

Ethylenebis(tetrabromophthalimide)
[CASRN 32588-76-4]

Review of Toxicological Literature

Prepared for

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EXECUTIVE SUMMARY

Ethylenebis(tetrabromophthalimide) was nominated by NIEHS because of its high production volume and potential for human exposure as a flame retardant in plastics and fabrics.

Ethylenebis(tetrabromophthalimide) is used as a fire retardant additive in high impact polystyrene, polyethylene, polypropylene, thermoplastic polyesters, polyamides, ethylene propylene-diene terpolymers (EPDM), synthetic rubber, polycarbonate, ethylene copolymers, ionomer resins, and textile treatments. The properties that are favorable in ethylenebis(tetrabromophthalimide) are its thermal stability, resistance to bloom, and UV stability. Ethylenebis(tetrabromophthalimide) is produced from the reaction of tetrabromophthalic anhydride with ethanediamine. According to the Interagency Testing Committee (ITC), production in 1990 was less than 1 million pounds, whereas 1986 and 1994 production was greater than 1 million pounds.

Environmental exposure to ethylenebis(tetrabromophthalimide) would most likely occur from production, use, and disposal of materials treated with the chemical. Carp were exposed for 8 weeks at levels of 2.09 and 0.199 ppm of ethylenebis(tetrabromophthalimide), the bioaccumulation factors were 3.3 and 0.3, respectively. After 28 days, no ethylenebis(tetrabromophthalimide) had been degraded in biodegradation tests using soil microflora.

Only two cases of possible human exposure to ethylenebis(tetrabromophthalimide) have been reported. One worker suffered a respiratory attack and had to be hospitalized but recovered completely. The other worker complained of cough and related symptoms, but was asymptomatic after removal from the production area. Since these exposures occurred in an area where production of ethylenebis(tetrabromophthalimide) and tetrabromophthalic anhydride occurred, so it could not be determined which compound may have caused these symptoms.

Ethylenebis(tetrabromophthalimide) was recommended, along with several other brominated flame retardants, for further testing for chemical fate (chemical properties and persistence), health effects (chronic toxicity), and ecological effects (chronic toxicity) in the TSCA Interagency Testing Committee's 25th Report to the EPA Administrator in 1989. After review by the EPA, the ITC recorded in its 33rd Report that ethylenebis(tetrabromophthalimide) would be removed from the Priority List because it was not known to be domestically produced or imported in substantial quantities. Ethylenebis(tetrabromophthalimide) is included in the EPA OPPT's HPV Challenge Program and is sponsored by the Albemarle Corporation (Baton Rouge, LA) for Screening Information Data Sets (SIDS) testing by 2003.

Ethylenebis(tetrabromophthalimide) was mainly excreted in the feces (65% of dose), urine (15% of dose), and breath (1% of dose) twenty-four hours after oral dosing in laboratory rats. The organs containing the highest concentrations of the compound were the liver, kidney, and muscles. Lower levels were detected in the brain and fat.

The acute oral LD₅₀ in the rat was greater than 7.5 g/kg. No dermal irritation or reactivity was observed in rabbits treated with 0.5 g or 2.0 g/kg ethylenebis(tetrabromophthalimide).

Ethylenebis(tetrabromophthalimide) was determined to be an eye irritant when tested in rabbits at a dose of 100 mg/eye. It was mildly toxic to rats when inhaled.

In two subchronic exposure studies in rats, ethylenebis(tetrabromophthalimide) caused no remarkable changes according to the histopathological examination. No reproductive or teratological effects were seen in rats or rabbits.

Ethylenebis(tetrabromophthalimide) was not genotoxic when tested in strains of *Salmonella typhimurium*, *Saccharomyces cerevisiae*, or *Escherichia coli* with and without metabolic activation.

No porphyrinogenic activity was seen in chick embryo liver cells.

No information was found on the carcinogenicity or chronic toxicity of ethylenebis(tetrabromophthalimide).

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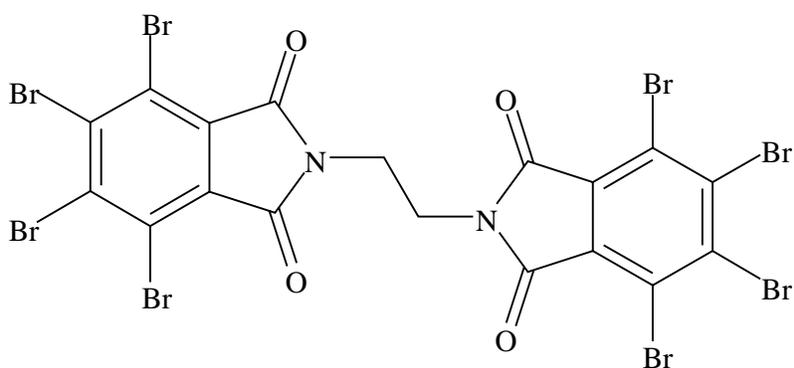
1.0 BASIS FOR NOMINATION

Ethylenebis(tetrabromophthalimide) was nominated by NIEHS because of its high production volume and potential for human exposure as a flame retardant in plastics and fabrics. Its was previously nominated to NTP in 1981 for genotoxicity testing (NTP, 1999).

2.0 INTRODUCTION

Ethylenebis(tetrabromophthalimide)

[CASRN 32588-76-4]



2.1 Chemical Identification

Ethylenebis(tetrabromophthalimide) (C₁₈H₄N₂O₄Br₈; mol. wt. = 951.47) is also called:

2,2'-(1,2-Ethanediy)bis[4,5,6,7-tetrabromo-1*H*-isoindole-1,3(2*H*)-dione]
 1,2-Bis(tetrabromophthalimido)ethane
N,N'-Ethylenebis-3,4,5,6-tetrabromophthalimide
 Saytex BT-93[®]

2.2 Physical-Chemical Properties

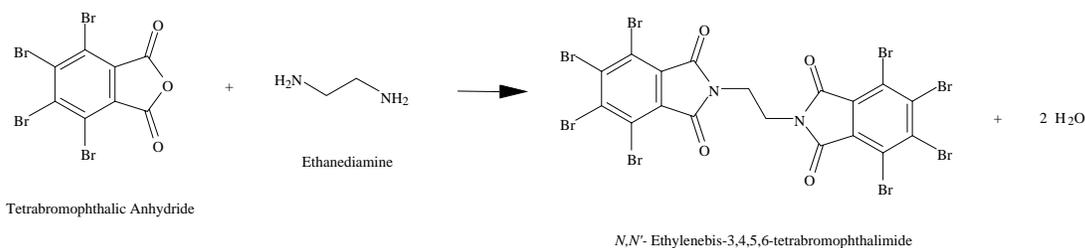
Property	Information	Reference
Physical State	Light yellow crystalline powder	Chemical Biotesting Center (CBC), (1981)
Melting Point (°C)	446	Radian (1991)
Density (18 °C/4 °C)	2.67 g/mL	Radian (1991)
Insoluble in:	Water, DMSO, and 95% ethanol	Radian (1991)
Slightly Soluble in:	Tetrahydrofuran (150 ppm)	Chemical Biotesting Center (1982)

2.3 Commercial Availability

Ethylenebis(tetrabromophthalimide) is available from Albemarle Corporation in two chemical grades—a white powder (BT-93W) and a yellow powder (BT-93) (Albemarle Corporation, 1999). Shipping amounts are not available.

3.0 PRODUCTION PROCESSES

There are two classes of fire retardants that are added to plastic polymers, additive and reactive retardants. Additive retardants are added to a polymer mixture to produce a blend and reactive retardants are reacted with the polymer and become part of the polymer linkages (Jackisch, 1992). Ethylenebis(tetrabromophthalimide) is an additive fire retardant. Additive bromine fire retardant compounds are typically produced by catalytic bromination of organic substrates. Ethylenebis(tetrabromophthalimide) is prepared from ethylenediamine and tetrabromophthalic anhydride (Pettigrew, 1992). Specifics of this reaction, such as amount of bromine, catalysts, and by-products are proprietary. The general reaction is:



4.0 PRODUCTION AND IMPORT VOLUMES

Ethylenebis(tetrabromophthalimide) is produced by the Albemarle Corporation (formerly Ethyl Corporation), located in Magnolia, Arkansas (SRI, 1997).

In the United States, the consumption of brominated flame retardants for polymers was 15,000 tons in 1984 (Dumler et al., 1989), 34,000 tons in 1986, and 54,000 tons in 1991 (IPCS, 1997), with a worldwide demand of 150,000 tons in 1992 (IPCS, 1997). It is not listed on the 1990 EPA OPPT High Production Volume (HPV) Chemicals List but is listed on the 1994 HPV List; however, no production values are given.

5.0 USES

Ethylenebis(tetrabromophthalimide), is used as an additive flame retardant in high impact polystyrene (HIPS), polyethylene, polypropylene, thermoplastic polyesters, polyamide, ethylene propylene-diene terpolymers (EPDM rubbers) and other synthetic rubbers, polycarbonate, ethylene copolymers, ionomer resins, epoxies, and textile treatments (IPCS, 1997). Its use in engineering thermoplastics and polyolefins is due to its thermal stability and resistance to bloom (Pettigrew, 1992). Its use in HIPS is favored due to its high stability to ultraviolet light exposure (Albemarle, 1999).

There are many more brominated fire retardants in use than the chlorine-substituted retardants because of their higher efficacy. They are about twice as effective as chlorine compounds and 1.7 times as dense (IPCS, 1997; Larsen, 1980). The bromine-substituted flame retardants included in plastics degrade at a somewhat lower temperature than the polymers.

The plastics industry is the largest consumer of flame retardants, estimated at about 95% for the United States in 1991 (IPCS, 1997). About 10% of all plastics contain flame retardants (Wolf and Kaul, 1992).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

Environmental exposure would most likely occur as a result of manufacture, transportation, use, and disposal of ethylenebis(tetrabromophthalimide) or items treated with the fire retardant (IPCS, 1997). Routes of environmental exposure may include air, water, and soil. Factors which affect environmental exposure are the physical and chemical properties of the product, emission controls, disposal/recycling methods, volume, and biodegradability/persistence.

The Chemical Biotesting Center of Japan reported that, at 100 ppm (W/V), ethylenebis(tetrabromophthalimide) did not biodegrade within 28 days in an aqueous medium inoculated with standard activated sludge at a temperature of $25 \pm ^\circ\text{C}$ as determined by biological oxygen demand and ultraviolet spectrometry (Chemical Biotesting Center, 1981).

Bioaccumulation was tested in the carp, *Cyprinus carpio* (Chemical Biotesting Center, undated). The carp were exposed for 8 weeks in flow-through tanks with mean tank water concentrations of up to 2.07 ppm. The whole carp were chopped and homogenized for analysis by HPLC. Bioconcentration factors, calculated by dividing the concentration of

ethylenebis(tetrabromophthalimide) in the carp by the actual concentration of the chemical in the tank water, were less than 3.3, indicating little bioaccumulation potential.

Environmental contamination can occur when products containing flame retardants are incinerated. It has been observed that, upon heating, some plastics treated with brominated flame retardants can release polybrominated dibenzodioxins (PBDDs) and polybrominated dibenzofurans (PBDFs). For example, “at 400 °C polymers containing decabromodiphenyl ether and antimony trioxide as flame retardant can release up to 4,000 ppm tetrabromodibenzofurans, besides other brominated dibenzofurans.” One study tested several plastics with flame retardants as additives to determine the tendency to form dibenzofurans and dibenzodioxins under certain conditions. It was found that ethylenebis(tetrabromophthalimide) did not show any tendency to form PBDDs or PBDFs, even in the presence of antimony trioxide (Clausen et al., 1987).

In a separate study, pyrolysis and combustion of ethylenebis(tetrabromophthalimide) with antimony trioxide at 600 and 800 °C resulted in very low or undetectable quantities of PBDDs and PBDFs (Dumler et al., 1989). The PBDDs and PBDFs that were detected were mainly the mono- and tribrominated congeners, which are of less toxicological significance than the more highly brominated compounds.

7.0 HUMAN EXPOSURE

Human exposure in the general population is from sources such as consumer products, manufacturing and disposal facilities, and environmental media (IPCS, 1997). Potential routes of exposure are inhalation, ingestion, and dermal contact.

Occupational exposure may occur during manufacture, transport, processing, and disposal/recycling of flame retardants (IPCS, 1997). The extent of exposure is affected by such factors as industrial hygiene practices, engineering controls, manufacturing processes, and the type of product. Routes of exposure may include inhalation, ingestion, and dermal contact.

Only two cases of possible human exposure to ethylenebis(tetrabromophthalimide) resulting in adverse health effects have been reported. See **Section 9.1.1** for details.

8.0 REGULATORY STATUS

The Interagency Testing Committee (ITC), an independent advisory committee to the Administrator of the U.S. Environmental Protection Agency (EPA) established according to

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Section 4(e) of TSCA, reviews exposure and production information about many chemicals and decides if further testing is required. When the ITC recommends further testing of a substance, it is placed on the TSCA Section 4(e) Priority List for further consideration by the EPA. The EPA Administrator is given either one year or more than one year to reply with his or her recommendations, according to the urgency that the TSCA ITC places on testing of the substance(s). After receipt of the ITC's Report the EPA may promulgate TSCA Section 8(a) and 8(d) rules, requesting that manufacturers, producers, and suppliers submit production and exposure data (8a) and submit health and safety studies (8d) within two months. The ITC has made testing decisions on 129 brominated flame retardants (Walker et al., 1996). Twenty-three of these were recommended for further testing; 7 for chemical properties, persistence and chronic ecological and health effects testing (ITC's 25th Report) and 16 for chemical properties and persistence testing (ITC's 26th Report).

In the ITC's 25th Report to the EPA Administrator (Federal Register Vol.54, 51114-51130) in 1989, ethylenebis(tetrabromophthalimide) was recommended, along with several other brominated flame retardants, for further testing for chemical fate (chemical properties and persistence), health effects (chronic toxicity), and ecological effects (chronic toxicity) (ITC, 1989). The EPA was given more than a year to respond to the testing recommendations for the nominated flame retardants. After review by the EPA, the ITC recorded in its 33rd Report (Federal Register Vol.59, 1994, 3764-3769) that ethylenebis(tetrabromophthalimide) would be removed from the Priority List because it was "not known to be domestically produced or imported in substantial quantities (ITC, 1994)."

Ethylenebis(tetrabromophthalimide) is regulated as a brominated flame retardant under the Toxic Substances Control Act (TSCA). Under 40 CFR 712, manufacturers and processors of ethylenebis(tetrabromophthalimide) are required to report production, use, and exposure-related information to the U.S. EPA. Effective January 11, 1990, manufacturers and importers of ethylenebis(tetrabromophthalimide) must submit a Preliminary Assessment Information Manufacturers Report for each site at which they manufacture or import the compound by March 12, 1990 according to TSCA Section 8(a). Ethylenebis(tetrabromophthalimide) is included in the EPA OPPT's HPV Challenge Program and is sponsored by the Albemarle Corporation (Baton Rouge, LA) for Screening Information Data Sets (SIDS) testing by 2003 (EPA OPPT, 1999).

Ethylenebis(tetrabromophthalimide) is not regulated by the Occupational Safety and Health Administration (OSHA), Department of Transportation (DOT), or Consumer Product Safety Commission (CPSC); and the National Institute of Occupational Safety and Health (NIOSH) and American Conference of Governmental Industrial Hygienists (ACGIH) have not recommended any exposure limits.

U. S. government regulations pertaining to ethylenebis(tetrabromophthalimide) are summarized below.

Table 1. Regulations Relevant to Ethylenebis(tetrabromophthalimide)

	Regulation	Summary of Regulation
E P A	40 CFR 712.30	Effective January 11, 1990, manufacturers and importers of chemicals listed in 40 CFR 712.30 are required to submit a Preliminary Assessment Information Manufacturer's Report. This report summarizes production, use, and exposure information and is to be submitted to the U.S. EPA according to TSCA 8(a)
	40 CFR 716.120	This part sets forth requirements for the submission of lists and copies of health and safety studies on chemical substances that are selected for priority testing considerations under TSCA 4(a). Effective: 1/11/90, Sunset Date: 12/19/95

9.0 TOXICOLOGICAL DATA

9.1 General Toxicology

Most of the toxicology information in this section was extracted from TSCA test submissions. All of the studies in the submissions were sponsored by Ethyl Corporation.

9.1.1 Human Data

In a letter submitted to the EPA from Ethyl Corporation, two cases of respiratory problems were reported by workers at a plant in Arkansas which manufactured ethylenebis(tetrabromophthalimide) as well as tetrabromophthalic anhydride (Ethyl Corporation, 1987). One of the workers suffered a respiratory attack after he had gone home, requiring hospitalization. He recovered completely, but did not reenter the production area. The other worker, from the same process area, went home complaining of cough and related symptoms. He was asymptomatic after removal from the process area. These incidents were surprising,

because the production of these two chemicals had recently been moved from New Jersey, where no problems had been reported. Since the two processes were located in close proximity to each other it was difficult to determine which chemical, or a combination of the two, may have been responsible for the respiratory effects.

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

In a study using seven female Sprague–Dawley rats (b.w. = 200 – 250 g), ethylenebis(tetrabromophthalimide) (^{14}C -labeled [unspecified labeling site]) was administered by gavage at a concentration of 1 mg/mL in corn oil to five rats for 14 consecutive days (Cannon Laboratories, 1978a). Two rats were used as controls. The volume administered to the rats was not stated in the report; however, based on the mean, weight of the rats and the radioactivity present, a radioactivity dose of 0.67 mg/kg body weight was calculated. Two rats were sacrificed 24 hours after the last treatment, and the other three were sacrificed 7, 14, and 30 days after the last treatment. The compound was mainly excreted in the feces (65%) with 15% of the total dose found in the urine. The carbon dioxide and volatile organic traps together contained less than 1.0% of the daily dose during the 14-day treatment period. All organs contained radioactive residues. After 14 days, the highest levels were present in the leg muscle (0.065 – 0.112 ppm), kidney (0.318 – 0.320 ppm), and liver (0.366 – 0.424 ppm). Lower levels of radioactivity were detected in the brain (0.030 – 0.033 ppm) and fat (0.045– 0.106 ppm). By 30 days after cessation of treatment, concentrations had declined to < 0.0045 to 0.051 ppm, the lowest levels in fat and the highest levels in leg muscle. Only one animal in this study exhibited abnormal behavior. The animal showed decreased locomotor activity, piloerection, tremors, and loss of righting reflex. This animal was sacrificed after day 8 of treatment and was found to have an inflamed, reddish, distended intestinal tract which contained gelatinous-appearing material. All other animals in the study had normal weight gain and contained no gross tissue abnormalities at necropsy.

9.1.3 Acute Exposure

Acute toxicity values for ethylenebis(tetrabromophthalimide) are presented in **Table 2**. The details of studies discussed in this section are presented in **Table 3**.

Acute toxicity was determined in adult orange-red killifish, *Oryzias latipes* (Chemical

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Biotesting Center, undated). None of the test fish died during the 48-hour test period when exposed to the compound at a concentration of 500 ppm in a static chamber at pH 7.3 to 8.1. Thus, the 48-hour LC₅₀ value was calculated to be greater than 500 ppm.

Acute oral toxicity was determined by gavage in 5 male and 5 female Sherman-Wistar rats (Biosearch, Inc., 1976c). Rats administered a single dose of 7.5 g/kg observed for 14 days showed no mortality. It was thus concluded that the oral LD₅₀ was greater than 7.5 g/kg.

A dermal irritation test was employed using albino rabbits (number, strain, sex, and weight not specified) (Biosearch, Inc., 1976a). The rabbits were shaved over a wide area. One side of each rabbit's back was slightly abraded at one site with a lancet sufficiently deep to penetrate the stratum corneum but not to enter the derma and produce bleeding. The other side of the back was left intact. A 0.5 g portion (yellow powder) of ethylenebis(tetrabromophthalimide) was applied to the abraded skin of three rabbits and the intact skin of the other three. The sites were covered with gauze pads and an impervious material was wrapped around the trunk of the animal to hold the pads in place. The dressing was removed at 24 hours and 72 hours in order to observe the sites. The Draize method of scoring was used and a primary irritation score of 0 was assigned to the compound. No erythema, eschar, or edema formation occurred at 24 or 72 hours.

In an acute dermal toxicity test, the shaved backs (abraded or unabraded) of 6 albino rabbits (2.5 – 3.5 kg each, strain not specified) were exposed to ethylenebis(tetrabromophthalimide) at a dose of 2.0 g/kg of with occlusion for 14 days (Biosearch, Inc., 1976b). Since no mortalities were observed during the 14-day period, the dermal LD₅₀ was determined to be > 2.0 g/kg.

Acute eye irritation was tested in male and female albino New Zealand rabbits (2 – 3 kg each) (Pharmakon Research International, 1983). The powdered material, as received, was applied once directly to the rabbits' eyes in a dose of 100 mg/eye. The animals were observed at 1, 24, 48, and 72 hours and finally at day 7, when the study was terminated. Post-exposure positive responses occurred in all six rabbits at 1 hour, 2 rabbits at 24 hours, and none from 48 hours until the end of the study. Only the conjunctivae were affected. Grading of the irritation was according to the Draize method. Ethylenebis(tetrabromophthalimide) received a Draize score of 3.0 at 1 hour, indicating that it is considered to be a mild eye irritant. The Draize score was 0.3 at 72 hours and at 7 days after exposure.

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In an acute inhalation toxicity study, 5 female and 5 male albino Sprague-Dawley rats were exposed once, for 1 hour, to a dust atmosphere of ethylenebis(tetrabromophthalimide) equal to $4,500 \pm 3,000 \text{ mg/m}^3$ (International Research and Development Corporation, 1981). The rats were observed every 15 minutes during exposure, hourly for four hours following exposure, and daily during the 14-day post-exposure period for pharmacotoxic signs. Dyspnea was seen in all of the rats during the exposure and persisted for 1 to 5 days following the exposure. Dry, red brown matter was observed on or around the muzzle of 5 rats immediately following exposure, but was not seen after the day of exposure. One rat exhibited nasal discharge for one day following the exposure. The mean body weight gain of the rats was normal throughout the 14-day observation period. The occurrence of 1-mm red foci in the lungs of 2 male and 2 female rats was the principal lesion observed at necropsy.

Table 2. Acute Toxicity Values for Ethylenebis(tetrabromophthalimide)

Route	Species (sex and strain)	LD ₅₀	Reference
Oral	Rat; 5M and 5F, Sherman-Wistar	> 7500 mg/kg	Biosearch, Inc. (1976c) NTIS OTS0522912
Inhalation	Rat	1-hr LC ₅₀ > $4.5 \pm 3 \text{ g/m}^3$	International Research and Development Corporation (1981) NTIS OTS0522915
Dermal	Rabbit	> 2 g/kg	Biosearch, Inc. (1976b) NTIS OTS0522917
	<i>Oryzias latipes</i> : Orange-red killifish (sex n.p.)	48-hr LC ₅₀ > 500 ppm	Biosearch, Inc. (1976b) NTIS OTS0522917

Abbreviations: n.p. = not provided

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Table 3. Details of Acute Toxicity Studies with Ethylenebis(tetrabromophthalimide)

Species and Strain	Number and Sex of Animals	Dose	Exposure Period/Study Duration	Results
Orange-red killifish	10 fish; sex and age n.p.	500 ppm, static, pH = 7.3 at start and 8.1 at end	Exposed for 48 hours	None of the test fish died during the 48-hour period. The hour LC ₅₀ was calculated to be >500 ppm.
<i>Oral</i>				
Sherman-Wistar Rats	5 M and 5 F	Single dose of 7.5 g/kg	Single dose then observed for 14 days	None of the rats died during the 14-day observation period. The oral LD ₅₀ was determined to be >7500 mg/kg.
<i>Dermal</i>				
Albino Rabbits (strain n.p.)	Number and sex, n.p.	0.5 g applied to abraded and intact skin	72-hour exposure and observation period	A Draize score of 0 was assigned. No erythema, eschar, or edema formation in 72 hours. Not an eye irritant.
Albino Rabbits (strain n.p.)	6 (sex n.p.)	2.0 g applied to abraded and intact skin	Exposed for 24 hours and observed for 14 days	No mortalities occurred in either group. The dermal LD ₅₀ determined to be >2.0 g/kg
<i>Ocular</i>				
New Zealand Rabbits	3 M and 3 F	100 mg applied once directly to each eye	Observed for 7 days	Positive responses occurred in all rabbits at 1 hour, 2 rabbits at 24 hours and none after 48 hours. Draize test score of 1 at one hour which indicated that ethylenebis(tetrabromophthalimide) is a mild eye irritant.
<i>Inhalation</i>				
Sprague-Dawley Rats	5 M and 5 F	4.5 ± 3.0 g/m ³ for 1 hour	14-day observation period	Dyspnea was observed in all of the rats during exposure and for 1-5 days following exposure. Dry red brown matter was seen on or around the muzzle of 5 rats immediately following exposure, but did not persist beyond the day of exposure. One rat exhibited nasal discharge for one day following exposure. The principal lesion was 1-mm red foci in the lungs.

Abbreviations: F = female; M = male, n.p. = not provided

9.1.4 Short-Term and Subchronic Exposure

The details of these studies are presented in **Table 4**.

Ethylenebis(tetrabromophthalimide) was fed to Sprague-Dawley rats (15 of each sex per dose level) in NIH-07 Rat Mash at concentrations of 0.01%, 0.1%, or 1.0% for 90 days followed by a 46-day period in which the rats were fed the control diet (Cannon Laboratories, 1978b).

One male in the control group died from multiple hemorrhages of the lung and one female in the 1.0% diet group died on study day 11 from an intestinal hemorrhage that was probably attributable to the test compound. Two male rats in the 0.01% diet group exhibited jaw swelling, while 1 male and 1 female in the 0.1% and the 1.0% groups, respectively, also showed these signs. Females in the 1.0% diet group had significantly higher body weights than either of the other three groups at weeks 2-8 and higher than the control and 0.01% groups at week 11.

Hematological and clinical chemistry evaluations did not reveal any significant changes in the test groups when compared to the controls that could be attributed to the treatment. The absolute and relative weights of the kidneys, heart, liver and thyroid of the rats ingesting the 1.0% diet were not significantly different from those of the controls. At necropsy, the tissues did not reveal any remarkable changes between those of the treatment groups and the controls.

Histopathological examination of the organs and tissues revealed no gross differences at necropsy between the rats dosed at any level and the controls.

A 28-day feeding study was conducted with weanling Sprague-Dawley male rats (Warf Institute, 1976). A total of 40 rats was divided into four groups: one control group and three test groups. The three test groups received ethylenebis(tetrabromophthalimide), mixed into a basal diet of Purina Lab Chow, equivalent to 0.01, 0.1, and 1.0% of the diet. Animals received the test diets from initiation of the experiment until their sacrifice. Daily observations of the animals revealed no treatment-related abnormal behavior or appearance that could have distinguished any one group from another. The average body weights of all groups were normal and there were no differences that could be attributed to the test compound. No significant differences in mean body weight, food consumption, or blood chemistry were noted between the test groups and control group. The liver, heart, spleen, kidney and gonad weight data showed no statistically significant difference ($P = 0.05$) among the four groups. A slightly larger left gonad was seen in all of the rats in the low-dose group, but no difference in the right gonad. There was a slightly larger relative liver weight in the low-dose group rats when compared to controls, 5.38% vs.

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5.00%. There were no differences for rats in the two highest dose groups regarding absolute or relative organ weights and the difference from the low-dose group was not considered to be toxicologically significant. Gross and microscopic examination of tissues from each test group revealed no alterations. Microscopic tissue alterations that did occur were limited to the tubules of the testicles, which appeared acellular. This acellular appearance was seen in both the control group and high-dose test animals; however, the frequency in the control group was 4/10 and the frequency in the high-dose group was 10/10. The laboratory regarded the lesions as insignificant and attributed them to the loss of cells during the embedding and sectioning and not related to the test compound.

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Table 4. Short-Term and Subchronic Toxicity Studies of Ethylenebis(tetrabromophthalimide)

Type and Age of Subjects	Number and Sex of Animals	Route/Dose	Study Duration	Results/Comments
<i>Rats</i>				
Sprague-Dawley Weanling	40 M (10 per dose group)	Oral, in diet: 0.01, 0.10, and 1.0% of the diet for 28 days	28 days	The tubules of the testicles appeared acellular in 4/10 controls and 10/10 of high-dose rats. The lesions were regarded as insignificant. Slightly larger relative liver weight in mid-dose rats was considered to be toxicologically insignificant. All other observations were normal for all groups.
Sprague-Dawley, age n.p.	60 M and 60 F (15 of each sex per dose group)	Oral, in diet: 0.01, 0.1, and 1.0% of the diet for 90 days	136 days	Low number of rats exhibited swelling in the lower jaw region of each of the treatment groups. There were no histopathological differences between the treated rats and the controls.

Abbreviations: F = female; M = male; n.p. = not provided

9.1.5 Chronic Exposure

No chronic exposure studies were found for ethylenebis(tetrabromophthalimide).

9.1.6 Synergistic and Antagonistic Activities

No studies were found detailing synergistic or antagonistic actions of ethylenebis(tetrabromophthalimide) with other compounds.

9.2 Reproductive and Teratological Effects

The details of these studies are presented in **Table 5**.

A teratology study was conducted for ethylenebis(tetrabromophthalimide) using 100 12-week-old Sprague-Dawley COBS/CD rats (Springborn Life Sciences, 1998a). Ethylenebis(tetrabromophthalimide) dissolved in corn oil was administered by gavage daily from gestation day 6 to gestation day 15. Dosing was determined by an earlier range-finding study (Springborn Life Sciences, 1988b). The animals were divided into 4 groups of 25 each. Controls received the corn oil vehicle (4 mL/kg daily) and the test groups received ethylenebis(tetrabromophthalimide) in doses of 100 mg/kg/day, 500 mg/kg/day, and 1000 mg/kg/day. All animals in this study survived until the termination of the experiment on gestation day 20, when they were sacrificed. No abortions, resorptions, or premature deliveries were reported and the pregnancy rate was 100% in all groups. Mean maternal body weights were comparable in all groups. There was no significant difference in food intake between the control rats and those dosed with ethylenebis(tetrabromophthalimide). Malformations and developmental variations were observed in all groups and at similar frequencies. The malformations that were observed were known to occur in this strain of rat. They included edema and micrognathia in the control group, vertebral agenesis with filamentous tail in the 500 mg/kg/day group, and anal atresia with an absent tail, and right-sided retroesophageal aortic arch in the 1000 mg/kg/day group.

Artificially inseminated rabbits were employed in another teratology study (Springborn Life Sciences, 1988c). Twenty New Zealand white rabbits were gavaged with ethylenebis(tetrabromophthalimide) at a dose of 1000 mg/kg body weight in a vehicle of 1% aqueous carboxymethyl cellulose (5 mL/kg). Another 20 rabbits served as a control group and were gavaged with the vehicle only (5 mL/kg). The animals were dosed from gestation day 7

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through gestation day 19. All rabbits were sacrificed on gestation day 29. No mortalities were observed in either the test group or the control group. No abortions or premature deliveries were observed. The pregnancy rate was 90% in the control group and 95% in the test group. No treatment-related clinical signs were observed in the test group. Some rabbits did exhibit soft stool, reduced defecation, fecal or urine staining, and hair loss from various body regions. However, these occurred in the control group as well and was considered incidental. Body weights were comparable in both control and test groups. Mean food intake was not remarkably different between the two groups. Necropsy of the animals showed no remarkable morphopathological changes. Cesarean sections on the animals revealed 18 and 19 gravid rabbits in the control and ethylenebis(tetrabromophthalimide)-treated groups, respectively. The mean number of corpora lutea, implantation sites, viable and dead fetuses, early and late resorptions, mean fetal weight, and mean fetal sex ratios were similar between the two groups. There were 3 malformed fetuses in the control group and 6 in the test group. The malformations in the control group included fetal edema, micrognathia, malaligned sternbrae. The malformations observed in the treated groups were anal atresia and absent tail, vertebral agenesis with filamentous tail, and right-sided retroesophageal aortic arch. The increased incidence of malformations in the test group was not statistically significant when compared to the controls. These malformations occur spontaneously in this strain of rabbit and the incidence and type of malformations was concluded not to be indicative of a teratogenic effect of ethylenebis(tetrabromophthalimide) in rabbits.

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Table 5. Reproductive Toxicity Studies with Ethylenebis(tetrabromophthalimide)

Species and Strain of Animal	Sex, Number, and Age of Animal	Dose	Study Duration	Results/Observations
<i>Rats</i>				
Sprague-Dawley COBS [®] CD rats	36 F, 80 – 100 days old (6 per dose group)	200, 500, 1000, 1500, and 2000 mg/kg/day from gestation days 6 – 15	Sacrificed on gestation day 20	This was a range-finding study only. Histopa examinations were conducted, but the results published. In the following study the dose range determined to be 100 – 1000 mg/kg/day.
Sprague-Dawley COBS [®] CD rats	100 F, 12 weeks old (25 per dose group)	100, 500, and 1000 mg/kg/day from gestation day 6 – 15	Sacrificed on gestation day 20	No fetal malformations or other developmental morphopathological variations could be attributed to ethylenebis(tetrabromophthalimide)
<i>Rabbits</i>				
New Zealand white rabbits	40 F, age n.p. (20 per dose group)	Oral; 1000 mg/kg from gestation day 7 – 19	Sacrificed on gestation day 29	A higher number of fetal malformations did occur in the ethylenebis(tetrabromophthalimide)-treated group but the number was not significantly different from the control level. No other developmental effects in the treated group were significantly different from the control group.

Abbreviations: F = female

9.3 Carcinogenicity

No carcinogenicity studies were found for ethylenebis(tetrabromophthalimide).

9.4 Initiation/Promotion Studies

No initiation/promotion information was found for ethylenebis(tetrabromophthalimide).

9.5 Anticarcinogenicity

No anticarcinogenicity information was found for ethylenebis(tetrabromophthalimide).

9.6 Genotoxicity

Ethylenebis(tetrabromophthalimide) was tested in the Ames Salmonella/Microsomal assay for mutagenicity (Chemical Inspection and Testing Institute, 1982). Six strains were used: *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, TA100), and *Escherichia coli* (WP2 uvrA). The concentrations of ethylenebis(tetrabromophthalimide) used in this study were 10, 50, 100, 500, 1,000, and 5,000 µg/plate. No mutagenic activity was detected in any of the strains, either with or without metabolic activation.

Ethylenebis(tetrabromophthalimide) was determined to be nonmutagenic, both with and without metabolic activation, at concentrations of 1, 10, 100, 500, and 1,000 µg/plate in *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, and TA100) and *Saccharomyces cerevisiae* (D4) (Cannon Laboratories, 1978c).

In another study with *Salmonella typhimurium*, ethylenebis(tetrabromophthalimide) was found not to induce mutations, either with or without metabolic activation, in strains TA98, TA100, TA1535, and TA1537 (Zeiger et al., 1985).

9.7 Cogenotoxicity

No co-genotoxicity information was found for ethylenebis(tetrabromophthalimide).

9.8 Antigenotoxicity

No antigenotoxicity information was found for ethylenebis(tetrabromophthalimide).

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Table 6. Genotoxicity Studies with Ethylenebis(tetrabromophthalimide)

Organisms and Strains Employed	Endpoint	Doses	Results
Prokaryotes			
<i>Salmonella typhimurium</i> (TA1535, TA1537, TA1538, TA98, TA100)	mutation, gene reversion	0, 10, 50, 100, 500, 1,000, and 5,000 µg/plate	No mutagenic activity was detected in any of the strains, either with or without metabolic activation
<i>Salmonella typhimurium</i> (TA1535, TA1537, TA1538, TA98, and TA100)	mutation, gene reversion	0, 1, 10, 100, 500, and 1,000 µg/plate	No mutagenic activity was detected in any of the strains, either with or without metabolic activation
<i>Salmonella typhimurium</i> (TA1535, TA1537, TA98, TA100)	mutation, gene reversion	0, 100, 333, 1000, 3333, and 10,000 µg/plate	No mutagenic activity was detected in any of the strains, either with or without metabolic activation
<i>Escherichia coli</i> (WP2 uvrA)	mutation, gene reversion	0, 10, 50, 100, 500, 1,000, and 5,000 µg/plate	No mutagenic activity was detected in any of the strains, either with or without metabolic activation
Lower Eukaryotes			
<i>Saccharomyces cerevisiae</i> (D4)	mutation, gene reversion	0, 1, 10, 100, 500, and 1,000 µg/plate	No mutagenic activity was detected in any of the strains, either with or without metabolic activation

9.9 Immunotoxicity

No immunotoxicity information was found for ethylenebis(tetrabromophthalimide).

9.10 Other Data

The porphyrinogenic activity of ethylenebis(tetrabromophthalimide) was tested using chick embryo liver cells (Koster et al., 1980). Some cultures were pretreated with β -naphthoflavone for 20 hours (β -NF, 3 μ g/mL medium) to induce drug enzymes P-450 and P-448. β -NF alone in the medium causes no porphyrinogenic activity. After 24 hours the culture medium was replaced with 2 mL of fresh medium containing ethylenebis(tetrabromophthalimide) suspended in dimethyl sulfoxide (DMSO) to give a concentration of 10 μ g/mL medium. The author determined that DMSO at 1 μ L/mL did not harm the cells or cause any accumulation of porphyrins. After another 24 hours, the fluorescence of the cultures was determined semiquantitatively by fluorescence microscopy. The culture showed trace microscopic fluorescence when β -NF was used as a pretreatment, but no porphyrinogenic activity was detected with ethylenebis(tetrabromophthalimide) alone.. The poor solubility of the ethylenebis(tetrabromophthalimide) could have been a factor responsible for its low activity.

8.0 STRUCTURE-ACTIVITY RELATIONSHIPS

No structure-activity information was found for ethylenebis(tetrabromophthalimide).

11.0 ONLINE DATABASES AND SECONDARY REFERENCES

11.1 Online Databases

Chemical Information System Files

SANSS (Structure and Nomenclature Search System)
TSCATS (Toxic Substances Control Act Test Submissions)

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS	EMBASE	Registry
CANCERLIT	HSDB	RTECS
CAPLUS	MEDLINE	TOXLINE
CHEMLIST		

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC [®]	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

In-House Databases

CPI Electronic Publishing Federal Databases on CD

Current Contents on Diskette®

The Merck Index, 1996, on CD-ROM

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APPENDIX A

UNITS AND ABBREVIATIONS

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µg = microgram(s)

b.w. = body weight

C = Celsius

CASRN = Chemical Abstracts Service Registry Number

cm = centimeter(s)

EPA = U.S. Environmental Protection Agency

g = gram(s)

HPLC = high-pressure liquid chromatography

HPV = High Production Volume

IPCS = International Programme on Chemical Safety, World Health Organization

ITC = Interagency Testing Committee

kg = kilogram(s)

L = liter(s)

m³ = cubic meter(s)

mg = milligram

mg/kg = milligram per kilogram

mL = milliliter(s)

NIEHS = National Institute of Environmental Health Sciences

NIOSH = National Institute of Occupational Health and Safety

NTIS = National Technical Information Service

NTP = National Toxicology Program

OPPT = Office of Pollution Prevention and Toxics

PBDD = Polybrominated dibenzodioxin

PBDF = Polybrominated dibenzofuran

ppm = parts per million

TSCA = Toxic Substances Control Act

W/V = weight/volume