Tetrabromophthalic Anhydride
[CASRN 632-79-1]

Review of Toxicological Literature

Prepared for

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EXECUTIVE SUMMARY

Tetrabromophthalic anhydride was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicity and carcinogenicity testing based on its high production volume and the potential exposure of humans to the chemical through its use as a flame retardant. It is listed on the U.S. Environmental Protection Agency High Production Volume (HPV) Chemicals list with an estimated annual production volume of 4.7 to 6.6 million lb (2100 to 3000 metric tons).

High yields (95%) of tetrabromophthalic anhydride are achieved by the bromination of phthalic anhydride in 60% oleum (concentrated sulfuric acid with sulfur trioxide). The compound can also be prepared by the reaction of phthalic anhydride and bromine in a mixture of concentrated sulfuric acid and hydrogen peroxide in the presence of iodine or in chlorosulfonic acid containing small amounts of sulfur.

Tetrabromophthalic anhydride is expected to be persistent in soils. Its bioaccumulation potential, however, in aquatic environments is low. When applied to silica gel surfaces and irradiated with UV light, the compound was quickly hydrolyzed to its acid form, as was also observed in moist soil. Release of polybrominated dibenzofurans and dibenzodioxins is not expected; pyrolysis and combustion of polymers containing tetrabromophthalic anhydride resulted in undetectable amounts of bromine-containing by-products.

Tetrabromophthalic anhydride, which first appeared on the Interagency Testing Committee's (ITC's) *Priority Testing List* in the 25th Report to the Administrator of EPA as a chemical recommended without intent-to-designate, was also added to the Toxic Substances Control Act (TSCA) section 8(a) Preliminary Assessment Information Rule, requiring the reporting of production volume, use, exposure, and release information and the TSCA section 8(d) Health and Safety Data Report Rule, requiring the reporting of unpublished health and safety studies of the compound. It was later removed from the list in the 33rd Report "to give adequate priority to recently identified testing needs for other chemicals." Tetrabromophthalic anhydride is included in the U.S. EPA HPV Challenge Program.

A single oral dose of tetrabromophthalic anhydride (4.38-5.75 mg/kg; 9.45-12.4 µmol/kg) given to rats was hydrolyzed to its acid form and partly absorbed in the gastrointestinal tract. The latter was then rapidly eliminated in the urine, while the unabsorbed portion was excreted in the feces. After two days, total residues in all tissues were <0.2% of the administered dose. The absorbed portion is therefore not expected to persist or accumulate.

Numerous toxicity studies have been conducted with tetrabromophthalic anhydride. For rats, rabbits, and mice, a maximum acute oral and/or dermal toxicity value (LD_{50}) of >10,000 mg/kg (21.565 mmol/kg) was found. For guinea pigs, the oral LD_{50} was >1000 mg/kg (2.156 mmol/kg). The 4-hour LC_{50} in rats was 10.9 mg/L (575.8 ppm). In fish and water fleas, LC_{50} values of >10 mg/L (0.022 mM) and >5.6 mg/L (0.012 mM), respectively, were determined.

In rabbits, acute dermal application of tetrabromophthalic anhydride (200-10,000 mg/kg body weight; 0.431-21.656 mmol/kg body weight) resulted in no signs of irritation. Short-term dermal exposure of the compound (50, 500, and 5000 mg/kg [0.11, 1.08, and 10.78 mmol/kg] per day for 5 days per week for 4 weeks) produced very slight to moderate erythema in the animals. When instilled into the conjunctival sac of the eye at a dose of 100 mg (0.216 mmol), redness, chemosis, and discharge were observed. A later study reported no positive ocular scores under the same conditions.

In rats, oral administration of tetrabromophthalic anhydride (200-10,000 mg/kg; 0.431-21.6 mmol/kg) resulted in moderate weakness and kidney congestion. Common symptoms of inhalation experiments included decreased motor activity, eye squint, slight dyspnea, lacrimation, and nasal discharge.

When administered daily to pregnant rats on days 6-15 of gestation at dose levels ranging from 30 to 10,000 mg/kg (0.065-21.565 mmol/kg), no compound-related effects were seen in the number of viable or nonviable fetuses, resorptions, implantations, or corpora lutea at 3000 mg/kg or less. The deaths of 4 of 5 animals at the highest dose, however, were linked to treatment.

In genotoxicity experiments, tetrabromophthalic anhydride failed to give a positive mutagenic response in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 or in *Saccharomyces cerevisiae* strain D4, in the presence and absence of metabolic activation. Although under the test conditions the result implies that acylation of nucleic acids would not take place, the ability of tetrabromophthalic anhydride to acylate protein amino groups in dimethylformamide solutions suggests that it could acylate amino and other functional groups in DNA. This is contrary to the expectation of the compound to be a poor biological alkylating agent due to the relatively inert nature of its aromatic carbon-bromide bonds.

In guinea pigs, dermal application of tetrabromophthalic anhydride induced sensitization. Based upon the results, the authors of one study concluded that the compound is a potentially sensitizing agent in man. However, in a human study in which male and female subjects received 9 induction patches of the compound for a contact time of 24 hours, followed by a single challenge dose 12 days later, no erythema or edema and no sensitization was observed.

No chronic toxicity or carcinogenicity studies were available.

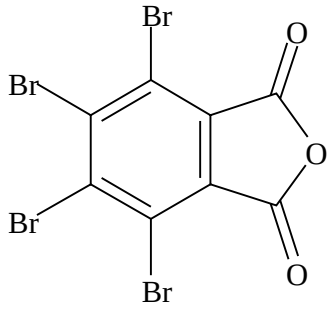
The NTP has conducted comprehensive toxicology studies of the structurally related tetrachlorophthalic anhydride. In male and female rats, administration of the compound by oral gavage resulted in death at doses of 750 and 1500 mg/kg. Average final body weights and body weight gains were lowered in males at doses of 375 mg/kg and greater and in females at doses ranging from 94 to 1500 mg/kg. At concentrations of 187 mg/kg and higher, liver weights in both sexes were slightly increased. In addition, dose-dependent increases in kidney weights and in the incidence and severity of renal tubule necrosis and/or dilation were observed for both groups. In mice no chemical-related effects on survival, body weights, or organ weights were observed. Several *in vitro* and *in vivo* tests have been conducted with tetrachlorophthalic anhydride. Like tetrabromophthalic anhydride, tetrachlorophthalic anhydride was not mutagenic in *S. typhimurium* in the presence and absence of metabolic activation.

1.0 BASIS FOR NOMINATION

Tetrabromophthalic anhydride was selected by the National Institute of Environmental Health Sciences (NIEHS) Nominating Faculty for toxicity and carcinogenicity testing based on high production volume and potential human exposure through use as a flame retardant.

2.0 INTRODUCTION

Tetrabromophthalic Anhydride
[632-79-1]



2.1 Chemical Identification

Tetrabromophthalic anhydride ($C_8Br_4O_3$; mol. wt. = 463.72) is also called:

Bromophthal
FG-4000
Firemaster PHT 4
1,3,-Isobenzofurandione, 4,5,6,7-tetrabromo-
Phthalic acid, tetrabromo-, anhydride
Phthalic anhydride, tetrabromo-
4,5,6,7-Tetrabromo-1,3-isobenzofurandione
3,4,5,6-Tetrabromophthalic anhydride

(Esposito, 1999)

2.2 Physical-Chemical Properties

Property	Information	Reference
Physical State	Pale yellow crystalline solid or needles; bromine content of 68.6 weight %	Esposito (1999); Larsen (1990)
Odor	Faint pungent	Doyle and Elsea (1964)
Melting Point (^oC)	279.5-280.5	Weast and Astle (1979)
Specific Gravity	2.87	Pettigrew (1992)
Water Solubility (ppm)	149 (15 °C), 241 (25 °C), 242 (35 °C); Decomposes	Yu and Atallah (1978b); Esposito (1999)
Slightly Soluble in:	Benzene and DMSO	Esposito (1999)

Tetrabromophthalic anhydride, as a liquid, is combustible. It may decompose on exposure to moist air or water, emitting toxic fumes of carbon monoxide, carbon dioxide, and hydrogen bromide gas (Esposito, 1999). Thermal disintegration of the compound gives a high mineralization degree (93% recovery of organic bromine) (Stachel et al., 1994).

2.3 Commercial Availability

Tetrabromophthalic anhydride is available in crystalline form from the Albemarle Corporation (under the trade name SAYTEX RB-49) and from Great Lakes Chemical Corporation (under the trade name PHT-4) in off-white crystalline powder grades. Both companies ship tetrabromophthalic anhydride in 50-lb bags (Chemcyclopedia Online, 1999).

3.0 PRODUCTION PROCESSES

Tetrabromophthalic anhydride is prepared by bromination of phthalic anhydride in 60% oleum (fuming sulfuric acid containing 45-65% sulfur trioxide), rendering a 95% yield (Dagani et al., 1985; Larsen, 1990; Pettigrew, 1992). Because the halogenating agent is bromine, an excess of oleum is used to oxidize the by-product hydrogen bromide to bromine (Dagani et al., 1985). As a result, some sulfonation of the aromatic ring occurs, which is then removed by reacting the anhydride with dilute sodium hydroxide, filtering, and acidifying with dilute hydrochloric acid. The precipitated acid, washed with hot water, is reconverted to the anhydride by heating at 150 °C for several hours (Larsen, 1990; Pettigrew, 1992).

Tetrabromophthalic anhydride can also be prepared by the reaction of phthalic anhydride and bromine in a mixture of concentrated sulfuric acid and 70% hydrogen peroxide in the presence of iodine or in chlorosulfonic acid containing sulfur (Dagani et al., 1985).

4.0 PRODUCTION AND IMPORT VOLUMES

Tetrabromophthalic anhydride is produced by the Albemarle Corporation in Magnolia, Arkansas, and by the Great Lakes Chemical Corporation in El Dorado, Arkansas (SRI, 1998). It is listed on the U.S. Environmental Protection Agency High Production Volume Chemicals list with an estimated annual production of 4.7 to 6.6 million lb (2100 to 3000 metric tons) (U.S. EPA, 1998). In 1979 production was probably greater than 2.26×10^6 g (2.27 metric tons) and in

1981 greater than 6.81 x 10^6 (6.81 metric tons). In 1979 U.S. imports were 2.61 x 10^6 g (2.61 metric tons) (HSDB, 1999).

5.0 USES

Tetrabromophthalic anhydride is a reactive flame retardant incorporated into unsaturated resins. It is also used as a starting material for the manufacture of other flame retardants, such as bromine-containing urethane polyols and diallyl tetrabromophthalate (Dagani et al., 1985; Chemcyclopedia Online, 1999). It is used to manufacture sulfobromophthalein, a compound used as a diagnostic aid for the determination of liver function (NLM, 1995; Budavari, 1996).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

Tetrabromophthalic anhydride was found to be rapidly hydrolyzed to tetrabromophthalic acid but not further degraded in moist soil (1% was identified in 0- and 28-day samples). When tested at 1 and 10 µg/g, little volatilization occurred and a large proportion (24% and 32%, respectively) became soil-bound after 28 days. Tetrabromophthalic anhydride is, therefore, expected to be persistent in soils (Butz, 1979). It was found to have a slight positive effect (i.e., increased the number) on soil bacterial population at the higher dose but not at the lower dose, while soil fungal population was not affected at either 1 or 10 µg/g (Butz and Atallah, 1979).

The bioaccumulation potential of the compound in aquatic environments is low; an average partition coefficient of 96 was obtained in a 1,2-dichlorobenzene/water system (Yu, 1978). Combustion analysis indicated that tetrabromophthalic anhydride was not accumulated in bluegill sunfish (Nye, 1978). Its water solubility is also very low: 149 ppm at 15 °C, 241 ppm at 25 °C, and 242 ppm at 35 °C (Yu and Atallah, 1978b).

When applied to silica gel surfaces and irradiated with UV light, its quick hydrolysis (half-life <5 min) to the dicarboxylic acid was demonstrated (Yu and Atallah, 1978a). Release of polybrominated dibenzofurans (PBDFs) and dibenzodioxins (PBDDs) is not expected; pyrolysis and combustion of polymers (flame retardants) containing tetrabromophthalic anhydride at 600 °C to 900 °C resulted in undetectable amounts of bromine-containing by-products (Thoma et al., 1986b; Dumler et al., 1989). In analytical grade tetrabromophthalic anhydride, PBDFs and PBDDs were also not detected (Thoma et al., 1986a).

7.0 HUMAN EXPOSURE

Exposure to tetrabromophthalic anhydride is possible during its manufacture, processing, use, and disposal. Symptoms of exposure may include coughing, sneezing, respiratory system irritation, dermatitis, and eye irritation (Radian Corp., 1991).

8.0 REGULATORY STATUS

Tetrabromophthalic anhydride is regulated by the U.S. Environmental Protection Agency (EPA) under the Clean Air Act NESHAPs provisions and under the Toxic Substances Control Act (TSCA). In its 25th Report to the Administrator of EPA which revised the *Priority Testing List*, the Interagency Testing Committee (ITC), established under TSCA section 4(e), listed tetrabromophthalic anhydride as a chemical recommended without intent-to-designate and authorized the compound for chemical properties, persistence, and health and ecological effects testing (ITC, 1989). Tetrabromophthalic anhydride was also added to the TSCA section 8(a) Preliminary Assessment Information Rule (40 CFR part 712), requiring the reporting of production volume, use, exposure, and release information and the TSCA section 8(d) Health and Safety Data Report Rule (40 CFR part 716), requiring the reporting of unpublished health and safety studies of the compound. Based on the TSCA submissions, available production data, and EPA's testing priorities, the class of brominated flame retardards was removed from the *Priority Testing List* in ITC's 33rd Report (ITC, 1994). Tetrabromophthalic anhydride was removed specifically "to give adequate priority to recently identified testing needs for other chemicals."

Tetrabromophthalic anhydride is included in the U.S. EPA High Production Volume (HPV) Challenge Program. Under this program, EPA has sought private-sector sponsors to conduct voluntary research on HPV chemicals. Tetrabromophthalic anhydride is fully sponsored for Screening Information Data Set (SIDS) testing by Albemarle Corp., Ameribrom, Inc., and Great Lakes Chemical Corp., as members of the Chemical Manufacturers Association (CMA) Brominated Flame Retardant Industry Panel (BFRIP). The tests agreed to are acute toxicity, chronic toxicity, development/reproductive toxicity, mutagenicity, ecotoxicity, and environmental fate (U.S. EPA, 1999).

Table 1. Regulations Relevant to Tetrabromophthalic Anhydride

	Regulation	Summary of Regulation
EPA	40 CFR 63	Subpart F—National Emission Standards for Organic Hazardous Air Pollutants [NESHAPs] from the Synthetic Organic Chemical Manufacturing Industry. §63.100 Applicability and designation of source. This subpart provides requirements applicable to chemical manufacturing process units that manufacture tetrabromophthalic anhydride as a primary product.
-	40 CFR 712	Subpart B—Manufacturers Reporting—Preliminary Assessment Information. §712.30 Chemical lists and reporting periods. Effective January 11, 1990, manufacturers and importers of tetrabromophthalic anhydride were required to submit a Preliminary Assessment Information Manufacturer's Report by March 12, 1990, for each site at which they manufactured or imported the chemical.
-	40 CFR 716	Subpart B—Specific Chemical Listings. §716.120 Substances and listed mixtures to which this subpart applies. Effective January 11, 1990, tetrabromophthalic anhydride was subjected to all provisions of part 716 until December 19, 1995. Manufacturers, importers, and processors of the chemical were subjected to the reporting requirements of subpart A, which called for the submission of lists and copies of health and safety studies on tetrabromophthalic anhydride for priority consideration for testing rules under section 4(a) of the Toxic Substances Control Act (TSCA).

9.0 TOXICOLOGICAL DATA

9.1 General Toxicology

9.1.1 Human Data

Fifty male (29- to 65-years-old) and female (24- to 62-years-old) subjects receiving induction patches of tetrabromophthalic anhydride on the upper arm and upper back, respectively, for 9 weeks (24 hours' contact each week), followed 12 days later by a single challenge patch test of the compound applied 24 hours to an adjacent site, exhibited no erythema or edema and no skin sensitization (Wenzel, 1976).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

Male and female Holtzman albino rats given a single oral dose of tetrabromophthalic anhydride (4.38-5.75 mg/kg; 9.45-12.4 µmol/kg) by oral intubation hydrolyzed the compound to its acid form. Tetrabromophthalic anhydride was also partly absorbed in the gastrointestinal tract, which was then rapidly eliminated in the urine (almost 20% of absorbed dose within 24 hours) mostly as the acid. The unabsorbed portion was excreted in the feces (almost 75% within 48 hours). Additionally, the pharmacokinetics of tetrabromophthalic anhydride was observed to be the same in both sexes. After 48 hours, total residues in all tissues were <0.2% of the administered dose; the rate constant of elimination ranged from 0.211 to 0.100, and the retention half-life was <7 hours. In blood, the respective values were 0.081 and 8.5 hours. The absorbed dose is therefore not expected to persist or accumulate (Diaz, 1978).

9.1.3 Acute Exposure

Acute toxicity values for tetrabromophthalic anhydride are presented in **Table 2**. The details of studies discussed in this section are presented in **Table 3**.

Table 2. Acute Toxicity Values for Tetrabromophthalic Anhydride

Route	Species (strain and sex)	LC_{50}/LD_{50}	Reference
Mammalian Animals			
oral	Rat (strain and sex n.p.)	LD_{50} >3200 mg/kg (6.901 mmol/kg)	Roudabush and Rouse (1965)
-	Rat (strain and sex n.p.)	LD_{50} >50 mg/kg (0.11 mmol/kg)	Velsicol Chem. Corp. (1977)
-	Rat (Dublin Sprague-Dawley, M)	LD_{50} >10,000 mg/kg (21.565 mmol/kg)	Doyle and Elsea (1964)
-	Mouse (Charles River CD-1, M and F)	LD_{50} >10,000 mg/kg (21.565 mmol/kg)	Dean and Jessup (1978)
dermal	Guinea pig (strain and sex n.p.)	LD_{50} >1000 mg/kg (2.156 mmol/kg)	Roudabush and Rouse (1965)
-	Rabbit (strain and sex n.p.)	LD_{50} >10,000 mg/kg (21.565 mmol/kg)	Doyle and Elsea (1964)
-	Rabbit (strain n.p., F)	LD_{50} >200 mg/kg (0.431 mmol/kg)	Velsicol Chem. Corp. (1977)
inhalation	Rat (Spartan, M and F)	LC_{50}, 4-h >10.92 mg/L (10,920 mg/m^3; 575.8 ppm)	Wazeter and Goldenthal (1974a)
Aquatic Organisms			
-	Bluegill sunfish (*Lepomis macrochirus*, sex n.p.)	LC_{50}, 96-h >10 mg/L (0.022 mM)	Calmbacher (1978a)
-	Rainbow trout (*Salmo gairdneri*, sex n.p.)	LC_{50}, 96-h >10 mg/L (0.022 mM)	Calmbacher (1978b)
-	Water flea (*Daphnia magna*, sex n.p.)	LC_{50}, 48-h >5.6 mg/L (0.012 mM)	Morrissey (1978)

Abbreviations: F = females; h = hour(s); LC_{50} = concentration lethal to 50% of test animals; LD_{50} = dose lethal to 50% of test animals; M = males; n.p. = not provided

9.1.3.1 Rabbits

In New Zealand White rabbits, tetrabromophthalic anhydride (200 mg/kg body weight [0.431 mmol/kg] and 500 mg [1.08 mmol]) applied to the back with patches for 24 hours, resulted in no edema formation at the intact or abraded sites. One animal given the 500 mg dose (occluded), however, showed a very slight erythema at an abraded site at 72 hours (Wolven and Levenstein, 1958; Wazeter and Goldenthal, 1974c). When applied to the intact abdominal skin under a binder of rubber dental damming for 24 hours at levels ranging from 1.00 to 10.0 g/kg (2.16-21.6 mmol/kg) body weight, no signs of dermal irritation occurred. During the exposure period, the animals at the highest level showed depressed righting and placement reflexes. Afterward, they appeared normal (Doyle and Elsea, 1964). When tetrabromophthalic anhydride

(100 mg; 0.216 mmol) was instilled into the conjunctival sac of the eye, redness, chemosis, and discharge were observed at 24, 48, and 72 hours (Wazeter and Goldenthal, 1974b). Using the same test system, Mallory et al. (1986), in contrast, found the chemical to not be an eye irritant.

9.1.3.2 Rats

Male Dublin Sprague-Dawley rats treated by gavage with tetrabromophthalic anhydride at levels ranging from 0.215 to 10.0 g/kg body weight (0.464-21.6 mmol/kg) exhibited wheezing, while gross necropsy revealed kidney congestion (Doyle and Elsea, 1964). In rats given 200 to 3200 mg/kg (0.431-6.901 mmol/kg) tetrabromophthalic anhydride orally, moderate weakness resulted (Roudabush and Rouse, 1965). In albino rats exposed to an atmospheric concentration of approximately 10.92 mg/L (575.8 ppm) of tetrabromophthalic anhydride for 4 hours in a glass chamber, decreased motor activity, eye squint, slight dyspnea, and erythema occurred. At 24 hours, one rat exhibited nasal porphyrin discharge (Wazeter and Goldenthal, 1974a). Rats receiving whole-body exposure to an atmosphere consisting of pyrolysis products of 100.05 g of HIPS (high-impact polystyrene) resin/tetrabromophthalic anhydride/Sb_2O_3 (atmospheric concentration of test compound not provided) for 4 hours in a glass chamber resulted in decreased motor activity, eye squint, and lacrimation. At 24 and 48 hours, decreased motor activity was observed. At 72 hours to the end of the experiment, all rats appeared normal. No gross lesions were obtained at terminal necropsy following 14 days of observation (Wazeter and Goldenthal, 1975a). Whole-body exposure of the animals to an atmosphere containing pyrolysis products of 200.03 g of HIPS resin/tetrabromophthalic anhydride/Sb_2O_3 for 6 hours resulted in eye squint, lacrimation, salivation, slight dyspnea, and a white deposit around the nares. At termination, two rats exhibited nasal porphyrin discharge. At 24 to 72 hours, eye squint and clear ocular discharge were observed. At 4 days, eye squint continued in two rats. From 5 days to the end of the 14-day study period, most rats appeared normal. No gross lesions were observed (Wazeter and Goldenthal, 1975b). In Sprague-Dawley rats, a polyester sample containing tetrabromophthalic anhydride (sample weight: 3.6 g), heated to produce smoke and fumes (atmospheric concentration of test compound not provided), resulted in no incapacitation during exposure and no mortality using a smoldering mode. The flaming mode (sample weight: 4.2 g), however, resulted in 5 out of 6 animals incapacitated and 1 rat dead (Drozdowski, 1978).

Table 3. Acute Exposure to Tetrabromophthalic Anhydride

Species Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose/Duration	Observation Period	Results/Comments
Rabbits					
strain and age n.p.	10F	tetrabromophthalic anhydride, purity n.p.	dermal: 200 mg/kg (0.431 mmol/kg) body weight with patches for 24 h	48 h	No signs of an erythema or edema obse
strain and age n.p.	F, number n.p.	tetrabromophthalic anhydride, purity n.p.	dermal: 1.00, 2.15, 4.64, and 10.0 g/kg (2.16, 4.64, 10.0, 21.6 mmol/kg) body weight applied to intact abdominal area (occluded) for 24 h	15 days	No signs of dermal irritation observed. the highest dose showed depressed righ placement reflexes during exposure pe then appeared normal afterward. No g pathology observed.
New Zealand White, age n.p.	3M, 3F	tetrabromophthalic anhydride, purity n.p.	dermal: 500 mg (1.08 mmol) applied to back (occluded) for 24 h	24 and 72 h	No edema formation occurred at intact abraded sites. One animal showed a ve erythema at the abraded site at 72 h.
New Zealand White, age n.p.	3M, 3F	tetrabromophthalic anhydride, purity n.p.	ocular: 100 mg (0.216 mmol) instilled into conjunctival sac of right eye	24, 48, and 72 h, and at 7 days	Redness: moderate to marked cases at to moderate cases at 48 h and 72 h Chemosis: very slight to moderate at 2 slight at 48h and 72 h Discharge: very slight to marked at 24 at 48 h to end of observation period
New Zealand White, "adult"	3M, 3F	tetrabromophthalic anhydride, purity n.p.	ocular: 100 mg (0.216 mmol) instilled into conjunctival sac of right eye	72 h	No positive ocular scores observed.
Rats					
Dublin Sprague-Dawley albino, age n.p.	5M/dose	tetrabromophthalic anhydride, purity n.p.	gavage; 0.215, 0.464, 1.00, 2.15, 4.64, and 10.0 g/kg (0.464, 1.00, 2.16, 4.64, 10.0, and 21.6 mmol/kg) body weight	14 days	All rats exhibited wheezing. Gross nec showed kidney congestion in all anima congestion at the lower levels and mod marked congestion at the highest level)
strain and age n.p.	10, sex n.p.	tetrabromophthalic anhydride, purity n.p.	p.o.; 200-3200 mg/kg (0.431-6.901 mmol/kg); specific dose levels n.p.	n.p.	Moderate weakness observed.

Table 3. Acute Exposure to Tetrabromophthalic Anhydride (Continued)

Species Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose/Duration	Observation Period	Results/Comments
Spartan, age n.p.	5M, 5F	tetrabromophthalic anhydride, purity n.p.	inhalation: whole-body exposure to ~10.92 mg/L (575.8 ppm) for 4 h	14 days	During the 4-h exposure period, decrea activity, eye squint, slight dyspnea, and were observed. At 24 h, one rat exhibi porphyrin discharge.
Spartan, age n.p.	5M, 5F	HIPS resin/ tetrabromophthalic anhydride/Sb_2O_3, purity n.p.	inhalation: whole-body exposure to pyrolysis products of 100.05 g (atmospheric concentration of test compound n.p.) for 4 h	14 days	During exposure period, decreased mot eye squint, and lacrimation observed. 48 h, decreased motor activity was see days, 2 rats showed very slight corneal All rats exhibited normal body weight gross lesions obtained at terminal necr
Spartan, age n.p.	5M, 5F	HIPS resin/ tetrabromophthalic anhydride/Sb_2O_3, purity n.p.	inhalation: whole-body exposure to pyrolysis products of 200.03 g (atmospheric concentration of test compound n.p.) for 6 h	14 days	During exposure period, eye squint, lac salivation, slight dyspnea, and white de around snares observed. At end of exp rats exhibited nasal porphyrin discharg h, eye squint and clear ocular discharge and at 4 days, eye squint in 2 rats. At 6 rats exhibited very slight corneal opaci All rats exhibited normal body weight gross lesions obtained at terminal necr
Sprague-Dawley, "adult"	3M, 3F	polyester containing tetrabromophthalic anhydride; purity n.p.	inhalation: whole-body exposure to smoke and fumes (atmospheric concentration of test compound n.p.) smoldering mode: sample weight of 3.6 g for 30 min flaming mode: sample weight of 4.2 g for 20 min	n.p.	Smoldering mode: no incapacitation d exposure but some slight loss of contro mortality. Necropsy of survivors show animals with slight hemorrhaging. Flaming mode: 5/6 animals (note: tabl indicated 6/6 rats) incapacitated during 1/6 animals died during test. Necropsy survivors showed all lungs near normal

Abbreviations: F = females; h = hour(s); M = males; min = minutes; n.p. = not provided; p.o. = perorally

9.1.4 Short-Term and Subchronic Exposure

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

In Spartan albino rats exposed to a dust atmosphere of tetrabromophthalic anhydride (2 or 8 mg/L; 104 or 422 ppm) for 4 hours daily 5 days a week for 3 weeks in a sealed glass chamber, salivation, lacrimation, nasal discharge, and nasal porphyrin discharge were reported (Wazeter and Goldenthal, 1975e). At 20 days hematological, biochemical, and urinalysis studies showed no changes related to the chemical. Decreases in liver weights and increases in lung weights, however, were considered compound-related. The higher incidence of inflammatory lung lesions in both exposure groups compared to that in the control group may have also been compound-related. Necropsy showed no gross pathological lesions.

Tetrabromophthalic anhydride applied dermally to the dorsal skin of New Zealand White rabbits at dose levels of 50, 500, and 5000 mg/kg (0.11, 1.08, 10.78 mmol/kg) daily for 5 days per week for 4 weeks resulted in very slight to moderate erythema (Wazeter and Goldenthal, 1975d). At 5000 mg/kg/day, 3 rabbits showed moderate desquamation, while 1 rabbit showed marked ataxia, the inability to lift its head or right itself, and dyspnea. The deaths or condition requiring sacrifice of the high-dose animals were considered compound-related. At the lower doses, statistically significant increases in bromine concentration in skin were found.

9.1.5 Chronic Exposure

No chronic exposure data were available.

9.1.6 Synergistic and Antagonistic Activity

No synergistic and antagonistic activity data were available.

Table 4. Short-Term and Subchronic Exposure to Tetrabromophthalic Anhydride

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose/Duration	Observation Period	Results/Comments
Spartan albino rats, age n.p.	15M, 15F	tetrabromophthalic anhydride, purity n.p.	inhalation: 2 and 8 mg/L (104 and 422 ppm) for 4 h/day, 5 days/wk for 3 wk	21 days	At both levels, clinical observations salivation, lacrimation, nasal discha nasal porphyrin discharge. Hemato biochemical, and urinalysis studies 20 days showed no compound-relat Decreases in liver weights and incre weights, however, were compound- necropsy, no gross lesions observed
New Zealand White rabbits, age n.p.	3M, 3F per dose level	tetrabromophthalic anhydride, purity n.p.	dermal: 50, 500, and 5000 mg/kg (0.11, 1.08, 10.78 mmol/kg) per day for 5 days/wk for 4 wk as a paste to dorsal skin	28 days	At all dose levels, very slight to mo erythema observed. At the highest dose, several had pal accentuated liver lobulation, and ga irritation, which may have been con related. Three animals showed mod desquamation. The 1 survivor had a with lymphopenia, nucleated erythr marked increase in glucose and urea and albumin in the urine. Statistically significant increases in concentration of bromine in skin at 500 mg/kg/day levels.

Abbreviations: F = females; M = males; n.p. = not provided; wk = week(s)

9.2 Reproductive and Teratological Effects

The details of this study are presented in **Table 5**.

In pregnant Charles River CD rats, tetrabromophthalic anhydride was administered by gavage at levels ranging from 30 to 10,000 mg/kg (0.065-21.565 mmol/kg) per day from day 6 to 15 of gestation. At levels between 30 to 3000 mg/kg/day, no changes in appearance or behavior were observed. Furthermore, no compound-related effects were seen in the number of viable or nonviable fetuses, resorptions, implantations, and corpora lutea. Rats receiving 10,000 mg/kg/day exhibited staining of the anogenital area and red nasal and/or oral discharge after the third day of treatment. All animals survived the 3000 mg/kg/day or less dose levels. At the highest dose, however, 4 out of 5 animals died by day 14. The deaths were linked to the treatment. The one surviving rat showed severely reduced body weight gains throughout the experiment (Goldenthal, 1978).

9.3 Carcinogenicity

No carcinogenicity data were available.

9.4 Initiation/Promotion Studies

No initiation/promotion studies were available.

9.5 Anticarcinogenicity

No anticarcinogenicity data were available.

9.6 Genotoxicity

The details of these studies are presented in **Table 6**.

In *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *Saccharomyces cerevisiae* strain D4, tetrabromophthalic anhydride (doses ranging from 0.1-10,000 µg/plate [0.2 nmol-21.565 µmol per plate]), in the presence and absence of Aroclor 1254-induced rat liver S9, showed no mutagenic response (Brusick, 1976; MacGregor and Friedman, 1977; Atherholt, 1979; Zeiger et al., 1985). Using Aroclor 1254-induced Syrian hamster liver S9 did not alter the results (Zeiger et al., 1985).

Table 5. Reproductive Toxicity and Teratology Study of Tetrabromophthalic Anhydride

Species, Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose/Duration	Observation Period	Results/Comments
Rats, Charles River CD, 12-wk-old at mating	5F/dose level	tetrabromophthalic anhydride, purity n.p.	orally by gavage: 30, 100, 300, 1000, 3000, and 10,000 mg/kg (0.065, 0.216, 0.647, 2.156, 6.469, 21.565 mmol/kg) per day from day 6 to day 15 of gestation	20 days	30-3000 mg/kg/day dose: No mo occurred. No compound-related c appearance, behavior, and the nun viable or nonviable fetuses, resorp implantations, or corpora lutea ob 10,000 mg/kg/day dose: 4/5 anim gestation day 14. The deaths were treatment. After 3rd day, staining anogenital area and red nasal and/ discharge were observed. The sur also showed severely reduced bod gains throughout the experiment.

Abbreviations: F = females; n.p. = not provided; wk = week(s)

Table 6. Genotoxicity Studies of Tetrabromophthalic Anhydride

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form and Purity	Dose	Endpoint Response	Comments
Lower Eukaryotic Systems						
Saccharomyces cerevisiae strain D4	Try^+ gene conversions	+/-	tetrabromophthalic anhydride, purity n.p.	0.05, 0.25, 0.5, 5, and 50 µg/plate (0.1, 0.54, 1.1, 11, 110 nmol/plate)	negative	-
Prokaryotic Systems						
Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538	*his* gene mutations	+/-	tetrabromophthalic anhydride, purity n.p.	0.05, 0.25, 0.5, 5, and 50 µg/plate (0.1, 0.54, 1.1, 11, 110 nmol/plate)	negative	-
S. typhimurium strains TA98, TA100, TA1535, and TA1537	*his* gene mutations	+/-	tetrabromophthalic anhydride, purity n.p.	10, 100, 1000, and 10,000 µg/plate (0.022, 0.216, 2.156, 21.565 µmol/plate)	negative	-
S. typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538	*his* gene mutations	+/-	tetrabromophthalic anhydride, purity n.p.	0.1, 1.0, 10, 100, and 1000 µg/plate (0.2, 2.2, 22, 216, 2156 nmol/plate)	negative	Without S9, 100 µg/ strain TA1537 result twofold increase in t number of colonies b considered not signi
S. typhimurium strains TA98, TA100, TA1535, and TA1537	*his* gene mutations	+/-	tetrabromophthalic anhydride, 98% pure	3, 10, 33, 100, 333, 1000, 3333, 6666, and 10,000 µg/plate (0.006, 0.022, 0.071, 0.216, 0.718, 2.156, 7.188, 14.38, and 21.565 µmol/plate)	negative	In addition to rat live Aroclor 1254-induce hamster liver S9 was

Abbreviations: n.p. = not provided; "+" = presence; "-" = absence

9.7 Cogenotoxicity

No cogenotoxicity data were available.

9.8 Antigenotoxicity

No antigenotoxicity data were available.

9.9 Immunotoxicity

The details of these studies are presented in **Table 7**.

Tetrabromophthalic anhydride, applied as various formulations to the backs of male and female Hartley albino guinea pigs with patches occluded with dental dam for 6 hours at weekly intervals, induced sensitization in the test group versus control (Lewis, 1986). In another study using only male guinea pigs, all animals responded to the challenge dose of 0.1% (given via intradermal injection). Four of the eight showed an average flare response that was greater than twice that obtained with the sensitizing dose, while the other half had responses 158 to 186% of that induced by the sensitizing dose (Wazeter and Goldenthal, 1975c). In three guinea pigs administered 0.25-1.0 g/kg (0.54-2.2 mmol/kg) of a solid form via cuff, slight edema and erythema resulted in 24 hours, while peeling was observed for up to two weeks. When tested as a 1% solution in acetone, dioxane, and guinea pig fat in 5 animals, tetrabromophthalic anhydride was found to not be a skin sensitizer (study not included in table) (Roudabush and Rouse, 1965). These last results were in agreement with the one human study conducted (see section 9.1.1).

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

Because the aromatic carbon-bromide bonds in tetrabromophthalic anhydride are relatively inert, the compound is not expected to act as a biological alkylating agent (MacGregor and Friedman, 1977). However, in dimethylformamide solutions, it has been found to acylate protein amino groups (Friedman and Koenig, 1976; Whitfield and Friedman, 1973; both cited by MacGregor and Friedman, 1977), which suggests that it could acylate amino and other functional groups in DNA (Friedman, 1977; cited by MacGregor and Friedman, 1977).

Table 7. Immunotoxicity Studies of Tetrabromophthalic Anhydride

Species Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose/Duration	Observation Period	Results/Comments
Guinea Pigs—Sensitization Experiments					
Hartley albino, age n.p.	10M, 10F	tetrabromophthalic anhydride, purity n.p.	test material as a 95% w/v formulation in acetone for 6 h once per wk for a total of 3 applications as patches occluded with dental dam primary challenge: test material as a 50% w/v formulation in acetone for 6 h 2 wk later rechallenge: test material as a 5.0% w/v formulation in acetone for 6 h 1 wk later	24 and 48 h after each treatment	Primary challenge: slight patchy eryth and slight patchy erythema and cases o confluent or moderate patchy erythema The same results were found in the rec experiment.
albino, strain and age n.p.	8M	tetrabromophthalic anhydride, purity n.p.	0.1% in NaCl solution injected i.d. into back and right flanks every other day 3x/wk for a total of 10 doses: first dose, 0.05 mL; remaining 9 doses, 0.10 mL challenge dose: 0.05 mL given 2 wk later	24 and 48 h after each treatment	Half exhibited an average flare respons than twice the average response obtain sensitizing dose; remaining 4 exhibited which were 158 to 186% of that induce sensitizing dose.
strain and age n.p.	3, sex n.p.	tetrabromophthalic anhydride, purity n.p.	0.25-1.0 g/kg (0.54-2.2 mmol/kg) via cuff; specific dose levels n.p.	24 h and at 1 and 2 wk	Slight edema and erythema was observ while desquamation occurred at 1 and

Abbreviations: F = females; h = hour(s); i.d. = intradermally; M = males; n.p. = not provided; wk = week(s)

Tetrachlorophthalic Anhydride

The NTP (1993) has previously conducted comprehensive toxicology studies of the structurally related tetrachlorophthalic anhydride which are briefly summarized below.

In 10 male and 10 female F344/N rats given tetrachlorophthalic anhydride (TCPA) (94, 187, 375, 750, and 1500 mg/kg) by oral gavage for 5 days per week for 13 weeks, 1 female died at a dose of 750 mg/kg and 5 males and 1 female died at a dose of 1500 mg/kg. Average final body weights and body weight gains were lowered in males given $\geq$375 mg/kg and in females at all dose levels. Relative liver weights were found to be slightly increased in both sexes at $\geq$187 mg/kg. Furthermore, dose-dependent increases in kidney weights and in the incidence and severity of renal tubule necrosis and/or dilatation were observed in the two groups.

Under the same test conditions, $B6C3F_1$ mice exhibited no chemical-related effects on survival, body weights, or organ weights; the mice did show decreases in red blood cell measurements.

In *in vitro* tests, TCPA (doses not provided) was not mutagenic in *Salmonella typhimurium* in the presence and absence of metabolic activation. In Chinese hamster ovary cells, sister chromatid exchanges and chromosomal aberrations were not induced. In mouse bone marrow cells, chromosomal aberrations were not induced with TCPA after 17 hours after intraperitoneal injection; however, an increase in sister chromatid exchanges was seen after 23 hours. In *in vivo* tests with *Drosophila melanogaster*, TCPA (doses not provided) gave equivocal results in the induction of sex-linked recessive lethal mutations when administered by feeding and negative results when administered by injection.

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
CANCERLIT
CAPLUS
CHEMLIST
EMBASE
HSDB
MEDLINE
Registry
RTECS
TOXLINE

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
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APPENDIX A: UNITS AND ABBREVIATIONS

°C = degrees Celsius

µg = microgram(s)

µg/mL = microgram(s) per milliliter

µM = micromolar

µmol = micromole(s)

BFRIP = Brominated Flame Retardant Industry Panel

µmol/kg = micromole(s) per kilogram

bw = body weight

CMA = Chemical Manufacturers Association

DMSO = dimethyl sulfoxide

EPA = Environmental Protection Agency

F = female(s)

g = gram(s)

g/kg = gram(s) per kilogram

g/mL = gram(s) per milliliter

GC/MS = gas chromatography/mass spectrometry

h = hour(s)

HIPS = high-impact polystyrene

HPV = high production volume

i.d. = intradermal(ly)

L = liter(s)

lb = pound(s)

LC_{50} = concentration lethal to 50% of test animals

LD_{50} = dose lethal to 50% of test animals

M = male(s)

mg/kg = milligram(s) per kilogram

mg/L = milligram(s) per liter

min = minute(s)

mL = milliliters

mmol = millimole(s)

mmol/kg = millimole(s) per kilogram

mmol/L = millimole(s) per liter

mol. wt. = molecular weight

NIEHS = National Institute of Environmental Health Sciences

nmol = nanomole(s)

n.p. = not provided

ppm = parts per million

p.o. = peroral(ly), per os

wk = week(s)