201-15090

HPV

DATA SUMMARY AND TEST PLAN

FOR

1H-Isoindole-1,3(2H)-dione, 2,2'-(1,2-ethanediyl)bis(4,5,6,7-tetrabromo-

(a.k.a Ethylene bis tetrabromophthalimide)

CAS No. 32588-76-4

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1.0 INTRODUCTION

1H-Isoindole-1,3(2H)-dione, 2,2'-(1,2-ethanediyl)bis(4,5,6,7-tetrabromo- (CAS# 32588-76-4) is also known as Ethylene bis tetrabromophthalimide (EBTBP). Its manufacturer, Albemarle Corporation, sponsors EBTBP under the U.S. Environmental Protection Agency's voluntary High Production Volume Program. EBTBP is manufactured in a closed system. EBTBP is used solely as a flame retardant.

2.0 STRUCTURE AND PROPERTIES

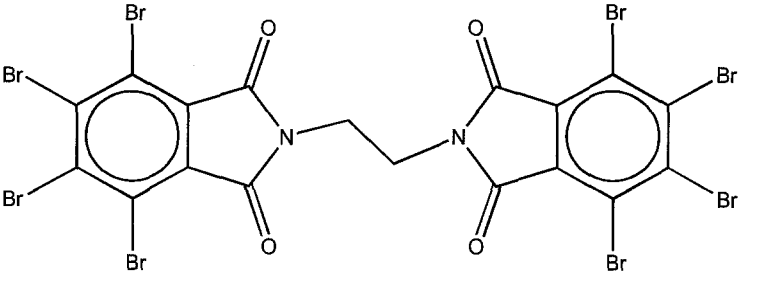

Figure 1. Ethylene bis tetrabromophthalimide (EBTBP)

The structure of EBTBP ($C_{18}H_{16}O_4Br_8N_2$) is shown in Figure 1. The product has a molecule weight of 951.47, and is an off-white powder at room temperature. EBTBP's estimated (EPIwin, v3.04) water solubility and vapor pressure are 3 x 10^{-9} mg/L and 2.5 x 10^{-22} mm Hg, respectively, at 25 deg C. Albemarle Corporation's technical data sheet reports the following solubilities (Wt. %, 25°C):

Water..... < 0.01
Acetone..... .... < 0.01
Methanol ..... < 0.01
Toluene ..... < 0.01

3.0 APPLICATIONS

EBTBP is a unique additive flame retardant that combines stable, aromatic bromine with an imide structure. It finds use in polyolefins, high-impact polystyrene (HIPS), thermoplastic polyesters (PBT, PET, etc.), polycarbonate and elastomers whose applications include electrical and electronics components, wire and cable insulation, switches, and connectors.

4.0 TOXICOLOGY DATA SUMMARY

4.1 Environmental Fate

EBTBP measured and predicted environmental fate parameters are provided in Table 1.

EBTBP is predicted to partition in the environment primarily to sediment and to a lesser extent to soil. Partitioning to air and water are expected to be minimal. EBTBP's

estimated half-life in sediment is 1600 days, and therefore may be persistent in that matrix. EBTBP may also be persistent in water and soil, but not air. EBTBP is expected to bind to organic carbon, be essentially immobile in sediment or soil, and is not expected to leach through soil or enter groundwater due to its high Log Koc. EBTBP is not expected to volatilize from water based on its river and lake volatilization half-lives and air-water partition coefficient. Sewage treatment plants are predicted to remove EBTBP from the influent through partitioning to sludge. Actual test data indicates EBTBP is not ready biodegradable.

Using EPA's PBT Profiler software, EBTBP is expected to be persistent, and is not expected to be bioaccumulative in the food chain and is not expected to exert chronic toxic to fish due to its very low water solubility. Thus, EBTBP does not fulfill EPA's criteria of a Persistent, Bioaccumulative and Toxic (PBT) chemical.

4.1.1. Ready Biodegradation

EBTBP was not readily biodegradable by activated sewage sludge over a 28-day period when tested under Japanese MITI/OECD Ready Biodegradability 301C Modified MITI guidelines. This test was performed according to Good Laboratory Practices guidelines. (The Biodegradability Test of S-502 (Ethylene-1,2-bis(3,4,5,6-tetrabromophthalimide. November 5, 1981. Chemical Biotesting Center, Chemicals Inspection & Testing Institute, Tokyo, Japan)

TABLE 1. Environmental Fate Parameters for EBTBP.

Parameter	Estimation Program or Test Result	Result
Photodegradation	-	Not likely to be a significant route of environmental degradation due to negligible portioning to air.
Hydrolysis	Estimated (EPI win, V.3.04)	Calculation not performed by EPIwin, because of amide group. Hydrolysis rate of amide group extremely slow or t1/2 > 1 year. Not expected to be a significant route of environmental degradation due to negligible partitioning to water.
Distribution	Estimated (EPI win, V.3.04)	Level III Fugacity Model predicts at emissions to Air, Water, Soil and Sediment of 1,000, 1,000, 1,000 and 0 kg/hr, respectively: Air 0.00003%, Water 0.4 %, Soil80.6.3%; Sediment 19.1%.
	Estimated (PBT Profiler)	Air 0%; Water 1%; Soil 51%; Sediment 49%
Atmospheric Oxidation	Estimated (EPI win, V.3.04)	Overall OH Rate Constant = 39.5 x 10-12 cm3/molecule-sec Half-Life = 0.27 Days (12-hr day; 1.56 x 10+6 OH/cm3) Half-Life = 3.3 Hrs
Henry's Law Constant	Estimated (EPI win, V.3.04)	3.6 x 10-21 atm-m3/mole at 25 °C
Soil Koc	Estimated (EPI win, V.3.04)	800,000
Log Kow	Estimated (EPI win, V.3.04)	9.79
Air-Water Partition Coefficient	Estimated (EPI win, V.3.04)	1.4 x10-19
Biomass to Water Partition Coefficient	Estimated (EPI win, V.3.04)	1.3 x 10+9
Volatization from Water	Estimated (EPI win, V.3.04)	Half life: 5.6x10+13 years (River); 6.2x10+14 years (Lake)
Sewage Treatment Plant Fugacity Model	Estimated (EPI win, V.3.04)	Total Removal: 94%, Total Biodegradation: 0.78%, Primary Sludge: 59.9%, Waste Sludge: 33.4%, Final Water Effluent: 5.9%
Level III Fugacity Model	Estimated (EPI win, V.3.04)	At Emissions to Air, Water, Soil and Sediment of 1,000, 1,000, 1,000 and 0 kg/hr, respectively: *Fugacity (atm):* Air 2.6 x 10-25, Water 1 x 10-30, Soil 2.9 x 10-32, Sediment 1.8 x 10–30 *Reaction (kg/hr):* Air 234, Water 43, Soil 1.7 x10+3, Sediment 570 *Advection (kg/hr)*: Air 22, Water 226, Soil 0, Sediment 237 *Reaction (%):* Air 7.8, Water 1.4, Soil 56, Sediment 19 *Advection (%):* Air 0.7, Water 7.5, Soil 0, Sediment 7.9
Biodegradation	Estimated (EPI win, V.3.04)	Not expected to biodegrade fast Ultimate Biodegradation Time Frame: Recalcitrant Primary Biodegradation Time Frame: Recalcitrant
Half-lives	Estimated (EPI win, V.3.04) and based on Biowin (Ultimate) and AOPwin	Air: 6.5 Hr Water: 3600 Hr Soil: 3600 Hr Sediment 1.4 x 10+4 Hr
	Estimated (PBT Profiler)	Air: 0.41 Days Water: 180 Days Soil: 360 Days Sediment: 1600 Days Overall Persistence: 1100 Days

4.2 Ecotoxicology

EBTBP's estimated properties are provided in Table 2. EBTBP is not expected to bioconcentrate and its estimated chronic toxicity value in fish is below that of its estimated water solubility. Thus, EBTBP is not expected to concentrate in higher organisms to levels that may be toxic.

Table 2. Ecotoxicology parameters for EBTBP.

Parameter	Estimation Program or Test Result	Result
Log Kow	Estimated (EPI win, V.3.04)	9.79
Water Solubility (mg/L)	Estimated (EPI win, V.3.04)	3 x 10-9
Fish LC50 96 Hr (mg/L)	Estimated (EPIwin, V.3.04, Imides)	0.000612; Not expected to be soluble at this level
	Estimated (PBT Profiler – Imides)	0.000612; Not expected to be soluble at this level
	Measured (CITI, 48 hr)	> 500 ppm
Dapnid LC50 48 Hr (mg/L)	Estimated (EPIwin, V3.04)	Not estimated; Log Kow above cutoff (5)
Green Algae EC50 96 Hr (mg/L)	Estimated (EPIwin, V3.04)	Not estimated; Log Kow above cutoff (6.4)
Fish ChV (mg/L)	Estimated (EPIwin, V3.04, Neutral Organics)	0.0002; Not expected to be soluble at this level; Log Kow above cutoff (8.0)
	PBT Profiler	0.0002; ; Not expected to be soluble at this level; Log Kow above cutoff (8.0)
Bioconcentration (BCF)	Estimated (EPI win, V.3.04)	9.5
	PBT Profiler	9.5
	Measured	<3.3

4.2.1 Fish Acute Toxicity

A semi static dose range-finding study conducted in Orange-red killifish (*Oryzias latipes*) for the fish bioconcentration study provided a 48 hr LC50 of > 500 ppm (w/v). This study was conducted according to Japanese MITI guidelines and Good Laboratory Practices guidelines. (The Bioaccumulation of Compound S-503 (Ethylene-1,2-bis(3,4,5,6-tetrabromophthalimide) by Carp. 1982. Chemical Biotesting Center, Chemical Inspection & Testing Institute, Tokyo, Japan)

4.2.2. Fish Bioconcentration

EBTBP did not bioconcentrate in fish *(Cyprnus carpio)* when tested over an 8-week period. The bioconcentration factor (BCF) was < 3.3 at a water concentration of 0.2 ppm (w/v) and 1.3 at a water concentration of 2.0 ppm (w/v) after an 8-week exposure period with a continuous flow system. A semi static dose range-finding study conducted in Orange-red killifish (*Oryzias latipes*) for this study provided a 48 hr LC50 of > 500 ppm (w/v). This study was conducted according to Japanese MITI guidelines and Good Laboratory Practices guidelines. (The Bioaccumulation of Compound S-503 (Ethylene-

1,2-bis(3,4,5,6-tetrabromophthalimide) by Carp. 1982. Chemical Biotesting Center, Chemical Inspection & Testing Institute, Tokyo, Japan)

4.3 Mammalian Toxicology

4.3.1 Acute Toxicity

4.3.1.1 Acute Oral LD50, Rat.

One group of 5 male and 5 female Sherman-Wistar rats was administered a single dose of EBTBP by gavage in corn oil at 7,500 mg/kg. The animals were observed for 14 days. No animals died on test. The oral LD50 was > 7,500 mg/kg. (Acute Oral Toxicity – Rats. Cities Service Company – LTW-31-1. 1976. Biosearch, Inc. Philadelphia, PA)

4.3.1.2 Acute Dermal LD50, Rabbit

EBTBP was administered as a single dose of 2,000 mg/kg to the clipped skin of 6 albino rabbits. The skin of three of the animals was abraded prior to treatment. The test site was wrapped with an impervious material. The wrapping was removed at 24 hr, any excess test article removed, and the animals observed for 14 days. No animals died during the test. The dermal LD50 was > 2,000 mg/kg. (Acute Dermal Toxicity – Rabbits. Cities Service Company – LTW-31-1. 1976. Biosearch, Inc. Philadelphia, PA)

4.3.1.3 Acute Inhalation LC50, Rat

One group of 5 male and 5 female albino rats was exposed to EBTBP at a nominal concentration of 203 mg/L for 1 hour. Dyspnea and nasal discharge were the principal signs observed during the exposure. No deaths occurred during treatment or the during the 14 day observation period. The inhalation LC50 was > 203 mg/L for 1 hour. This study was performed according to Good Laboratory Practices. IRDC 1981.

4.3.1.4 Eye Irritation

EBTBP (100 mg) was instilled in the right eye of six albino rabbits. The treated eyes were observed at 1, 24, 48 and 72 hours and 5 and 7 days post treatment. No effects were observed at any time point in any animal with respect to the cornea, iris, or conjunctiva. The test article was not an eye irritant. (Primary Eye Irritation Study – Rabbits. Cities service Company – LTW-31-65. 1976. Biosearch, Inc. Philadelphia, PA)

4.3.1.5 Skin Irritation

EBTBP (500 mg) was applied to the clipped abraded and intact skin of 6 albino rabbits. The test site was wrapped with an impervious material. The wrapping was removed at 24 hr and the test site scored by the Draize method. The test site was also scored at 72 post-treatment. No positive scores for erythema, eschar formation or edema were found in any animal at any time point. The material was not a skin irritant. (Primary Skin Irritation Study – Rabbits. Cities service Company – LTW-31-65. 1976. Biosearch, Inc. Philadelphia, PA)

4.3.2 Repeated Dose Toxicity

4.3.2.1 28-Day Subchronic, Rat

EBTBP was fed to Sprague Dawley male rats (n=10/group) at 0, 0.01, 0.1 and 1% of the diet for 28 days. No mortality occurred during the study. No clinical signs of toxicity were observed. Mean body weights, body weight gains, food consumption and organ weights were not affected by treatment. Organs weighed at necropsy were liver, heart, spleen, kidney, and testes. Hematology and serum chemistry parameters were not affected by treatment. No gross or microscopic lesions attributable to test article were detected at necropsy or on light microscopy. The 28-day NOEL was ∞ 1% of the diet. This is estimated to be ~ 1,000 mg/kg/d using the assumption of consumption of 25 g diet per 250 g rat per day. This study was performed prior to the adoption of Good Laboratory Practices or EPA/OECD guidelines. (Report Cities Service Company, CITEX BT-93. Rat – 28-Day Feeding Study – Study Code T-626. 1976. Warf Institute, Inc. Madison, WS)

4.3.2.2 90-Day Subchronic, Rat

EBTBP was administered to four groups of Sprague Dawley rats (n=15/sex/group) at 0, 0.01, 0.1 and 1.0% of the diet for 90 days followed by 46 days during which the rats were fed control diet. No changes in hematology or serum chemistry values related to treatment were detected on study days 0, 45, 92. No effect of treatment was found on urinalysis (d 0, 45 and 90). The mean relative and absolute organ weights of the liver, kidney, heart, and thyroids from the control and 1.0% groups were statistically comparable. Several animals died on test from non-test article related causes (most deaths were related to collection of blood for hematology and serum chemistry evaluations). Gross necropsy from animals dieing on test and sacrificed on days 92, 134, 135 and 136 revealed no test article-related gross lesions. No test article related lesions were detected on histopathology. The 90-day NOEL was 1% of the diet. This is estimated to be ~ 1,000 mg/kg/d using the assumption of consumption of 25 g diet per 250 g rat per day. This study was performed prior to the adoption of Good Laboratory Practices or EPA/OECD guidelines. (Report: 90-Day Feeding Study in Rats Evaluating Cities Service Compound RW-4-178B. Laboratory Number: 8E-0183. September 19, 1978. Cannon Laboratories, Inc. Reading, PA)

4.3.3 Developmental

4.3.3.1 Rat

EBTBP was administered to four groups of 25 mated female Sprague Dawley rats by gavage in corn oil at doses of 0, 100, 500 or 1000 mg/kg/d on gestation days 6-15. The animals were observed daily for clinical signs of toxicity. Body weights were measured on gestation days 0, 6, 9, 12, 16, and 20. Food consumption was measured daily. All females were sacrificed on gestation day 20 and subjected to a cesarean section. Fetuses were individually weighed sexed and examined for external, visceral and skeletal abnormalities. No maternal mortality or clinical signs of toxicity were observed during

the study. No treatment-related differences were noted among the groups with respect to maternal body weights, food consumption, necropsy or caesarean section data. No treatment-induced fetal malformations or developmental variations were detected. The maternal and fetal NOEL was 1,000 mg/kg/d. This study was conducted according to US TSCA Guidelines and Good Laboratory Practices. (D. E. Rodwell. Teratology Study in Rats with BT-93. Final Report. SLS Study No. 3196.4. 1988. Springborn Life Sciences, Inc. Spencerville, OH).

4.3.3.2 Rabbit

EBTBP was administered to two groups of 20 mated female New Zealand White rabbits each by gavage in methyl cellulose at dose of 0 or 1,000 mg/kg/d on gestation days 7-19. The animals were observed daily for clinical signs of toxicity. Body weights were measured on gestation days 0, 7, 10, 13, 19, 24 and 29. Food consumption was measured daily. All females were sacrificed on gestation day 29 and subjected to a cesarean section. Fetuses were individually weighed sexed an examined for external, visceral and skeletal abnormalities. No maternal mortality, abortions or clinical signs of toxicity were observed during the study. Maternal body weights, weight gain, food consumption, necropsy observations and cesarean section data were generally comparable among the groups. No treatment-related malformations or developmental variations were observed. The maternal and fetal NOEL was 1,000 mg/kg/d. This study was conducted according to US TSCA Guidelines and Good Laboratory Practices. (D. E. Rodwell. Teratology Study in Rabbits with BT-93. Final Report. SLS Study No. 3196.5. 1988. Springborn Life Sciences, Inc. Spencerville, OH).

4.3.4 Excretion And Tissue Distribution

^{14}C-labelled EBTBP (~0.67 mg/kg) was administered to 5 female Sprague Dawley rats by gavage in corn oil for 14 consecutive days. Two additional female rats served as controls. Two animals were sacrificed 24 hr after the last dose, and the remainder sacrificed after 7, 14 and 30 days of withdrawal. Feces, urine and expired air were collected during the dosing period: One test animal sacrificed on day 14 was housed in a Roth metabolism cage to allow collection of expired C02, volatile organics, feces, and urine. The other animal sacrificed on day 14 was housed in a plastic metabolism cage to allow collection of feces and urine. Skeletal muscle, brain, kidney, liver and fat were collected at each sacrifice from all animals.

The ^{14}C-label was excreted primarily in the feces; ~65% of the total 14-day dose was recovered in the feces during the dosing period. Approximately 15% of the total 14-day dose was detected in the urine during the dosing period. Negligible ^{14}C-activity was detected in expired air. Thus, 80% of the total dose was recovered in the feces and urine during the 14 days of dosing.

At the end of dosing, the tissues with the highest ^{14}C-activity were liver (~0.39 ppm) and kidney (~0.32 ppm). Levels in both dropped rapidly (by ~50%) during the first 7 days of withdrawal, and continued to drop over the withdrawal period. Levels in muscle (~0.08

ppm), fat (~0.075 pm) and brain (~0.032 ppm) were substantially below that of the liver and kidney after 14 days of dosing. By day 14 of the withdrawal period, no ^{14}C-activity was detected in fat. ^{14}C-activity in the liver, kidney, muscle and brain continued to fall between 14 and 30 days of withdrawal, and were below 0.05 ppm by 30 days post-treatment. The highest level at 30 day post-treatment was found in the skeletal muscle (0.05 ppm). (Excretion and Tissue Distribution of ^{14}C-RW-4-178B Administered Orally to Rats. Laboratory Number: 8E-0188. 1978. Cannon Laboratories, Inc. Reading, PA)

4.3.5 Genetic Toxicity - Mutagenicity

In the Ames assay, the tester strains used were *Salmonella* TA98, TA100, TA1535, TA1537, and TA1538 and *E. coli*, WP2 uvrA. Each strain was tested with and without a source of exogenous metabolic activation of Arochlor-induced rat liver microsomes. EBTBP dose levels were 0, 1, 10, 100, 500, 1,000 and 5,000 ug/plate. Positive and negative controls were included, and performed as expected. No increase in revertant colonies was found at any EBTBP dose level either in the presence or absence of microsomal enzymes. EBTBP was not genetically active in this assay. (Mutagenicity Evaluation of Ethylene-1,2-bis(3,4,5,6-tetrabromophthalimie) in the Ames Salmonella/Microsome Assay. February 18, 1982. Chemical Inspection & Testing Institute, Japan, Induced Mutation Division)

5.0 TEST PLAN

EBTBP's database consists of mammalian and ecotoxicity studies. With respect to mammalian testing, EBTBP has a NOEL in a 90-day study of 1% of the diet (~1,000 mg/kg/day), and a NOEL in developmental studies in the rat and rabbit of 1,000 mg/kg. A mammalian pharmacokinetic study indicates 85% of the total dose administered over a 14-day period was recovered in the feces and urine during dosing. Thus, EBTBP is not expected to bioaccumulate. EPA's PBT Profiler reports that the EBTBP's chemical structure is not a member of the 19 chemical categories for which EPA may have human health concerns. This indicates that no relationship between EBTBP's structure and known human health effects has been developed to date. EBTBP's results in repeated dose studies in the rat and developmental studies in the rat and rabbit also raise no concerns. The data indicate EBTBP does not affect reproduction: No effect was found on reproductive organs in a 90-day study at doses up to 1% of the diet. No developmental toxicity was founds in developmental toxicity studies in two species at doses up to 1,000 mg/kg/day. A lack of mutagenicity in the Ames test and no other alerts reduces the need for additional mutagenicity tests. Thus, no mammalian testing is proposed under the HPV program (Table 3).

No physical/chemical property testing is proposed under this program because the estimated values are considered sufficient (Table 3). Likewise, no additional environmental fate testing is proposed based on EBTBP's use pattern (the electrical and electronics industries), anticipated minimal releases to the environment, negligible partitioning to air and water, and modeling results.

No ecotoxicity tests are proposed under the HPV program (Table 3). EBTBP is not expected to bioconcentrate nor is it expected to exert chronic toxicity to aquatic organisms. This is based on a combination of actual data and model predictions. Both actual data (CITI 1982) and model predictions (EPIWIN, PBT Profiler) indicate a lack of bioconcentration. Model predictions (PBT Profiler/ECOSAR) indicate EBTBP is not expected to exert chronic toxicity.

Table 3. Testing proposed for EBTBP.

Study Type	Data Available	Data Acceptable	Estimation Available	Testing Proposed
Physical/Chemical				
Melting Point	Y	Y	Y	N
Boiling Point	N	Y	Y	N
Vapor Pressure	N		Y	N
Water Solubility	N		Y	N
Environmental Fate				
Photodegradation	N		Y	N
Stability in Water (Hydrolysis)	N		Y	N
Biodegradation	Y	Y	Y	N
Transport (Fugacity)	N		Y	N
Ecotoxicity				
Acute Toxicity to Fish	Y	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	N		Y	N
Toxicity to Aquatic Plants	N		Y	N
Toxicology Data				
Acute Toxicity	Y	Y	N	N
Repeated Dose Toxicity	Y	Y	N	N
Genetic Toxicity – Mutation	Y	Y	N	N
Genetic Toxicity – Chromosome Aberration	N		N	N
Developmental Toxicity	Y	Y	N	N
Reproductive Toxicity	Y	Y	N	N