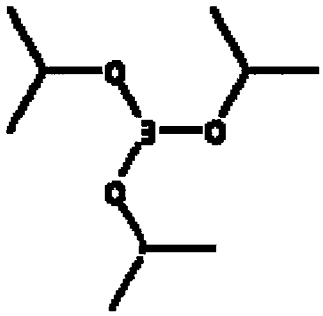
201-16697A

RECEIVED
OPPT CBIC
2005 MAR 18 AM 7:45

Summary and Test Plan for:

Triisopropylborate (TIPB)

CAS#: 5419-55-6



U.S. EPA HPV Challenge Program Submission

Submitted by:

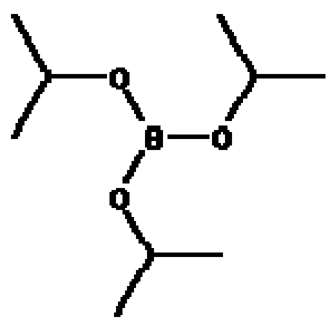
INVISTA S.à r.l.

SUMMARY

Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program, INVISTA S.à r.l. is completing a commitment by DuPont to voluntarily compile a Screening Information Data Set (SIDS) that can be used for an initial hazard assessment of Triisopropylborate (TIPB), CAS Registry No. 5419-55-6. Robust summaries have been prepared for all key studies. The information described in this test plan is a summary of the data presented in the Robust Summaries and should only be used for the purposes of the HPV Program.

This assessment includes data for physicochemical, environmental fate, and mammalian and environmental effect endpoints included in the U.S. HPV Program in a manner consistent with the requirements of an OECD SIDS Level 1 data package. Data/ information on use and exposure have also been supplied with this submission. Because TIPB rapidly hydrolyzes to isopropanol and boric acid, when in contact with water (across a broad pH range), read-across data from isopropanol and boric acid are included. OECD, NTP, and ACGIH have also reviewed and summarized information on isopropanol and/or boric acid. Based on a literature search, combined with data from accepted models, adequate information is available for all endpoints and no further testing is proposed.

Triisopropylborate (TIPB) is a colorless, moisture-sensitive liquid. It has a melting point of -72 to -70 °C, a boiling point of 140 °C, and density of 0.8251 g/cm^3 at 20 °C. TIPB has a measured vapor pressure of 8.6 mm Hg at 25 °C, is unstable in water (hydrolyzes rapidly, <15 minutes), and an estimated log Kow of 0.83. TIPB has the following chemical structure:



Molecular Formula: $C_9H_{21}O_3B$

Molecular Weight: 188

TIPB is sold commercially at ≥ 99 wt. % pure and contains very minor amounts of Triisopropoxyboroxine (CAS RN 10298-87-0). Common synonyms for Triisopropylborate include:

- Triisopropylborate (TIPB)
- Boric acid, triisopropyl ester
- Boric acid (H_3BO_3), triisopropyl ester
- Boron isopropoxide
- Boron triisopropoxide
- Isopropyl borate
- Triisopropoxy borane
- Triisopropoxy boron
- Triisopropyl orthoborate
- Triisopropoxyborane

A stability-in-water test, conducted in general accordance with OECD Guideline 111, determined that TIPB is unstable in water and rapidly hydrolyzes (<15 minutes) to the point where no parent compound remains. Analytical tests confirmed that sequential loss of isopropanol groups formed the end constituents of boric acid (CAS Registry No. 10043-35-3) and isopropanol (CAS Registry No. 67-63-0). The rapid hydrolysis to boric acid and isopropanol occurred over a broad range of pH values including the physiologically important pH of 1.2. Boric acid will form soluble salts with monovalent cations (e.g. $Na_2B_4O_7 \cdot 10H_2O$, 6% in water) and insoluble salts with divalent cations (e.g. $CaB_4O_7 \cdot 6H_2O$, almost insoluble in cold water) (Budavari, 1989). Isopropanol is water-soluble.

TIPB possesses very low to slight acute toxicity with an oral LD_{50} in rats and mice of 8,126 mg/kg and 2,500 mg/kg, respectively. TIPB was neither a skin irritant nor a skin sensitizer when tested in guinea pigs, and produced no to mild eye irritation when tested in rabbits. TIPB was negative in *Salmonella typhimurium* when tested in the *in vitro* bacterial reverse mutation assay.

No data are available to evaluate the potential repeated dose, reproductive, or developmental effects of TIPB. Because the water stability test results indicate that TIPB rapidly hydrolyses at the physiologically important pH of 1.2, repeated dose, reproductive and developmental studies for boric acid and isopropanol are appropriate to address these endpoints.

Boric Acid has been well studied in animals and, to a lesser degree, in humans. In repeat dose studies completed by the National Toxicology Program, groups of male and female $B6C3F_1$ mice were fed boric acid for 14 days, 13 weeks, and 2 years. In the 14-day studies, hyperplasia and dysplasia of the forestomach constituted the principal histopathologic findings. In the 13-week study at doses, in feed, ranging from 1,200 ppm to 20,000 ppm (5 days/week), the testis, stomach, and spleen were again identified as potential target organs. In the 2-year study, a dose-related reduction in body weight gain was observed in both sexes at the low dose of 2,500 ppm and the high dose of 5,000 ppm, and a decrease in the survival rate of male mice was observed at both doses by week 84. Histological examination of the survivors showed that statistically significant dose-related effects were limited to testicular atrophy and interstitial cell hyperplasia in male mice, with no evidence of carcinogenicity. A No Observable Adverse Effect Level (NOAEL) was not determined (NTP, 1987).

Boric acid has been tested for reproductive and development effects by oral administration in rats and mice. A statistically significant dose-related increase in the incidence of testicular atrophy and interstitial cell hyperplasia was observed in both species. In a 2-year chronic feeding study, a reproductive NOAEL at 17.5 mg boron/kg body weight/day (350 ppm boron in the diet) was reported (Weir and Fisher, in ACGIH, 2005). In addition, testicular atrophy is reported to have been observed in male Beagle dogs at 29.3 mg boron/kg body weight/day, with a reproductive NOAEL of 8.8 mg boron/kg body weight/day (ACGIH, 2005). The relevance of these findings to humans in occupational settings has not been fully characterized, but the NTP researchers concluded that it is unlikely that nuisance dust levels of boric acid found in occupational settings would pose a threat of reproductive toxicity in humans. Epidemiological investigations of male workers exposed to sodium borate compounds have not uncovered a statistically significant impact on reproduction, which lends some support to the NTP conclusion.

Isopropanol has also been well studied in animals and there is a long track record of human exposures without apparent chronic effects. High quality repeat-dose studies have been completed in rats and mice, by oral and inhalation routes. Nephrotoxicity has been the only dose-related statistically significant chronic effect commonly observed, but only at doses / exposure levels above those which would typically be encountered in the workplace.

Isopropanol has also been tested for reproductive and developmental effects in rats and in rabbits. No significant effects on reproduction or developmental outcomes were observed at doses that were not otherwise toxic to the test animals. A range of reproductive / developmental NOAELs have been reported from 400 mg/kg/day to 1200 mg/kg/day (OECD, 1997). A benchmark dose (BMD) assessment was conducted for the CMA Isopropanol Panel as a way of clarifying issues surrounding the derivation of effect levels for these studies. This assessment resulted in calculated BMDL dosages of 449 and 418 mg/kg/day for the F1 and F2 generations, respectively (OECD, 1997).

Modeling of environmental fate indicates that TIPB is estimated to have a half-life of 10.55 hours in air (AOPWIN modeled, by the method of Harris, 1990). Moisture may shorten the half-life in air. Emission to dry soil could possibly result in a moderate soil half-life in the absence of any moisture input. However, the hydrolytic instability of TIPB was highlighted by the fact that isopropanol was detected in the TIPB reference standard although precautions were utilized in order to ensure that reagents were dry. Therefore, the expectation is that the half-life of TIPB in soil will be relatively short. The Mackay Level III fugacity model (assuming equal emissions to air, water, and soil) predicts that TIPB will mainly occupy water, with a lesser amount occupying soil, little occupying air, and virtually none occupying sediment.

Because TIPB hydrolyzes, its aquatic toxicity potential is expected to be that of its hydrolysis products - isopropanol and boric acid. Modeled data indicate that isopropanol and boric acid have little tendency to bioaccumulate (estimated log BCF = 0.5). Isopropanol is readily biodegradable, while boric acid is not subject to biodegradation.

Isopropanol is of low concern for aquatic toxicity. Isopropanol has 96-hour LC_{50}s in fathead minnows and mysid shrimp of 9,640 - 10,400 mg/L and 4,050 mg/L, respectively (Veith, 1983). In another study, the 24-hour EC_{50} for daphnids was determined to be 159,000 μmol/L (29,906 mg/L) (Calleja, 1994). The 16-day log NOEC for growth and the log EC_{50} for reproduction in *Daphnia magna* were 3.37 μmol/L (0.63 mg/L) (Hermens, 1985) and 4.73 μmol/L (0.89 mg/L) (De Wolf, 1988), respectively. Isopropanol had very low toxicity to green algae with a 5-day algistatic concentration of 54,294 ppm (Exxon, 1983).

Boric acid is also of low concern for acute aquatic toxicity to fish with 96-hour LC_{50}s of >100 to 725 mg/L (Hamilton, 1995). Boric acid had a 48-hour LC_{50} in *Daphnia* of 133 mg/L (Gersich, 1984), an 8-day EC_{50} in *Ceriodaphnia dubia* of >100 mg/L (DuPont, 1993), and a 21-day LC_{50} in *Daphnia magna* of 52.2 mg/L (Gersich, 1984). In another study with *Daphnia magna*, the 14-day NOEL was approximately 14 mg/L (Gersich, 1984). The 7-day NOEC for boron using *Lemna minor* L. was >20 mg/L (Frick, 1985).

Because TIPB readily hydrolyzes with no parent compound remaining within 15 minutes, it is not possible to perform an *in vitro* chromosome aberration assay, such as an OECD Guideline 473 study, that was recommended previously. Boric acid and isopropanol micronucleus assays were negative.

During manufacturing and shipment, the potential for TIPB exposure is the greatest during shutdown work and loading and unloading. To control exposure, INVISTA's manufacturing site has implemented safety, health, and environmental practices and procedures in addition to engineering controls, environmental controls, and personal protective equipment. Safety equipment, such as safety showers, eyewash fountains, and washing facilities, is available in the event of an occupational exposure.

Individuals handling TIPB should wear coverall chemical splash goggles. A face shield should be worn where the possibility exists for face contact due to splashing or spraying of material. NIOSH-approved respiratory protection should be worn, as appropriate. Where there is potential for skin contact, impervious gloves, apron, pants, and jacket should be worn as appropriate.

References for Summary

ACGIH (2005). Borate Compounds, Inorganic. Documentation of TLVs® and BEIs®, 7th Edition. American Conference of Governmental Industrial Hygienists.

AOPWIN, v1.91 module of EPIWIN v.3.11. Meylan, W. M. and P. H. Howard (1993). Chemosphere, 26:2293-99. The model used assumptions of a 24-hour day and an ambient hydroxyl radical concentration of $0.5x10^6$ molecules/cm^3.

Budavari, S. (ed.) (1989). The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biological, 11^{th} ed., Merck and Co., Inc., Rahway, NJ.

Calleja, M. C. et al. (1994). Arch. Environ. Contam. Toxicol., 26:69-78.

De Wolf, W. et al. (1988). Aquatic Toxicol., 12:39-49.

DuPont Co. (1993). Unpublished Data, Haskell Laboratory Report HLO-418-93, "Chronic Toxicity to *Ceriodaphnia dubia*" (June 2).

Exxon Corp. (1983). EG&G Report No. BP-83-2-9, TSCA Fiche OTS0510685.

Frick, H. (1985). J. Plant Nutr., 8(12):1123-1129.

Gersich, G. M. (1984). Environ. Toxicol. Chem., 3:89-94.

Hamilton, S. J. (1995). Ecotoxicol. Environ. Safety, 30:134-142.

Harris, J. C. (1990). Rate of Aqueous Photolysis, Chapter 8, In: Handbook of Chemical Property Estimation Methods, Lyman, W. J. et al. (eds.), American Chemical Society, Washington, D.C.

Hermens, J. et al. (1985). Aquatic Toxicol., 6:209-217.

NTP (1987) U.S. National Toxicology Program: Toxicology and carcinogenesis studies of boric acid (CAS No. 10043-35-3) in B6C3F1 mice (feed studies). NTP TR 324. DHHS (NIH) Pub. No. 88-2580. NTP, Research Triangle Park, NC (1987).

OECD (1997). 2-Propanol CAS #67-63-0 Screening Information Data Set (SIDS) Initial Assessment Report (SIAR). Organization for Economic Co-Operation and Development (OECD). March 1997.

Veith, G. D. et al. (1983). Can. J. Fish. Aquatic. Sci., 40:743-748.

TEST PLAN

Subsequent to the earlier test plan submission, a stability-in-water test has been performed and indicates that TIPB completely hydrolyzes to boric acid and isopropanol over a broad range of pH values including the physiologically important pH of 1.2. No parent compound was left within 15 minutes.

Given the measured and estimated data available, the known hazards of the material, and the circumstances under which it is processed and used, no additional testing is proposed. The Test Plan matrix below summarizes the existing data for Triisopropylborate (TIPB).

TEST PLAN FOR TRIISOPROPYLBORATE

Triisopropylborate (5419-55-6)	Data Available	Data Acceptable	Testing Required
PHYSICAL/CHEMICAL CHARACTERISTICS			
Melting Point	Y	Y	N
Boiling Point	Y	Y	N
Vapor Pressure	Y	Y	N
Partition Coefficient	Y	Y	N
Water Solubility	Y	Y	N
ENVIRONMENTAL FATE			
Photodegradation	Y	Y	N
Stability in Water	Y	Y	N
Transport (Fugacity)	Y	Y	N
Biodegradation	Y	Y	N
ECOTOXICITY			
Acute Toxicity to Fish	Y*	Y	N
Acute Toxicity to Invertebrates	Y*	Y	N
Acute Toxicity to Aquatic Plants	Y*	Y	N
MAMMALIAN TOXICITY			
Acute Toxicity	Y	Y	N
Repeated Dose Toxicity	Y*	Y	N
Developmental Toxicity	Y*	Y	N
Reproductive Toxicity	Y*	Y	N
Genetic Toxicity Gene Mutations	Y	Y	N
Genetic Toxicity Chromosomal Aberrations	Y**	Y	N

*Data are available for hydrolysis products boric acid and isopropyl alcohol.

**Data are available for hydrolysis products boric acid and isopropyl alcohol for in vivo genetic toxicity studies, but not for in vivo clastogenicity studies. However, carcinogenicity studies have been conducted for boric acid and isopropanol.