Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*)
fungicide	PT-08	Timbor (=DOT)	*Lenzites trabea* Pers ex Fr FPLV 47B syn *Gloeophyllum trabeum*	Ponderosa pine sapwood treated by vacuum impregnation. No ageing or leaching. Soil block test, mass loss in weight and total carbon dioxide evolution measured by GC-FID (after reduction to methane). ASTM D1413 (1961). Blocks were placed on feeder strips, placed on the soil surface.	Concentration range not stated. Blocks exposed for 12 weeks at 23 °C.	Due to incomplete study report toxic threshold values could not be evaluated (figure 4 and table 2 are missing). Data are required because G. trabeum is considered the most boron tolerable decay fungus.	Smith, 1969
fungicide	PT-08	boric acid	Two species *Lentinus lepideus* BK C-1 highest boron tolerancy, but not relevant for present evaluation. Relevant species for toxic threshold concentration: *Gloeophyllum trabeum* (A570)	Pinus sylvestris L. sapwood treated by vacuum/pressure process. Blocks air dried for 24 hrs. No ageing or leaching. Agar block test, mass loss in weight. Blocks were placed on a nylon net, which was placed on the agar surface.	Retentions in blocks 0.1-1.0 kg/m^3 BAE. Blocks exposed for 6 months at 50°C.	Highest boron tolerancy for *Gloeophyllum trabeum* (A570) on pine (*Pinus sylvestris*) sapwood: Toxic threshold concentration determined as 0.08%-0.18% w/w BAE (0.40-0.92 kg/m^3 BAE). Conversion factor kg/m^3 → % w/w multiply by 0.2.	Bechgaard, 1979
fungicide	PT-08	boric-acid triethanolamine (BTEA); boric acid or Timbor (= DOT)	Four species. *Chaetomium globosum* Kunze IAM 8059 highest boron tolerancy, but not relevant for present evaluation. Relevant species for toxic threshold concentration in sequence of highest boron tolerancy: *Coriolus versicolor* L ex. Fr. Quel FFPR 1030 and *Serpula lacrymans* FFPR 0739.	Yezo spruce (Picea jezoensis) and Japanese beech (Fagus crenata) sapwood treated by vacuum impregnation. JIS A9201 (1991) test without weathering. Soil block test or agar block test (C. globosum only), mass loss in weight. Blocks were placed directly on the soil or agar surface. Toxic threshold levels on Japanese beech (Fagus crenata) were higher than on Yezo spruce (only tested for C. versicolor), but dose rates were not high enough to deduce a toxic threshold level for Japanese beech (> 1.45 or >1.53 kg/m^3 BAE for Timbor and boric acid,	Retention in blocks 0, 0.39-4.29 kg/m^3 BAE for Tim-bor and 0, 0.40-1.65 kg/m^3 BAE for boric acid. Blocks exposed for 120 days at 26 °C or 20 °C (S. lacrymans only). BTEA is considered not relevant for the present evaluation, because the tri-ethanol amine has synergic effects on boron efficacy. Toxic threshold levels for Timbor and boric acid are similar:0.85 and 0.83 kg/m^3 BAE, respectively. for *S. lacrymans* on Yezo spruce,	Highest boron tolerancy for *Coriolus versicolor* L ex. Fr. Quel FFPR 1030 on Yezo spruce (*Picea jezoensis*) sapwood: For **Tim-bor** toxic threshold concentration determined as 0.77%-0.86% w/w BAE (3.84-4.29 kg/m^3 BAE). **Boric acid** was not tested on the combination C. versicolor and Yezo spruce. Conversion factor kg/m^3 → % w/w multiply by 0.2. Toxic threshold levels in this study were higher compared to other studies, because leaching was not prevented during test. This study is	Doi et al., 1994

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*)
				respectively).		therefore considered as not reliable and results are not used in efficacy assessment.	
fungicide	PT-08	Boric acid	Several species *Gloeophylum abietineum* (Fr.) Karst 13851 highest boron tolerancy Other relevant species: *Gloeophyllum trabeum* (Fr.) Murr. 7520, *Serpula lacrymans* S.F. Gray 16508, *Coniophora olivacea* (Fr.) Karst, *Poria sp.* 2422, *Poria subcrassa* Rodway & Cleland 11040, *Trametes versicolor* (L.:Fr.) Pil. syn *Coriolus versicolor*.	Pinus radiata D Don sapwood and Eucalyptus regnans F. Muell heartwood treated by vacuum impregnation and diffusion. Blocks were air dried for 6 weeks (ageing). No leaching. Soil block test, mass loss in weight. Blocks were placed on a plastic mesh square, but not in contact with the feeder strips which were placed on the soil surface. Agar block test resulted in higher toxic threshold levels, results are considered not reliable because of larger concentration intervals. Results from agar block tests are not used for derivation of toxic threshold levels. Toxic threshold levels for pine and eucalyptus were similar for *Poria sp.* 2422, *Poria subcrassa* Rodway & Cleland 11040. The other relevant species were only tested on pine	Mean retentions in blocks of 0 and 0.5-2.0 kg/m^3 BAE for soil block test or 0 and 0.1-10.0 kg/m^3 BAE for agar block test. Blocks exposed for 12 weeks at 25°C.	Highest boron tolerancy for *Gloeophylum abietineum* (Fr.) Karst 13851 on pine (Pinus radiata) sapwood: Toxic threshold concentration determined as 0.4% w/w BAE (2.0 kg/m^3 BAE) in the soil block test. Conversion factor kg/m^3 → % w/w multiply by 0.2.	Cookson & Pham 1995
insecticide	PT-08	Sodium metaborate (assumed $NaBO_2$)	Egg larvae and larger larvae of *Lyctus brunneus* Stephens	Starch-free and starch-containing sapwood of Eucalyptus regnans or Eucalyptus obliqua treated by immersion in boiling solution. Blocks were air dried (period not stated). No ageing or leaching. Larval survival and mass loss in weight of wood.	Test concentrations 0.4-2.3 lb/ft^3 for larger larvae and 0.04-2.8 lb/ft^3 for beetle test (egg larvae). Duration of the test not stated, but at least 9 weeks. Large larvae hardly eat from the wood and pupate almost	Highest boron tolerancy for Lyctus brunneus on starch-free Eucalyptus obliqua: Toxic threshold concentrations for egg larvae determined as 0.30% w/w BAE (1.5 kg/m^3 BAE or 0.1 lb/ft^3 sodium metaborate) assuming wood density is 500 kg/m^3. Not effective against larger larvae	Cummins & Wilson 1936

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*)
				Wood-boring in starch free wood is generally lower than in starch containing wood. Because of the reduced amount of toxic material passed through the digestive tract, toxic threshold levels for starch free wood is higher. Experiments with larger larvae were only carried out on Eucalyptus obliqua. Results from egg larvae on Eucalyptus obliqua and Eucalyptus regnans were similar.	immediately. Therefore tests were carried out with very small, small and medium sized larvae which have sufficient gluttony to ensure proper assessment of efficacy.	at highest level tested: 6.9% w/w BAE (35 kg/m^3 BAE, 2.3 lb/ft^3 sodium metaborate). Conversion factor lb/ft^3 → kg/m3 multiply by 15.99. Conversion factor kg/m^3 → % w/w multiply by 0.2. Conversion factor metaborate (MW 657996) → BAE multiply by 0.94.	
insecticide	PT-08	boric acid or borax or boric acid plus borax	Egg larvae of *Lyctus brunneus* Stephens	Starch containing yellow carrabeen (Sloanea woolsii). Wood treatment not stated. Visual damage to wood. Experimental conditions not stated.	Test concentrations 0.01-0.24 lb/ft^3 BAE for boric acid or 0.04-0.3 lb/ft^3 for borax. Duration of the test not stated.	Boron tolerancy for Lyctus brunneus on yellow carrabeen (Sloanea woolsii) For boric acid, toxic threshold concentration is 0.16% w/w BAE (0.80 kg/m^3 BAE, 0.05 lb/ft^3 BAE). For borax, toxic threshold concentration is 0.08% w/w (0.42 kg/m^3 BAE, 0.04 lb/ft^3 as borax). Toxicity of boric acid, borax or mixtures of borax and boric acid, is considered equal. Because of differences in concentration ranges, final endpoints are slightly different. Conversion factor lb/ft^3 → kg/m3 multiply by 15.99. Conversion factor kg/m^3 → % w/w multiply by 0.2. Conversion factor borax → BAE multiply by 0.65.	Cummins, 1939
insecticide	PT-08	Boric acid	Egg larvae of *Anobium punctatum*	Pinus radiata D. Don sapwood and Podocarpus dacrydoides sapwood;	Test concentrations 0.004-3.25 % (w/w) in wood. Duration of the test	Highest boron tolerancy for *Anobium punctatum* on pine (Pinus	Spiller 1948

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*)
			de Geer	wood treatment not stated. Larval survival. Efficacy results for Pinus radiata D. Don sapwood and Podocarpus dacrydoides sapwood are similar.	not stated.	radiata) and kabikatea (Podocarpus Dacrydoides) sapwood: Toxic threshold concentrations determined as 0.022 – 0.043% (w/w) BAE (0.11 – 0.21 kg/m^3 BAE) assuming wood density is 500 kg/m^3. Conversion factor % w/w → kg/m^3 multiply by 5.	
insecticide	PT-08	Borax or DOT	Egg larvae and larger larvae of two species *Anobium punctatum* de Geer highest boron tolerancy Other relevant species: *Hylotrupes bajulus*	Corsican pine sapwood treated by vacuum impregnation. Details on wood treatment not stated. BS 3651 and BS 3652 newly hatched (egg larvae) or larger larvae introduced into holes. Larval survival and mass loss in weight of wood.	Borax test concentrations 0.068-3.4 kg/m3 or 0.013-0.70 % w/w (0.008-0.45 % w/w BAE) for egg larvae and larger larvae (1-3 mg). DOT test concentrations 0.077-7.7 kg/m3 or 0.016-1.6 % w/w (0.019-1.9% w/w BAE). for egg larvae and larger larvae (1.5-5.5 mg). Duration of the test 6-18 months.	Highest boron tolerancy for *Anobium punctatum* on pine sapwood. For borax the toxic threshold concentrations determined as 0.45% w/w BAE (2.2 kg/m^3 BAE, 3.4 kg/m^3 borax) for larger larvae. For DOT the toxic threshold concentrations determined as 1.9% w/w BAE (9.5 kg/m^3 BAE, 7.7 kg/m^3 DOT) for larger larvae. For DOT the toxic threshold concentrations determined as 0.09% w/w BAE (0.45 kg/m^3 BAE, 0.39 kg/m^3 DOT) for egg larvae. Toxicity of boric acid and DOT, is considered equal. Because the test conditions for DOT differ from test conditions for boric acid (length of larvae, test duration), final endpoints are different Conversion factor % w/w → kg/m^3 multiply by 5.	Taylor 1967
termiticide	PT-08	DOT	*Reticulitermes flavipes*	Slash pine (Pinus elliottii Engelm.	DOT loadings equivalent to 0.37-	Boron tolerancy for *Reticulitermes*	Mauldin and

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*)
				variety elliottii) treated by vacuum/pressure impregnation. Air dried for 24 hrs. No ageing or leaching. Laboratory test with no choice (only treated wood) or choice (both treated and untreated wood available). Subterranean termite attack in a field test in Gulfport, MS, USA (non-leaching conditions and protected from rain). Termite mortality and mass loss of weight in wood.	2.9 kg/m^3 BAE or 0.10-0.54% (w/w) BAE (by analytical determination). Duration of the laboratory test 4 weeks at 25-28 °C. Duration of the field test 18 months.	*flavipes* on pine (Pinus elliottii). For DOT, toxic threshold concentrations determined as 0.30% BAE (1.5 kg/m^3 BAE) in the choice laboratory test. Field tests in USA are considered not relevant for EU. No conversion factors used, actual values from study report.	Kard, 1996
fungicide; insecticide	PT-08	Boric acid or borax or sodium borate (assumed to be borax)	Review article on decay fungi (e.g. *Coniophora cerebella* syn *Coniophora puteana, Lenzites trabea* syn *Gloeophyllum trabeum, Poria vaporaria* syn *Poria placenta, Polystictus versicolor* syn *Coriolus versicolor, Merulius lacrymans* syn *Serpula lacrymans*) and wood boring insects (egg larvae and larger larvae of *Anobium punctatum, Hylotrupes bajules, Lyctus brunneus*).	Not stated	Not stated	For boric acid highest toxic threshold levels for decay fungi were determined as 0.12%-0.40% w/w BAE (0.6-2.0 kg/m^3 BAE). For egg larvae, highest toxic threshold levels were 0.04%-0.12% w/w BAE (0.2-0.6 kg/m^3 BAE). For borax (or sodium borate) highest toxic threshold levels for decay fungi were determined as 0.065%-0.38% w/w BAE (0.32-1.9 kg/m^3 BAE, 0.5-2.9 kg/m^3 borax) Toxicity of boric acid and borax, is considered equal. Because the test conditions for borax differ from test conditions for boric acid, final endpoints are slightly different Conversion factor kg/m^3 → % w/w multiply by 0.2. Conversion factor % w/w → kg/m^3 multiply by 5.	Findlay, 1959

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*)
						Conversion factor borax → BAE multiply by 0.65.	
fungicide; insecticide	PT-08	Boric acid or borax	Review article on decay fungi (e.g. *Coniophora cerebella* syn *Coniophora puteana*, *Lenzites trabea* syn *Gloeophyllum trabeum*, *Poria vaporaria* syn *Poria placenta*, ,*Merulius lacrymans* syn *Serpula lacrymans*) and wood boring insects (egg larvae and larger larvae of *Anobium punctatum*, *Hylotrupes bajules*, *Lyctus brunneus*).	Not stated	Not stated	For boric acid highest toxic threshold levels for decay fungi were determined as 0.072%-0.28 % w/w BAE (0.36-1.4 kg/m^3 BAE) if American test methods are omitted. Highest toxic threshold levels for egg larvae were 0.03%-0.12% w/w BAE (0.15-0.6 kg/m^3 BAE) after 12 weeks. Highest toxic threshold levels for larger larvae were 0.072%-1.5% w/w BAE (0.36-7.4 kg/m^3 BAE) after 16-24 weeks. For borax toxic highest threshold levels for decay fungi were determined as 0.065%-0.21% w/w BAE (0.32-1.0 kg/m^3 BAE, 0.5-1.6 kg/m^3 borax) if American test methods are omitted. Highest toxic threshold levels for egg larvae were 0.023%-0.084% w/w BAE (0.12-0.42 kg/m^3 BAE, 0.18-0.65 kg/m^3 borax) after 12 weeks. Highest toxic threshold levels for larger larvae were 0.091%-0.34% w/w BAE (0.46->1.7 kg/m^3 BAE, 0.7->2.6 kg/m^3 borax) after 24 weeks. Toxicity of boric acid and borax, is considered equal. Because the test conditions for borax differ from test conditions for boric acid, final endpoints are slightly different Conversion factor kg/m^3 → % w/w multiply by 0.2. Conversion factor % w/w → kg/m^3 multiply by 5. Conversion factor borax → BAE	Becker, 1959

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*)
						multiply by 0.65.	
fungicide; insecticide	PT-08	Boric acid or borax or DOT (=TIMBOR = Polybor) or sodium metaborate	Review article on decay fungi (*Coniophora puteana, Gloeophyllum trabeum, Poria placenta, Coriolus versicolor, Serpula lacrymans*) and wood boring insects (egg larvae and larger larvae of *Anobium punctatum, Hylotrupes bajules, Lyctus brunneus*).	Not stated.	Not stated	Highest toxic threshold concentrations determined as 0.016%-0.42% w/w BAE (0.08-2.1 kg/m^3 BAE) for decay fungi (if ASTM values are deleted) and 0.008%-0.2% w/w BAE (0.04-1.0 kg/m^3 BAE) for egg larvae and 0.008%-1.8% w/w BAE (0.04-9.2 kg/m^3 BAE) for larger larvae assuming wood density is 500 kg/m^3. Conversion factor kg/m^3 → % w/w multiply by 0.2.	Bravery & Carey 1983

A6.1.1.1 Acute Toxicity

Annex Point IIA6.1

A6.1.1.1 Acute Oral Toxicity: Limit Test: Male Rats

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	8 REFERENCE	
8.1	**Reference**	[redacted] 1996, Final Report: Anhydrous Boric Acid. Acute Oral Toxicity Study in the Rat. [redacted]
		Electronic file
8.2	**Data protection**	Yes
8.2.1	Data owner	[redacted]
8.2.2	Companies with letter of access	To be advised
8.2.3	Criteria for data protection	Data on new a.s. for first entry to Annex I/IA
	9 GUIDELINES AND QUALITY ASSURANCE	
9.1	**Guideline study**	Yes
		Directive 92/69/EEC, B.1 OECD 401.
9.2	**GLP**	Yes
9.3	**Deviations**	Yes
		This study was carried out to confirm a previous study, which indicated that the LD_{50} was greater than 2000 mg/kg, but where 40% of the male rats died at 2000 mg/kg. See Section A6.1.1.1
		Dose levels were selected on the basis of clinical observations and time of onset of signs or death in the previous study, to straddle the regulatory limit dose, with the intention of establishing mortality rates of 0 - 20% in the lower dose group and 40 - 100% in the higher group, such that a calculation of the LD_{50} would be possible.
	10 MATERIALS AND METHODS	
		.
10.1	**Test material**	As given in section 2
		Anhydrous Boric Acid
10.1.1	Lot/Batch number	5C183709
10.1.2	Specification	As given in section 2
10.1.2.1	**Description**	White powder
10.1.2.2	**Purity**	>99%

A6.1.1.1	**Acute Toxicity**
Annex Point IIA6.1	A6.1.1.1 Acute Oral Toxicity: Limit Test: Male Rats
10.1.2.3 Stability	Stable

A6.1.1.1 Acute Toxicity

Annex Point IIA6.1

A6.1.1.1 Acute Oral Toxicity: Limit Test: Male Rats

10.2	**Test Animals**	
10.2.1	Species	Rat
10.2.2	Strain	Crl:CD.BR
10.2.3	Source	Charles River (UK)
10.2.4	Sex	Male
10.2.5	Age/weight at study initiation	5-8 weeks old; 142-217 grams
10.2.6	Number of animals per group	*5*
10.2.7	Control animals	No
10.3	**Administration/ Exposure**	Oral
10.3.1	Postexposure period	14 days
		Oral
10.3.2	Type	Gavage
10.3.3	Concentration	1540; 2600 mg/kg bw
10.3.4	Vehicle	Corn Oil
10.3.5	Concentration in vehicle	Adjusted to weight of animal
10.3.6	Total volume applied	10ml/kg
10.3.7	Controls	None
10.4	**Examinations**	Clinical observations, necropsy, histopathology or other
10.5	**Method of determination of LD_{50}**	Limit test
10.6	**Further remarks**	
		11 RESULTS AND DISCUSSION
11.1	**Clinical signs**	No deaths occurred. No effects at 1540 mg/kg. At 2600 mg/kg, piloerection observed in one animal that recovered by day 2 and 2 animals were lethargic and one displayed increased breathing rate, but both had recovered by Day 2
11.2	**Pathology**	The only effects observed were a few red foci in the thymus of one animal and pale lungs and distension of the jejunum in a second animal at 1540 mg/kg.

A6.1.1.1 Acute Toxicity

Annex Point IIA6.1

A6.1.1.1 Acute Oral Toxicity: Limit Test: Male Rats

11.3 Other	None
11.4 LD_{50}	> 2600 mg/kg bw males
	12 APPLICANT'S SUMMARY AND CONCLUSION
12.1 Materials and methods	Directive 92/69/EEC, B.1 OECD 401. Dose levels of 1540; 2600 mg/kg bw given to males only were selected on the basis of clinical observations and time of onset of signs or death in the previous study (A6.1.1.1), to straddle the regulatory limit dose, with the intention of establishing mortality rates of 0 - 20% in the lower dose group and 40 - 100% in the higher group, such that a calculation of the LD_{50} would be possible
12.2 Results and discussion	In this study no deaths occurred and no significant clinical or pathological findings were observed The mortality from the two studies gave a non-monotonic response, 0/5 male rats died at 1540 mg/kg, 2/5 died at 2000 mg/kg and 0/5 died at 2600 mg/kg. Probit analysis of this mortality pattern was unable to produce a value for LD_{50}. However, if it is assumed that the next dose level in the sequence will elicit mortality, then the range within which the LD50 must lie can be determined. In doing the dose interval of 1.3, the next higher dose would be 3380 mg/kg. It was assumed that one rat would be killed at this level. The acute median lethal oral dose (LD_{50}) could them be computed and the result obtained was 47,371 mg/kg. If it was assumed that complete mortality was elicited at 3380 mg/kg, then the value obtained by extrapolation was 2665 mg/kg. If 3380 elicited no mortality, then the LD_{50} would exceed 48 g/kg. It can therefore be concluded that the LD_{50} is greater than 2600 mg/kg bw (and is less than 48 g/kg). This data is consistent with the LD_{50} data obtained with boric acid and various sodium borates (LD_{50}s all >2000 mg/kg)..
12.3 Conclusion	LD_{50} > 2600 mg/kg (based on 2 studies)
12.3.1 Reliability	1
12.3.2 Deficiencies	No

A6.1.1.1 Acute Toxicity

Annex Point IIA6.1

A6.1.1.1 Acute Oral Toxicity: Limit Test: Male Rats

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	23 February 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.
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	

A6.1.1.2 Acute Toxicity

Annex Point IIA6.1

A6.1.1.2 Acute Oral Toxicity: Limit Test: Male Rats

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	13 REFERENCE	
13.1	**Reference**	[redacted] 1995, Final Report: Anhydrous Boric Acid. Acute Oral Toxicity Study in the Rat. [redacted]
		Electronic file
13.2	**Data protection**	Yes
13.2.1	Data owner	[redacted]
13.2.2	Companies with letter of access	To be advised
13.2.3	Criteria for data protection	Data on new a.s. for first entry to Annex I/IA
	14 GUIDELINES AND QUALITY ASSURANCE	
14.1	**Guideline study**	Yes
		Directive 92/69/EEC, B.1 OECD 401.
14.2	**GLP**	Yes
14.3	**Deviations**	No
	15 MATERIALS AND METHODS	
		.
15.1	**Test material**	As given in section 2
		Anhydrous Boric Acid
15.1.1	Lot/Batch number	5C183709
15.1.2	Specification	As given in section 2
15.1.2.1	**Description**	White powder
15.1.2.2	**Purity**	>99%
15.1.2.3	**Stability**	Stable

15.2	**Test Animals**	
15.2.1	Species	Rat
15.2.2	Strain	Crl:CD.BR
15.2.3	Source	Charles River (UK)
15.2.4	Sex	Male & Female
15.2.5	Age/weight at study initiation	5-87weeks old; Males; 160 -221 grams; Females: 137-207 grams
15.2.6	Number of animals per group	5
15.2.7	Control animals	No
15.3	**Administration/ Exposure**	Oral
15.3.1	Postexposure period	14 days
		Oral
15.3.2	Type	Gavage
15.3.3	Concentration	2000 and 200 mg/kg bw
15.3.4	Vehicle	Corn Oil
15.3.5	Concentration in vehicle	Adjusted to weight of animal
15.3.6	Total volume applied	10ml/kg
15.3.7	Controls	None
15.4	**Examinations**	Clinical observations, necropsy, histopathology or other
15.5	**Method of determination of LD_{50}**	Limit test
15.6	**Further remarks**	

16 RESULTS AND DISCUSSION

16.1	**Clinical signs**	One male at 2000 mg/kg died 15 mins after dosing and a second died on Day 3. There were no clinical signs prior to death. A slight loss of body weight was recorded in these rats. In the remainder of the males, three were noted with an unkempt appearance and one had vasodilation. At 200 mg/kg, apart from one male rat with an unkempt appearance no other clinical signs were observed. No females died and clinical signs were restricted to salivation in three females during the first hour of treatment and vasodilation in one female on Day 2
16.2	**Pathology**	The only effects observed were a distended stomach and darkened lungs in one rat that died and an enlarged liver, dark inflated lungs and

	red fluid in the thoracic cavity of the second rat that died.
16.3 Other	None
16.4 LD_{50}	> 200 mg/kg bw Males; >2000 mg/kg Females.
	17 APPLICANT'S SUMMARY AND CONCLUSION
17.1 Materials and methods	Directive 92/69/EEC, B.1 OECD 401. Limit dose Acute Oral Toxicity Study in male and female rats dosed at 200 and 2000 mg/kg bw
17.2 Results and discussion	At 2000 mg/kg 2/5 rats male rats died. No clinical signs were observed in these rats. Only minor clinical signs were observed in surviving rats including three with an unkempt appearance and one with vasodilation. The only pathological effects observed were a distended stomach and darkened lungs in one rat that died and an enlarged liver, dark inflated lungs and red fluid in the thoracic cavity of the second rat that died. At 200 mg/kg, apart from one male rat with an unkempt appearance no other clinical signs were observed No females died and clinical signs were restricted to salivation in three females during the first hour of treatment and vasodilation in one female on Day 2. No pathological effects were observed The LD_{50} was estimated to be > 200 mg/kg bw Males; >2000 mg/kg Females.
17.3 Conclusion	The LD_{50} was estimated to be > 200 mg/kg bw Males; >2000 mg/kg Females. A further study was carried out to clarify the LD_{50} in the males (See A6.1.1.1)
17.3.1 Reliability	1
17.3.2 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	23 February 2005
Materials and Methods	Animals were 5-7 weeks old. Otherwise the version of the applicant is acceptable.
Results and discussion	The LD50 is considered to be > 2000 mg/kg bw.
Conclusion	LD50> 2000 mg/kg bw
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 A6.1.2 Acute Toxicity

Annex Point IIA6.1

Section A6.1.2; Dermal Route; Rat; LD_{50} Limit Test

Official use only

18 REFERENCE

18.1	**Reference**	[redacted] (1982). Acute Dermal Toxicity Screen in Rabbits; Primary skin irritation study in rabbits of boric acid. [redacted]
		Electronic file
18.2	**Data protection**	Yes
18.2.1	Data owner	[redacted]
18.2.2	Companies with letter of access	To be advised
18.2.3	Criteria for data protection	Data on new a.s. for first entry to Annex I/IA

19 GUIDELINES AND QUALITY ASSURANCE

19.1	**Guideline study**	Yes
		FIFRA (40 CFR 163) Acceptable protocol at the time
19.2	**GLP**	No data
		Although not carried out to modern protocols and GLP, the data is acceptable particularly as data is available to indicate the absorption through humans skin is negligible > 0.5%. In addition, acceptable data on other borates indicates that dermal acute toxicity is not an issue. Therefore further testing is not warranted.
19.3	**Deviations**	See above

20 MATERIALS AND METHODS

Section A6.1.2

Annex Point IIA6.1

Acute Toxicity

Section A6.1.2; Dermal Route; Rat; LD_{50} Limit Test

20.1	**Test material**	Boric Acid Boric oxide is the anhydride of boric acid (CAS No.14003-35-3). It is hygroscopic and takes up water to form boric acid. Therefore for practical purposes one part of boric oxide is equivalent to 1.776 parts of boric acid in aqueous solution. The data for boric acid is therefore relevant for boric oxide and in the interests of animal welfare testing is not warranted.
20.1.1	Lot/Batch number	OA 107-3
20.1.2	Specification	As given in Boric Acid Dossier

Section A6.1.2 Annex Point IIA6.1	Acute Toxicity Section A6.1.2; Dermal Route; Rat; LD_{50} Limit Test	
20.1.2.1 Description	White powder	
20.1.2.2 Purity	>99%	
20.1.2.3 Stability	Stable	

Section A6.1.2 Acute Toxicity

Annex Point IIA6.1

Section A6.1.2; Dermal Route; Rat; LD_{50} Limit Test

20.2	**Test Animals**	Non-entry field
20.2.1	Species	Rabbit
20.2.2	Strain	New Zealand White
20.2.3	Source	Harlan F Plummer
20.2.4	Sex	Male and Female
20.2.5	Age/weight at study initiation	1623 –2922 grams
20.2.6	Number of animals per group	5 male; 5 female
20.2.7	Control animals	No
20.3	**Administration/ Exposure**	Dermal
20.3.1	Post exposure period	14 days
		Dermal
20.3.2	Area covered	Not specified but implies > 10 % of body surface The skin of all of the animals was abraded longitudinally every 2-3 cm , deep enough to penetrate the stratum corneum, but not cause bleeding.
20.3.3	Occlusion	Semi occlusive
20.3.4	Vehicle	Physiological saline
20.3.5	Concentration in vehicle	Substance moistened with 1.5 ml saline
20.3.6	Total volume applied	Dosage to 2 g/kg bw
20.3.7	Duration of exposure	24 h
20.3.8	Removal of test substance	Moist towel
20.3.9	Controls	None
20.4	**Examinations**	Clinical observations, necropsy, histopathology or other
20.5	**Method of determination of LD_{50}**	Not relevant – Limit test
20.6	**Further remarks**	On removal of binders the binders and exposed areas were moist or dry with sample indicating incomplete absorption of sample.
		21 RESULTS AND DISCUSSION
21.1	**Clinical signs**	Clinical changes were limited t transient diarrhoea in 2 rabbits and some incidences of erythema (9), oedema (3), atonia (2), desquamation (4) at

Section A6.1.2 **Acute Toxicity**

Annex Point IIA6.1 **Section A6.1.2; Dermal Route; Rat; LD_{50} Limit Test**

24 hours and later times after treatment.

Section A6.1.2 Acute Toxicity

Annex Point IIA6.1

Section A6.1.2; Dermal Route; Rat; LD_{50} Limit Test

21.2 Pathology	No gross necropsy findings were observed. Observations included one animal with gas filled intestine, one animal with pale yellow coloured kidneys; 5 animals with enlarged or swollen or pale fallopian tubes.
21.3 Other	
21.4 LD_{50}	LD_{50} > 2000 mg/kg bw No lethal effect at limit dose
	22 APPLICANT'S SUMMARY AND CONCLUSION
22.1 Materials and methods	Protocol to FIFRA (40 CFR 163), which was an acceptable protocol at the time. Limit test in which rabbits were treated with 2g/kg bw boric acid. The skin of all of the animals was abraded longitudinally every 2-3 cm , deep enough to penetrate the stratum corneum, but not cause bleeding. Although not carried out to modern protocols and GLP, the data is acceptable particularly as data is available to indicate the absorption through humans skin is negligible > 0.5%. In addition, acceptable data on other borates indicates that dermal acute toxicity is not an issue. Therefore further testing is not warranted.
22.2 Results and discussion	Boric oxide is the anhydride of boric acid (CAS No.14003-35-3). It is hygroscopic and takes up water to form boric acid. Therefore for practical purposes one part of boric oxide is equivalent to 1.776 parts of boric acid in aqueous solution. The data for boric acid is therefore relevant for boric oxide and in the interests of animal welfare testing is not warranted. The LD_{50} > 2000 mg/kg bw for boric acid indicated no acute dermal toxicity. Clinical changes were limited to transient diarrhoea in 2 rabbits and some incidences skin irritation 24 hours and later times after treatment. No gross necropsy findings were observed. It can be concluded that the dermal LD_{50} for boric oxide is > 2000 mg/kg bw
22.3 Conclusion	LD_{50} > 2000 mg/kg bw
22.3.1 Reliability	2
22.3.2 Deficiencies	See above

Section A6.1.2 Acute Toxicity

Annex Point IIA6.1

Section A6.1.2; Dermal Route; Rat; LD_{50} Limit Test

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 February 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.
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 A6.1.3 Acute Toxicity

Annex Point IIA6.1 **Section A6.1.3; Inhalation Route; Rat; LC_{50} Limit Test**

Official use only

23 REFERENCE

23.1	**Reference**	[redacted] 1997. Acute inhalation toxicity limit on boric acid MG [redacted] [redacted] Electronic file
23.2	**Data protection**	Yes
23.2.1	Data owner	[redacted]
23.2.2	Companies with letter of access	To be advised
23.2.3	Criteria for data protection	Data on new a.s. for first entry to Annex I/IA

24 GUIDELINES AND QUALITY ASSURANCE

24.1	**Guideline study**	Yes OECD Guide-line 403 "Acute Inhalation Toxicity" (USEPA.FIFRA 40 CFR Part 160.
24.2	**GLP**	Yes
24.3	**Deviations**	Yes The stability; characterisation, identity and verification of the test substance was the responsibility of the study sponsor. Also highest dose was limited. However, this was a repeat study carried out at the request of the US EPA to confirm that the highest dose obtainable was 2 mg/l. It was deemed by the US EPA to be an acceptable study

25 MATERIALS AND METHODS

Section A6.1.3 Acute Toxicity

Annex Point IIA6.1

Section A6.1.3; Inhalation Route; Rat; LC_{50} Limit Test

25.1	**Test material**	Boric Acid [redacted] Boric oxide is the anhydride of boric acid (CAS No.14003-35-3). It is hygroscopic and takes up water to form boric acid. Therefore for practical purposes one part of boric oxide is equivalent to 1.776 parts of boric acid in aqueous solution. The data for boric acid is therefore relevant for boric oxide and in the interests of animal welfare testing is not warranted. In addition, the inhalation route is not a specific route of exposure for Biocidal Uses of boric oxide
25.1.1	Lot/Batch number	Lot #7B10
25.1.2	Specification	As given in section 2
25.1.2.1	**Description**	White powder
25.1.2.2	**Purity**	>99%
25.1.2.3	**Stability**	Stable

Section A6.1.3 Acute Toxicity

Annex Point IIA6.1

Section A6.1.3; Inhalation Route; Rat; LC_{50} Limit Test

25.2	**Test Animals**	Non-entry fieLC	
25.2.1	Species	Rat	
25.2.2	Strain	Sprague-Dawley	
25.2.3	Source	Ace animals Inc; Boyertown, PA	
25.2.4	Sex		
25.2.5	Age/weight at study initiation	Young adults: Males 205-255 grams; Females 179-208 grams	
25.2.6	Number of animals per group	5 male; 5 female	
25.2.7	Control animals	No	
25.3	**Administration/ Exposure**	Inhalation	
25.3.1	Postexposure period	14 days	
		Inhalation	
25.3.2	Concentrations	Nominal concentration	2000 mg/m³
		Analytical concentration	2120 ±140 mg/m³
25.3.3	Particle size	Not an aerosol study	
25.3.4	Type or preparation of particles	Sample was ground in a ball mill for 24 hours MMAD 3.5 µm ± GSD 1.81µm Top dose ~ 2 mg/l was the highest that was obtainable under the conditions of the test	
25.3.5	Type of exposure	Whole body	
25.3.6	Vehicle	Not relevant	
25.3.7	Concentration in vehicle	Not relevant	
25.3.8	Duration of exposure	4 h	
25.4	**Examinations**	Clinical observations, Pathology	
25.5	**Method of determination of LC_{50}**	Not relevant – Limit Test	
25.6	**Further remarks**	This study was a repeat study carried out at the request of the US EPA to confirm that the highest dose obtainable was 2 mg/l.	
25.6.1	Controls	None	

Section A6.1.3 Acute Toxicity

Annex Point IIA6.1

Section A6.1.3; Inhalation Route; Rat; LC_{50} Limit Test

26 RESULTS AND DISCUSSION

26.1 Clinical signs

Animal observations were limited due to the accumulation of test material on the walls of the exposure chamber. During the first 1.5 hours of exposure, ocular and nasal discharge, hypoactivity and haunched posture were noted. Ocular discharge and or nasal discharge persisted in most animals after removal from the chamber. All animals recovered by day two after removal from chamber.

26.2 Pathology

No specific findings observed except red lung discolouration consistent with CO2 inhalation (caused by euthanasia technique). All tissue sand organs were normal.

26.3 Other

26.4 LC_{50}

LC_{50} > 2.12.mg/L (2g/m^3)
No lethal effect at limit dose

27 APPLICANT'S SUMMARY AND CONCLUSION

27.1 Materials and methods

Acute inhalation toxicity limit on boric acid. The Sample was ground in a ball mill for 24 hours to give a MMAD 3.5 µm ± GSD 1.81µm
Top dose ~ 2 mg/l was the highest that was obtainable under the conditions of the test

27.2 Results and discussion

Boric oxide is the anhydride of boric acid (CAS No.14003-35-3). It is hygroscopic and takes up water to form boric acid. Therefore for practical purposes one part of boric oxide is equivalent to 1.776 parts of boric acid in aqueous solution. The data for boric acid is therefore relevant for boric oxide and in the interests of animal welfare testing is not warranted.

In addition, the inhalation route is not a specific route of exposure for Biocidal Uses of boric oxide

The LC_{50} for boric acid was > 2.12.mg/L (2g/m^3). Animal observations were limited due to the accumulation of test material on the walls of the exposure chamber. This was a repeat study carried out at the request of the US EPA to confirm that the highest dose obtainable was 2 mg/l. It was deemed by the US EPA to be an acceptable study

It can be concluded that the oral LC_{50} for boric oxide is> 2.12.mg/L bw

27.3 Conclusion

LC_{50} > 2.12.mg/L (2g/m^3).

27.3.1 Reliability

1

27.3.2 Deficiencies

No

Section A6.1.3 Acute Toxicity

Annex Point IIA6.1

Section A6.1.3; Inhalation Route; Rat; LC_{50} Limit Test

	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 Feb 2005
Materials and Methods	In the study report it is stated that the sponsor characterized the composition of test substance to be 100 % boric acid. The nominal concentration of boric acid is reported to 26.06 mg/L (26.06 g/m^3).
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_1-1. Table for Acute Toxicity (modify if necessary)

Dose [unit]	*Number of dead / number of investigated*	*Time of death (range)*	*Observations*
0			
x			
xx			
xxx			
LC_{50} value			

Section 6.1.4 Acute Eye Irritation

Annex Point IIA6.1.4

Specify section no., heading and species as appropriate

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] 1990, Evaluation of the Occular Irritation of Anhydrous Boric Acid in Rabbits. (P01875). [redacted] Electronic file
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]
1.2.2	Companies with letter of access	To be advised
1.2.3	Criteria for data protection	Data on new a.s. for first entry to Annex I/IA

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes EPA Guideline 81-4; 40 CFR158. Although not carried out to an OECD protocol, the study has been carried out to an US EPA acceptable protocol.
2.2	**GLP**	Yes *(If no, give justification, e.g. state that GLP was not compulsory at the*
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	Anhydrous Boric Acid
3.1.1	Lot/Batch number	OA12D
3.1.2	Specification	As given in section 2
3.1.2.1	**Description**	White crystalline powder
3.1.2.2	**Purity**	>97.5%
3.1.2.3	**Stability**	Stable

Section 6.1.4 Acute Eye Irritation

Annex Point IIA6.1.4

Specify section no., heading and species as appropriate

3.2	**Test Animals**	Non-entry field
3.2.1	Species	Rabbit
3.2.2	Strain	New Zealand White
3.2.3	Source	Irish Farms (Norco, CA)
3.2.4	Sex	Not reported
3.2.5	Age/weight at study initiation	2.07 –2.47 kg
3.2.6	Number of animals per group	6 for No rinsing group; 3 for rinsing group
3.2.7	Control animals	No (used left eye as no treatment)
3.3	**Administration/ Exposure**	
3.3.1	Preparation of test substance	Test substance was used as delivered
3.3.2	Amount of active substance instilled	0.1 g.
3.3.3	Exposure period	6 animals: sample not removed
		3 animals; sample rinsed out immediately with normal saline
3.3.4	Postexposure period	The irritation remaining was slight and not considered significant and therefore the study was terminated at 72 hours
3.4	**Examinations**	
3.4.1	Ophthalmoscopic examination	yes
3.4.1.1	**Scoring system**	Scoring in report according to Draize, but scoring reported here according to EU 67/548/EEC
3.4.1.2	**Examination time points**	24h, 48h, 72h or other
3.4.2	Other investigations	Effect of rinsing
3.5	**Further remarks**	
		4 RESULTS AND DISCUSSION
4.1	**Clinical signs**	Table A6_1_4E-1.and Table A6_1_4E-2
4.2	**Average score**	
4.2.1	Cornea	No rinsing: 0.11
		Rinsing: 0.00
4.2.2	Iris	No rinsing: 0.06
		Rinsing: 0.00

Section 6.1.4 Acute Eye Irritation

Annex Point IIA6.1.4 *Specify section no., heading and species as appropriate*

4.2.3	Conjunctiva	
4.2.3.1	**Redness**	No rinsing: 0.78 Rinsing: 0.78
4.2.3.2	**Chemosis**	No rinsing: 0.78 Rinsing: 0.89
4.3	**Reversibility**	The irritation remaining was slight and not considered significant and therefore the study was terminated at 72 hours
4.4	**Other**	
4.5	**Overall result**	Not classifiable in the EU under Directive 67/548/EEC. Classified in US Category IV (40 CFR 156) Minimal Effects US CPS (16 CFR 15000.42) - Irritant

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Eye irritation study in New Zealand white rabbits to EPA Guideline 81-4; 40 CFR158. 100 mg boric oxide was instilled in the eyes. It was either rinsed out immediately with normal saline or left in for the entire period of the study.
5.2	**Results and discussion**	In the rinsing study, irritation was confined to redness and slight swelling of the conjunctival tissue which retuned to normal in 2/3 rabbits 72 hours after exposure. A more pronounced reaction occurred in the rabbits without rinsing including slight corneal swelling and iritis in one animal. However the effects improved by 48 hours and the irritation remaining in 2/3 animals was slight and not considered significant and the test was terminated at 72 hours. Boric oxide is the anhydride of boric acid (CAS No.14003-35-3). It is hygroscopic and takes up water to form boric acid. Boric acid is used up to 5% in eye washes
5.3	**Conclusion**	Not classifiable in the EU under directive 67/548/EEC.
5.3.1	Reliability	2
5.3.2	Deficiencies	Although the study on boric oxide was not been carried out to OECD protocols, it was carried out to US Government Guidelines and evaluated under EU 67/548/EEC rules and indicate that boric oxide is not an eye irritant. Further testing of boric acid is therefore not justified in the interests of protecting laboratory animals.

Section 6.1.4 Acute Eye Irritation

Annex Point IIA6.1.4

Specify section no., heading and species as appropriate

	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 February 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
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	

Appendix

Table A6_1_4E-1. Results of Non Rinsing eye irritation study – Boric Oxide

Use this table, if re

	Cornea	Iris	Conjunctiva	
			redness	chemosis
24 h	0.33	0.17	1.5	1.5
48 h	0.00	0.00	1.00	0.33
72 h	0.00	0.00	0.33	0.50
Average 24h, 48h, 72h	0.11	0.06	0.78	0.78
average time for reversion		By 48 h	*	*

* The irritation remaining was slight and not considered significant and therefore the study was terminated at 72 hours

Table A6_1_4E-2. Results of Rinsing eye irritation study – Boric Oxide

Use this table, if re

	Cornea	Iris	Conjunctiva	
			redness	chemosis
24 h	0.00	0.00	1.33	1.33
48 h	0.00	0.00	0.67	1.00
72 h	0.00	0.00	0.33	0.33
Average 24h, 48h, 72h	0.00	0.00	0.78	0.89
average time for reversion		By 48 h	*	*

* The irritation remaining was slight and not considered significant and therefore the study was terminated at 72 hours

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Section A6.1.4 : Rabbit Skin Irritation Study

Official use only

6 REFERENCE

6.1	**Reference**	[redacted], 1973. Corrosivity study on a series of seven materials [redacted] Electronic file
6.2	**Data protection**	Yes
6.2.1	Data owner	[redacted]
6.2.2	Companies with letter of access	To be advised
6.2.3	Criteria for data protection	Data on new a.s. for first entry to Annex I/IA

7 GUIDELINES AND QUALITY ASSURANCE

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Section A6.1.4 : Rabbit Skin Irritation Study

7.1	**Guideline study**	Title 49 of the Code of Federal Regulations Section 173.240. Although not carried out to an OECD protocol, the study has been carried out to an US EPA acceptable protocol.
7.2	**GLP**	GLP not regulated at that time
7.3	**Deviations**	Although not carried out to modern protocols, data from other irritation studies boric acid confirm the results Therefore further testing is not warranted in the interest of animal welfare. NB Boric oxide is the anhydride of boric acid (CAS No.14003-35-3). It is hygroscopic and takes up water to form boric acid. Therefore for practical purposes one part of boric oxide is equivalent to 1.776 parts of boric acid in aqueous solution.
	8 MATERIALS AND METHODS	
8.1	**Test material**	As given in section 2
8.1.1	Lot/Batch number	
8.1.2	Specification	As given in section 2
8.1.2.1	**Description**	*100 mesh fine white powder*
8.1.2.2	**Purity**	*> 97.5%*
8.1.2.3	**Stability**	*Stable*
8.2	**Test Animals**	Non-entry field
8.2.1	Species	Rabbit
8.2.2	Strain	White albino
8.2.3	Source	
8.2.4	Sex	Not reported
8.2.5	Age/weight at study initiation	Not reported
8.2.6	Number of animals per group	6
8.2.7	Control animals	No
8.3	**Administration/ Exposure**	Dermal
8.3.1	Application	Non entry field

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Section A6.1.4 : Rabbit Skin Irritation Study

8.3.1.1	**Preparation of test substance**	Test substance was used as delivered.
8.3.1.2	**Test site and Preparation of Test Site**	Hair was clipped from the saddle area of rabbit and one areas on each rabbit was abraded by making epidermal incisions with a hypodermic needle sufficiently deep to penetrate the epidermis, but not to induce bleeding Each rabbit was treated on one intact and one abraded areas
8.3.2	Occlusion	Occlusive
8.3.3	Vehicle	Not relevant
8.3.4	Concentration in vehicle	Not relevant
8.3.5	Total volume applied	0.5grams
8.3.6	Removal of test substance	Moistened towel
8.3.7	Duration of exposure	4 h or
8.3.8	Postexposure period	48 hours
8.3.9	Controls	None
8.4	**Examinations**	
8.4.1	Clinical signs	Yes
8.4.2	Dermal examination	Yes
8.4.2.1	**scoring system**	**S 191.11. – Regulations under the Federal Hazardous Substances Act (based on Draize)*
8.4.2.2	**Examination time points**	4 h; 24h; 48h
8.4.3	Other examinations	None
8.5	**Further remarks**	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Section A6.1.4 : Rabbit Skin Irritation Study

9 RESULTS AND DISCUSSION

.

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Section A6.1.4 : Rabbit Skin Irritation Study

9.1	**Average score**	Non-entry field
9.1.1	Erythema	0
9.1.2	Edema	0
9.2	**Reversibility**	Not relevant
9.3	**Other examinations**	No other effects observed
9.4	**Overall result**	Negative

10 APPLICANT'S SUMMARY AND CONCLUSION

10.1	**Materials and methods**	Method: Title 49 of the Code of Federal Regulations Section 173.240. Hair was clipped form the saddle area of rabbit and one area on each rabbit were abraded by making epidermal incisions with a hypodermic needle sufficiently deep to penetrate the epidermis, but not to induce bleeding, therefore each rabbit was treated on two intact and two abraded areas with 0.5 grams boric acid under and occlusive dressing
10.2	**Results and discussion**	No irritancy was observed and although not carried out to modern protocols, data from other irritation studies on boric acid confirm the results since boric oxide is the anhydride of boric acid (CAS No.14003-35-3). It is hygroscopic and takes up water to form boric acid. Therefore further testing is not warranted in the interest of animal welfare.
10.3	**Conclusion**	Non-irritant
10.3.1	Reliability	*2*
10.3.2	Deficiencies	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Section A6.1.4 : Rabbit Skin Irritation 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	24 February 2005
Materials and Methods	The version of the applicant is acceptable
Results and discussion	The test material was not moistened, so good contact with the skin is not ensured. However, virtually no sign of skin irritation was observed after application of boric oxide on the intact or abraded skin. Furthermore, boric oxide is reported to be hygroscopic, and takes up water to form boric acid. Skin irritation studies with other borates, among others boric acid, are also negative. All evidence together indicates that boric oxide does not cause skin irritation.
Conclusion	It is concluded that boric oxide is not a skin irritant.
Reliability	3
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 A6.1.5 Skin sensitisation

Annex Point IIA6.1.5 Buehler Test

			Official use only
		11 REFERENCE	
11.1	**Reference**	[redacted] (1994), Dermal sensitization test-Buehler method on boric acid. [redacted] [redacted] Electronic File	
11.2	**Data protection**	Yes	
11.2.1	Data owner	[redacted]	
11.2.2	Companies with letter of access	**Curent Access** [redacted]	
11.2.3	Criteria for data protection	Data on new a.s. for first entry to Annex I/IA	
		12 GUIDELINES AND QUALITY ASSURANCE	
12.1	**Guideline study**	Yes OECD Guide-line 406 "Skin Sensitization"	
12.2	**GLP**	Yes	
12.3	**Deviations**	No	
		13 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 A6.1.5 Skin sensitisation

Annex Point IIA6.1.5 Buehler Test

13.1 Test material	As given in section 2
13.1.1 Lot/Batch number	Lot #4H25-3611
13.1.2 Specification	As given in section 2
13.1.2.1 Description	White powder
13.1.2.2 Purity	>99%
13.1.2.3 Stability	Stable
13.1.2.4 Preparation of test substance for application	*a) <u>for induction:</u> used as delivered moistened with distilled water (95%w/v)* *b) <u>for challenge:</u> used as delivered moistened with distilled water (95%w/v)*
13.1.2.5 Pre-test performed on irritant effects	Yes

Section A6.1.5 Skin sensitisation

Annex Point IIA6.1.5 Buehler Test

13.2	**Test Animals**	Non-entry field
13.2.1	Species	Guinea pigs
13.2.2	Strain	Hartley albino
13.2.3	Source	Davidson's Mill Farms, South Brunswick, NJ
13.2.4	Sex	
13.2.5	Age/weight at study initiation	Young adult males: 314 -411 grams; Young adult females: 282-376 grams
13.2.6	Number of animals per group	Test Group: 20 animals Naive Control: 10 animals Positive Control: 20 animals Positive Naive Control: 10 animals
13.2.7	Control animals	Yes
13.3	**Administration/ Exposure**	State study type: Non-Adjuvant
13.3.1	Induction schedule	day 0 – day –7 – day 21 *Table A6_1_5-1.*
13.3.2	Way of Induction	Topical
13.3.3		Occlusive
13.3.4	Concentrations used for induction	0.4 g 95% w/w/boric acid moistened with distilled water to enhance skin contact
13.3.5		
13.3.6	Challenge schedule	Day 28; Table A6_1_5-1.
13.3.7	Concentrations used for challenge	95% w/w/boric acid moistened with distilled water to enhance skin contact
13.3.8	Rechallenge	No
13.3.9	Scoring schedule	24h, 48h after challenge
13.3.10	Removal of the test substance	After 6 hours test substance wiped off with water
13.3.11	Positive control substance	Dinitrochlorobenzene
13.4	**Examinations**	Non-entry field
13.4.1	Pilot study	No
13.5	**Further remarks**	
		14 RESULTS AND DISCUSSION
14.1	**Results of pilot studies**	No pilot study

Section A6.1.5	**Skin sensitisation**
Annex Point IIA6.1.5	Buehler Test

14.2	**Results of test**	See Table A6_1_5-2
14.2.1	24h after challenge	0/20
14.2.2	48h after challenge	0/20
14.2.3	Other findings	
14.3	**Overall result**	Non -sensitiser
14.4		**APPLICANT'S SUMMARY AND CONCLUSION**
14.5	**Materials and methods**	OECD Guide-line 406 "Skin Sensitisation" method (Buehler test) using 95% w/w boric acid moistened with distilled water to enhance skin contact
14.6	**Results and discussion**	Very faint erythema seen in one animal at induction stage and 2 animals at challenge stage and also in one naïve control. No other adverse effect observed
14.7	**Conclusion**	Non-sensitiser
14.7.1	Reliability	1
14.7.2	Deficiencies	No

Evaluation by Competent Authorities		
		Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
14.8		**15 EVALUATION BY RAPPORTEUR MEMBER STATE**
15.1	**Date**	2 Feb 2005
15.2	**Materials and Methods**	In the study report it is stated that the sponsor characterized the composition of test substance to be 100 % boric acid. The induction schedule was day 0 - day 7- day 14. On day 28 a challenge dose was applied.
15.3	**Results and discussion**	The version of the applicant is adopted.
15.4	**Conclusion**	The version of the applicant is adopted.
15.5	**Reliability**	1
15.6	**Acceptability**	acceptable
15.7	**Remarks**	
15.8		**16 COMMENTS FROM ...**
16.1	**Date**	*Give date of comments submitted*
16.2	**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*
16.3	**Results and discussion**	*Discuss if deviating from view of rapporteur member state*
16.4	**Conclusion**	*Discuss if deviating from view of rapporteur member state*
16.5	**Reliability**	*Discuss if deviating from view of rapporteur member state*
16.6	**Acceptability**	*Discuss if deviating from view of rapporteur member state*
16.7	**Remarks**	

Table A6_1_5-1. Detailed information including induction/challenge/scoring schedule for skin sensitisation test

Treatments	Buehler test	Observations/Remarks *give information on irritation effects*
	day of treatment	
Induction 1	day 0	Very faint erythema (0.5) observed at one test site at 24 hours after first induction dose. No other irritation observed
Induction 2	7	No irritation observed
Induction 3	14	No irritation observed
challenge	28	No irritation observed
(rechallenge)		
scoring 1	29	Very faint erythema (0.5) observed at two test sites at 24 hours after challenge dose. Irritation persisted at one site for 48 hours. Very faint erythema (0.5) observed at one test site at 24 hours in one naive control.
scoring 2	30	

Table A6_1_5-2. Result of skin sensitisation test

	Number of animals with signs of allergic reactions / number of animals in group		
	Negative control	**Test group**	**Positive control**
scored after 24h	***0 / 10***	***0 / 20***	***10/20***
scored after 48h	***0 / 10***	***0 / 20***	***7/20***

Section A6.2 Percutaneous absorption (in vivo test)

Annex Point IIA6.2

Section A6.2 Human In vivo

Official use only

17 REFERENCE

17.1 Reference

[redacted]. (1996). In Vivo Percutaneous Absorption of Boric Acid, Borax and Octaborate Tetrahydrate (DOT) in Man. [redacted]

Electronic File

17.2 Data protection Yes

17.2.1 Data owner [redacted]

17.2.2 Companies with letter of access: To be advised

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

18 GUIDELINES AND QUALITY ASSURANCE

Section A6.2 Percutaneous absorption (in vivo test)

Annex Point IIA6.2 Section A6.2 Human In vivo

18.1 Guideline study	No Human Study specifically designed and therefore no specific guidelines available, but designed to comply with US 40 CFR, 160
18.2 GLP	Yes
18.3 Deviations	Not relevant (If yes, describe deviations from test guidelines or refer to respective field numbers where these are described, e.g. "see 3.x.y")
	19 MATERIALS AND METHODS
19.1 Test material	Boric oxide is the anhydride of boric acid (CAS No.14003-35-3). It is hygroscopic and takes up water to form boric acid. Therefore for practical purposes one part of boric oxide is equivalent to 1.776 parts of boric acid in aqueous solution. The data for boric acid is therefore relevant for boric oxide and in the interests of animal welfare testing is not warranted.
19.1.1 Lot/Batch number	
19.1.2 Specification	As given in section 2
19.1.2.1 Description	White powder
19.1.2.2 Purity	>99%
19.1.2.3 Stability	Stable
19.1.2.4 Radiolabelling	^{10}B
19.2 Test Animals	Non-entry field
19.2.1 Species	Humans
19.2.2 Strain	
19.2.3 Source	
19.2.4 Sex	Male & female
19.2.5 Age/weight at study initiation	Age 22 -50
19.2.6 Number of animals per group	8/groups
19.2.7 Control animals	Internal controls (i.e. baseline boron measured)
19.3 Administration/ Exposure	Dermal both intact and abraded skin

19.3.1	Preparation of test site	Skin was washed and a 30 cm x 30 cm area marked on back
19.3.2	Concentration of test substance	5% Boric acid ; 5% Borax or 10% DOT in distilled water
19.3.3	Specific activity of test substance	
19.3.4	Volume applied	3 ml/900 cm^2
19.3.5	Size of test site	900 cm^2
19.3.6	Exposure period	After 5 days during which urine samples were collected the test substance was applied topically; air-dried and a commercial white T-shirt worn for 24 hours during which time urine was collected. At 24 hours the T-shirt was removed and analysed. The exposed areas were analysed for transepidermal water loss (TEWL) and then washed carefully with soap and distilled deionised water and all washing analysed. On day 11 the TEWL was measured and the treatment site dosed with 1.8 ml of 2% SDS (sodium lauryl sulphate) to cause irritation. On day 12 the TEWL was measured and the test substance was applied again topically; air-dried and a commercial white T-shirt worn for 24 hours during which time urine was collected. At 24 hours the T-shirt was removed and analysed. The exposed areas were analysed for transepidermal water loss (TEWL) and then washed carefully with soap and distilled deionised water and all washing analysed.
19.3.7	Sampling time	See above – Sample time 24 hours
19.3.8	Samples	Urine sampled as well as T-shirts worn and skin washings samples – see above

20 RESULTS AND DISCUSSION

20.1 Toxic effects, clinical signs No adverse effects

20.2 Dermal irritation No skin Irriation observed

20.3 Recovery of labelled compound BA -76.5%; Borax 72%; DOT 78.5% Since the skin was washed 10 times and less 1 % was found I the last wash, it is assumed that most of the substance unaccounted for was in lost to outside clothing (over the T-shirt) an bedding during the 24 hour dosing period

20.4 Percutaneous absorption

Substance	% Dose Absorbed (95% CI)	Flux $\mu g/cm^2/hr$	Permeability Kp cm/hr.
5 % Boric Acid	0.226 ± 0.125	0.009	1.8×10^{-7}
5 % Borax[1]	0.210 ± 0.194	0.009	1.8×10^{-7}
10% DOT[2]	0.122 ± 0.10	0.010	1.0×10^{-7}

[1] Disodium tetraborate decahydrate

[2] Disodium octaborate tetrahydrate

21 APPLICANT'S SUMMARY AND CONCLUSION

21.1 Materials and methods

This study was designed to address absorption of typical solutions used in wood preservation and other biocidal uses.

Human Volunteers (8 per group) Group I, group II, and group III received two separate topical application of B^{10}-enriched 5% Boric Acid, 5% Borax, and 10% DOT solutions on their back skin, respectively and the in vivo percutaneous absorption was determined for a 24-hour dosing period. One dose was applied on day 5 under normal skin conditions and the other on day 12 under irritated skin conditions created by applying 2% SLS solution. Twenty- four hours after each topical dose, residual chemical on the dosed skin site was removed by skin wash. Urine samples were collected every 24 hours for 17 days. Urine samples from day 1 to day 4 were used to establish base boron levels and isotope ratios in the urine. The samples from day 5 to day 11 and day 12 to the end were used to compare absorbed level under normal skin and irritated skin conditions. To evaluate the dosing site skin condition, TEWL measurement and skin visual scoring were taken each time before dosing (including SLS treatment) and washing. To control any boron intake some food/beverage restrictions were instituted and daily detailed records were required. Boron analysis was done using inductively coupled mass spectrometry

21.2 Results and discussion

Approximately one-half of the administered topical dose was recovered after 24 hours in the T-shirt covering the dosed skin area and the skin washes. Pre-treatment with the potential skin irritant 2~ sodium lauryl sulphate had no effect on boron skin absorption for all three different dosage forms. No skin irritation was noted for any of the dosage forms.

Substance	% Dose Absorbed (95% CI)	Flux $\mu g/cm^2/hr$	Permeability Kp cm/hr.
5 % Boric Acid	0.226 ± 0.125	0.009	1.8×10^{-7}
5 % Borax[1]	0.210 ± 0.194	0.009	1.8×10^{-7}
10% DOT[2]	0.122 ± 0.10	0.010	1.0×10^{-7}

[1] Disodium tetraborate decahydrate

[2] Disodium octaborate tetrahydrate

Since boric oxide is the anhydride of boric acid (CAS No.14003-35-3). It is hygroscopic and takes up water to form boric acid. The data for boric acid is therefore relevant for boric oxide. No confirmatory animal testing is necessary in the interests of animal welfare testing is not warranted..

21.3 Conclusion

Low skin absorption. For risk assessment where an absorbed dose is used the mean plus the standard deviation is used as a conservative absorption figure Boric acid and Boric Oxide = 0.351% absorption; Borax = 0.404 % absorption; DOT = 0.132 % absorption.

21.3.1 Reliability 1

21.3.2 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	24 February 2005
Materials and Methods	The version of the applicant is accepted.
Results and discussion	In the studies total recovery of the applied dose ranged from 48.8-63.6%. Accordingly 36.4-51.2% of the applied dose is not accounted for. This may be due to loss to outside clothing and bedding, as suggested by the study authors. However, part of the lost dose may be located in the body or in the skin at the application site, which in that case should be considered as being absorbed. As such, the absorption estimates from this study are unreliable. On the other hand, toxicokinetic studies also indicate that borates have a low dermal absorption and low potential for accumulation in the body. In this respect the present data are in line with dermal absorption data from other studies. Therefore, based on this study and other data a dermal absorption borates of 0.5% can be assumed as a reasonable worst case estimate.
Conclusion	The read across to data on boric acid is justified. Reasonable worst case estimate for dermal absorption of borates is 0.5%.
Reliability	3
Acceptability	acceptable
Remarks	Boric oxide is the anhydride of boric acid. The data for boric acid is therefore relevant for boric oxide and in the interests of animal welfare testing is not warranted.
	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 A6.2-A10 Doc III A Read Across to Boric Acid

Annex Point Section A6.2-A10

16 APPLICANT'S SUMMARY AND CONCLUSION

Since all the borates will exist as undissociated boric acid under physiological and environmental conditions, the toxicology and the ecotoxicology of all these simple borates is similar on an equivalent boric acid basis or boron basis. Therefore the data for boric acid and disodium tetraborate decahydrate can be read across to the other borates for both toxicological and ecotoxicological effects

Conversion factors are given below. These conversion factors are important as some studies express dose in terms of B, whereas other studies express the dose in units of boric acid or disodium tetraborate decahydrate. The B equivalents used are a generic designation rather than a designation of the element boron. For comparative purposes, dose levels of borates are expressed in terms B in most toxicology studies

Conversion factors to Boron Equivalents

		Conversion Factor for Equivalent dose of B
Boric acid	H_3BO_3	0.175
Boric oxide	B_2O_3	0.311
Disodium tetraborate decahydrate (Borax)	$Na_2B_4O_7 \bullet 10H_2O$	0.113
Disodium tetraborate pentahydrate	$Na_2B_4O_7 \bullet 5H_2O$	0.148
Disodium tetraborate anhydrous	$Na_2B_4O_7$	0.215
Disodium octaborate tetrahydrate	$Na_2B_8O_{13} \bullet 4H_2O$	0.210

The simple inorganic borates (for example, boric acid, boric oxide, sodium tetraborates and octaborates) are highly water-soluble. The mode of dissolution of metal borates as well as of boric acid is complex and depends on the conditions (pH, temperature, and concentration). Boric acid is a weak acid and is considered a Lewis acid. As such it is an electron acceptor, rather than a proton donor, so will accept hydroxide. 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 + H2O --> [B(OH)4]+ + H+ pKa = 9,15

0,025M <= [B(OH)3] <= 0,4/0,6M
[B3O3(OH)4]-; [B3O3(OH)5]2- predominant

[B(OH)3] > 0,6M