivalent to 100 (17.5) mg boric acid (mg B)/kg bw.*
15.1.1.8 Parent females	*350 ppm boron in the diet, equivalent to 100 (17.5) mg boric acid (mg B)/kg bw*
15.1.1.9 F1 males	*as above*
15.1.1.10 F1 females	*as above*
15.1.1.11 F2 males	*as above*
15.1.1.12 F2 females	*as above*
Reliability	*2*
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 welfare and protecting laboratory animals*

Section A6.8.2.1	**Multigeneration Reproduction Toxicity Study**
Annex Point IIA6.8.2	6.8.2.1 Rat Three Generation Study – Boric Acid

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18 February 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 boric acid, in which histopathological examination demonstrated lack of viable sperm in the males received food containing 6690 ppm of boric acid. It should be mentioned that the control group in the present study also served as the control group for the multigeneration reproduction study with borax (disodium tetraborate decahydrate) 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 70 % 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 boric acid.
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 A6.8.2.1 **Multigeneration Reproduction Toxicity Study**

Annex Point IIA6.8.2 6.8.2.1 Rat Three Generation Study – Boric Acid

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 A6.8.2.1 **Multigeneration Reproduction Toxicity Study**

Annex Point IIA6.8.2 6.8.2.1 Rat Three Generation Study – Boric Acid

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	1	0	0	0	0	0	0		
		F_1	0	1	0	0	0	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 wt. of thyroid in low dose group 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)	%	62	88	81	0	80	94	94	69	94	94	
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	96	97		99	99	98	100	99	99	
Gestation index												
Litter size	Mean	12	11	11		12	13	12	12	13	11	

Section A6.8.2.1 **Multigeneration Reproduction Toxicity Study**

Annex Point IIA6.8.2 6.8.2.1 Rat Three Generation Study – Boric Acid

Litter weight	Mean											
Pup weight at 24h (g)	Mean	**7.0**	**7.2**	**6.7**		**6.4**	**6.5**	**6.7**	**6.0**	**7.0**	**7.0**	
Sex ratio	Male/female	**6/6**	**6/5**	**5/6**		**6/6**	**7/6**	**6/6**	**6/6**	**7/6**	**6/5**	
Survival index												
Viability index												
Lactation index: Pup wt. at weaning		**55**	**50**	**52**		**56**	**53**	**51**	**48**	**51**	**55**	

Section A6.12 **Medical Data/Surveillance Data/Health Record**

Annex Point IIA VI 6.9 **Section IIA6.12.1/6.12.3**

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APPLICANT'S SUMMARY AND CONCLUSION

[redacted]
Information

On all sites several different borates are handled including other borates not subject to the Biocides Directive. Therefore unless a specific medical issue arises by someone using a particular borate, the medical surveillance does no distinguish between the borates.

Main Borates handled at [redacted]

	[redacted]	[redacted]	[redacted]
Boric Acid	x	x	x
Boric oxide		x	
Sodium tetraborate decahydrate	x	x	x
Sodium tetraborate pentahydrate	x	x	x
Sodium tetraborate (anhydrous		x	
Potassium pentaborate	x		
Potassium tetraborate	x		
Sodium metaborate 8 mol	x		
Sodium metaborate 4 mol	x		
Disodium octaborate tetrahydrate	x	x	
Zinc borate	x	x	

[redacted] has had no indication for any medical surveillance. In compliance with our group [redacted] Occupational Health Standards a risk assessment has been carried out at all our operational sites. This risk assessment included consideration of all industrial hygiene data and records of occupational disease at our sites. In the last 4 years we have recorded only 2 cases in all our European operations.

Our group [redacted] Occupational Health standards only require health monitoring in certain circumstances where a disease is likely to occur under the circumstances found in the site; there is a test that can detect that effect reliably; the detection of any disease or change from normal is of benefit to the employees.

Having carried out the risk assessment we do not consider that any form of medical monitoring of health is required.

Of the 2 cases recorded one was dermatitis in a worker, which was deemed not to be a reportable official occupational disease and occurred only when the person sweated highly. The symptoms did not occur in the worker at all in 2003. There has been one case, in 2003, where a truck driver who, purely on clinical grounds, developed a dermal sensitisation to an unspecified company product which. The rash recurred when he worked in a warehouse. He no longer works in the warehouse.

It was decided that no medical monitoring was necessary, given the extreme rarity of the event. Also there are no indications of a sensitisation effect in any other worker world wide in over 50 years of experience, no indications in animal studies and in a human sensation study.

In compliance with good practice we monitor the number of

Section A6.12 **Medical Data/Surveillance Data/Health Record**

Annex Point IIA VI 6.9 **Section IIA6.12.1/6.12.3**

sickness/absentees taken by our employees. Nothing has been noted that could be related to exposure to borates

Section A6.12 Medical Data/Surveillance Data/Health Record

Annex Point IIA VI 6.9 **Section IIA6.12.1/6.12.3**

[redacted] **Information**

In the past three years, 14.957 periodic heath control of staff and personnel have been completed over 5 operating sites in [redacted] and no occupational disease has been found.

[redacted]

Year 2003

During the calendar year 2003, I applied the health agreement decided upon, and specifically undertook the following activities:

I carried out 30 medical examinations and issued the related certificates of medical fitness for specified tasks.

12 spirometric check-ups and 12 audiometric tests in acoustically silent cabins were made.
Of the 30 certificates of medical fitness issued, two necessitated prescriptions.
In the course of 2003 I effected the inspections foreseen by the legal decree 626/94.
I believe that during the course of the calendar year 2004 it would be wise to insist on proper formation programmes for every level.

In the light of the [redacted], it would also be opportune to carry out new formation programmes for the personnel assigned to first aid.

The following health protocol is proposed for the calendar year 2004;

- **day and shift workers, maintenance staff**; annual medical examination, biennial spirometric check-up, biennial audiometric tests #
- **laboratory staff**; six-monthly medical examination, biennial spirometric check-up, annual haematological and urinary tests *
- **technical staff**; annual medical examination and biennial ergophthalmological examination (if in contact with VDT)
- **office and managerial staff**; biennial medical and ergophthalmological examination (if in contact with] VDT)

All workers with hypacusia between classes 1 and 6 of the Merluzzi scale will be subject to annually recurring audiometric tests.

Any further examinations deemed necessary to integrate the programme will be proposed by the doctor in charge.
The practice regarding **new personnel** is made up of spirometric check-ups, audiometric tests in acoustically silent cabins, ECG at rest, Rx of the thorax, haematological and urinary tests *, and ergophthalmological examination, if in contact with VDT.
* Haemochrome, platelets, azotemia, creatinemia, transaminase, glycaemia, complete urinary examination, including if necessary the arsenic quotient present in urine.

The Occupational Health-Care Doctor

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18 April 2005
Materials and Methods	-
Results and discussion	From the data reported above there is no indication of health effects of workers exposed in their working environment to substances containing boron. It is noted that the reporting is very concise. [redacted] considers health monitoring of the employees not required since only one case of dermatitis and one case of dermal sensitisation were recorded over the past 4 years. [redacted] reports that no occupational disease were found during about 15000 health checks over the past 3 years. No details are provided. The occupational health care doctor of the [redacted] reports that he performed 30 health check on 30 employees. It is not reported whether occupation-related diseases were observed.
Conclusion	The data described above suggest that there are no obvious indications for occupational diseases for workers exposed to borates. Detailed monitoring data on occupation-related diseases for workers exposed to boron containing substances are not available.
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 A6.12 **Medical Data/Surveillance Data/Health Records**

Annex Point IIA VI6.9 Section IIA6.12.2

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APPLICANT'S SUMMARY AND CONCLUSION

5.1 Reference

Culver BD and S A Hubbard Inorganic boron health effects in humans: An aid to risk assessment and clinical judgement. J Trace Elements in Experimental Medicine, **9**, 175 -184, 1996

Additional references can be found in the IUCLID database

Data protection

No

5.1 Summary

There is a large database of accidental or intentional poisoning incidents for humans. Many were the result of accidental use as an antiseptic for irrigating body cavities, treating wounds or as a treatment for conditions such as epilepsy. Such medical uses are now obsolete. Also, accidental misuse in the preparation of baby formula (1 – 14 g in boric acid in the formula) and the topical use of pure boric acid powder for infants has led to poisonings in the past. This database is reviewed in several papers of data from poisoning centres as well as a detailed review of the literature cases from the mid 1800s to the 1970s. Humans display different acute symptoms compared with most animals. In the literature, the human oral lethal dose is regularly quoted as 2--3 g boric acid for infants, 5-6 g boric acid for children and 15-30 g boric acid for adults. This data is largely unsubstantiated. In most cases it is difficult to make a good quantitative judgement particularly since medical intervention occurred in most cases and there were often other unrelated medical conditions. Of 784 more recent reports of accidental ingestion, none were reported as fatal and 88.3% were asymptomatic. The estimated dose range was 10 mg to 88.8 g while a single intake of 30 g of boric acid was fatal in one case. Symptoms of acute effects may include nausea, vomiting, gastric discomfort, skin flushing, excitation, convulsions, depression and vascular collapse.

In humans multiple exposure (high levels > 1g) results in various symptoms which may appear singly or together and include dermatitis, alopecia, loss of appetite, nausea, vomiting, diarrhoea, and focal or generalised central nervous system irritation or convulsions. Much data comes from the mid 1800s to around 1940, when boric acid and disodium tetraborate decahydrate were used systematically for a variety of medical conditions including amenorrhea, malaria, epilepsy, urinary tract infection and exudative pleuritis. Daily oral doses in adults ranged from 1-14 g per day. Repeated doses in the 6 10 g/day range were given for as long as several weeks. In one extreme case a 28 year old women ingested around 0.5 g of boric acid (in baby powder) every day for two years and suffered anaemia, which reversed on ceasing ingestion. Doses greater than 3 –5 g/day regularly caused vomiting and/or diarrhoea in the first instance often accompanied by dermatitis and appetite suppression. As the dose became higher and the dosing period longer, symptoms included alopecia, disseminated maculopapular eruption followed by widespread desquamation, focal or generalised central nervous system irritation, and convulsions. The symptoms of dermatitis, nausea, diarrhoea and vomiting symptoms also occurred in some patients receiving doses of 2 g boric acid/day (29 mg boric acid/kg/day) and above. In one such case, reduction of the dose from 2 g/day of boric (29 mg boric acid/kg/day) acid to 1g/day (14 mg boric acid/kg/day) resulted in resolution of the effects (vomiting and dermatitis). In all cases where withdrawal of treatment was reported, recovery occurred with no lasting effects. The lowest recorded adult dose causing symptoms was 2 g/day boric acid.

Section A6.12 **Medical Data/Surveillance Data/Health Records**

Annex Point IIA VI6.9 Section IIA6.12.2

In children, where low levels can be estimated, infants aged from 6 to 19.5 weeks ingested borax (as a honey-borax mixture which had been applied to pacifiers) for periods of 4 to 12 weeks. The mean intake was 0.98 g boric acid/day (range 0.55g to 2 g) for a 10 kg child. The effects seen, which disappeared on withdrawal of the honey borax mixture, relate to effects on CNS such as convulsions, generalised seizures and focal seizures. There were no dermal effects. Minor occurrences of vomiting and loose stools were also described.

5.2 Conclusions

A no effect level for humans based on the acute and chronic symptoms of nausea, vomiting and diarrhoea can be established at about 1 g of boric acid/day (2.5 mg B/kg/day). The level at which adverse effects of anorexia, indigestion and exfoliative dermatitis will be seen is 5.0 mg boric acid/kg/day. Although chronic absorption data at these levels is not available in the literature for infants, their responses at high does are similar enough to the human adult to assume that children are not more sensitive to the effects of 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	18 April 2005
Materials and Methods	The version of the applicant is acceptable
Results and discussion	The version of the applicant is adopted
Conclusion	The version of the applicant is adopted
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 A6.12.4 **Epidemiological Study**

Annex Point IIA6.12.4 Sayli – Cohort Epidemiology Study on Turkish Population

Official use only

16 REFERENCE

16.1 Reference

Sayli B S, Tuccar E, Elhan A H. 1998. An assessment of fertility in boron-exposed Turkish subpopulations. Reproductive Toxicology, 12, 297 –304

Copyright

No

16.2 Data protection

16.2.1 Data owner

16.2.2 Companies with letter of access

16.2.3 Criteria for data protection

No data protection claimed

17 GUIDELINES AND QUALITY ASSURANCE

Not applicable

18 MATERIALS AND METHODS

18.1 Test material	Boron	x
18.1.1 Lot/Batch number	List lot/batch number if available	
18.1.2 Specification	As given in section 2	
18.1.2.1 Description	Natural boron as found in drinking water	
18.1.2.2 Purity	Give purity in % of active substance	
18.1.2.3 Stability	Describe stability of test material	
18.2 Type of study	Cohort study	
18.3 Method of data collection	Interviewer	
18.4 Test Persons / Study Population	Non-entry field	
18.4.1 Selection criteria	cohort study : Relationships between elevated boron intake and fertility were sought by comparing reproduction in the residents of two Turkish villages with high levels of boron in their drinking water (one with 8.5 to 29 mg B/L and the other with 2.05 to 2.5 mg B/L), with three nearby villages with more typical lower boron levels (0.03 to 0.45 mg B/L). The two high boron villages were designated as Region I, and the three villages with lower boron in the drinking water were designated Region II. In addition to exposure to elevated boron in drinking water, 28.3% of the probands in Region I were employed in borate mining or processing, whereas in Region II, 11.7% were so employed. The data on fertility from these two populations was also compared with that from an area with a very low boron concentration in drinking water and no occupational exposure, and also from data for the whole Turkish population.	
18.4.2 Number of test persons per group/cohort size	The group with the high boron exposures in Regions I and II comprised 927 probands and by the use of a pedigree technique covering three generations, fertility data on 5934 marriages were investigated.	
18.4.3 Sex	males and females	

18.4.4 Age	40% of the probands were 30-39 y; 35% 40-60 y; and 15% <30 y.
18.4.5 Diseases	none specific, general population
18.4.6 Smoking status	smokers and non-smokers
18.5 Controls	Yes two separate control groups
18.5.1 Type of control	Cohort: Fertility data from: National population of Turkey 49,856 randomly chosen families Regional population of Camlidere (relatively boron free soils) 625 families covering three generations.
18.5.2 Number of test persons per group/cohort size	National population of Turkey 49,856 randomly chosen families Regional population of Camlidere (relatively boron free soils) 625 families covering three generations.
18.5.3 Sex	Males and females
18.5.4 Age	not specified
18.5.5 Diseases	General population, generally healthy
18.5.6 Smoking status	smokers and non-smokers
18.6 Administration/ Exposure	No Entry field
18.6.1 Exposure Route	Environmentally and drinking water mainly.
18.6.2 Exposure Situation	Mostly environmental but 12-28% of the index population were also occupationally exposed in boron mining but no details of specific exposure scenarios were reported.
18.6.3 Exposure concentration(s)	Drinking water levels of boron were measured at up to 29 mg B/L in the highest region.
18.6.4 Method(s) to determine exposure	Exposure was assessed only from the drinking water concentrations.
18.6.5 Postexposure period	none
18.7 Examinations	No Entry field

18.7.1 Type of disease

Infertility

18.7.2 Parameters

The questions first asked of the proband were about age at marriage, age at first pregnancy, number and gender of offspring, miscarriages and stillbirths, congenital malformations and early infant deaths. General questions of other aspects of health status and lifestyle were asked, as well as demographic data about age, sex, place of birth and residence, education, occupation. The proband was then questioned in the same way about each member of his/her family, covering three generations. Any unknown or doubtful data were omitted.

18.8 Further remarks

19 RESULTS AND DISCUSSION

19.1 Exposure

19.1.1.1 Number of measurements

Exposure was based on drinking water levels of boron in the different regions of Turkey studied.

19.1.1.2 Average concentrations

In high areas it ranged from 0.7-29.0 mg B/L. In other lower boron areas 0.05- 0.45 mg B/L. Drinking water in 5 supplies from the very low control area of Camlidere had levels <0.1mgB/L.

19.1.1.3 Standard deviation

19.1.1.4 Date(s) of measurement(s)

19.1.2 Other

Not relevant

19.2 Number of cases for each disease / parameter under consideration

Not relevant

19.3 SMR (Standard mortality ratio), RR (relative risk), OR (Odds ratio)

19.4 Other Observations

The outcome studied was infertility as assessed by childless families. In the high boron exposure region the infertility rate was 3.17% in the probands and 3.0% averaged over 3 generations. In the very low exposure control area infertility was 4.48%, and in the general Turkish population was 3.84% . No difference in fertility was observed between 399 men with occupational exposure to boron, and 222 men with similar occupations but not exposed to boron. It was concluded that within the limits of the study, there was no evidence that boron interfered with human fertility and reproduction.

20 APPLICANT'S SUMMARY AND CONCLUSION

20.1 Materials and methods

This is a study of fertility in populations from different regions of Turkey selected because of wide differences in boron content in the drinking water. Three generations of population were studied. The study covered regions which contained boron mines and had very high drinking water boron concentrations, and also included areas with low and very low boron concentrations, as well as comparison with the general Turkish population.

20.2 Results and discussion

The infertility rates in three generations of people, generally living their whole lives, in the high boron drinking water areas were no higher than in the low and very low areas. No difference was found in fertility between men occupationally exposed to boron and those not so exposed.

20.3 Conclusion

It was concluded that within the limits of the study, there was no evidence that boron interfered with human fertility and reproduction.

20.3.1 Reliability

2

20.3.2 Validity

Discuss critical points i.e.: The probands chosen for the study were not randomly chosen in a formal way, but were a convenience sample. Information was obtained by interview and national records of births were not available.

20.3.3 Deficiencies

The deficiencies of the study are counterbalanced by the number of families studied and the deficiencies applied equally to the comparator groups. Multiple types of comparison failed to reveal any systemic bias in the results. The results over the three generations did not differ significantly. These deficiencies apply to many large cohort epidemiology studies.

20.4 Other

	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 February2005
Materials and Methods	The version of the applicant is acceptable.
Results and discussion	The version of the applicant is adopted.
Conclusion	The present study provide no evidence for an increased infertility rate in three generations of people exposed to high born levels through drinking water. However, it should be noted that the conclusion of the study is based solely on the number of children born. Other reproductive effects, such as time to pregnancy were not investigated.
Reliability	2
Acceptability	acceptable
Remarks	Assuming an average body weight of 60 kg and a daily water consumption of 2L per person, the exposure to boron due to drinking water containing 29 mg/L (highest concentration measured) would amount to approximately 1 mg/kg bw/day.
	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 A6.12.4 **Epidemiological Study**

Annex Point IIA6.12.4 Section A6.12.4 Cohort study on US Borax Employees

Official use only

21 REFERENCE

21.1 Reference

[redacted] 1992) Reproductive effects of inorganic borates on male employees: birth rate assessment. [redacted]

[redacted]

Electronic File

21.2 Data protection

Yes

21.2.1 Data owner

[redacted]

21.2.2 Companies with letter of access

Current Access:

[redacted]

21.2.3 Criteria for data protection

Data on new a.s. for first entry to Annex I/IA

22 GUIDELINES AND QUALITY ASSURANCE

Not applicable

23 MATERIALS AND METHODS

23.1 Test material	Sodium borate dust
23.1.1 Lot/Batch number	Not relevant
23.1.2 Specification	Occupational Setting
23.1.2.1 Description	Sodium borate minerals tincal and kernite are mined in an open pit, and refined on site to disodium tetraborate decahydrate, disodium tetraborate pentahydrate, and disodium tetraborate anhydrous.
23.1.2.2 Purity	variable depending on product.
23.1.2.3 Stability	Stable
23.2 Type of study	Cohort study
23.3 Method of data collection	Questionnaire and Interviewer and some record inspection. The fertility data were obtained primarily by self administered questionnaire, and a section of the group by telephone interview. A 10% sample of questionnaires was checked against the relevant medical insurance records. The work and exposure data was provided from Company records. Non-entry field
23.4 Test Persons / Study Population	
23.4.1 Selection criteria	cohort study: All male employees at the U.S. Borax mine and production facility in Southern California with more than 6 months service were invited to participate in the study.
23.4.2 Number of test persons per group/cohort size	Of the 753 eligible male employees with more than 6 months service, 542 (72%) participated. The demographic data, length of employment, age and year at hire and medical insurance records of the non-participants and the participants were compared and no significant differences were found.
23.4.3 Sex	males
23.4.4 Age	Wide range with average duration of employment in the facility of 16 years.
23.4.5 Diseases	Essentially healthy
23.4.6 Smoking status	smokers and non-smokers

Section A6.12.4 **Epidemiological Study**

Annex Point IIA6.12.4 Section A6.12.4 Cohort study on US Borax Employees

23.5 Controls	No specific local control group was studied, but the results expressed as the Standardised Birth Ratio (SBR) were compared with the SBR for the general US population adjusted for maternal age, parity, race and calendar year.
23.5.1 Type of control	cohort study: National population of USA
23.5.2 Number of test persons per group/cohort size	US population
23.5.3 Sex	*female*
23.5.4 Age	*adjusted*
23.5.5 Diseases	-
23.5.6 Smoking status	smokers and non-smokers
23.6 Administration/ Exposure	No Entry field
23.6.1 Exposure Route	Combined but mainly inhalation
23.6.2 Exposure Situation	Workplace: Mine in Southern California Mining, transport, processing, packaging, shipping.
23.6.3 Exposure concentration(s)	Personal sampling data of dust exposures for the most exposed jobs were available since the early 1980's. Sodium borate dust exposure categories for 8-hours were arbitrarily assigned three categories described as "high" (> 8 mg/m3), "medium" (3 - 8 mg/m3) and "low" (< 3 mg/m3). The range of exposure in one year was 2 to 35.7 mg/m3 (sodium borates). Base in an average of 23.2 mg/m3, Whorton et al, (1994), calculated the average exposure to borate dusts to be 203 mg/day assuming a 7 hour day and a respiratory volume of 8.75 m3 (based on 10 m3 for 8 hours). They assumed an average or usual boron content of 14% of the dust which, for the high exposure group, is equivalent to a mean of 28.4 mg B/d or 0.4 mg B/kg/d for a 70kg worker.
23.6.4 Method(s) to determine exposure	Based on previous studies in the facility, and the personal work record of each employee to allocate amount of time and dates spent in low, medium or high exposure areas..
23.6.5 Postexposure period	None

Section A6.12.4 **Epidemiological Study**

Annex Point IIA6.12.4 Section A6.12.4 Cohort study on US Borax Employees

No Entry field

23.7 Examinations

23.7.1 Type of disease

Infertility

23.7.2 Parameters

The summary index for assessing the risk of infertility is the Standardised Birth Ratio (SBR). The number of live children born to wives of the workers was compared to the number of births that would be expected in the general USA population (SBR) adjusted for maternal age, parity , race and calendar year. Total, male and female births were analysed.

23.8 Further remarks

24 RESULTS AND DISCUSSION

24.1 Exposure

24.1.1.1 Number of measurements

There was a highly significant excess of offspring fathered by the male employees at the mine and production facility (529 observed births compared with 466.6 expected). A statistically significant excess in the standardised birth ratio (SBR) of 113, significant at $p < 0.01$. The SBR for the workers with 'low' exposures was not different from the SBR of those with 'medium' and 'high' exposures, and both exceeded 100. There was no evidence of a relation between exposure and this excess of offspring, nor were there any temporal differences during the more than 30 year period of observation. The SBR was also evaluated in 5 year periods from 1950-1990 and in every period the SBR was greater than 100.

Nine percent of workers tried unsuccessfully to conceive for more than one year which compares with the national average of 15% of the adult population.

An excess in the percentage of female offspring (52.7% compared with 48.8% expected) were fathered by these male employees, this increase was not statistically significant, and was not due to a deficit of boys since 249 were observed compared with 238 expected. Thus there was an excess of 11 boys and 51 girls. There was no evidence of an exposure relationship to sodium borate exposures of the fathers and the excess of female offspring, nor was there any temporal differences. There was an inverse relationship between the increase percentage of female offspring and the sodium borate exposures of their fathers.

24.1.1.2 Average concentrations

24.1.1.3 Standard deviation

24.1.1.4 Date(s) of measurement(s)

24.1.2 Other

24.2 Number of cases for each disease / parameter under consideration	not relevant
24.3 SMR (Standard mortality ratio), RR (relative risk), OR (Odds ratio)	not relevant
24.4 Other Observations	A 36% vasectomy rate was observed among the workers which is about five times the national average, but similar to that found by the authors in 2 other worker studies in California.

25 APPLICANT'S SUMMARY AND CONCLUSION

Section A6.12.4 **Epidemiological Study**

Annex Point IIA6.12.4 Section A6.12.4 Cohort study on US Borax Employees

25.1 Materials and methods

[redacted] et al studied the reproductive effects of male employees at the U.S. Borax mine and production facility in Southern California. The standardised birth ratio (SBR) was used to assess fertility of these employees. Live births were the measured end-point. The ratio of female to male offspring was also assessed. This group of workers was selected for study as they have the highest and longest measured exposures of any worker or community group in the United States and probably the world. The method employed was a questionnaire to examine any anti-fertility influence of occupational exposures by studying the reproductive performance in terms of live births to the wives of workers, subsequent to specific occupational exposures to sodium borate dust.

25.2 Results and discussion

When compared with the SBR for the USA population adjusted for maternal age, parity, race and calendar year the SBR for the wives of workers was 113 ($P<0.01$) and exceeded 100 for every 5 year period from 1950-1990. Nine percent tried unsuccessfully to conceive for more than one year compared with a national average of 15%. An excess of girls was found but this was not due to a deficit of boys which were also in excess of expected numbers.

25.3 Conclusion

Exposure to inorganic borates up to an estimated maximum of 28.4mg B/day over a working lifetime did not lead to a reduction in birth rate.

25.3.1 Reliability

2

25.3.2 Validity

Strengths: Non-invasive methodology; sufficient statistical power; adequate assessment of non-participants; no demonstrable bias;births used as measure of fertility.

Weaknesses: questionnaire response lower than optimal; historical exposure categorisations based on incomplete data; no direct measure on the gonads so subtle effect on semen parameters would not be detected.

25.3.3 Deficiencies

Some deficiencies as reported above but overall is a clear demonstration of absence of any adverse effect of borate exposure on a most highly exposed population of workers with repeated exposures for up to 40 years.

25.4 Other

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted

	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18 February 2005
Materials and Methods	The version of the applicants is acceptable.
Results and discussion	The present study provide no evidence for an adverse effect on fertility of borates on a highly exposed population of workers. It should be noted that the conclusion of the study is based solely on the number of children born. Other reproductive effects, such as time to pregnancy were not investigated.
Conclusion	The version of the applicants is adopted.
Reliability	2
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	

Section A6.12 **Medical Data/Surveillance Data/Health Records - 2**

Annex Point IIAVI6.9 *Section A6.12.5/6.12.7/6.12.8*

APPLICANT'S SUMMARY AND CONCLUSION

Official use only

6.12.5 /6.12.7/6.12.8

6.12.5 Symptoms of poisoning from to borates have been associated with deliberate ingestion of very high doses or absorption through large areas of damaged skin in obsolete medical treatments (See 6.12.2). These may include nausea, vomiting, and diarrhoea, and anaemia, with delayed effects of skin redness and peeling.

6.12.6

No sensitisation or allergic responses have been observed. Borates are not sensitisers.

6.12.7

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.

For Excessive Inhalation Exposure: If symptoms such as nose and throat irritation are observed, remove to fresh air.

For Excessive Exposures: Observation only is required for adult ingestion of a few grams of borates. For more excessive ingestion, maintain adequate kidney function and force fluids. Gastric lavage is recommended for symptomatic patients only. Haemodialysis should be reserved for massive acute ingestion or patients with renal failure. Boron analyses of urine or blood are only useful for documenting exposure and should not be used to evaluate severity of poisoning or to guide treatment

6.12.8

Prognosis depends of speed of treatment and level of intake. Death rarely occurs where medical intervention has taken place – see (6.12.2) occurs unless

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18 April 2005
Materials and Methods	The version of the applicant is acceptable
Results and discussion	The version of the applicant is adopted
Conclusion	The version of the applicant is adopted
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 A6.14 **Human Case Report**

Annex Point IIA6.14 Section IIA6.14

Official use only

26 Reference

Reference

Sensory Perception study in Boric acid at Occupationally Relevant Concentrations: [redacted]

Study ongoing – FINAL report due July 2004

Data produced for sodium tetraborates – see Doc IIIA Sodium Tetraborates

Electronic File

Data protection

Yes

Data owner

[redacted]

Companies with letter of access

Curent Access

[redacted]

Criteria for data protection

Data on new a.s. for first entry to Annex I/IA

	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	not applicable
Results and discussion	not applicable
Conclusion	The data form the tetraborate study 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 this 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 with no evidence of an effect on pulmonary function. In the toxicological review of boron by US-EPA in 2004 they concluded that these data are inadequate to support derivation of an RfC for boron compounds. 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 6.15 Annex Point IIA VIA	Food and Feeding Stuff Section: 6.15 Food and Feedingstuffs	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [x]	**Other justification [ ]**	
Detailed justification:	Borates that are active ingredients or other biocidal products containing the borate active ingredient do not go in to wood products that are used for food preparation or feedingstuffs. Furthermore finished wood products containing borates and manufactured for structural and building material are not appropriate to be used and would not be used to make products that would come in to contact with food or feedingstuffs. Boric acid is permitted as a food preservative (Directive 95/2/EC) in caviar at a level of 4g/kg.	
Undertaking of intended data submission [ ]		

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	10-Febr-05
Evaluation of applicant's justification	No comments.
Conclusion	As indicated by the notifier
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	

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

Annex Point IIA7.6.2.1

Official use only

Reference

1. [redacted] 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] Electronic File
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]

Data protection

Yes on [redacted].

Data owner

[redacted]

Curent Access

Companies with letter of access

[redacted]

Criteria for data protection

Data on new a.s. for first entry to Annex I

GUIDELINES AND QUALITY ASSURANCE

Guideline study

No.

GLP

Yes

Deviations

No

MATERIALS AND METHODS

Test material

Disodium Octaborate Tetrahydrate [redacted]

Sodium Tetraborate Decahydrate (Borax, [redacted]

144-99-303

Lot/Batch number

[redacted].

Specification

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%

Purity

[redacted] >98%

Borax [redacted] >99%

Further relevant properties

none

Reference substance

Yes

Orthoboric acid (Boric Acid, [redacted])

Initial concentration of reference substance

0.02 $mol.l^{-1}$

Test solution

Solutions of [redacted] (Disodium octaborate tetrahydrate) tech., Borax [redacted] and Boric Acid [redacted], with a final solution concentration of 0.02$mol.l^{-1}$ 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.

Testing procedure

Non-entry field

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], 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] Technical and Borax, [redacted] are comparable to those of Boric Acid, [redacted].
Temperature	Room temperature
pH	See Tables
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.
Number of replicates	Non reported
Sampling	Stable system, therefore sampling interval and storage not relevant
Analytical methods	Raman Spectrometry
Preliminary test	No

RESULTS

Concentration and hydrolysis values	*See table A7_1_1_1_1-4*
Hydrolysis rate constant (k_h)	Not determined. Inorganic material speciation under consideration.
Dissipation time	Not relevant – Inorganic Material
Concentration – time data	Concentration is constant in all cases (0.02M).
Specification of the transformation products	There are no transformation products (inorganic material). Reference Farmer, 1982

APPLICANT'S SUMMARY AND CONCLUSION

Materials and methods

The objective of the study was to identify and compare the dissociation products of [redacted], and Borax, [redacted], in aqueous solution with those of Boric acid, [redacted], using Raman spectrometry.

The Raman spectra of dilute solutions of [redacted] and Borax [redacted] were measured and compared to Boric Acid, 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.

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)

$[B(OH)_3] < 0{,}02M$
$B(OH)_3 + H_2O \rightarrow [B(OH)_4]^+ + H^+$ 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 $[B_3O_3(OH)_5]^{2-}$

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

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.

k_H Not determined

DT_{50} Not determined

r^2 Not determined

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).

Reliability 1

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	14-02-2005
Materials and Methods	Applicant's version is acceptable
Results and discussion	Applicant's version is acceptable
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-values.
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			
[redacted]	8.62	6.03	6.99	8.03	9.00
Borax [redacted]	9.18	5.99	6.99	8.03	9.02
Boric Acid [redacted]	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 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, [redacted], contain a band at 745cm^{-1} in the natural pH and at pH 9.0. Boric acid, [redacted], has a vibration at 490cm^{-1} at pH 7.0, pH 8.0 and pH 9.0 apart from the band at 872 cm in all samples. The Raman spectra of [redacted]. show a band at 565cm^{-1} (non-buffered, pH 6.0, pH7.0 and pH 8.0), a band at 524/525 cm (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^{-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. *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.

Section 7.1 **Annex Point VII7.6.1.1**	**Ready biodegradability** Section 7.1.1.2.1	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	Boric acid behaves like a weak inorganic acid in water due to its reaction with water forming the tetrahydroborate anion ($[B(OH)_4]^-$) and releasing H^+ ions. The equilibrium constant is small enough that the proportion of boric acid in dilute solutions with a neutral pH is >99%. The relative concentration of tetrahydroborate anion becomes dominant at pH values >9 (7.1.1.1.1). The determination of inherent biodegradability is only relevant for organic compounds. Therefore no ready biodegradability test needs to be carried out with boric acid. Boric acid would be equivalent to the mineral degradation products resulting from ultimate degradation of organic compounds **Reference** [redacted] (2004). Boric Acid (CAS No. 10043-35-3): Statement on ready biodegradability [redacted]	
Conclusion **Remarks**	*Indicate whether applicant's justification is acceptable or not. If unacceptable because of the reasons discussed above, indicate which action will be required, e.g. submission of specific test/study data*	

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	14-02-2005
Evaluation of applicant's justification	Applicant's justification is considered valid
Conclusion	Justification for non-submission of data is accepted, with the addition that the 7th line of the justification should read "The determination of readily *or inherent* biodegradability ..."
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	

Section 7.1 **Annex Point VII7.6.1.2**	**Inherent biodegradability** Section 7.1.1.2.2.	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [x]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	Boric acid behaves like a weak inorganic acid in water due to its reaction with water forming the tetrahydroborate anion ($[B(OH)_4]^-$) and releasing H^+ ions. The equilibrium constant is small enough that the proportion of boric acid in dilute solutions with a neutral pH is >99%. The relative concentration of tetrahydroborate anion becomes dominant at pH values >9 (7.1.1.1.1). The determination of inherent biodegradability is only relevant for organic compounds. Therefore no inherent biodegradability test needs to be carried out with boric acid. Boric acid would be equivalent to the mineral degradation products resulting from ultimate degradation of organic compounds. **Reference** [redacted] (2004). Boric Acid (CAS No. 10043-35-3): Statement on inherent biodegradability [redacted]	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	14-02-2005	
Evaluation of applicant's justification	Applicant's justification is considered valid	
Conclusion	Justification for non-submission of data is accepted	
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		

Section A7.1.3 **Adsorption / Desorption screening test**

Annex Point IIA7.7 **Section A7.1.3**

Official use only

27 REFERENCE

27.1 Reference

[redacted]. 2000. "A study on the adsorption/desorption of Boric acid Manufacturing Grade to soil particulates in four soil types." [redacted]

27.2 Data protection

Yes

Data owner

[redacted]

Criteria for data protection

Data on existing or new a.s. to [maintain or vary a.s. Annex I/IA entry

GUIDELINES AND QUALITY ASSURANCE