VOLUNTARY CHILDREN'S CHEMICAL EVALUATION PROGRAM (VCCEP)

DATA SUMMARY

DECABROMODIPHENYL ETHER

(A.K.A. DECABROMODIPHENYL OXIDE, DBDPO)

CAS # 1163-19-5

Prepared by

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DBDPO SUMMARY FOR TECHNICAL AUDIENCES

The American Chemistry Council's Brominated Flame Retardant Industry Panel (BFRIP) volunteered under the U.S. EPA's Voluntary Children's Chemical Evaluation Program (VCCEP) pilot to prepare the Data Summary for decabromodiphenyl oxide (DBDPO). This compound (CAS No. 1163-19-5) is also known as decabromodiphenyl ether. DBDPO is a data-rich chemical having valid guideline studies or other information for all VCCEP Tiers I, II and III and Screening Information Data Set (SIDS) endpoints.

The Environmental Protection Agency (EPA) included DBDPO in the VCCEP pilot on the basis of its detection in human milk as reported by Noren et al. 1998 (see Table 1, page 81704, Federal Register, Vol. 65, No. 248, December 26, 2000). However, Noren et al. did not report DBDPO in human breast milk, and DBDPO has not been reported in human breast milk in publications appearing prior to or since 1998. Noren et al.'s, and other authors, use of the terminology "PBDEs" rather than specifying the isomers or congeners detected is likely the cause for this error.

The DBDPO product is one of three commercial polybrominated diphenyl oxide (a.k.a. ether) products manufactured, and accounts for approximately 83% of all polybrominated diphenyl oxide/ether (e.g. "PBDE") production worldwide. DBDPO is used solely as a flame retardant to prevent or delay ignition of combustible materials. DBDPO's flame retardant activity is derived from the bromine atoms on the diphenyl oxide molecule. Bromine is one of the few elements able to provide flame retardancy in the gas phase; a property needed by some plastic resins as a result of the way the plastic burns. DBDPO's high bromine content makes it a very effective flame retardant which in turn makes DBDPO extremely cost-effective. This combination has resulted in DBDPO's becoming the second largest volume brominated flame retardant in production and use. DBDPO's main application is in high impact polystyrene (HIPS) used for electronic enclosures, e.g. television set cabinet backs. A comparatively minor, but important, use of DBDPO is to flame retard upholstery fabric where it is applied as a fabric back coat encapsulated in latex. Two companies manufacture DBDPO in the U.S.

Flame retardants such as DBDPO are a component of efforts to control and reduce the risk of fires. Despite the best efforts of fire departments, building codes, sprinklers and fire alarms, fires in the United States are a serious problem and the United States has one of the highest fire incidence and mortality rates of developed nations. The National Fire Protection Association reports that in the year 2000:

- A fire department responded to a fire somewhere in the United States every 18 seconds.
- Public fire departments attended 1,708,000 fires, of which 505,500 occurred in structures, 348,500 occurred in vehicles, and 854,000 occurred in outside properties.
- Nationwide, there was a civilian (non-firefighter) fire death every 130 minutes. There were 4,045 fire deaths, a significant increase of 13.3% from the previous year.
- The majority of fire deaths (85%) occur in home fires. There were 3,420 deaths from fires in the home, an increase of 18.1% from the previous year.
- The civilian fire death rate in the United States was 14.8 deaths per million people.

- Nationwide, there was a civilian fire injury every 23 minutes. There were an estimated 22,350 civilian fire injuries, of which 16,975 occurred in homes.
- Smoking materials were the leading cause of civilian deaths, accounting for roughly one-fourth of the total.

Populations at high-risk of death, injury or burns in fires are the very young, the elderly, and the poor. Based on annual averages for the five-year period from 1994 through 1998, children five and under made up about 9% of the country's population, but accounted for 17% of the home fire deaths. A child's risk of dying in a fire is twice the national average. Adults 65 and older also face a risk twice the average, while people 85 and older had a risk that is almost four-and-a-half times more than average.

The life safety benefits derived from brominated flame retardants (BFRs) in the U.S. were determined (Clarke 1997). Four product classes were identified in which BFRs are widely used and which could be directly associated with fire data: television/appliances, wire/cable insulation, curtains/draperies and upholstered furniture. Using fire data from the National Fire Protection Association (NFPA), BFRs' use in television cabinets (primarily DBDPO) were estimated to save 190 lives annually. For electrical insulation and draperies, less product and fire data were available, but 80 and 10 lives, respectively, were estimated saved annually through the use of BFRs in these products. Again, DBDPO is a major flame retardant used in electrical insulation and in draperies. In total, BFRs are estimated to avoid 280 deaths in the U.S. annually, at a minimum. A large portion of these lives saved are likely attributable to DBDPO. Clarke also found that another 140-220 fire deaths per year could be avoided if upholstered furniture fabrics were backcoated with fire retardant latex as is now done to meet California standards for upholstered furniture.

DBDPO, a solid at room temperature, is a fully brominated (e.g. 10 bromine atoms) diphenyl oxide with a molecular weight of 959.17. The composition of the commercial product is typically ≥ 97% DBDPO with the remainder composed of nonabromodiphenyl oxide. DBDPO's measured water solubility (<0.1 ug/L) and vapor pressure (4.63×10^{-6} Pa) are negligible. DBDPO's solubility in organic solvents is also extremely low: acetone 0.05%, benzene 0.48%, methylene bromide 0.42%, xylene 0.87%, and 0.2% in toluene. DBDPO is often assumed to be lipophilic due its presumed similarity to PCBs. However, no formal fat solubility study has been performed, and pharmacokinetic studies show no appreciable affinity of DBDPO for adipose tissue. DBDPO's blood:liver:adipose ratio in the rat was 1:7:2 compared to Arochlor 1254's ratio of 1:22:359. DBDPO's measured octanol/water partition coefficient (Log K_{ow}) was 6.265, but its Log K_{ow} estimated by EPIwin, v3.4, was 12.61. It is apparent that DBDPO has a very low solubility coefficient in water and most organic solvents. Further, DBDPO's estimated K_{ow} appears to be a better predictor of it behavior in biological systems than its measured value, based on mammalian pharmacokinetic studies and fish bioconcentration data. This is likely due to its very poor solubility in both water and octanol so that any small change in concentration produces a large change in the measured K_{ow} value.

DBDPO has been extensively tested in acute through two year studies. DBDPO was not acutely toxic, was not irritating to the skin or eye, and did not induce skin sensitization in a human patch

test. Repeated dermal application to rabbits' ears did not induce a chloracne-like response. The soot and char combustion products from a high impact polystyrene/DBDPO/antimony trioxide matrix also were not acutely toxic and did not induce a chloracne-like response. Gavage administration of DBDPO (0.1 nmol/kg/day) to rats over 14 days did not induce hepatic cytochrome P450, cytochrome P450 reductase, UDP-glucuronyl-transferase, benzo[a]pyrene hydroxylase, p-nitroanisole demethylase, or EPN detoxification. Taken as a whole, the no-observable-adverse-effect-level (NOAEL) for DBDPO in repeated dose studies is at least 1,000 mg/kg body weight. DBDPO's low toxicity is likely related to its poor absorption and rapid elimination. Pharmacokinetic studies have shown that DBDPO is poorly absorbed (0.3 -2% of an oral dose), has a short half-life (24 hr) compared to PCB 153 (<2% of an oral dose was eliminated by rats in 21 days), can be metabolized, and is rapidly eliminated in the feces (>99% in 72 hr). No adverse effects in either parent or F1 animals were noted in a dietary one-generation reproduction test utilizing doses up to and including 100 mg of a 77% DBDPO mixture/kg body weight. No evidence of maternal or fetal toxicity or developmental effects was detected in a developmental test in the rat (n=25 pregnant females/dose) at 1,000 mg/kg body weight utilizing a composite of today's commercial DBDPO product produced by three manufacturers and administered from days 0 - 19 of gestation. The test article composition was 97.34% DBDPO, 2.66% nona- and octabromodiphenyl oxide. No evidence of a genotoxic effect was detected in the Ames Salmonella, chromosome aberration, mouse lymphoma, or sister chromatid exchange tests. No cytogenic changes were observed in the bone marrow of rats (parents and offspring) undergoing a one-generation reproduction test using a former DBDPO-commercial mixture of 77% purity (Dow FR-BA-300). No evidence of carcinogenicity was observed in female mice receiving 2.5 or 5% DBDPO in the diet (~3,760 or 7,780 mg/kg/d). Equivocal evidence of carcinogenicity was observed in male mice by an increase in the combined incidence of hepatocellular adenomas or carcinomas in both dose groups (~3,200 or 6,650 mg/kg/d); however, this finding may have been influenced by the larger number of early deaths in control male mice compared to the treated male mice. The large number of early deaths in the control males may have decreased expression of hepatocellular adenomas or carcinomas in this group. The combined incidence of hepatocellular adenomas and carcinomas in male mice treated with DBDPO was well within the historical range. Some evidence of carcinogenicity in male and female rats was observed by increased incidences of neoplastic nodules of the liver in low dose (2.5%, ~1,120 mg/kg/d) males and high (5%, ~2,240 mg/kg/d -males, ~2,550 mg/kg/d -females) dose groups of each sex. (The term "neoplastic nodule" is no longer used by NTP to describe hepatoproliferative lesions in rats. This change in nomenclature was made subsequent to a peer review of representative hepatoproliferative lesions from two-year carcinogenicity studies. The peer review found the use of this poorly defined and understood term had permitted some potentially useful drugs and chemicals to be unfairly categorized as carcinogens.) DBDPO is not listed as a carcinogen by NTP, the International Agency for Research on Cancer (IARC) or the U.S. Occupational Safety and Health Administration (OSHA).

Exposure scenarios considered are occupational, the general population through use of consumer goods, and the general population via food or breast milk. Reasonable occupational exposure routes/scenarios are a) inhalation of dust and/or dermal contact at manufacture and b) at formulation prior to encapsulation in polymer or inclusion in the textile dispersion. The most likely point at which exposure could occur during manufacture is when the flame retardant is

transferred into bags for shipping. Likewise, the point at which worker exposure is most likely during formulation into the polymer dispersion is when the bags of DBDPO are emptied into a hopper prior to mixing the dispersion. Once formulated into the polymer dispersion, DBDPO is encased in the polymer matrix and the potential for worker exposure is negligible.

Theoretically, workplace exposure could occur via the dermal or inhalation routes. DBDPO's physical and chemical properties make the probability of systemic absorption following dermal or inhalation exposure very low. DBDPO is a large molecule of high molecular weight (959.17) with negligible water solubility (<0.1 ug/L), and is likely to diffuse through biological membranes only with great difficulty. This assumption is borne out with pharmacokinetic studies that demonstrate DBDPO's poor oral bioavailability (0.3-2% of an oral dose). DBDPO's negligible water solubility and high molecular weight effectively preclude significant skin absorption, and DBDPO's skin absorption is estimated at <<0.03% of a dermally applied dose. DBDPO's vapor pressure (4.63×10^{-6} Pa) is such that volatilization is not expected to be a source of inhalation exposure. Occupational exposures to dusts may occur; however, DBDPO is a large poorly absorbed molecule that exhibits little toxicity, and for which the American Industrial Hygiene Association assigned a Workplace Environmental Exposure Level of 5 mg/kg/d. The combined effects of poor absorption and minimal toxicity (NOAEL μ 1,000 mg/kg/d) indicate adverse effects should not occur as a result of occupational exposure. Nonetheless, workplace controls should focus on points where fine-particle-size-DBDPO may become airborne to limit inhalation exposure. This would be during bagging at manufacture and at formulation prior to inclusion in the resin or polymer dispersion.

Theoretically, the flame retardant textile backcoat could crumble during fabrication of upholstered furniture. Any particles generated would likely be too large to be respirable. In addition, for systemic absorption to occur, not only would the particles need to be inhaled or ingested, but also DBDPO would have to diffuse out of the polymer prior to its absorption. Systemic absorption of significant amounts as a result of crumbling of the backcoat is highly unlikely.

An additional occupational exposure scenario explored in the published literature is electronics recycling and computer repair. A graduate student's research reports the detection of DBDPO, and other polybrominated diphenyl oxide (a.k.a. ether) isomers, in Swedish workers engaged in dismantling electronic equipment and in Swedish computer technicians. The mean DBDPO blood levels, characterized by the original author as "high", were 5 pmol/g lipid in the Swedish electronics recycling workers, and 1.6 pmol/g lipid in the Swedish computer technicians. DBDPO air levels in the recycling workplace were 0.0002 mg/m^3. The DBDPO blood levels were substantially below those of PCB 153 (dismantlers, 760 pmol/g lipid; technicians, 290 pmol/g lipid) measured in the same workers. The electronics dismantling workers' internal DBDPO dose (1.2 ng/kg body weight) based on their measured blood level was comparable to the level expected (0.57 ng/kg body weight) calculated from the measured air levels. A similar comparison was not possible for the computer technicians because air values were not reported for that workplace. The DBDPO air level (0.0002 mg/m^3) measured in the electronics recycling plant was approximately 25,000 times below the AIHA WEEL of 5 mg/m^3. No impact on

human health from DBDPO is expected in either the electronics dismantlers or computer technicians based on available data.

DBDPO is not sold directly to the public, but may be present in various consumer goods. A typical U.S. example is in the cabinet backs of television sets where DBDPO is used at a level of approximately 12% (weight). Upholstered furniture in commercial settings in the U.S. is required to met federal flammability standards and may utilize upholstery textiles that are flame retarded with a backcoating containing DBDPO at ~5 mg/m^2. Residential furnishings, except in the state of California, are not required to met a comparable standard, although the Consumer Product Safety Committee (CPSC) is considering implementing such a standard. CPSC is also considering a standard for mattresses.

Potential consumer exposure could theoretically occur via the dermal or inhalation routes (e.g. from dermal contact with the television cabinet back or upholstery textile or via inhalation of a vapor given off by the appliance). DBDPO's physical/chemical properties make these unlikely exposure scenarios. In infants or small children, another route could be oral through chewing or sucking on the upholstery textile. In addition, exposure to the general population could occur if DBDPO were present in food or in breast milk.

DBDPO's potential risk to the consumer, including children, in the upholstery application was recently reviewed by the National Academy of Sciences (NAS). The NAS evaluated the potential risk to the consumer posed by DBDPO-treated upholstery textiles. In all scenarios evaluated, dermal, oral or inhalation exposure for carcinogenic or non-carcinogenic risks, DBDPO was determined not to present a risk of adverse health effects to the consumer, including children.

A similar conclusion is reached for DBDPO's use in electrical and electronic applications. DBDPO is a large poorly absorbed molecule that exhibits little toxicity. These features coupled with DBDPO's low potential for migration out of plastic resin indicate this use also would not be expected to present a risk of adverse effects to the consumer. Further, the protection provided by DBDPO in terms of enhanced fire safety reduces the very real risk of death or injury that consumers face in the home from fires.

Laboratory studies have shown DBDPO is not bioconcentrated in fish, probably due to its poor solubility and large molecular weight. DBDPO has not been detected in limited sampling of fish and poultry in the U.S., and based on its properties, is not anticipated to be present in these food items or in meat or dairy products. Likewise, leafy vegetables and root crops are not expected to be a source of DBDPO exposure to the general public, and a risk of adverse health effects is not anticipated.

DBDPO transfer to breast milk is likely to be slow and limited, if at all. The combination of low absorption from the gut, rapid elimination in the feces, poor and/or slow diffusion into breast milk should effectively preclude DBDPO in milk. Build-up of concentrations in breast milk is not expected due to its slow diffusion into milk and periodic emptying of breast milk. A risk to the nursing infant is not anticipated based on current information.

Data is available on DBDPO for essentially all VCCEP Tier I, II and III endpoints. The NAS concluded no additional information was needed to evaluate DBDPO's risk to the consumer through the use of flame-retarded upholstery textiles. BFRIP concurs with that assessment, and extend it to DBDPO's use in electrical and electronic equipment as well.

DBDPO SUMMARY FOR NON-TECHNICAL AUDIENCES

The American Chemistry Council's Brominated Flame Retardant Industry Panel (BFRIP) volunteered under the U.S. EPA's Voluntary Children's Chemical Evaluation Program (VCCEP) pilot to prepare the Data Summary for decabromodiphenyl oxide (DBDPO). This compound (CAS No. 1163-19-5) is also known as decabromodiphenyl ether. DBDPO's toxicology has been extensively investigated and information is available on virtually all end-points listed in VCCEP's Tiers I, II and III.

DBDPO was identified for the VCCEP pilot on its assumed detection in human milk (see Table 1, page 81704, Federal Register, Vol. 65, No. 248, December 26, 2000 citing Noren et al. 1998). However, Noren et al. did not report DBDPO in human breast milk, and DBDPO has not been reported in human breast milk in publications appearing prior to or since 1998. Noren et al.'s, and other authors, use of the terminology "PBDEs" rather than specifying the isomers or congeners detected is likely the cause for this error.

DBDPO has been extensively tested for toxicity and exhibits minimal effects. These tests have shown that DBDPO is not toxic in a single large dose nor does it induce gene mutations. Tests have also shown DBDPO is not toxic to the developing embryo and fetus and does not interfere with reproduction. No harmful effects were seen in studies where DBDPO was repeatedly administered to rats and mice in doses of at least 1,000 mg/kg every day for several months. This is roughly equivalent to someone weighing ~150 pounds swallowing ~2.5 ounces of DBDPO every day for many years throughout his or her life or to a 44 pound child consuming about 0.7 ounces of DBDPO every day.

One reason that DBDPO has such little toxicity is that it is minimally absorbed into the body. Studies in rats show they absorb only 0.3 – 2% of the DBDPO added to their feed. DBDPO's low absorption leads to its quick elimination in the feces. More than 99% of a given dose exits the body in the feces within 72 hours. Because of this, DBDPO does not accumulate, or build-up, in the body.

DBDPO is used solely as a flame retardant to prevent or delay ignition in burnable materials. DBDPO's main application is in high impact polystyrene (HIPS) used for electronic enclosures, e.g. television set cabinet backs. A comparatively minor, but important, use of DBDPO is to flame retard upholstery fabric where it is applied to the back of the fabric encapsulated in latex. At a minimum, an estimated 280 deaths are avoided in the U.S. every year because of the use of brominated flame retardants in the applications where DBDPO is used.

Fires in the United States are a serious problem with our country having one of the highest fire incidence and mortality rates in developed nations. The National Fire Protection Association reports that in the year 2000:

- A fire department responded to a fire somewhere in the United States every 18 seconds.
- Public fire departments attended 1,708,000 fires, of which 505,500 occurred in structures, 348,500 occurred in vehicles, and 854,000 occurred in outside properties.

- Someone died in a fire in the United States every 130 minutes. There were 4,045 fire deaths, a significant increase of 13.3% from the previous year. This death rate was for civilians only and did not include firefighters.
- People are at greatest risk of death and injury from a fire in their homes – 85% of fire deaths occur at home. There were 3,420 deaths from fires in the home, an increase of 18.1% from the previous year.
- The civilian fire death rate in the United States was 14.8 deaths per million people.
- Someone was injured in a fire in the United States every 23 minutes. There were an estimated 22,350 civilian fire injuries, of which 16,975 occurred in homes. This injury rate was for civilians only and did not include firefighters.
- Smoking materials were the leading cause of civilian deaths, accounting for roughly one-fourth of the total.

Those at high-risk of death, injury or burns in fires are children, the elderly, and the poor. Fires are a leading cause of unintentional injury-related death among children in the United States. Each year, more than 600 children ages 14 and under die, and nearly 47,000 are injured, in fires. Based on annual averages for the five-year period from 1994 through 1998, children five and under made up about 9% of the country's population, but accounted for 17% of the home fire deaths. A child's risk of dying in a fire is twice the national average. Adults 65 and older also face a risk twice the average, while people 85 and older had a risk that is almost four-and-a-half times more than average.

The circumstances surrounding the potential for a deadly fire have changed in the last few decades. Today's homes and businesses store more contents than in the past - the fire load in a typical home has more than doubled in the past 50 years on a pound per square foot basis. Furnishings are often constructed of synthetics that are made from petrochemicals and that can actually enhance a fire's growth. Homes and offices are also more energy efficient and hold heat better than in the past and this also can enhance the seriousness of a fire. This combination of more synthetic materials and higher energy efficiency increases the risk of a serious fire, if a fire starts.

These factors have intensified the need for flame retardancy in many applications, especially electrical and electronic products such as television sets, computers, and wire and cable that combine a potentially flammable plastic with a source of ignition (e.g. electricity). Flame retardants can reduce the risk of death or injury in fires by preventing or delaying ignition, reducing the rate the fire releases heat, reducing the quantity of toxic gases produced, and increasing the time available to leave the burning building. Studies have shown that flame retardants can increase the time available to escape a burning building by a factor of 15. In a fire where every second counts, this can literally mean the difference between life and death.

The U.S. National Academy of Sciences (NAS) concluded DBDPO did not present a health risk to consumers, including children, when used in upholstery textiles. NAS did not review DBDPO's use in electrical and electronic products, but one can draw a similar conclusion about these uses by considering DBDPO's properties and toxicology. DBDPO is a large poorly absorbed molecule that has been shown to cause little toxicity. When used in television cabinet

backs, it is part of a dense hard plastic with minimal possibility of exposure to the user. The combination of these factors indicates DBDPO's use in electrical and electrical products would not be expected to be a health risk to consumers, including children. Further, the protection provided by DBDPO in terms of enhanced fire safety reduces the very real risk of death or injury one faces in the home.

Two other exposure possibilities are food and breast milk. Laboratory studies have shown DBDPO is not absorbed to any significant amount in fish. This is probably due to its poor solubility and large molecular weight. DBDPO has not been detected in limited sampling of fish and poultry in the U.S., and based on its properties, is not anticipated to be present in these foods or in meat or dairy products. Likewise, vegetables and root crops like lettuce or potatoes are not expected to be an exposure source because plants would not absorb DBDPO. This, coupled with DBDPO's very limited toxicity, indicates negligible health risk due to food exposure.

DBDPO's very poor absorption means that the nursing mother would have negligible amounts to pass on to her infant. Also, DBDPO is such a large molecule that transfer to breast milk, if it occurs at all, will be slow and limited and build-up of concentrations in breast milk is not expected. Taken together, the combination of poor absorption by the nursing mother, and poor and/or slow movement into breast milk should effectively preclude DBDPO in milk. A risk to the nursing infant is not anticipated.

Occupational exposure to DBDPO dust could occur when DBDPO is bagged at the manufacturer or when the user empties the bags. The American Industrial Hygiene Association (AIHA) established a Workplace Environmental Exposure Level (WEEL) of 5 mg/m^3. This was based on DBDPO's toxicology and is equivalent to a nuisance dust. A WEEL is the level that workers could be exposed to every day with the expectation of no harmful effects. Inhalation of vapor and absorption through the skin are not realistic sources of occupational exposure to DBDPO due to its negligible vapor pressure and predicted skin absorption. Theoretically, the flame retardant textile backcoat could crumble during fabrication of upholstered furniture, but absorption of significant amounts as a result of crumbling of the backcoat is highly unlikely.

In conclusion, DBDPO has undergone extensive testing and shows minimal toxicity. No additional tests are proposed. DBDPO's toxicology is such that harmful effects to workers, the general public or children are not anticipated. DBDPO provides significant benefits to consumers and their children by lessening the very real danger presented by fires in the home.

1.0 INTRODUCTION

The Brominated Flame Retardant Industry Panel (BFRIP) was formed in the 1980s to address issues related to the brominated flame retardants that its members manufacture in common, conduct research, and interact with regulatory agencies and other interested parties. Its members, who are global manufacturers of brominated flame retardants, are Albemarle Corporation, Ameribrom Inc. (a subsidiary of Dead Sea Bromine Group), and Great Lakes Chemical Corporation. Akzo-Nobel is an associate member. BFRIP, organized under the American Chemistry Council, volunteered under the U.S. EPA's Voluntary Children's Chemical Evaluation Program (VCCEP) pilot to prepare the Data Summary for decabromodiphenyl oxide (DBDPO). This compound (CAS No. 1163-19-5) is also known as decabromodiphenyl ether. As discussed below, DBDPO is a data-rich chemical having valid guideline studies or other information for all Screening Informational Data Set (SIDS) endpoints.

DBDPO was included in the VCCEP pilot on the basis of its detection in human milk (see Table 1, page 81704, Federal Register, Vol. 65, No. 248, December 26, 2000 citing Noren et al. 1998). However, Noren et al. did not report DBDPO in human breast milk, and DBDPO has not been reported in human breast milk in publications appearing prior to or since 1998. Noren et al.'s, and other authors, use of the terminology "PBDEs" rather than specifying the isomers or congeners detected is likely the cause for this error. BFRIP volunteered to sponsor DBDPO under the VCCEP pilot in an effort to rectify this, and to provide a publicly accessible summary of DBDPO's toxicology.

2.0 STRUCTURE AND PROPERTIES

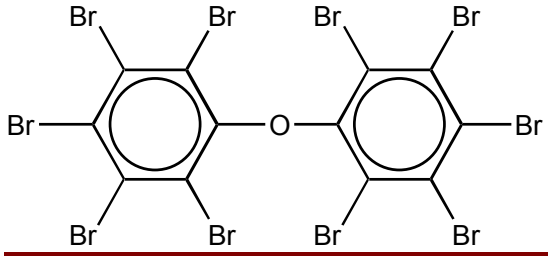

Figure 1. Decabromodiphenyl oxide (DBDPO).

DBDPO, a solid at room temperature, is a fully brominated (e.g. 10 bromine atoms) diphenyl oxide with a molecular weight of 959.17 (Figure 1). The composition of the commercial product is typically ≥ 97% DBDPO with the remainder composed of nonabromodiphenyl oxide. DBDPO's measured water solubility (<0.1 ug/L) (Stenzel and Markley 1997) and vapor pressure (4.63×10^{-6} Pa) (Stenzel and Nixon 1997) are negligible. DBDPO's solubility in organic solvents is also extremely low: acetone 0.05%, benzene 0.48%, methylene bromide 0.42%, xylene 0.87%, and 0.2% in toluene (WHO 1994; Norris et al. 1973). DBDPO is often assumed to be lipophilic due its presumed similarity to PCBs (Hardy 2002a). However, no formal fat solubility study has

been performed, and pharmacokinetic studies show no appreciable affinity of DBDPO for adipose tissue. Using NTP's (1986) pharamacokinetic data, DBDPO's blood:liver:adipose ratio in the rat was 1:7:2 compared to Arochlor 1254's ratio of 1:22:359 (Kodavanti et al. 1998). DBDPO's measured octanol/water partition coefficient (Log K_{ow}) was 6.265 (Macgregor and Nixon 1997), but its Log K_{ow} estimated by EPIwin, v3.4, was 12.61 (Meyland and Howard 1999). It is apparent that DBDPO has a very low solubility coefficient in water and most organic solvents. Further, DBDPO's estimated K_{ow} appears to be a better predictor of it behavior in biological systems than its measured value, based on mammalian pharmacokinetic studies and fish bioconcentration data. This is likely due to its very poor solubility in both water and octanol so that any small change in concentration produces a large change in the measured K_{ow} value.

The DBDPO commercial product has been analyzed for trace quantities of 15 2,3,7,8-substituted polybrominated-p-dibenzodioxins (PBDD) and dibenzofurans (PBDF) under a U.S. Environmental Protection Agency (EPA) test rule. None of the analytes were present at or above the quantitation limits established by the agency (Ranken et al. 1994). Resins containing DBDPO have also been analyzed for PBDD/PBDF content. A high impact polystyrene (HIPS) resin containing antimony trioxide and DBDPO was molded using normal (215-220℃; 30 sec.), abusive (235-245℃; 5 min.) or extreme (265-270℃, 7 min.) processing conditions (McAllister et al. 1990). The molded resin was cryogenically ground and analyzed for six 2,3,7,8-substituted PBDD/PBDFs. None were detected. Polybutyleneterephthalate (PBT) resin containing antimony trioxide and DBDPO was also molded under similar conditions, and analyzed. No 2,3,7,8-substituted PBDD/PBDFs were detected. Donnelly et al. also analyzed molded HIPS/DBDPO/Sb2O3 and molded PBT/DBDPO/Sb2O3, and detected no 2,3,7,8-TBDF and no 1,2,37,8-PeBDF. Brenner and Knies (1990) also reported no PBDDs in their analysis of an extruded PBT/DBDPO blend. Virgin molded HIPS/DBDPO/Sb2O3 and repeatedly ground and injection molded (e.g. "recycled") HIPS/DBDPO/Sb2O3 resins meet the requirements of the German Chemicals Banning Ordinance with respect to 2,3,7,8-substituted PBDD/F content (Hamm 1999; Hamm et al. 2001). The concentrations of relevant PBDD/F congeners were at least one order of magnitude below the regulated limit values for PBDD/F (1 ppb for the sum of four congeners, 5 ppb for the sum of all eight regulated congeners).

The DBDPO product is one of three commercial polybrominated diphenyl oxide (a.k.a. ether) products manufactured, and accounts for approximately 83% of all polybrominated diphenyl oxide/ether (e.g. "PBDE") production. The other two commercial polybrominated diphenyl oxide/ether products are known as octabromodiphenyl oxide/ether (OBDPO, CAS# 32536-52-0) and pentabromodiphenyl oxide/ether (PeBDPO, CAS# 32534-81-9) and are listed in the VCCEP's pilot. OBDPO, a mixture of brominated diphenyl oxide congeners ranging from nona- to hexa-, is used to flame retard business equipment constructed of acrylonitrile-butadiene-styrene (ABS) plastic. PeBDPO, a highly viscous liquid composed of tetra-, penta- and hexaBDPO congeners, is used to flame retard polyurethane foam that is used as cushioning in upholstery.

3.0 APPLICATIONS

DBDPO is used solely as a flame retardant for the purpose of preventing or delaying ignition in combustible materials (See Sections 3.1-3.6 for information on the fire hazard in the U.S. and Apppendix I for information on the importance of flame retardants in today's plastics). DBDPO's flame retardant activity is derived from its bromine content. Bromine is one of the few elements able to provide flame retardancy in the gas phase; certain plastics require a flame retardant active in the gas phase due to the way they burn. DBDPO's high bromine content makes it very effective as a flame retardant that in turn makes it extremely cost-effective. As a result, DBDPO is the second largest volume brominated flame retardant in production and use. Global market demand in 1999 for DBDPO was estimated at 54,800 metric tons (BSEF 2001). Market demand, 1999, for DBDPO in the regions of the America's, Europe and Asia was 24,300, 7,500 and 23,000 metric tons, respectively (BSEF 2001). These regional differences reflect differences in the location of end product manufacture. Two companies manufacture DBDPO in the U.S. Production facilities of both manufacturers are located in Arkansas to take advantage of the underground brine fields as a source of bromine.

DBDPO's main application is in high impact polystyrene (HIPS) used for electronic enclosures, e.g. television set cabinet backs (Hardy 2002b). A comparatively minor, but important, use of DBDPO is to flame retard upholstery fabric where it is applied as a fabric back coat encapsulated in latex (Hardy 2002b). DBDPO's potential risk to the consumer, including children, in the upholstery application was recently reviewed by the United States National Academy of Sciences (NAS 2000). DBDPO is not used to flame retard children's clothing or sleepwear.

3.1 U.S. Fire Risks

Fires in the United States are a serious problem. The U.S. has one of the highest fire incidence and mortality rates of all developed countries. This is despite all our modern efforts including fire departments, building codes, fire drills, fire alarms, smoke detectors, fire sprinklers, fire extinguishers, UL ratings, and flame retardants.

The National Fire Protection Association (NFPA 2001) reports that in the year 2000:

- Every 18 seconds, a fire department responded to a fire somewhere in the United States.
- Public fire departments attended 1,708,000 fires, of which 505,500 occurred in structures, 348,500 occurred in vehicles, and 854,000 occurred in outside properties.
- Nationwide, there was a civilian (non-firefighter) fire death every 130 minutes. There were 4,045 fire deaths, a significant increase of 13.3% from the previous year.
- About 85% of all fire deaths occurred in home fires. There were 3,420 deaths from fires in the home, an increase of 18.1% from the previous year.
- The civilian fire death rate in the United States was 14.8 deaths per million people.
- Nationwide, there was a civilian fire injury every 23 minutes. There were an estimated 22,350 civilian fire injuries, of which 16,975 occurred in homes.
- Smoking materials were the leading cause of civilian deaths, accounting for roughly one-fourth of the total.

3.2 Basic Fire Concepts

Fire is dark. In television and movies, fire is often portrayed as a bright light, but the fire environment is actually pitch black due to the dense smoke produced. Escape plans must be memorized (USFA 2002; Education World 2002).

Smoke from fire kills. Fire victims typically succumb to smoke inhalation before flames reach them. More fire deaths occur when people are sleeping—between 2 a.m. and 6 a.m (USFA 2002; Education World 2002).

Many people believe – falsely - that they would awaken in a fire. But toxic gases, typically carbon monoxide, actually put people into a deeper sleep (USFA 2002; Education World 2002).

Fire is intensely hot. This might seem obvious, but few understand that fire can cause the temperature to rise *several hundred degrees* in seconds. That degree of heat can prompt the human body to stop functioning and lose consciousness, making escape impossible (USFA 2002; Education World 2002).

Fire is fast. A home can be completely consumed by fire in less than five minutes. In less than 30 seconds a small flame can get completely out of control and turn into a major fire. It takes only minutes for thick black smoke to fill a house. Time is the biggest enemy and every second counts (USFA 2002; Education World 2002).

Flame retardants prevent or delay ignition, reduce the rate of heat release, reduce the quantity of toxic gases generated, and increase the time available for escape. Studies have shown that flame retardants can increase escape time by a factor of 15. In a fire where every second counts, this can literally mean the difference between life and death. See Section 3.5 for additional information.

3.3 Children and Elderly at High Risk of Death and Injury in Fires

Populations at high-risk of death, injury or burns in fires are the very young, the elderly, and the poor (NSKC 2002; Stevens and Mann 1999). Based on annual averages for the five-year period from 1994 through 1998, children five and under made up about 9% of the country's population, but accounted for 17% of the home fire deaths. A child's risk of dying in a fire is twice the national average. Adults 65 and older also face a risk twice the average, while people 85 and older had a risk that is almost four-and-a-half times more than average.

3.4 Why Children Are at Special Risk in Fires

Fires are a leading cause of unintentional injury-related death among children in the United States. Each year, more than 600 children ages 14 and under die, and nearly 47,000 are injured, in fires (NSKC 2002).

Picture a fire from a child's point of view: smoke and flames suddenly sweep through his room. It is dark, hot, loud and scary. A large stranger comes in, wearing equipment that makes him

look like a monster or an alien – or worse. Children's first instincts are often to hide from things that frighten them. But in the case of a fire, those instincts can be deadly (NSKC 2002).

Kids are at grave risk of injury and death from residential fires because they have less control of their environment than adults and limited ability to react appropriately. More than 40 percent of residential fire-related deaths among children ages 9 and under occur when the child is attempting to escape, is unable to act or is acting irrationally. Although an escape plan may help to reduce these deaths, only 26 percent of households have developed and practiced a plan (NSKC 2002).

The youngest children are at greatest risk. Children ages 5 and under are more than twice as likely to die in a fire as the rest of the population. More than half of the children in this age group who die are asleep at the time of the fire, and another one-third of them are too young to react appropriately (NSKC 2002).

Older children are often at risk due to their own curiosity. Studies indicate that an estimated 38 percent of children ages 6 to 14 have played with fire at least once. Child-play home fires tend to begin in a bedroom where children are left alone. Children playing with matches or lighters start 80 percent of these. Boys are nearly twice as likely as girls to play with fire (NSKC 2002).

Other risk factors especially related to children include the following. Children in homes without working smoke alarms are at the greatest risk. Households without working smoke alarms are approximately two and a half times more likely to experience a fire in their homes (NSKC 2002).

Home cooking equipment is the leading cause of residential fires and fire-related injuries. However, residential fires caused by smoking materials (i.e. cigarettes) are the leading cause of fire-related death, accounting for nearly 23 percent of all fatalities (NSKC 2002).

Home fires and fire-related deaths are more likely to occur during the cold weather months December through February, when there is a significant rise in the use of portable or area heating equipment such as fireplaces, space heaters and wood stoves (NSKC 2002).

Children living in rural areas have a dramatically higher risk of dying in a residential fire. Death rates in rural communities are more than two times higher than in large cities, and more than three times higher than in large towns and small cities (NSKC 2002).

3.5 Flame Retardants – Protection Through Prevention

Years ago, most combustible building contents were made of cellulosic materials commonly found in nature (Leihbacher 1999). Chairs and tables were made of wood, sofas and bedding with cotton batting and jute, carpeting with wool and cotton fibers, and draperies with linen and other natural materials. Rapidly spreading fires were uncommon and generally indicated the use of a petroleum-based accelerant like gasoline. Today, the furnishings in homes and businesses include those constructed of petrochemicals such as polyurethane foams and rigid polystyrene

plastic. These materials can behave in a fire as if they have built-in-accelerant, and can produce quantities of heat exceeding those of ordinary combustibles.

Another change from the past is that today's buildings and homes have more contents. The fire load in residential structures has more than doubled in the past 50 years on a pound per square foot basis (Leihbacher 1999). Flashover, when the room bursts into flame and the most dangerous time of a fire, has become more common as a result of the greater fire load and the use of synthetic furnishings. Synthetics, especially foams and plastics, produce more heat than natural products - the heat produced by burning foams and plastics can approach that of highly volatile flammable liquids. This contributes to the development of flashover so that flashover now occurs rapidly - generally within 3-10 minutes after ignition. Flashover is caused by the radiation feedback of heat. Heat from the growing fire is absorbed into the upper walls and contents of the room, heating combustible gases and furnishings to their auto-ignition temperature. This build up of heat in the room triggers flashover. Flashover signals the end of an effective search and rescue in a room; it means the death of any person trapped in the blazing room — either civilians or firefighters. Flashover signals the change from a contents to a structure fire and the beginning of the structural collapse danger.

Another change in modern buildings and homes is increased energy efficiency (Leihbacher 1999). Buildings are designed to hold heat inside in the winter and exclude heat in the summer. Over the last 20 years new energy-efficiency standards have come into effect, and better and more insulation of walls, floors, ceilings, roofs, and windows has occurred. This higher energy efficiency influences the building's behavior in the event of a fire. Energy efficient upper walls and ceilings are less able to conduct heat away from the fire room, resulting in a higher temperature fire in the room of origin. Energy efficient thermal pane windows are more break resistant than older window types, and are less likely to break and vent the fire's heat outdoors. The net result of enhanced energy efficiency, in the event of a fire, is rooms that burn hotter and hold heat better.

The combination of higher energy efficiency and a greater quantity of synthetic materials increases the potential for a serious fire if ignition occurs (Leihbacher 1999). Thus, the extensive use of synthetic polymers has intensified the need and concern for flame retardancy in many applications. Flame retardants are especially useful for flammable foams and plastics where they act to delay ignition and slow flame spread. Flame retarded products also generate a lower rate of heat release once ignited which in turn influences the development of flashover. A slower rate of heat release also lowers the quantity of toxic gases produced. These factors all translate into longer escape times for occupants - the use of flame retardants can increase escape times by a factor of 15 (FRCA 1987; Babrauskas et al. 1988) – and provide life safety benefits (Clarke 1997).

The life safety benefits derived from the use of brominated flame retardants (BFRs) in the U.S. were determined using fire data from the National Fire Protection Association (NFPA) (Clarke 1997). Four product classes were identified in which BFRs are widely used and which could be directly associated with fire data: television/appliances, wire/cable insulation, curtains/draperies and upholstered furniture. An estimated 190 lives are saved annually through the use of BFRs

(e.g. DBDPO) in television cabinets. For electrical insulation and draperies, less product and fire data were available, but 80 and 10 lives, respectively, were estimated saved annually through the use of BFRs in these products. Again, DBDPO is a major flame retardant used in electrical insulation and in draperies. Thus, an estimated 280 deaths are avoided each year in the U.S. due to the use of BFRs. A large portion of these lives saved are likely attributable to DBDPO. Another 140-220 fire deaths per year could be avoided if upholstered furniture fabrics were backcoated with BFR-latex as is now done to meet California standards for upholstered furniture.

3.5 Sources of Additional Information on Fires and Their Impact

Additional information on fires in the U.S. and their impact on children can be found on the following websites. This is only a partial list and there are many other excellent sources of information on this topic. The State Fire Marshall in each of the 50 states can also provide information on the local situation as well as educational tools and services.

The United States Fire Administration (USFA): www.usfa.fema.gov.

The USFA's Kid's Page: www.usfa.fema.gov/kids.

National Fire Protection Association (NFPA): www.nfpa.org.

Consumer Product Safety Commission (CPSC): www.cpsc.gov.

International Association of Fire Chiefs: www.iafc.org.

Education World, Lesson Planning, Fire Safety Activities: www.education-world.com.

National Safe Kids Campaign: www.safekids.org.

4.0 DBDPO HAZARD ASSESSMENT

4.1 Mammalian Toxicology (VCCEP Tiers I, II, and III)

DBDPO has undergone extensive testing in mammalian species (Table 1). All studies were performed using a commercial DBDPO product unless otherwise stated. In brief, the studies show that DBDPO is not acutely toxic or mutagenic, and is not a developmental or reproductive toxicant. The NOAEL for DBDPO in subchronic and/or chronic studies in the rat or mouse is at least 1,000 mg/kg/d. DBDPO's low toxicity is likely related to its poor absorption and rapid elimination (NTP 1986). Pharmacokinetic studies have shown that DBDPO is poorly absorbed (0.3 -2% of an oral dose), has a short half-life (24 hr) compared to PCB 153 (<2% of an oral dose was eliminated by rats in 21 days), can be metabolized, and is rapidly eliminated in the feces (>99% in 72 hr) (NTP 1986; Norris et al. 1973, 1975; El Dareer et al. 1987; Moreck and Klassen-Wheler 2001).

4.1.1 Acute Toxicology (Tier I)

TABLE 1. DBDPO Mammalian Toxicology Summary.

TEST	RESULTS
Water Solubility +	< 0.1 ug/L (Stenzel and Markley 1997)
Vapor Pressure+	4.63 x 10-6 Pa (Stenzel and Nixon 1997)
Octanol/Water Partition Coefficient +	6.265 (measured) (MacGregor and Nixon 1997)
Rat Oral LD50	> 2,000 mg/kg (Norris et al. 1973)
Rabbit Dermal LD50	> 2,000 mg/kg (Great Lakes 1974b)
Rat Inhalation LC50	> 48.2 mg/L (Great Lakes 1974c)
Rabbit Eye Irritation	Not an irritant (Great Lakes 1974e)
Rabbit Skin Irritation	Not an irritant (Norris et al. 1973, 1974)
Human Skin Sensitization	Not a skin sensitizer (Norris et al. 1973, Industrial Biotest 1975)
Ames+	Not mutagenic (Wagner and Klug 1998)
Mouse Lymphoma*	Not mutagenic (NTP 1986)
Sister Chromatid Exchange*	Did not induce (NTP 1986)
Chromosome Aberration*	Did not induce aberrations (NTP 1986)
14 Day Rat & Mice Oral (Diet)*	NOEL $\geq$ 100,000 ppm (10% of diet or ~ 10,000 mg/kg/d) (NTP 1986)
90 Day Rat & Mice Oral (Diet)*	NOEL $\geq$ 50,000 ppm (5% of diet or ~5,000 mg/kg/d) (NTP 1986)
30 Day Rat (Diet)**	NOEL = 0.01% (8 mg/kg/d) (Norris et al. 1973, 1974, 1975)
Rat 1 Generation Reproduction**	NOEL $\geq$ 100 mg/kg/d (highest dose tested) (Norris et al. 1975)
Rat Developmental, Days 0-19 Gestation* +	NOEL $\geq$ 1,000 mg/kg/d (maternal & fetal) (Hardy et al. 2002)
Rat Developmental, Days 6-15 Gestation**	NOEL ≥ 1,000 mg/kg/d (maternal) NOEL = 100 mg/kg/d (fetal) (Norris et al. 1973, 1974, 1975)
Rat & Mouse Carcinogenicity (Diet)*	25,000 (2.5%) or 50,000 (5%) ppm for 2 years (~3,200 – 7,780 mg/kg/d Mice; ~1,120 – 2,550 mg/kg/d Rats) Negative, equivocal or some evidence of carcinogenicity No effect body weight or mortality Minimal evidence of chronic toxicity (NTP 1986)
Rat Carcinogenicity (Diet)**	NOEL $\geq$ 1 mg/kg/d for 2 years (highest dose tested) (Kociba et al. 1975)
Rat Hepatic Enzyme Induction	Did not induce hepatic enzymes: cytochrome P450, cytochrome P450 reductase, UDP-glucuronyl-transferase, benzo[a]pyrene hydroxylase, p-nitroanisole demethylase, or EPN detoxification. (Carlson 1980)
Rabbit Skin Acnegenicity	Not acnegenic; Soot and char not acnegenic (Pinkerton et al 1989)
Rat Pharmacokinetics (Oral & IV)*	Poorly absorbed (<0.3-2%) from GI tract Rapidly Eliminated (>99% in 72 hours) Half life < 24 hours (NTP 1986; El Dareer et al 1987)

*Test article 94-99% DBDPO.
** Test article only 77% DBDPO.
+Studies Performed under Good Laboratory Practices and using today's commercial DBDPO product as test article.

DBDPO was not acutely toxic, was not irritating to the skin or eye of rabbits, and did not induce skin sensitization in a human patch test (Norris et al. 1973, 1974, 1975; NTP 1986). The $LD50_{oral,\ dermal}$ in rats and rabbits, respectively, was > 2,000 mg/kg. The rat 1 hr $LC50_{inhalation}$ was > 48.2 mg/L. The soot and char combustion products of a DBDPO plastic matrix were also not acutely toxic (Pinkerton et al. 1989).

4.1.1.1 Acute Studies

Intragastric intubation of a single dose of a 10% corn oil suspension of DBDPO (Dow FR-300-BA: 77.4% DBDPO, 21.8% NonaBDPO and 0.8% OBDPO) to female Sprague Dawley rats resulted in the survival of all rats at doses of 126, 252, 500, 1,000 or 2,000 mg/kg. No indication of toxicity after intubation or during the 14-day period was observed. No gross pathological changes were observed at necropsy carried out on one rat/dose level (Norris et al., 1973).

Groups of 2 male and 2 female New Zealand White rabbits were administered single doses of 200 or 2,000 mg/kg of DBDPO (DE-83) applied neat under occlusive wraps for 24 hours: all the animals survived. Animals were observed for 14 days. At the 2,000 mg/kg dosage level all rabbits exhibited normal body weight gains. Local and general signs of toxicity were not reported and necropsies not performed (Great Lakes 1974b).

Groups of 5 male and 5 female Spartan rats were exposed for one hour to 2 or 48.2 mg/l DBDPO (DE-83) in air and subsequently observed for 14 days. All rats survived. Dyspnea and ocular discharge were noted from 2 mg/l concentration (one animal); moreover, in the 48.2 mg/l group, eye squint and increasing motor activity were observed. All rats were normal at the end of 14-day-observation period. Necropsies were not performed (Great Lakes 1974c).

Norris et al. (1973 and 1974) reported that DBDPO applied as dry solid on shaved skin of New Zealand albino rabbits caused essentially no response on intact skin and a slight erythematous and edematous response on abraded skin after a single confined exposure of 24 hours. Repeated exposures to intact skin for five days/week for two weeks and to abraded skin for three days did not alter the responses observed following a single administration.

DBDPO as dry solid (500 mg), cause no irritation on intact or abraded skin when applied to shaved skin under occlusion to 2 groups of 3 New Zealand White rabbits. No erythema or edema was observed after a single exposure for 24h and followed by an observation period of 72h (Great Lakes 1974d).

Studies with 3 male and 3 female New Zealand White rabbits showed that 100 mg DBDPO (93 - 98.5% purity) as dry solid caused transient (reversible in 48h) mild irritation of the conjunctival membranes. The cornea, iris and lens were unaffected (Great Lakes 1974e). This study was carried out in accordance with the GLP procedures.

4.1.1.2. Human Sensitization

In 50 human subjects, repeated application of a suspension of 5% DBDPO in petrolatum 3 times a week for 3 weeks and challenged two weeks subsequent to the last induction application did not result in skin sensitisation. Skin irritation was observed in 9 out of the 50 persons (Norris et al., 1974; WHO, 1994).

Human volunteers (80 males and 120 females) were treated with 9 induction patches of 2 batches of DBDPO. The first sample was evaluated as received, and the second as a 2% (w/v) aqueous solution. The patches were applied once every 2 days, allowed to contact the skin for 24h, and the skin was graded for irritation. Fifteen (15) subjects among the 200 volunteers showed some slight irritation reactions: very slight erythema - barely perceptible in 14/1,800 patches and mild – well defined erythema in 2/1,800 patches and very slight edema – barely perceptible in 1/1,800 patches. After a non-patching period of 12 days, the challenge patch was applied to detect sensitisation. No evidence of skin sensitisation with either of the test materials in any of the subjects tested was observed (Industrial Bio-Test Laboratories, 1975).

4.1.1.3 Soot and Char Combustion Products

The soot and char combustion products from a high impact polystyrene/DBDPO/antimony trioxide matrix also were not acutely toxic in rats (LD_{50} > 2,000 mg/kg) (Pinkerton et al. 1989). Six groups of 5 male and female Sprague-Dawley rats were treated with a single dose via gavage in 1% methylcellulose with 0, 0.5, 5, 50, 500 or 2,000 mg/kg of the combined soot and char generated from the combustion of a DBDPO/high impact polystyrene/antimony trioxide matrix and observed for 28 days. No animals died during the study and clinical signs of toxicity were observed. No histologic lesions were detected in the examined organs – thyroid, parathyroid, adrenal gland, spleen, gonads, heart, liver, lung, brain, kidneys and thymus. The $LD50_{oral}$ of the soot and char combustion products of a high impact polystyrene/DBDPO/antimony trioxide matrix was > 2,000 mg/kg body weight (Pinkerton et al. 1989). Based on these results, toxicologically significant amounts of polybrominated dioxins or polybrominated dibenzofurans were not present in the soot and char, or if present, were not biologically available.

4.1.2 Repeated Dose Toxicology (VCCEP Tiers I and II)

DBDPO administered at 10% and 5% of the diet for 14 and 90 days, respectively, produced no adverse effects in F344/N rats and $B6C3F_1$ mice (NTP 1986).

4.1.2.1 U.S. NTP 14-Day Repeated Dose Studies in Rats and Mice (1986) (Tier I)

Groups of five males and five females were fed diets containing 0, 5,000, 10,000, 20,000, 50,000 or 100,000 ppm DBDPO for 14 days. Male and female F344/N rats and B6C3F1 mice were obtained from Charles River Breeding Laboratories and held for approximately 3 weeks before the studies began. Animals were assigned to groups such that cage weights were approximately equal at initiation of the study. Animals were housed 5 per cage (polycarbonate) on heat-treated hardwood chips. Formulated or control diets and water were available ad libitum. The formulated diets were checked for homogeneity and correctness of concentration.

Rats and mice were observed daily for clinical signs of toxicity and were weighed on days 1, 7 and 14. A necropsy was performed on all animals in all doses. Organs examined at the gross necropsy included gross lesions, skin, mandibular lymph nodes, mammary glands, salivary glands, thigh muscle, sciatic nerve, sternebrae, femur or vetebrae including marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, tissue masses, ileum, colon, cecum, rectum, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary gland, spinal cord and eyes.

DBDPO doses up to 10% (100,000 ppm) of the diet in F344/N rats and $B6C3F_1$ mice produced no mortality, no effect on body weight, and no compound-related clinical signs or gross pathologic effects (histopathology was not performed). The test article in the 14 day study was 99% pure DBDPO.

4.1.2.2 U.S. NTP 13-Week Repeated Dose Studies in Rats and Mice (1986) (Tier II)

In the 13-week study, DBDPO doses up to 5% of the diet in F344/N rats (n = 10 rats/sex/dose) and $B6C3F_1$ mice (n = 10 mice/sex/dose) produced no mortality, no effect on body weight, and no compound related gross or microscopic pathologic effects. The dietary dose levels were 0, 3, 100, 6,200, 12,500, 25,000 or 50,000 ppm DBDPO and were fed for 13 weeks.

Four-week-old male and female F344/N rats and 5-wek-old B6C3F1 mice were obtained from Charles River Breeding Laboratories, observed for 4 weeks, and assigned to cages according to a table of random numbers. The cages were then assigned to dosed and control groups according to another set of random numbers. Animals were housed five per cage (polycarbonate) on heat-treated hardwood chips. Formulated or control diets and water were available ad libitum. The formulated diets were checked for homogeneity and correctness of concentration. Animals were checked twice daily; moribund animals were sacrificed. Feed consumption was measured weekly by cage. Animal weights were recorded weekly. Clinical signs and behavior was recorded weekly. At the end of the 13-week studies, survivors were sacrificed and a necropsy was performed on all animals. Approximately 30 tissues were examined histologically in the control and high dose groups: gross lesions and tissue masses, mandibular or mesenteric lymph nodes, salivary gland, sternebrae, femur or vertebrae including marrow, thyroid, parathyroids, small intestine, colon, liver, gallbladder (mice), prostate/testes or ovaries/uterus, lung and mainstem bronchi, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, spinal cord (if neurologic signs present), eyes if grossly abnormal), and mammary gland. The test article used in this study consisted of two lots of DBDPO; one lot was that used in the 14 day study and the second was ~97% pure DBDPO.

4.1.2.3 U.S. NTP Two Year Studies in Rats and Mice (1986) (Tier III)

Doses of 2.5 or 5% DBDPO in the diet for two years (103 weeks) were also well tolerated by F344/N rats (n=50 rats/sex/dose) and $B6C3F_1$ mice (n=50 mice/sex/dose) with no effect on body

weight or mortality and only minimal evidence of organ effects (NTP 1986). The U.S. National Toxicology Program (NTP) estimated the average amount of DBDPO consumed per day in the two year study to be 1,120 mg/kg and 2,240 mg/kg for low and high dose male rats, respectively, and 1,200 mg/kg and 2,550 mg/kg for low and high dose female rats, respectively. Likewise, NTP estimated the average DPDPO consumed per day by mice in the two year study was 3,200 and 6,650 mg/kg for low and high dose male mice, respectively, and 3,760 and 7,780 mg/kg for low and high dose female mice, respectively. The test article used in this study consisted of two lots of DBDPO that were 96% or 94-97% pure DBDPO, respectively.

Animals used in the 2-year study were produced under strict barrier conditions at Charles River Breeding Laboratories. Animals were shipped to the test laboratory at 5-6 weeks of age, quarantined for 14 (rats) or 16 (mice) days, and placed on the study when 7-8 (rats) and 9 (mice) weeks old. Animals were housed in polycarbonate cages with heat-treated hardwood chips. Rats and female mice were housed 5/cage, male mice 5/cage until month 8 and then 1/cage for intermittent periods, and 1/cage after 15 months. The animal room environment was 68-80 degrees F, 15-90% humidity, fluorescent lighting 12 hours/d, and with 10-12 room air changes/hour. Animals were randomized to groups by weight class and then to dose groups. Formulated or control diets and water were available ad libitum. The formulated diets were checked for homogeneity and correctness of concentration.

Animals were observed twice per day, weighed initially and then once/week for 12 weeks and monthly thereafter until wk 100 or 101 when observations were performed every 2 weeks. All animals were subjected to a necropsy and histologic examination of tissues. The tissues examined histologically were gross lesions, skin, mandibular lymph nodes, mammary glands, salivary glands, sternum (including bone marrow), thymus, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, pancreas, gallbladder (mice), small intestine, colon, mesenteric lymph nodes, liver, spleen, kidneys, adrenal glands, urinary bladder, prostate/testes or ovaries/uterus, brain, pituitary gland, tissue masses, and regional lymph nodes. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

Organ effects reported in high dose male rats (~2,240 mg/kg/d) at the conclusion of NTP's two year study consisted of thrombosis and degeneration of the liver, fibrosis of the spleen, and lymphoid hyperplasia. Degeneration of the eye was observed in low dose female rats (~1,200 mg/kg/d). This later effect has been correlated with exposure to artificial light due to cage placement, and as a result, long term studies presently incorporate cage rotation into the study design. The DBDPO two-year study was conducted prior to NTP instituting cage rotation as a part of their experimental protocols. In mice, granulomas in the liver of low dose males and hypertrophy in the liver of low (~3,200 mg/kg/d) and high (~6,650 mg/kg/d) dose males were observed. Follicular cell hyperplasia was observed in thyroid glands of dosed male mice. The U.S. NTP concluded " ... effects observed in these studies must be attributed to the approximately 95% pure preparation used rather than to pure decabromodiphenyl oxide" (NTP 1986).

4.1.2.4 30-Day Repeated Dose Study (1973) (Tier I)

An earlier repeated dose study using a DBDPO material of lower (77%) purity, Dow FR-BA-300 (Norris et al. 1973, 1974, 1975), produced somewhat different results from those of NTP which used a test article of ≥ 95% DBDPO (NTP 1986). This DBDPO mixture is no longer manufactured, and has not been manufactured since the mid-1980s.

In a 30-day feeding study 5 male Sprague-Dawley rats/group were administered the DBDPO mixture in the diet at 0, 0.01, 0.1 and 1.0%, which corresponded approximately 0, 8, 80 and 800 mg/kg body weight (Norris et al. 1973, 1974, 1975). No overt signs of toxicity were detected in any dose group. Liver weights were statistically increased in the 1.0 and 0.1 % dose groups compared to the control group. Gross pathologic changes were limited to hepatomegaly in 2 of 5 rats at the 1.0% dose level. Centrilobular cytoplasmic enlargement with minimal vacuolation was observed in 2 of 5 rats at the 1.0% dose level. Thyroid hyperplasia was detected in a non-dose-related manner: in 1 of 5 rats at the 1.0% dose level and in 3 of 5 rats at the 0.1% dose level. Hyaline droplet tubular cytoplasmic changes were detected in the kidneys of 4 of 5 rats at the 1.0% dose level. A dose of 8 mg/kg per day was established as a no-effect level and 80 mg/kg per day as a marginal-effect level. The 77% DBDPO commercial product is no longer manufactured and the results of the 1974 30-day study are not applicable to the ≥ 97% DBDPO commercial product in use today.

4.1.3 Reproductive and Developmental Toxicology (Tiers I and II)

4.1.3.1 One Generation Reproduction Study (1975) (Tier I)

No adverse effects in either parent or F1 offspring were noted in a dietary one-generation reproduction test in male and female Sprague-Dawley rats utilizing doses up to and including 100 mg of a 77% DBDPO mixture (FR-300 BA)/kg body weight (Norris et al. 1975). The test article was composed of 77.4% DBDPO, 21.8% nonabromodiphenyl oxide, and 0.8% octabrmodiphenyl oxide. This DBDPO mixture is no longer manufactured, and has not been manufactured since the mid-1980s.

Groups of male and female rats were maintained on diets containing sufficient test article to provide dose levels of 0, 3, 30 or 100 mg/kg/d for 60 days prior to mating, during mating, and subsequently throughout gestation and lactation. There were 10 males and 20 females at the 2 lower dose levels, and 15 and 30 males and females, respectively at the high dose level. Twenty male and 40 female rats served as controls. The additional males and females were included with the controls and the group receiving the high dose level for tissue analysis for content of DBDPO. After 60 days on the test diet, each male was placed with 2 female from the same treatment regimen for 15 days (3 estrus cycles). After the 15-day mating period, the males and females were separated and maintained on the appropriate treatment diets. The females continued to receive the test diets throughout gestation and for 21 days following parturition. After 21 days of lactation, the females and their young were killed and necropsied. The brain, heart, liver, kidneys, and testes of 10 adult males and females in each group were removed and weighed. Microscopic examination of approximately 30 tissues was performed on 5 animals/sex

in the control and high dose groups. Serum chemistries (BUN, alkaline phosphatase, and serum glutamic pyruvic transaminase) and urinalysis were performed on the control and high dose animals at termination (~ day 120). Sections of brain, liver, kidney, pancreas, spleen, heart, lung, testes/ovaries, adrenal gland, small intestine, large intestine, urinary bladder, and uterus were preserved from one male and one female of each litter for microscopic examination. After gross exam, the remaining weanlings of each litter were prepared for skeletal exam. Bone marrow was saved from 5 male and 5 female adults and weanling animals/dose level at termination of the study for cytogenic evaluation. Statistical evaluation of the indices of reproduction was made by the Fisher exact probability test. Analysis of the neonatal and maternal body weights and organs weights were made by an analysis of variance and the means were compared to control values by Dunnett's test. The level of significance chosen for all was $P<0.05$.

The results of this study indicate that incorporation of the DBDPO mixture in the diet of rats for 60 days prior to mating, and subsequently throughout mating, gestation and lactation had no effect on reproductive parameters. No signs of toxicity were observed in the adult rats or the neonates during the study or at necropsy. Unaffected parameters included body weight gain and food consumption by adults, reproductive parameters (the percent pregnant and neonatal growth, survival and development), pre-terminal urinalyses and clinical chemistry measures in adult rats, gross examination of all adult and weanling animals and microscopic examination of selected tissues from both age groups. Cytogenic aberrations were not detected in bone marrow collected from the femurs of adults or weanlings. Thus, no toxicological manifestations were associated with ingestion of the DBDPO mixture at the highest dose level tested, 100 mg/kg/d.

4.1.3.2 Developmental Toxicity (Tier II)

4.1.3.2.1 Rat Developmental Toxicity Study (2002) (Tier II)

No evidence of maternal or fetal toxicity or developmental effects was detected in a developmental test in the Sprague Dawley rat (CD [Crl:CD(SD)GS BR) (n = 25 pregnant females/dose) at 1,000 mg/kg body weight utilizing a composite of today's commercial DBDPO product produced by three manufacturers and administered from days 0 - 19 of gestation (Hardy et al. 2002 (APPENDIX II); Schroeder 2000). The test article composition was 97.34% DBDPO, 2.66% nona- and octabromodiphenyl oxide congeners. This study was performed according to current EPA and GLP guidelines.

In this study, female rats (25 mated females/group) received 0, 100, 300 or 1,000 mg DBPDO/kg/day via gavage in corn oil from Gestation Day 0-19. All dams survived until scheduled sacrifice. No clinical signs of toxicity were observed. Pregnancy rates in the control and treated groups ranged from 96-100% and provided 23 or more litters in each group for evaluation on Gestation Day 20. No effect of treatment was detected in maternal gestational parameters (body weight, body weight gain and food consumption), uterine implantation data, liver weight or necropsy findings. Likewise, no treatment-related effect was detected in fetal body weights, fetal sex distribution, or from the fetal external, visceral, or skeletal examinations.

The NOEL (No Observable Effect Level) for maternal and developmental toxicity was 1,000 mg DBPDO/kg/day, the highest dose level tested.

4.1.3.2.2 Rat Developmental Toxicity Study (1973) (Tier II)

An earlier developmental study, using the former commercial product of only 77% DBDPO purity (Dow FR-BA-300) and administered to female Sprague-Dawley rats (n=20/treatment group and 30/control) on gestation days 6-15 at doses of 0, 10, 100, or 1,000 mg/kg/day, also was negative for maternal toxicity and developmental effects (Norris et al. 1973; 1974; 1975). The test article used by Norris et al., FR-300 BA, was a product composed of 77.4% DBPDO, 21.8% NBDPO, and 0.8% OBDPO, and is no longer manufactured.

No maternal toxicity or mortality was observed, and the mean maternal liver weights of the treated groups were statistically comparable to the control mean. No statistical differences between the control and treated groups were observed for the position and number of fetuses *in utero*, number of corpora lutea/dam, individual pup weight, crown rump ratio, sex ratio, number of litters, implantation sites/litter, live fetuses/litter, litters totally resorbed, or resorptions/litters with resorptions. The numbers of resorptions/implantation sites and the number of litters with resorptions was statistically significantly increased in the treated groups compared to control.

The statistical increase in resorption rate was secondary to an unusually low control value, showed no dose-response relationship, and was comparable to historical control values. Soft tissue variations detected in higher incidence in the 1,000 mg/kg dose group, but not in the 100 or 10 mg/kg groups, compared to control group were subcutaneous edema and delayed ossification of the interparietal bones of the skull.

4.1.4 Genotoxicity (Tiers I and II)

No evidence of a genotoxic effect was detected in the Ames Salmonella, chromosome aberration, mouse lymphoma, or sister chromatid exchange tests (Wagner and Klug 1998; WHO 1994; NTP 1986; McGregor et al. 1988). No cytogenic changes were observed in the bone marrow of rats (parents and offspring) undergoing a one-generation reproduction test using a former DBDPO-commercial mixture of 77% purity (Dow FR-BA-300) (Norris et al. 1975).

4.1.4.1 Ames Test (Tier I)

DBDPO (>98% purity) was tested in the bacterial reverse mutation assay using S. typhimurium tester strains TA98, TA100, TA 1535 and TA 1637 and E. coli tester strain WP2 uvrA in the presence and absence of Arochlor-induced rat liver S9 (Wagner and Klug 1998). The assay was performed in two phases, using the plate incorporation method. The first phase, the preliminary toxicity-mutation assay, was used to establish the dose range for the mutagenicity assay and to provide a preliminary mutagenicity evaluation. The second phase, the mutagenicity assay, was used to evaluate and confirm the mutagenic potential of the test material. Positive controls plated concurrently were 2-aminoantracene, 2-nitrofluorene, sodium azide, 9-aminoacridine, and methyl methanesulfonate.

Dimethyl sulfoxide was selected as the solvent based on solubility of the test article and compatibility with the target cells. Concentrations from 50 to 250 mg/ml were workable suspensions.

In the preliminary assay, the maximum dose tested was 5,000 ug/plate; this dose was achieved using a concentration of 100 mg/ml and a 50 uL plating aliquot. The test article was soluble but cloudy in dimethyl sulfoxide at $\leq$ 3.0 mg/ml and soluble and clear at $\leq$ 0.3 mg/ml. Precipitate was generally observed at $\geq$ 500 ug/plate but no appreciable toxicity was observed. Based on the findings of the toxicity-mutation assay, the maximum dose plated in the mutagenicity assay was 5,000 ug/plate.

In the mutagenicity assay, no positive response was observed (Table 4-2). Precipitate was generally observed at >500 ug/plate but no appreciable toxicity was observed.

Under the conditions of this study, DBDPO was concluded to be negative in the Bacterial Reverse Mutation Assay. This study was conducted according to US EPA and OECD guidelines and Good Laboratory Practices.

Similar results were reported by the U.S. NTP in their own tests (NTP 1986).

TABLE 4-2. DBDPO Ames test results.

S9 Activation	Overall Evaluation[a] and Dose Range Tested (ug/plate)									
	TA98		TA100		TA1535		TA1537		WP2 uvrA	
	Low	High	Low	High	Low	High	Low	High	Low	High
None	-	-	-	-	-	-	-	-	-	-
	15	5000	15	5000	15	5000	15	5000	15	5000
Rat Liver	-	-	-	-	-	-	-	-	-	-
	15	5000	15	5000	15	5000	15	5000	15	5000

[a] - = negative; + = positive (maximum fold increase)

4.1.4.2 Mouse Lymphoma (In excess of Tier III)

DBDPO (the test article used in the NTP 2 carcinogenicity studies) was tested for muagenicity in L5178Y/TK$^{+/-}$ mouse lymphoma cells in the presence and absence of S9 (NTP 1986). Experiments were performed twice, and all doses were tested in duplicate, except the solvent control (DMSO), which was tested in triplicate. Cells (6 x 10^5/ml) were treated for 4 hours at 37 degrees C in medium, washed, resuspended in medium, and incubated fro 48 hrs at 37 ®C. After expression, 3 x 10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells. DBDPO did not induce mutations in this mouse lymphoma assay (Tables 4-3 and 4-4).

TABLE 4-3. DBDPO Mouse lymphoma results in presence of S9.

Compound	Dose (ug/ml)	Total Mutant Clones	Cloning Efficiency (%)	Relative Total Growth (%)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO		117	78	100	50
		90	77	100	39
		90	66	100	45
		87	68	100	43
Ethylmethanesulfonate	2.5	544	53	35	344
		474	36	31	437
DBDPO	7	75	57	74	44
		91	53	84	57
	8	58	64	84	30
		97	124	158	26
	9	51	55	70	31
		85	60	76	48
	10	114	83	104	46
		94	52	72	61

TABLE 4-4. DBDPO mouse lymphoma results in absence of S9.

Compound	Dose (ug/ml)	Total Mutant Clones	Cloning Efficiency (%)	Relative Total Growth (%)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO		134	98	100	45
		102	105	100	33
		140	115	100	41
		178	100	100	59
Ethylmethanesulfonate	15	750	57	32	436
		762	70	36	365
DBDPO	7	77	89	87	29
		143	90	88	53
	8	97	81	85	40
		180	118	125	51
	9	49	90	86	35
		130	99	93	44
	10	115	97	91	40
		152	104	99	49

4.1.4.3 *In vitro* Sister-Chromatid Exchange (In excess of Tier III)

DBDPO (the test article used in the NTP 2 year carcinogenicity studies) was tested for the induction of sister-chromatid exchanges in Chinese hamster ovary cells in the presence or absence of S9 (NTP 1986). In the absence of S9, Chinese hamster ovary cells were incubated with DBDPO or solvent for 2 hr at 37 degrees C. BrdU was added, and incubation was continued for 24 hr. Cells were washed, fresh medium containing BrdU (10 uM) and colcemid (0.1 ug/ml) was added, and incubation was continued for 2-3 hrs. Cells were collected by mitotic shake-off, treated for 3 minutes with potassium chloride (75 mM), washed twice with

fixative, dropped onto slides and air dried. Staining was by a modified technique (after Perry and Wolff, 1974; Goto el al., 1978). In the presence of S9, cells were incubated with DBPDO or solvent for 2 hrs at 37 degrees C. Cells were washed, and medium containing 10 uM BrdU was added. Cells were incubated for a further 26 hrs, with colcemid (0.1 ug/ml) for the final 2-3 hrs. S9 was derived from the livers of Arochlor 1254-induced male Sprague-Dawley rats. DBDPO did not induce sister-chromatid exchanges in Chinese Hamster Ovary cells when tested with or without metabolic activation (Table 4-5).

TABLE 4-5. DBDPO sister-chromatid exchange results in Chinese hamster ovary cells.

Without S9		With S9	
Dose (ug/ml)	SCE/cell	Dose (ug/ml)	SCE/Cell
DMSO (10 ul)	8.5	DMSO (10 ul)	9.3
DBDPO		DBDPO	
50	8.1	50	8.6
100	7.9	100	9.3
250	8.1	250	8.4
500	7.6	500	8.8
Mitomycin C		Cyclophosphamide	
0.001	11.1	0.3	12.9
0.01	49	2.0	35.6

4.1.5.4 *In vitro* Chromosome Aberration (Tier I)

DBDPO (the test article used in the NTP 2-year carcinogenicity studies) was tested for induction of chromosome aberrations in Chinese hamster ovary cells with and without metabolic activation (NTP 1986). In the absence of S9, Chinese hamster ovary cells were incubated with DBDPO or solvent of 8-10 hrs at 37 degrees C. Cells were washed and fresh medium containing colcemid (0.1 ug/ml) was added. After a further 2-3 hr incubation, cells were harvested by mitotic shake-off, fixed, and stained with 6% Giemsa. In the presence of S9, cells were incubated with DBDPO or solvent for 2 hrs at 37 degrees C. Cells were washed, medium added and incubation continued for 8-10 hrs. Colcemid (0.1 ug/ml) was added for the last 2-3 hrs of incubation. Cells were harvested and fixed as described for the sister-chromatid exchange test. S9 was derived from the livers of Arochlor 1254-induced male Sprague-Dawley rats. DBDPO did not induce chromosome aberrations in Chinese hamster ovary cells when tested with or without metabolic activation (Table 4-6).

TABLE 4-6. DBDPO chromosome aberration results in Chinese hamster ovary cells.

Without S9		With S9	
Dose (ug/ml)	Abs/100 Cells	Dose (ug/ml)	Abs/ 100 Cells
DMSO (10 ul)	1	DMSO (10 ul)	1
DBDPO		DBDPO	
50	0	50	0
100	0	100	2
250	1	250	0
500	0	500	1
Mitomycin C		Cyclophosphamide	
0.150	16	15	28
0.250	22	30	40

4.1.4.5 *In vivo* Bone Marrow Cytogenetics (Tier II)

No cytogenic changes were observed in the bone marrow of rats (parents and offspring) undergoing a one-generation reproduction test using a former DBDPO-commercial mixture of 77% purity (Dow FR-BA-300) (Norris et al. 1975). This one-generation study was described in the section 4.1.3.1.

In the one-generation study, bone marrow, obtained from the femur, was saved from 5 male and female adults and weanling animals per dose level at termination of the study for cytogenetic evaluation. The DBDPO mixture did not induce cytogenetic aberrations in the treated animals.

4.1.5 Hepatic Enzyme Induction (In excess of Tier III)

Gavage administration of DBDPO (0.1 nmol/kg/day) to rats over 14 days did not induce hepatic cytochrome P450, cytochrome P450 reductase, UDP-glucuronyl-transferase, benzo[a]pyrene hydroxylase, p-nitroanisole demethylase, or EPN detoxification (Carlson 1980).

4.1.6 Chloracne Potential (In excess of Tier III)

Repeated dermal application of DBDPO did not induce a chloracne-like response (Naismith and Matthews 1981; WHO 1994). Chloracnegenic activity was studied by applying the test article on the ear of each of 4 New Zealand White male and female rabbits. The test material (Saytech® 102) was administered once daily at 0.1 ml/d 5 times/wk for 4 weeks, at 1, 10, 100 or 1,000 g/kg in chloroform to rabbits' ears. Observations were recorded prior to the initial dose and at 7, 14, 21 and 28 days of dosing. No chloracne was observed.

Between 1971-1974, pilot plant samples of DBDPO were studied for chloracnegenic activity. The samples (0.1 ml) were applied as a 5 or 10% solution in chloroform on the rabbit ear 5 days per week for 4 weeks. No chloracne was observed (WHO 1994).

The soot and char combustion products from a high impact polystyrene/DBDPO/antimony trioxide matrix also did not induce a chloracne-like response (Pinkerton et al. 1989). Soot and char generated from the combustion of high impact polystyrene flame retarded with and without DBDPO and antimony trioxide were tested in New Zealand rabbits. The dose levels were 0.001, 0.003, 0.005, 0.008, 0.01, 0.3, 0.05, 0.08 and 0.1 grams. The materials were applied in 0.1 ml of water for 5 consecutive levels. Ears were examined on day –1, 0, and daily during dosing and one day post-dosing. Erythema was observed in the nonflame retarded and flame retarded groups.

Two groups of four male and female New Zealand White rabbits were used to test a mixture of soot and char generated from the combustion of high impact polystyrene or high impact polystyrene/DBDPO/antimony trioxide resin in a rabbit ear comedogenicity bioassay. Daily doses of 2, 5, 8, 20 or 50 mg were administered. Each daily dose was rubbed with 0.1 ml of water on the inner surface of the pinna of one ear of each rabbit. The animals were dosed 5 days per week for a total of 4 weeks. The total cumulative dose levels were 40, 100, 160, 400 and

1,000 mg. The ears were graded for irritation (Draize test) and for hyperkeratosis (Adams test). Dermal irritation was observed in all groups. No comedogenic responses were observed. A slight increase in hyperkeratosis of the sebaceous follicles was observed on histopathological examination of the skin at the 2 highest dose levels of the high impact polystyrene groups. No evidence of overt toxicity was seen, and results from the high impact polystyrene/DBDPO/antimony trioxide soot and char groups were comparable.

4.1.7 Carcinogenicity (Tier III)

Two two-year carcinogenicity bioassays have been conducted on DBDPO (Kociba et al. 1975; NTP 1986).

The first, a single species study performed at a top dose level of 1 mg/kg using a DBDPO material of only 77% purity, produced no evidence of carcinogenicity or toxicity in rats (Kociba et al. 1975).

The second, conducted at 2.5 and 5% of the diet in F344/N rats and $B6C3F_1$ mice using a DBDPO material more closely resembling today's commercial product, produced no, equivocal and some evidence of carcinogenicity depending on genus and sex (NTP 1986).

4.1.7.1 Two Year Carcinogenicity Studies in Rats (1975) (Tier III)

Groups of 25 male and 25 female Sprague-Dawley rats were fed 0, 0.01, 0.1 or 1 mg/kg body weight/day of a DBDPO-mixture (Dow FR BA-300: DBDPO 77.4%, NBDPO 21.8%, OBDPO 0.8%) in the diet for 100 to 105 weeks. Ingestion of up to 1 mg/kg/day of the DBDPO mixture did not influence survival rates; appearance, mean body weights, feed consumption, hematology, urinalysis, clinical chemistry (blood urea nitrogen, alkaline phosphatase and glutamic pyruvic transaminase activities) and organ weights of treated groups were similar to those of controls. Gross and microscopic examinations performed on all rats killed or dying during the course of the study, did not reveal any significant finding, all the observed changes or variations from normal occurred with similar frequency and severity in the treated and control groups of rats. All these changes were considered spontaneous in nature and unrelated to ingestion of the test article. No significant difference in the number of rats developing tumours, the total number of tumours or the specific type of tumours was observed between treated and control groups (Kociba et al. 1975).

4.1.7.2 U.S. NTP Two Year Carcinogenicity Study in Rats and Mice (1986) (Tier III)

Three groups of F344/N rats (n=50 rats/sex/dose) and $B6C3F_1$ mice (n=50 mice/sex/dose) were fed diets containing 0, 2.5% or 5% DBDPO for 2 years. The test article consisted of two lots of DBDPO that were of 96% and 94-97% pure, respectively. Doses up to 5% of the diet for two years were well tolerated by F344/N rats and $B6C3F_1$ mice with no effect on body weight or mortality and only minimal evidence of organ effects (NTP 1986). The U.S. National Toxicology Program (NTP) estimated the average amount of DBDPO consumed per day in the two year

study was 1,120 mg/kg and 2,240 mg/kg for low and high dose male rats, respectively, and 1,200 mg/kg and 2,550 mg/kg for low and high dose female rats, respectively. Likewise, NTP estimated the average DPDPO consumed per day by mice in the two year study was 3,200 and 6,650 mg/kg for low and high dose male mice, respectively, and 3,760 and 7,780 mg/kg for low and high dose female mice, respectively.

No evidence of carcinogenicity was observed in female mice receiving 2.5 or 5% DBDPO in the diet (~3,760 or 7,780 mg/kg/d). Equivocal evidence of carcinogenicity was observed in male mice by an increase in the combined incidence of hepatocellular adenomas or carcinomas in both dose groups (~3,200 or 6,650 mg/kg/d); however, this finding may have been influenced by the larger number of early deaths in control male mice compared to the treated male mice. The large number of early deaths in the control males may have decreased expression of hepatocellular adenomas or carcinomas in this group. The combined incidence of hepatocellular adenomas and carcinomas in male mice treated with DBDPO was well within the historical range.

Some evidence of carcinogenicity in male and female rats was observed by increased incidences of neoplastic nodules of the liver in low dose (2.5%, ~1,120 mg/kg/d) males and high (5%, ~2,240 mg/kg/d - males, ~2,550 mg/kg/d - females) dose groups of each sex. (The term "neoplastic nodule" is no longer used by NTP to describe hepatoproliferative lesions in rats. This change in nomenclature was made subsequent to a peer review of representative hepatoproliferative lesions from two-year carcinogenicity studies. The peer review found the use of this poorly defined and understood term had permitted some potentially useful drugs and chemicals to be unfairly categorized as carcinogens (Maronpot et al., 1986). DBDPO is not listed as a carcinogen by NTP (NTP 2001), the International Agency for Research on Cancer (IARC 1990) or the U.S. Occupational Safety and Health Administration (OSHA 1990).

The abstract from the NTP final report on this study is attached in Appendix V.

4.1.8 DBDPO Absorption, Distribution, Metabolism, Elimination (Tier II)

The uptake, distribution and elimination of DBDPO after oral or intravenous (IV) dosing in the rat have been evaluated in several studies (NTP 1986; Norris et al. 1973, 1974; El Dareer et al. 1987; Moreck and Klassen-Wheler 2001). These processes were monitored by following total ^{14}C-radioactivity after administration of labeled-DBDPO or by following total bromine content via neutron activation after administration of DBDPO. NTP evaluated the uptake and disposition of DBDPO in the rat as part of the two-year bioassay. Four studies were performed and the results were reported in the 1986 NTP report (NTP, 1986) and in the publication of El Dareer et al. (1987). Earlier studies are reported in Norris et al. (1974, 1975). Similar work was recently performed by Morck and Klassen Wheeler (2001).

In the dietary NTP-sponsored studies conducted by El Dareer et al. (1987; NTP 1986), DBDPO treatment for 7 days at varying dose levels preceded treatment with the radiolabeled compound. Pretreatment dose levels were 51,000, 25,400, 4,730,2,510, 496 and 238 ppm in the diet. Test articles used for pretreatment in the ^{14}C-DBDPO studies (NTP 1986; El Dareer et al. 1987) closely resembled today's commercial product which is ≥ 97% DBDPO. In the studies conducted

by Norris et al. (1973; 1975), a single dose of ^{14}C-DBDPO was administered orally or bromine tissue levels were monitored by neutron activation after repeated administration of DBDPO for 3, 6 or 12 months. The test article for the neutron activation experiments was the former low purity product "Dow FR-300-BA" composed of 77.4% DBDPO, 21.8% nonabromodiphenyl oxide and 0.8% octabromodiphenyl oxide. In the Morck and Kassen Wheeler (2001) study, ^{14}C-DBDPO was synthesized in the laboratory.

All studies showed similar results. The NTP studies by El Dareer et al. (NTP 1986; El Dareer et al. 1987) showed that DBDPO was poorly absorbed (2-0.28% of the oral dose) from the gastrointestinal tract at all pretreatment doses (277-50,000 ppm in the diet, respectively) and rapidly eliminated. The whole body half-life was < 24 hr. Excretion in the urine accounted for ≤ ~0.01% of the dose. Feces was the major route of elimination and > 99% of the dose was recovered in the feces by 72 hr post-dosing. At all oral doses tested (277 - 50,000 ppm in the diet), the majority of the test article (~98 - 70%, respectively) was eliminated as the parent molecule. Three metabolites were detected in the feces and ranged from ~2 to 30%, respectively, of the total recovered ^{14}C-label. The highest percentage of metabolites (~30% of the dose) was present in the feces of animals pretreated with higher doses of DBDPO (25,000 and 50,000 ppm) in the diet. The lowest percentage of metabolites (~2% of the dose) was present in the feces of animals pretreated with lower levels of DBDPO (277 ppm). The identity of the metabolites was not determined.

Only trace levels of the ^{14}C-label were detected in any organ or tissue at any time point (24, 48 or 72 hr post dosing with the radiolabel) (NTP 1986; El Dareer et al. 1987). The maximum total ^{14}C-activity detected in the body at any time was only ~1% of the oral dose. The maximum ^{14}C-activity, calculated as the sum of the radioactivity in liver, kidneys, lungs, spleen, brain, muscle, skin, fat, and blood, was detected in the 277 ppm treatment group 24 hr post-dosing. Studies utilizing intravenous (IV) administration of 1 mg ^{14}C-DBDPO/kg and bile duct canulation showed that the ^{14}C-label was excreted in the bile as the parent molecule and 3 metabolites. Approximately 60% of the dose was eliminated as metabolites after IV administration. The bile contained 7.17% of the IV dose within 4 hr post-doing, and 2.2% of the dose was excreted in the bile per hr.

The above results are consistent with earlier reports by Norris et al. (1973, 1975). Norris et al. (1975) administered 1 mg/kg ^{14}C-DBDPO orally to 3 male and 3 female rats. The level of radioactivity found in the expired air and urine, measured at 24 hr intervals over a 16-day period, was < 1 %. The principal route of excretion was the feces. The rate of excretion was the same for both sexes. Within the first 24 hr post-dosing, 90.6% of the administered dose was detected in the feces, and 99% of the ^{14}C-activity was accounted for by day 2. Tissues (adipose, heart, skin, adrenals, spleen, liver, pancreas) taken on day 16 post-dosing showed no ^{14}C-label with the exception of the adrenal (0.01% of the dose) and spleen (0.06% of the dose). The ^{14}C-activity in these two tissues was at the limit of detection. The half-life of the disappearance of ^{14}C-activity from the body of DBDPO-treated rats was < 24 hours.

Norris et al. (1973, 1975) also measured bromine concentrations (via neutron activation analysis) in the kidney, skeletal muscle, serum testes, liver and adipose tissue in male and female rats

maintained on diets providing 1, 0.1, 0.01 and 0 mg DBDPO mixture/kg/day for 6 or 12 months. The composition of the DBDPO mixture (Dow FR-300-BA) was 77.4% DBDPO, 21.8% nonabromodiphenyl oxide and 0.8% octabromodiphenyl oxide. After 180 days of treatment, mean bromine levels in the control and treatment groups in liver, kidney, skeletal muscle, serum and testes were statistically comparable. The mean bromine level in adipose tissue from the 0.1 mg/kg/day dose group (~3.3 ug/g) was statistically greater than the control mean (~1.7 ug/g). After 12 months on treatment, bromine concentrations in both the liver and adipose tissue were statistically comparable to controls.

Norris et al. (1975) evaluated the elimination of bromine from liver and adipose tissue. Male rats were maintained for 90 days on diets providing a dose of 1 mg DBDPO mixture (Dow FR-300-BA)/kg/day and then placed on control diet. Kidney, serum, adipose tissue, and liver were analyzed for bromine by neutron activation analysis. On recovery day 0 there was no difference in bromine content in kidney or serum between the control and treated rats. After 10 days on the control diet, bromine concentrations in the liver of treated rats were comparable to controls. Adipose bromine levels in the treated group (~2.5 - 4 ug/g) were higher than the controls (~0 - 2 ug/g) during the recovery period.

Morck and Klassen Wehler (2001) reported similar results. Male rats were gavaged with a single dose of ^{14}C-DBDPO (3 umol/kg; 0.00288 ug/kg). Feces were the predominant excretory route and contained ~90% of the dose within 3 days. Only trace amounts were eliminated in the urine (<0.5% of the dose). Approximately 9.5% of the dose was recovered in the bile within 3 days. Approximately 3% of the dose remained in tissues at 72 hr post-dosing. The majority of the ^{14}C-activity was detected in the liver followed in declining amount in the muscle, skin, adipose tissue and colon wall plus contents. Eight phenolic metabolites were reported in the feces, and included di-substituted penta- to octaBDPOs. Trace amounts of 3 nona-BDDPOs were also reported.

Based on the findings of NTP, El Dareer et al. and Norris et al. (NTP 1986; Norris et al. 1973, 1975; El Dareer et al. 1987), DBDPO is poorly absorbed from the gastrointestinal tract as would be expected for a molecule of this size, weight and poor solubility. Following oral administration of ^{14}C-DBDPO, only trace levels of radioactivity were found in organs/tissues at any time point. The parent molecule (and all metabolites) was rapidly eliminated - > 99% of the dose was recovered in the feces and gut contents within 72 hours of oral dosing. The overwhelming route and form of elimination was by fecal excretion as the parent molecule. Less than 0.01% of the oral dose was excreted in the urine. DBDPO was capable of being metabolized; the parent molecule and 3 metabolites were detected in feces following oral or IV dosing of rats. The lower the dietary dose the lower the percent eliminated as metabolites, e.g. at a pretreatment dose of 277 ppm in the feed, approximately 2% of the dose was eliminated as metabolites. Recent studies by Morck and Klassen Wheeler (2001) performed at a substantially lower dose reported similar findings to that of NTP and El Dareer.

4.1.9 Immunotoxicology (Tier II)

DBDPO has not been evaluated for immunotoxicity using the OPTS 870.7800 guideline that is intended to provide information on suppression of the immune system that might occur as a result of repeated exposure to a test chemical. However, data available from long-term studies conducted in two species at high doses indicate DBDPO is not immunotoxic. DBDPO at 2.5 and 5% of the diet and administered for two years to rats and mice did not affect mortality or body weight (NTP 1986). If DBDPO was toxic to the immune system, deaths, decreased body weights and histologic evidence of infections would be expected. This was not the case. Routine histopathology of organs/tissues of the immune system also provide no evidence of toxicity. Organs of the immune system examined histologically in the NTP studies were the mandibular lymph nodes, sternum including bone marrow, mesenteric lymph nodes, spleen, and regional lymph nodes. Complete blood counts in the 30-D and 2-year studies (Norris et al. 1973, 1974; Kociba et al. 1975) were considered normal, and no histologic evidence of immunotoxicity was observed in the mesenteric and thoracic lymph nodes or sternal bone marrow. DBDPO's poor bioavailability reinforces a low potential for an adverse effect on the immune system. No additional testing on this endpoint is proposed.

4.1.10 Neurotoxicity Screening Battery (Tier III)

The neurotoxicity screening battery (OPPTS 870.6200) consists of a functional observational battery, motor activity, and neuropathology. The functional observational battery consists of noninvasive procedures designed to detect gross functional deficits in animals and to better quantify behavioral or neurological effects detected in other studies. The motor activity test uses an automated device that measures the level of activity of an individual animal. The neuropathological techniques are designed to provide data to detect and characterize histopathological changes in the central and peripheral nervous system. This battery is designed to be used in conjunction with general toxicity studies and changes should be evaluated in the context of both the concordance between functional neurological and neuropatholgical effects, and with respect to any other toxicological effects seen. This test battery is not intended to provide a complete evaluation of neurotoxicity, and additional functional and morphological evaluation may be necessary to assess completely the neurotoxic potential of a chemical.

DBDPO has not been specifically tested according to OPPTS 870.6200. However, no indication of neurotoxicity was observed in the NTP lifetime studies in rats and mice at exceptionally high doses (2.5 and 5% of the diet for two years) or in any of the other tests performed on DBDPO. These studies all included frequent observations for clinical signs of toxicity or effects on behavior that are essential components of the functional observational battery. Histopathology of the nervous system was normal in all studies.

Considering the high doses administered in the NTP 14-D, 13-Wk and 2-Yr studies to two species, ample opportunity was provided for induction and/or development of neurotoxicity. The fact that no evidence was detected indicates DBDPO is not neurotoxic. DBDPO's poor bioavailability reinforces a low potential for an adverse effect on the nervous system. No additional testing on this endpoint is proposed.

4.1.11 Developmental Neurotoxicity (Tier III)

The developmental neurotoxicity study (OPPTS 870.6300) is designed to develop data on the potential functional and morphological hazards to the nervous system that may arise in the offspring from exposure of the mother during pregnancy and lactation. The test substance is administered to several groups of pregnant animals during gestation and early lactation, one dose level being used per group. Offspring are randomly selected from within litters for neurotoxicity evaluation. The evaluation includes observations to detect gross neurologic and behavioral abnormalities, determination of motor activity, response to auditory startle, assessment of learning, neuropathological evaluation, and brain weights. This protocol may be used as a separate study, as a follow-up to a standard developmental toxicity and/or adult neurotoxicity study, or as part of a two-generation reproduction study, with assessment of the offspring conducted on the second (F2) generation. Testing should be performed in the rat. Because of its differences in timing of developmental events compared to strains that are more commonly tested in other developmental and reproductive toxicity studies, it is preferred that the Fischer 344 strain not be used. If a sponsor wishes to use the Fischer 344 rat or a mammalian species other than the rat, ample justification reasoning for this selection must be provided.

While DBDPO has not undergone testing via OPPTS 870.6300, none of the repeated dose toxicology studies, including those administering DBDPO over the animals' lifetime, indicate an impact on the nervous system or on the developing embryo/fetus. The NOEL of DBDPO in a rat developmental toxicity study was 1,000 mg/kg/d administered on gestation days 0-19 (Hardy et al. 2002).

A non-guideline developmental neurotoxicity study of DBDPO in the mouse was briefly reported in 2001. DBDPO was reported to disrupt habituation in adult mice which were exposed on postnatal day 3 to a single oral dose of 20.1 mg lab-synthesized DBDPO/kg (Viberg et al. 2001; Appendix IV). Animals exposed on neonatal day 3 to 2.3 mg/kg were not similarly affected nor were animals treated with either dose on neonatal day 19 or on neonatal day 10 with 1.34, 13.4 or 20.1 mg/kg. No data was reported in the 4-page abstract, and much of the details relating to the performance of the study were not reported. The composition of the test article was not specified. According to the human health portion of the draft DBDPO EU risk assessment, the toxicological significance of these findings is unclear. The authors declined to provide data or specific details under the EU risk assessment process.

The neonatal mouse study was performed using an experimental design developed by P. Eriksson (Uppsala University, Sweden), and reported by Proff. Eriksson's graduate student. The design is not that typically used to investigate developmental neurotoxicity (e.g. is not equivalent to OPPTS 870.6300), and appears to be used exclusively in that laboratory. The probability is very low that DBDPO would produce an adverse effect in humans because of the very high dose administered in the Viberg et al. study, the lengthy exposure period required to cover a corresponding period in humans, DBDPO's poor oral absorption (less than 2% in the rat), rapid elimination (>99 % after 72 hours with a half-life less than 24 hours), poor solubility, and lack of bioaccumulation. These concepts are more fully developed below.

In several publications (Eriksson 1992; Eriksson and Talts, 2000; Eriksson 1997), Eriksson cites Davison and Dobbing (1968) as the source of information regarding the brain growth spurt, a key concept in the postnatal timing of dose administration in Eriksson's design. Davison and Dobbing (1968) state that the brain growth spurt occurs after birth in rats and mice, is almost complete at birth in guinea pigs, and occurs prior to birth in humans and primates: "The main fact which emerges is the very different timing of the brain growth spurt in relation to birth in different species, and it follows from this that such expression as 'foetal brain' or 'neo-natal' or 'post-natal brain' are quite meaningless unless one knows both the species being considered and the growth characteristics of its brain. Such an observation, which seems almost too obvious to mention, is very frequently ignored when interspecies extrapolations are being considered, especially when these are between man and other species." Eriksson and Talts (2000) state "The BGS does not take place at the same time point in all mammalian species. In the human, this period begins during the third trimester of pregnancy and continues throughout the first 2 years of life. In mouse and rat the BGS is neonatal, spanning the first 3-4 weeks of life."

Based on the timing of brain growth in humans, exposure would have occur during the last trimester of pregnancy and be followed by continued exposure during the first 2 years of the child's life in order to mimic exposure on neonatal mouse day 10. Assuming equal susceptibility in the child and mouse, absorption between 0.3-2% of an oral dose, and 100% transfer of the absorbed dose to the fetus, a 50 kg woman have to receive a total dose of 50 to 1,000 mg DBDPO every day during the later stages of pregnancy followed by additional exposure to the child during the first two years of its life to reach a dose equivalent to that administered to neonatal mice.

A similar calculation can be made with respect to mice. In terms of the dose a lactating mouse would have to receive in order to pass on an equivalent dose to her nursing offspring, neonatal day 3 is of interest with respect to Viberg's findings. On day 3 of life, the pup's total nutrition is received via nursing. Therefore, oral exposure to the pup at this age would be via milk. However, DBDPO's high molecular weight, its physical/chemical properties, and its pharmacokinetics, make it highly unlikely that DBDPO would be eliminated in the milk (see Section 5.3.7). Therefore, neonatal exposure via this route is not expected. Nonetheless, doses that a lactating mouse would have to receive in order to transmit in her milk doses equivalent to Viberg's are estimated below. The following conservative assumptions were used in calculating the dose received:

Weight of the female mouse = 20 g,
Weight of the day 3 neonate = 2.5 g based on an average birth weight of 1.5 g,
6 pups/litter (average litters range from 1-12 pups; Viberg did not provide the number pups/litter),
Female mouse produces 10 % of her body weight/day in milk,
3% absorption of an oral DBDPO dose by the lactating mouse,
100% transfer of the dose to milk and 100% absorption of the dose by the pup.

Based on these assumptions, each pup would consume 0.33 g of milk, and the 2.2 and 20.1 mg/kg dose administered to the day 3 neonates would be equivalent to a total dose of 0.005 or 0.05 mg/pup, respectively. To achieve a total dose of 0.005 or 0.5 mg, the milk would have to

contain 0.015 or 0.15 mg/g milk. The total day's milk production (2 g) would thus contain 0.03 or 0.3 mg total. Assuming the dam absorbed 3% of an oral dose, she would have to be exposed to doses of 50 or 500 mg/kg body weight in order to generate the estimated milk content. To achieve a dose of this amount, the dam would have to be exposed to 415.9 or 4,159 mg DBDPO/kg food. It is highly unlikely that lactating female mouse (or another mammalian species) could be exposed to a dose of 415.9 or 4,159 mg DBDPO/kg food except under laboratory conditions.

Using the results of the NTP mouse 2-year study, a dose of 25,000 ppm food, and assessment factor of 100, the oral predicted no effect concentration for a lifetime exposure would be 250 mg/kg food. The food exposure to a female mouse, 415.9 or 4,159 mg DBDPO/kg food, in order to generate doses in a day 3 neonate equivalent to those administered by Viberg (2001), are higher than the oral predicted no effect concentration calculated from the NTP two year mouse study.

4.2 Environmental Fate and Toxicology (Not included in Tiers I, II, or III)

4.2.1 Environmental Fate

DBDPO's measured and predicted environmental fate parameters are shown in Table 4-7. DBDPO is predicted to partition in the environment to soil and sediment (~99%) where it will bind extensively to organic carbon (estimated Koc_{soil} = 1.67 x 10^{12}) and to be essentially immobile in soil. Based on a release of 1,000 kg/hr to air, water and soil, the predicted partitioning is: air 0.12%, water 1.09%, soil 41.8% and sediment 57% (Level III Fugacity Model, EPIwin V3.04). DBDPO is not expected to volatilize from water based on its river and lake volatilization half-lives and air-water partition coefficient. DBDPO is expected to partition from water to organic carbon. Sewage treatment plants are predicted to remove DBDPO from the influent to a high degree (94%), but biodegradation in the treatment plant is not expected. Removal in the treatment plant is via partitioning to sludge. DBDPO leaching from polymers was insignificant (Norris et al., 1973,1974) as expected for a molecule of negligible water solubility and vapor pressure. DBDPO is not expected to undergo long range transport (Wania and Dugani 2002).

TABLE 4-7. Environmental fate parameters for DBDPO.

Property	Method	Result
Predicted Movement in the Environment: Expected to partition to sediment and soil and be essentially immobile.		
Water Solubility	Measured	< 0.1 ug/L
Vapor Pressure	Measured	4.63 x 10-6 Pa
Henry's Law Constant	Estimated	1.9 x 10-8 atm-m3/mole at 25®C (EPIwin, V.3.04)
		7.9 x 10-7 unitless at 25®C (EPIwin, V.3.04)
Soil Koc	Estimated	1.8 x 10+6 (EPIwin, V.3.04)
Log Octanol Water Partition Coefficient	Estimated	12.61 (EPIwin, V.3.04)
	Measured*	5.625 (MacGregor and Nixon 1997)
Air to Water Partition Coefficient	Estimated	7.9 x 10-7 (EPIwin, V.3.04)
Biomass to Water Partition Coefficient	Estimated	8.1 x 10+11 (EPIwin, V.3.04)
Volatilization from Water	Estimated	Half life: 10.7 years (river), 117 years (lake) (EPIwin, V.3.04)
Sewage Treatment Plant Fugacity Model	Estimated	Total Removal: 94%, Total Biodegradation: 0.78%, Primary Sludge: 60%, Waste Sludge: 33%; Final Water Effluent: 6% (EPIwin, V.3.04)
Level III Fugacity Model	Estimated	At Emissions to Air, Water, Soil and Sediment of 1,000, 1,000, 1,000 and 0 kg/hr, respectively (EPIwin, V.3.04):
		Distribution: Air 0.12%, Water 1.09%, Soil 42%, Sediment 57%
		Fugacity (atm): 3.1 x 10-16, Water 8.4 x 10-21, Soil 2.4 x 10-22, Sediment 1.5 x10-20.
		Reaction (kg/hr): Air 4.2, Water 43.4, Soil 1.7 x10+3, Sediment 570.
		Advection (kg/hr): Air 249, Water 226, Soil 0, Sediment 237.
		Reaction (%): Air 0.1, Water 1.5, Soil 56, Sediment 19.
		Advection (%): Air 8, Water 7.5, Soil 0, Sediment 8.
Long Range Transport Potential	Computer Modeling	Not expected to undergo long range transport (Wania and Dugani 2002)
Biodegradation: No evidence of biodegradation.		

Ready Biodegradation	MITI	Not readily degradable in a 2 week study (CITI 1992)
Sludge Respiration	OECD 209; EU67/548;EEC, Annex V, C.11; GLP	Not inhibitory to activated sewage sludge (limit dose = 15 mg/L) (Schaefer and Siddiqui 2001)
Anaerobic Sediment Degradation	Other; GLP* Other	Not degraded after 32 weeks (Schaeffer and Flaggs 2001) Not degraded after 2 years (de Wit 2000)

Abiotic degradation: Not likely a significant route of environmental degradation due to negligible vapor pressure & water solubility and expected environmental partitioning.

Aqueous Photodegradation	Other**	Half-life >> 90 days; Products not lower BDPOs (Norris et al. 1974, 1975)
Organic Solvent Photodegradation	Other	Half-life < 15 minutes; Sequential reductive debromination; PBDFs formed from degradants (Norris et al. 1974, 1975; Watanabe and Tatsukawa 1987; Eriksson et al. 2001)
Solid Surface Photodegradation	Other*	6 different exposure scenarios investigated; Less than 10% of the DBDPO decayed in a worst-case exposure scenario for inducing solar photochemical transformation in a model aqueous environment (e.g. DBDPO precipitated on humic acid-coated sand particles & exposed to 12 days of summer sunlight); No evidence for production of Tetra or PeBDPO congeners (Jafvert and Hua 2001)
	Other	Toluene half-life< 15 minutes; Sand half-life ~35 hr (rooftop sunlight); Sediment half-life ~ 100 hr (rooftop sunlight); Soil half-life ~200 hrs (rooftop sunlight); Some evidence of sequential reductive debromination but not as pronounced in sand/sediment/soil as in organic solvents; No evidence of 2,2',4,4'-TeBDPO formation (Sellstrom et al 1998; Tysklind et al. 2001)
Hydrolysis	Estimated	Not likely to be a significant route of environmental degradation due to low water solubility
Atmospheric Oxidation	Estimated	Overall OH Rate Constant = 0.6 x 10-12 cm3/molecule-sec; Half-Life = 169 Days (12-hr day; 1.5 x 10+6 OH/cm3 (EPIwin V3.04)

*Studies Performed under Good Laboratory Practices and using today's commercial DBDPO product (μ97%) as test article.
**Test article only 77% DBDPO.

4.2.1.1 Abiotic Degradation

Abiotic degradation may occur via hydrolysis or photolysis. DBDPO is not expected to undergo hydrolysis based on its chemical structure. DBDPO's negligible water solubility (< 0.1 ug/L) also does not lend hydrolysis to being a significant route of environmental degradation. Photodegradation requires exposure of the molecule to light, and is not expected to be a significant route of environmental degradation due to DBDPO's negligible vapor pressure that precludes substantial levels in air. Further, a Level III fugacity model predicts that only minimal amounts would partition to air. Nonetheless, questions regarding DBDPO's potential to undergo photolysis to lower brominated diphenyl oxides have been raised.

Norris et al. (1973, 1975) investigated the photolysis of DBDPO by sunlight in organic solvent or water (Norris et al. 1974, 1975), and predicted different routes/mechanisms of photodegradation for the DBDPO molecule in water or organic solvents based on the behavior of other halogenated aromatic compounds. Norris et al. found that halogenated aromatics photodegraded by reductive dehalogenation when dissolved in solvents capable of proton transfer. However, in water, photodegradation proceeded via an oxidative process of hydroxylation leading to the formation of phenolic compounds. Once photohydroxylation was initiated, its rate was expected to accelerate as electron-withdrawing halogens were replaced by electron releasing hydroxyl groups. The resulting hydroxylated species were expected to adsorb light more strongly and this ultimately could result in rupture of the aromatic ring.

Norris et al.'s laboratory findings correlated with the predictions. Minimal evidence of DBDPO (98% purity) aqueous photodegradation was found over a 3-month exposure to natural sunlight; degradants were not lower brominated diphenyl oxides. Evidence for degradation of only 0.57% of the amount initially present (10 g/8 l water) was detected after 98 days of exposure to sunlight. The minimal degradation was likely related to DBDPO 's extremely poor water solubility (<0.l ug/L) and its stability. However, Norris et al. also found that DBDPO (7 ppm) in octanol decomposed with a half-life of 4 h. In xylene (a strong absorber of UV light), DBDPO photodegraded by reductive debromination with a half-life of 15 h on exposure to a 125 watt Hg lamp. In comparison, neither Arochlor 1242 nor 1260 showed any evidence of degradation after 350 h.

DBDPO degradation via reductive debromination in organic solvents (hexane, toluene, methanol/water) to lower brominated diphenyl oxides was also reported by Wantanabe and Tatsukawa (1987) and Eriksson et al. (2001). A further stepwise formation of polybrominated dibenzofurans was also observed (Watanabe and Tatsukawa, 1987; Eriksson et al. 2001). However, organic solvent photodegradation of DBDPO is not anticipated to be an environmentally relevant degradation mechanism (WHO 1994; Existing Substances Regulation 793/93/EEC, 2000a).

The potential photodegradation of DBDPO adsorbed to sand, soil or sediment was also investigated (test article composition unknown but contained nonaBDPO and trace levels of octaBDPO) (Sellstrom et al. 1998). Sellstrom et al. reported a DBDPO half-life in sand of 37 h in natural sunlight. Evidence of reductive debromination was reported. However, the amounts

of nona-, octa- and heptaBDPO were not nearly as pronounced as in the toluene experiments carried out by this group. No 2,2',4,4'–TeBDPO was detected. Although small amounts of nonaBDPO formed, octaBDPO was a small fraction of this and heptaBDPO a small fraction of this. These results indicate that either a stepwise reductive debromination pathway was less significant in environmental media (e.g. sand, soil or sediment) or that in these media the lower brominated products themselves degrade at a faster rate than in toluene. Thus, although it appears possible for reductive debromination of DBDPO to occur under certain circumstances, the amounts of lower brominated diphenyl oxides formed would be very small and would also undergo similar degradation. Further, 2,2',4,4'-TeBDPO, the primary PBDPO detected in the environment, does not appear to be produced from DBDPO.

4.2.1.2 Biodegradation

DBDPO was not readily biodegradable (CITI 1992) nor was DBDPO degraded by anaerobic sediment over a 32 week (Schroeder 2001) or 2 year time frame (de Wit 2000).

Aerobic Biodegradation. DBDPO (100 mg/l) was incubated with activated sludge (30 mg/l) from mixed sources in Japan over a 2-week period (equivalent to MITI I test). No degradation (as measured by BOD) was observed; therefore DBDPO is not readily biodegradable (CITI, 1992). This result indicates that DBPDO is unlikely to biodegrade rapidly in the environment under aerobic conditions.

Anaerobic Biodegradation. Based on other halogenated aromatic substances, reductive dehalogenation of DBDPO may possibly occur under some conditions and anaerobic degradation studies were performed DBDPO and 2,2',4,4'-TetraBDE

KEMI (1994) and de Wit (2000) reported that no degradation/transformation of DBDPO was seen after four months incubation in sediment samples under anaerobic conditions. The inoculum used was an enrichment culture from a polybrominated diphenyl oxide-contaminated sediment. The incubation of one of the anaerobic cultures was extended to two years, but no degradation of decabromodiphenyl ether was seen. De Wit (2002) stated, "A study of anaerobic microorganisms' ability to break down DeBDE to lower brominated PBDE in sediment was carried out during 1994. DeBDE was applied to anaerobic sediment which was then inoculated with micro-organisms enriched from a PBDE-contaminated sediment. The sediment was then divided into smaller samples and allowed to gently shake. Samples were analyzed at different time points but no breakdown of DeBDE was seen during the experimental time of four months. The experiment was extended by letting one aliquot of sediment continue incubation. Subsamples were analyzed at several time points but no breakdown could be seen after an incubation of 2 years (unpublished results, Ulla Sellström; de Wit,1995; 1997)."

The anaerobic biodegradation of ^{14}C-DBDPO was also studied in a sediment-water system over 32 weeks at 5 or 500 mg/kg sediment (Schaefer and Flaggs, 2001a). ^{14}C-Glucose served as a positive control. The test article was a mixture of unlabelled substance (supplied as a composite sample from three manufacturers; purity 97.4% DBDPO, 2.5% NonaBDPO and 0.04%

OctaBDPO) with ^{14}C-DBDPO (radiochemical purity 96.8%). This study was conducted according to Good Laboratory Practices.

The sediment and accompanying overlying surface water used was collected from the Schuykill River, Valley Forge, Pennsylvania, USA. The redox potential of the sediment was -284 mV. The average moisture content of the sediment was 26%, its pH was 6.3, and the organic matter content was 1.4%. A 0.2 mg/l resazurin solution was prepared using the collected overlying surface water.

The test chambers consisted of 500 ml bottles containing 300 ml of the sediment and were prepared in an anaerobic chamber. The sediment was carefully added to the bottles in order to maintain the sediment column structure. Three replicate chambers were used at each concentration. In addition, a further six treatment groups at 5 mg/kg and 500 mg/kg were run to allow the concentrations of the test material and any metabolites to be determined at the start and end of the test. The test chambers were incubated in the dark at ambient room temperature (22^{o}C) in an anaerobic chamber. At the end of the incubation period, samples from each treatment group were analysed for DBDPO and the presence of any degradation products by a HPLC method using both UV and radiometric detection.

The mass balance results from the experiment are shown in Table 4-8.

TABLE 4-8. Mass balance results from a 32-week anaerobic sediment degradation of ^{14}C-DBDPO.

Nominal concentration	Mass balance at week 32			
	% as $^{14}CO_2$	% as $^{14}CH_4$	% ^{14}C in solids	Total % recovery of ^{14}C
5 mg/kg	0.4±0.04	0.4±0.04	129.9±24.1	130.9±24.1
500 mg/kg	0.4±0.03	0.4±0.06	122.5±7.9	123.3±7.9
Positive control (glucose, 5 mg/kg)	67.2±2.1	18.1±1.1	9.5±4.9	94.9±1.8

For the positive control, an average of 95% of the total radioactivity added as glucose was recovered with 85% converted to $^{14}CO_2$ and $^{14}CH_4$ and 10% associated with the sediment-phase. The degradation seen in the positive control indicated that the sample pre-treatment methods (e.g. use of tetrahydrofuran solvent) appeared to have had little effect on the viability of the microbial community present.

For DBDPO, <1% of the total radioactivity added was found as $^{14}CO_2$ and $^{14}CH_4$ indicating that essentially no mineralisation occurred. Parent compound analysis (mean of seven replicate samples) indicated that the concentrations of DBDPO in the nominal 5 mg/kg treatment were 6.64 ± 0.70 mg/kg at day 0 and 6.51 ± 2.15 mg/kg at week 32. Similarly, the measured concentrations of DBDPO in the nominal 500 mg/kg treatment were 543 ± 77 mg/kg at day 0 and 612 ± 158 mg/kg at week 32. The differences in concentration between day 0 and week 32

were not statistically significant. The composition of the sediment cores were found to account for some of the variability seen in the measured concentrations, with sediments containing a greater number of gravel/stones leading to a higher variability between replicate measurements of concentration.

The HPLC chromatographic profiles also indicated that traces of some ^{14}C-labelled components with shorter retention times than DBDPO were present in some of the 32-week samples in the 5 mg/kg treatment group. Similar components also were present in the stock solution of the ^{14}C-DBDPO. A more detailed GC-MS analysis was carried out on Day 0 and Week 32 sediment samples. No evidence for the formation of lower brominated congeners was found.

A similar anaerobic degradation study was performed with 2,2',4,4'-TetraBDE (Schaefer and Flaggs, 2001c). The substance tested was a mixture of ^{14}C-2,2',4,4'-TetaBPE (radiochemical purity 96.5%) and unlabelled 2,2',4,4'-TetraBDE (purity ~99%). The test concentrations were 5 and 500 mg/kg dry sediment. A positive control (^{14}C-Glucose) was also run. The test was carried out using the same sample preparation method, a similar sediment and the same test system as used for DBDPO. The mass balance results from the experiment are shown in Table 4-9.

TABLE 4-9. Mass balance results from a 32-week anaerobic sediment degradation study of ^{14}C-2,2',4,4'-TetraBDE.

Nominal concentration	Mass balance at week 32			
	% as $^{14}CO_2$	% as $^{14}CH_4$	% ^{14}C in solids	Total % recovery of ^{14}C
5 mg/kg	0.5±0.34	0.01±0.01	134.3±5.0	134.8±5.2
500 mg/kg	0.2±0.02	0.01±0.02	124.8±7.7	125.0±7.7
Positive control (glucose at 5 mg/kg)	73.4±8.5	7.8±4.7	19.6±4.0	100.9±0.25

The total recovery of ^{14}C from the positive control was 101%, with 81.2% converted to $^{14}CO_2$ and ^{14}C, and 19.6% associated with the sediment-phase. The degradation seen in the positive control indicates that the sample pre-treatment methods using tetrahydrofuran solvent appear to have had little effect on the viability of the microbial community present.

4.2.1.3 Transport (Fugacity)

If released in equal amounts to air, water and soil, DBDPO is predicted to partition to soil and sediment. Based on a release of 1,000 kg/hr to air, water and soil, the predicted partitioning is: air 0.12%, water 1.09%, soil 41.8% and sediment 57% (Level III Fugacity Model, EPIwin V3.04). The majority (73%) would be reacted in soil and sediment, with only 23% of the total undergoing advection.

A preliminary evaluation of DBDPO's potential for long-range transport in the atmosphere indicated that this was unlikely (Hardy and Smith 1999). Wania and Dugani (2002) recently concluded extensive computer modeling of the long-range transport potential of DBDPO. Four

multimedia models were used: Characteristic Travel Distance, Spatial Range, Arctic Accumulation Potential, and Globo-POP. All four models produced similar results, and Wania and Dugani concluded that DBDPO was unlikely undergo long-range transport. Instead, DBDPO released to the environment would deposit near the point of release. This behavior was very different from that predicted by the models for brominated diphenyl oxides having 2-4 bromine atoms/molecule. The Di- to TetraBDE molecules were predicted to have a long range transport potential similar to chlorinated biphenyls with 4-6 chlorine atoms/molecule known to undergo significant long-range transport.

4.2.1.4 Leaching from Polymers

The potential leaching of a DBDPO mixture (Dow FR-300-BA; 77.4% deca-, 21.8% nona- and 0.8% octabromodiphenyl oxide) from pellets of acrylonitrile-butadiene-styrene (ABS) polymer and polystyrene was studied. The pellets of either plastic contained 10% of the DBDPO mixture. The pellets were placed in 2 L of water and shaken mechanically. The results, expressed as the concentration of bromine in water, are shown in Table 4-10. The lack of increase of the bromine concentration with time and the erratic results are best explained by assuming that extraction of DBDPO was mainly due to erosion of surface particles (Norris et al., 1973 and 1974).

Little or no leaching into water, acetic acid or cottonseed oil at elevated temperature also occurred from ABS pellets containing 4.25% of DBPDO mixture (Dow FR-300-BA) (Table 4-11). No DBDPO was detected in water or acetic acid, and only about 0.03% of the total was extracted by cottonseed oil over 7 days at elevated temperatures (Norris et al., 1973 and 1974).

TABLE 4-10. Extraction of a DBDPO mixture from ABS or Polystyrene by water.

Time (hours)	Concentration (mg bromine/L water)	
	ABS	Polystyrene
3	1.8	<1
19	1.3	<1
27	1.0	<1
43	3.7	<1
51	<0.5 (not detected)	<0.5 (not detected)
187	<0.5 (not detected)	<0.5 (not detected)

TABLE 4-11. Solvent extraction of a DBDPO mixture from ABS.

Solvent	Time (days)	Temperature (°C)	Concentration of DBDPO in solvent (mg/l)
Water	1	48.9	<0.075 (not detected)
3% Acetic acid	1	48.9	<0.075 (not detected)
3% Acetic acid	7	48.9	<0.075 (not detected)
Cottonseed oil	7	57.2	1

4.2.2 Environmental Toxicology

DBDPO was not acutely toxic to fish (CITI 1992) or marine algae (Walsh et al.1987), and is not expected to be chronically toxic in aquatic species due to its large molecular weight, negligible water solubility, and the lack of toxicity exhibited by the OBDPO commercial product. DBDPO also was not toxic to the sediment oligochaete, *Lumbriculus variegatus* (Krueger et al. 2001), or to six species of terrestrial plants. DBDPO also did not bioconcentrate in fish, and no evidence of its degradation in fish to 2,2',4,4'-TeBDPO or 2,2',4,4',5-PeBDPO has been found.

4.2.2.1 Aquatic Organisms

A 48h-LC_{50} for orange-red killifish (*Oryzias latipes*) has been determined for DBDPO as part of a six-week bioconcentration study. The LC_{50} was >500 mg/l (CITI 1992).

Walsh et al. (1987) studied the toxicity of DBDPO to the marine unicellular algae *Skeletonema costatum*, *Thalassiosira pseudonana* and *Chlorella* sp. The tests were carried out at a salinity of $30^{o}/_{oo}$ for either 72 hours (*S. costatum* and *T. pseudonana*) or 96 hours (*Chlorella* sp.). The end-point measured was the EC_{50} for growth based on cell numbers. The exposure concentrations in the test solutions were verified by analysis. In the tests, the DBDPO was added as a solution in acetone (final acetone concentration around 1 ml/l). Six different growth media were used in the test, one natural seawater and five synthetic seawater formulations. The natural seawater had a salinity of 32‰ and was diluted to give a final test salinity of 30‰ to be comparable with that of the synthetic media. The pHs of the various test media were in the range 7.6-8.2. The EC50 for all three species was greater than the highest concentration tested (1 mg/l).

DBDPO is not expected to be chronically toxic to aquatic organisms owing to its lack of acute toxicity, negligible water solubility, and tests on the commercial OBDPO product. A long-term *Daphnia* test has been performed on the commercial OBDPO product, and no effects on survival, reproduction or growth were seen over 21-days at concentrations up to 2 µg/l (solubility limit). Taken as a whole, it is clear that the aquatic toxicity and bioaccumulation potential of the PBDPO products (penta-, octa- and decabromodiphenyl oxide) decreases with increasing bromination and therefore it is unlikely that DBDPO will show any toxic effects to invertebrates at concentrations below its solubility limit.

4.2.2.2 Fish Bioconcentation/Bioaccumulation

The bioconcentration of ^{14}C-DBDPO (20 ug/L) in rainbow trout under static conditions over a 48-hour period was compared to a known bioaccumulative substance, 2,2',4,4'-tetrachlorobiphenyl (TCBP) (16 ug/L). Little change in the DBDPO water concentration was seen in the water (initial concentration was 20 µg/l), indicating minimal uptake by the trout and insignificant losses by other means (e.g. volatilisation, adsorption onto surfaces etc.). DBDPO's lack of bioconcentration was confirmed by analysis of ^{14}C-residues in fish samples at intervals during the experiment (Table 4-12). Little or no uptake of DBDPO

occurred. The positive control, TCBP, was found to bioconcentrate at least 50 times over the initial exposure levels within 4 hours (Norris et al., 1973 and 1974).

TABLE 4-12. Concentrations of ^{14}C-DBPDO and TCBP (ppb) in fish on exposure to water concentrations of 20 or 16 ug/L, respectively.

Time (Hr)	14C-DBDPO (ppb)	TCBP (ppb)
0	-	<100
0.5	-7*	150
1	1	330
2	1	520
4	3	1,000
6	1	1,200
12	-2*	1,300
24	3	1,200
48	6	1,000

*Below background.

The bioconcentration of DBDPO in carp was studied over a six-week period in a study performed according to Japan's "Bioaccumulation test of chemical substance in fish and shellfish" (CITI 1992). The 48 hr LC50 was first determined in orange-red killifish (*Orizias latipes*), and the value was used along with the analytical detection limit of the test substance to select two test concentrations for the bioconcentration test in Japanese carp (*Cyprinus carpio*). Concentrations used in this design are typically 1/100, 1/1000 or 1/10,000 of the 48 hr LC50. The highest exposure concentration was 10 times that of the low exposure concentration. For DBDPO, the test concentrations were 6 and 60 ug/L. The control and test groups consisted of 15-20 fish each. The duration of exposure was 6-8 wks until equilibrium was reached in the fish. Test article concentrations in the aquaria and fish were determined twice/wk, and in 2-3 treated fish/exposure concentration every 2 weeks. The control fish were analyzed before test initiation and at termination of exposure for the test substance. The whole body of each fish was homogenized and extracted using an analytical method suitable for the test substance. Test article concentrations in fish and water were corrected for analytical recovery rates. Analytical method blanks were also performed. The BCFs measured at the end of the experiment were <5 at an initial concentration of 60 µg/l and <50 at an initial concentration of 6 µg/l (the two values are consistent if no DBDPO was detected in the fish, and the detection limit in fish was around 300 µg/kg, and indicate that little or no bioconcentration is occurring) (CITI, 1992).

Kierkegaard et al. (1997, 1999) investigated the uptake in trout of Dow FR-300-BA following administration in food. The Dow product has not been manufactured since the 1980s, contained only 77.4% of the DBDPO isomer with the remainder being nona- (21.8%) and octaBDPO isomers (0.8%) (Norris et al 1973, 1974, 1975). However, Kierkegaard et al. did not provide the composition of the mixture tested. Rainbow trout were force-fed homogenized cod containing the suspended test article for a period of 16, 49 and 120 d. Doses ranged between 7.5 and 10 mg/kg/d. Only a very small amount of the test material was taken up during the 120-day

exposure phase. Uptake was estimated to be 0.02 –0.13% of the dose after 120 days of exposure based on the muscle concentrations of the total hexa-to DBDPO isomers. Uptake of the DBDPO component was estimated at only 0.005% of the dose, and declined significantly during depuration. No evidence of debromination of the test article to 2,2',4,4'-TeBDPO, 2,2',4,4',5-PeBDPO or 2,2',4,4',6-PeBDPO was found, and the authors concluded "… possible metabolism seem not to be the major sources of tetra- and pentabromodiphenyl ethers found in wild fish".

Some hexa-, hepta-, octa- and nonaBDPO congeners' concentrations increased with exposure in liver and muscle. Some of these congeners were not detectable in the test article and Kierkegaard et al. speculated that their presence might be the result of a metabolic process or a more efficient absorption of trace amounts initially present in the food/test article. Kierkegaard et al. was not able to distinguish between these two possibilities. A third possibility, not considered in Kierkegaard et al., is that these hexa-, hepta-, octa- and nonaBDPO congeners were present in the test article but not detected, and slowly increased in fish tissue over time to detectable levels over the 120 d test period as a result of slow metabolism/elimination.

The results of this bioaccumulation study are consistent with previous work showing insignificant bioconcentration of DBDPO in fish, do not provide evidence that DBDPO is debrominated metabolically, and indicate that metabolic debromination of DBPDO is not the source of tetra- and pentaBDPO congeners detected in wild-caught fish.

4.2.2.3 Sediment Organisms

Prolonged sediment toxicity tests (28-D) on DBDPO were preformed with the oligochaete *Lumbriculus variegatus* using a flow-through test system with sediments of either 2.4% or 5.9% organic carbon content (Krueger et al. 2001a,b). The test was based on the ASTM E 1706-95b Guideline and USEPA Series 850 Ecological Effects Test Guidelines (OPPTS No. 850.1736) and performed according to Good Laboratory Practices.

The test substance was a composite sample from three manufacturers and had a purity of 97.9%. The total exposure period was 28 days. The nominal concentrations tested in the studies were 0, 313, 625, 1,250, 2,500 and 5,000 mg/kg dry weight. Each treatment and control group was replicated eight times with ten oligochaetes/replicate. Additional replicates were also run in each treatment and control group for analytical sampling of water and sediment. The endpoints were survival/reproduction (as measured by the total number of organisms present which is a combination of parent survival and reproduction) and growth (as determined by dry weight of organism).

In both the 2.4 and 5.9% organic carbon sediment, the NOEC for survival and growth ≥ 5,000 mg/kg dry sediment (nominal). Based on the measured sediment concentrations, the NOECs were 4,536 and 3,841 mg/kg dry weight for the 2.4 and 5.9% organic carbon sediments, respectively.

4.2.2.4 Sludge Microorganisms

An activated sludge respiration inhibition (OECD 209) test was performed on a composite sample of commercial DBDPO products from three manufacturers (Schaefer and Siddiqui, 2001). The purity of the test substance was 97.9% DBDPO. The substance was tested in triplicate at a concentration of 15 mg/l. The inoculum used in the test was activated sludge from a waste water treatment plant that received predominantly domestic waste. The test was carried out at 20-22^{o}C and the respiration rate of the activated sludge over 3 hours was determined. Two controls and a positive control (3,5-dichlorophenol at concentrations of 5, 15 and 50 mg/l) were also run. The respiration rates in the two controls were both 41.6 mg O_2/l/hour. The mean respiration rate in the DBDPO treatments was 41.1 mg O_2/l/hour and so no inhibition of respiration was seen at the concentration tested. The EC_{50} for the positive control was determined as 9.8 mg/l, which was within the normal range of 5 to 30 mg/l for this test. The NOEC for DBDPO from this test was therefore ≥ 15 mg/l. This indicates DBDPO's lack of ready biodegradation is not due to inhibition of the microorganisms present in sewage sludge.

4.3 Potential Degradation of DBDPO

There has been speculation that DBDPO may degrade in the environment or in biological systems to lower brominated diphenyl oxide/ether congeners. The apparent reasoning for this speculation is as follows: The commercial DBDPO product represents approximately 82% of the global commercial polybrominated diphenyl oxide/ether (PBDE) usage. Approximately 50-70% of "PBDEs" detected in biological samples is composed of a single isomer, 2,2',4,4'-TetraBDE, whereas DBDPO is rarely detected. 2,2',4,4'-TetraBDE is a component of only one PBDE product – the commercial pentabromodiphenyl oxide product – and the total content of tetra-substituted congeners in the pentabromodiphenyl oxide product is ~34%. Hence, the speculation that DBDPO may degrade to tetra and/or pentaBDE congeners either in the environment or in biological systems.

The above speculation does not take into consideration the impact that the differences in physical properties, potential for bioaccumulation, or the potential for environmental release between DBDPO and the tetra- and pentaBDE congeners. In addition, the available monitoring and experimental data do not support degradation of DBPDO to lower brominated diphenyl oxide congeners.

4.3.1 Differences Between DBDPO and Lesser Brominated Diphenyl Ether Isomers

The measured water solubility and vapor pressure of DBDPO are negligible (<0.1 ug/L and 4.63 x 10^{-6} Pa). Although small, the measured water solubility of 2,2',4,4'-TetraBDE (10.9 ug/L) is greater than that of DBDPO (Hardy 2002a). The vapor pressure of 2,2',4,4'-TetraBDE (2.5 x 10^{-4} Pa) (Wong et al. 2001), although small, is greater than that of DBDPO. Likewise, there are major differences in the potential bioaccumulation of DBDPO and the 2,2',4,4'-TetraBDE isomer. DBDPO has been shown not to bioconcentrate in fish (BCF < 50), is very poorly absorbed in rats (0.3-<2% oral dose) and rapidly eliminated (>99% in 72 hrs) and as a consequence does not bioaccumulate. The 2,2',4,4'-TetraBDE isomer, however, bioconcentrates in fish (BCF > 10,000) is readily absorbed (> 95% of an oral dose) by the rat and slowly

eliminated (14% in 5 days). DBDPO's predominant use is in hard dense plastics (e.g. television cabinets), which limit its potential for release. The 2,2',4,4'-TetraBPE isomer is a component in certain flame retarded flexible polyurethane foams. This foam has an open cell structure, which presents a large surface area to the environment and therefore the potential for release is likely to be greater than the hard dense plastics where DBPDO is used. In addition, this foam may become friable and crumble with age. Thus, small particles could thereby released could move into the environment and disperse its components. All of these factors working together likely contribute to the differences in the environmental behavior and detection of DBDPO and 2,2',4,4'-TeBDE.

4.3.2 Potential for Environmental Degradation of DBDPO

DBDPO's potential for degradation in the environment can be examined by reviewing environmental monitoring data and laboratory study results. In the environment, DBDPO is expected to partition predominantly (~99%) to soil and sediments where it will undergo extensive binding to particulate matter. DBDPO has been detected in sediments near point sources, and thus sediments are a logical matrix in which to look for evidence of degradation. The monitoring data does not support degradation of DBDPO to lower brominated diphenyl ether congeners.

European sediments have been monitored over a 20-year period (de Boer 2001), and do not support degradation of DBDPO. de Boer et al. concluded that significant amounts of lesser brominated diphenyl ethers were unlikely to be formed from DBDPO in sediment based on the results of a detailed survey of the levels of PBDPOs in various European sediment cores. Although the sediment concentration of DBDPO increased in recent years, no parallel increase in the concentrations of lesser brominated diphenyl ethers (e.g. tetra- to penta- congeners) occurred and there was no indication of increasing levels of nona- and octabromodiphenyl ethers.

The Mersey River estuary was used as a disposal site for U.K. sewage sludge for a number of years. (This practice has been discontinued.) DBDPO was used by industries in the area, and DBDPO was detected in sediment collected from this estuary. Samples of the Mersey River sediment were analyzed via HRGCMS for mono- to decabromodipnenyl oxide congeners. Hexa- to nona congeners would be expected if DBDPO were undergoing reductive debromination. However, only DBDPO and tetra/pentaBDPE congeners were detected. Thus, the monitoring data does not support the degradation of DBDPO to lower brominated diphenyl oxides.

With respect to laboratory degradation studies, the results indicate DBDPO is not biodegradable (see section 4.2.1.3). Abiotic degradation, e.g. hydrolysis or photolysis, is also not expected to be a significant route of environmental degradation. Hydrolysis is unlikely to occur based on DBDPO's chemical structure and negligible water solubility. Photolysis is not expected, because of DBPDO's negligible vapor pressure, negligible partitioning to air (~0.1%), and experimental photodegradation work showing little or no degradation under environmentally relevant conditions. Furthermore, in aqueous systems, halogenated organic compounds are expected to degrade via substitution of a Br atom with a hydroxyl group. Replacement of a Br

atom by a hydrogen atom (e.g. reductive debromination) is only anticipated in organic solvents (Norris et al 1975). Thus, if DBDPO were to photodegrade in the environment, reductive debromination would not be the expected pathway. Finally, in the environment, DBDPO is likely to be adsorbed to bulk matrices, and only a small fraction of that present (i.e. that near the exposed surface) would be exposed to light and therefore available for photodegradation to occur.

Studies carried out using organic solvents indicate that products such as lower brominated diphenyl ether congeners (which are potentially more toxic and accumulative than the parent compound) and in some cases polybrominated dibenzofurans are formed from DBDPO under UV or natural sunlight (Watanabe and Tatsukawa 1987). However, organic solvents act as hydrogen donors in these reactions and affect the products formed. Degradation of DBDPO under more environmentally relevant conditions using solid matrices in contact with water and either natural or artificial sunlight, provide little if any evidence for the photolytic degradation of DBPDO (Jaffvert and Hua 2001). Little or no evidence of photolysis of DBDPO was detected when the molecule was adsorbed to sand or humic acid coated sand and exposed to sunlight. Further, no evidence for the formation of 2,2',4,4'-TetraBDE was found (Jaffvert and Hua 2001, Sellstrom 1998).

4.3.3 Potential for Biological Degradation of DBDPO

No study has reported metabolism of DBDPO to lower brominated diphenyl ethers.

DBDPO is very poorly absorbed by the rat or fish. Oral absorption in the rat has been reported as 0.3-2% of the dose. The uptake of DBDPO from a DBDPO mixture (Dow FR BA 300) when force-fed to fish was <0.005% of the dose (Kierkgaard et al. 1999). DBDPO BCF in fish is < 50. Due to the very poor uptake, minimal levels of DBDPO would be available for systemic metabolism. Further, Kierkegaard et al. (1999) concluded that there was no evidence that DBDPO was debrominated in wild fish to the major PBDEs detected in fish, 2,2',4,4'-TetraBDE, 2,2',4,4',5-PentaBDE, or 2,2',4,4',5,6-PentaBDE, and that DBDPO was not a source of the Te/PeBDEs detected in wild fish.

Studies performed by NTP (1986) indicate at low levels in the diet (277 ppm pre-treatment) only about 2% of the dose was eliminated as DBDPO metabolites, and that much of this metabolism apparently took place in the gut. The percentage eliminated as metabolites increased with increasing dose so that at 50,000 ppm, about 30% of the dose was eliminated as metabolites. Based on this work, at environmental levels $\geq$ 98% of DBDPO is expected eliminated as the parent molecule.

NTP's work also demonstrated that DBDPO, and any metabolites, were rapidly cleared from the body. This rapid elimination of ^{14}C-DBDPO-associated activity argues against accumulation of metabolites. NTP's work, conducted at very high dose levels, also indicates a lack of toxicity associated with DBDPO and any metabolites.

5.0 EXPOSURE ASSESSMENT

The objective of the exposure assessment component of the VCCEP is to quantify the levels of exposure to DBDPO experienced by children. The U.S. Environmental Protection Agency (EPA) has suggested that this will involve quantification of the following:

- What are the sources of exposure (e.g., environmental releases, consumer products)?
- What are the pathways of exposure (e.g., breathing air, drinking water, eating food, contact with skin)?
- What are the chemical concentrations in the various media?
- What are the frequency and duration of chemical exposures?
- Who and how many children are exposed?

The VCCEP guidance suggests that a Tier I exposure assessment should contain "at a minimum…screening level (or, if available, better) information on exposure from manufacturing supplemented with relevant screening level data on downstream processing and use activities and specific information on children's exposures, if available." In addition, the VCCEP guidance suggests that the Tier I exposure assessment should "generate conservative, quantitative estimates of exposure." With regard to the availability of data, the VCCEP guidance suggests, "The screening approach generally involves using readily available measured data, existing release and exposure estimates and other exposure-related information."

There have been at least two recent evaluations conducted to address the potential health risks due to DBDPO (NAS 2000; ECB 2002) and one thorough review of the toxicology and exposures to DBDPO (WHO 1994). The National Academy of Sciences (NAS) evaluated the use of DBDPO in textiles, including child-specific activities that might result in their increased exposure potential (e.g. mouthing textiles). The European Chemicals Bureau (ECB) evaluated exposures to DBDPO via the general environment. Both evaluations concluded that exposures via these two pathways did not pose a health risk to the general population. The World Health Organization (WHO) (1994) concluded that exposures to DBDPO could occur in the course of manufacture and formulation into polymers, and that exposure of the general population to DBDPO was insignificant (WHO 1994). These three evaluations indicate that exposures to DBDPO are minimal and not likely to pose a health risk, but with the exception of NAS's assessment of upholstery textiles, did not explicitly address a child's exposure to DBDPO. The following outlines the approach to calculating a child-specific exposure assessment for DBDPO, per the requirements of the VCCEP program.

Based on DBDPO's applications, the following are plausible scenarios by which children might be exposed to DBDPO: exposures secondary to manufacturing of DBDPO, exposures related to consumer products containing DBDPO, and exposures from the general environment (food, water, air, soil, dust, etc.).

5.1 Occupational Exposure

The American Industrial Hygiene Association (AIHA) established a Workplace Environmental Exposure Level (WEEL) for DBDPO of 5 mg/m^3 based on DBDPO's toxicology data (AIHA 1996). A WEEL is the level at which at workers could be exposed every day for an 8-hour shift with the expectation of no adverse effects. The U.S. Occupational Safety and Health Agency (OSHA) has not set a Permissible Exposure Limit (PEL) for DBDPO. However, OSHA has set a PEL of 5 mg/m3 for the "respirable fraction of particulates not otherwise regulated", e.g. nuisance dusts. Thus, the AIHA WEEL for DBDPO is equivalent to that of a nuisance dust.

Workplace exposures to DBDPO may occur at a) manufacturing, and b) formulation into the resin or liquid polymer dispersion. DBDPO is manufactured in a closed system by the reaction of bromine with diphenyl oxide. The point at which exposure could occur during manufacture is when DBDPO is transferred into bags for shipping. Likewise, the point at which worker exposure is most likely during formulation is when the bags of flame retardant are emptied into a hopper prior to mixing. Once formulated, DBDPO is encased in the polymer matrix and the potential for worker exposure is negligible.

Theoretically, workplace exposure could occur via the dermal or inhalation routes. DBDPO's physical and chemical properties make the probability of systemic absorption following dermal (Section 5.1.1) or inhalation (Section 5.1.2) exposure very low. DBDPO is a large molecule of high molecular weight (959.17) with negligible water solubility (<0.1 ug/L), and is likely to diffuse through biological membranes only with great difficulty. This assumption is borne out with pharmacokinetic studies that demonstrate DBDPO's poor bioavailability. DBDPO's vapor pressure (4.63×10^{-6} Pa) is such that volatilization is not expected to be a source of inhalation exposure. Occupational exposure to dusts may occur, and the particle size of the DBDPO commercial product is within the inhalable and/or respirable range. The particle size used resin application is ~5 microns, whereas that used in textile applications is finely ground to ease its dispersion in latex coatings. Any DBDPO particles present in air are likely to be associated with larger dust particles due to DBDPO's affinity for adsorption (estimated $K_{oc} = 1.796 \times 10^6$) (Meyland and Howard 1999). It is likely that the primary routes of absorption in the workplace are via incidental ingestion resulting from inhalation (and mucociliary escalator effect) and contaminated clothing and surfaces.

Theoretically, the flame retardant textile backcoat could crumble during fabrication of upholstered furniture. Any particles generated would likely be too large to be respirable. In addition, for systemic absorption to occur, not only would the particles need to be inhaled or ingested, but also DBDPO would have to diffuse out of the polymer prior to its absorption. Systemic absorption of significant amounts as a result of crumbling of the backcoat is highly unlikely.

An additional occupational exposure scenario explored in the published literature is electronics recycling, computer repair and rubber manufacture. DBDPO, and other polybrominated diphenyl oxide (a.k.a. ether) isomers, was detected in Swedish workers engaged in dismantling electronic equipment (Sjodin et al. 1999; Sjodin 2000) and in Swedish computer technicians (Hagmar et al.

2000). This work was performed as a Ph.D. research project (Sjodin 2000). These findings are discussed in Section 5.1.2 where the measured workplace air levels (0.0002 mg/m^3) are compared to the AIHA WEEL for DBDPO of 5 mg/m^3. More recently, Thuresson et al. (2002a,b) also reported detection of DBDPO in Swedish workers engage in rubber manufacturing and electronic shredding operations. Occupational blood and air levels are summarized in Table 5-1.

Table 5-1. Measured DBDPO human serum and air concentrations in various occupations.

Type of Work	DBDPO Serum Levels (pmol/g lipid)		DBDPO Air Concentration	Reference
	Median	Number of Individuals		
U.S.				
Manufacture	N.D.*	39 (all male)	0.21-5.9 mg/m3	Bahn et al. 1980; Bialik 1982
Sweden				
Electronics Recycling	5	19 (15 males, 4 females)	36 ng/m3	Sjodin et al. 1999; Sjodin 2000
Computer Repair	2	19 (15 males, 4 females)	N.R.+	Hagmar et al. 2000
Rubber Manufacture	32	19 (all male)	7.6 $\pm$ 5.6 pmol/m3	Thuresson et al. 2002b
Electronics Shredding	3	5 **	13 pmol/m3	Thuresson et al. 2002a
Referents				
Hospital Cleaning	<0.7	20 (all female)	N.R.	Sjodin et al. 1999; Sodin 2000
Computer Clerks	<0.7	20 (all female)	N.R.	Sjodin et al. 1999; Sodin 2000
Abattoir Workers	3	18 (all male)	N.R.	Thuresson et al. 2002a,b

*N.D. = Not Detected (ng/ml serum)
**Gender distribution not provided.
+N.R. = Not Reported

Children's exposure to DBDPO could potentially occur during gestation or via ingestion of breast milk that might contain DBDPO resulting from lactating mothers who are exposed in the workplace. To assess the potential magnitude of exposure, we evaluated several occupational exposure scenarios for the working mother. These include workers involved in the actual manufacturing of DBDPO, or employees of companies using the chemical in specific processes (i.e., formulators). Some studies have reported detectable air concentrations and blood levels of DBDPO in workers at Swedish electronics recycling and computer repair facilities (Sjödin et al.

1999; Sjödin 2001a), and these occupations are included in this assessment. The estimated maternal occupational exposures were used to estimate an infant's exposure via breast milk.

5.1.1. Dermal

No *in vivo* dermal absorption studies of DBDPO have been performed. Nonetheless, the potential for absorption of DBDPO through the skin can be estimated based on known characteristics of dermal absorption, DBDPO's physical/chemical properties and pharmacokinetics, and the extent of dermal absorption of related compounds.

5.1.1.1.Characteristics of Dermal Absorption

The barrier function of the skin is the best that the human body possesses. "From an evolutionary standpoint, the skin did not develop as an epithelium through which absorption was intended. Quite the reverse; the architecture and biology of the skin are, in large part, directed towards the construction of a highly efficient barrier to the outward loss of water. The most superficial and least permeable skin layer, the stratum corneum, is a remarkable feat of bioengineering, both from a structural and compositional viewpoint, and provides a uniquely impressive resistance to molecular transport both from and into the body. This is the reason that transdermal delivery requires potent drugs - one simply cannot transfer very many micrograms of any compound across a small surface area in the period of a few hours. Because the principal function of the skin is to minimize transepidermal water loss, the stratum corneum is a predominantly lipophilic barrier that is particularly impermeable in a passive sense to hydrophilic drugs (including charged species)." (Guy 1996).

Dermal absorption is defined as penetration through the skin into capillary walls and the blood stream. Substances move through the skin via passive diffusion, and the anatomical structure of the skin limits absorption of most substances. Permeability is largely determined by the skin's least penetrable layer, the stratum corneum (SC). Penetration of high molecular weight substances, molecular aggregates, and particulate matter through the skin is virtually nil. In general, the criteria for significant skin absorption of foreign compounds include a molecular weight of < 500 and reasonable solubility in both water and lipid (Guy 1996). Water solubility is required because a prerequisite for absorption from any site, including the skin, is that the penetrant must be in aqueous (true) solution at the absorption site (Ritschel 1982) and is requirement for passage through the epidermis. The rate of penetration is limited more by penetration into the relatively water-rich viable epidermis than by penetration through the lipid-rich SC (Garner and Mathew 1998; Jackson et al. 1993). Nonetheless, diffusion into and through human skin is at least partially rate-limiting for all chemicals with a octanol water partition coefficient (K_{ow}) > 3 due to the lipid-rich SC intercellular space and the relatively aqueous epidermis. Dermal absorption actually decreases for those penetrants with high K_{ow}s because of this phenomena. Smaller molecules (i.e. those with relatively small molecular volumes) are more readily absorbed through the skin than larger ones. The rate of absorption is also less for large molecules than small molecules (Wester and Maibach 1983).

The relative impermeability of skin is much greater than other membranes in the body, and is much less permeable than the mucosal lining of the mouth cavity, gastrointestinal tract, rectum, and lung. In addition to being less permeable, the surface area of the skin is less than these other routes of entry into the body (Ritschel 1982). The surface area of the skin is only 1.73 m^2 in the Caucasian adult whereas the absorbing surface area of the lung is about 70 m^2. The gastrointestinal tract has an even larger surface area (120 m^2) due to small intestinal villi and microvilli. Thus, the total absorptive surface area of the skin is only ~1.4% of that of the gastrointestinal tract.

5.1.1.2 Potential for Dermal Absorption of DBDPO

DBDPO's potential for dermal absorption is low based on its physical and chemical properties and the known requirements for absorption of any compound through the skin.

DBDPO's negligible water solubility will reduce its skin absorption since a prerequisite for absorption is that the substance must be present in aqueous (true) solution at the absorption site. DBDPO's large molecular sizes and weight will also negatively impact its skin absorption since absorption of molecules weighting > 500 is severely limited. Because DBDPO's octanol water partition coefficient is > 3, diffusion into and through the epidermis is at least partially rate-limiting. This relative inability to move into and through the epidermis limits the rate at which systemic uptake could occur.

Passage through the SC and the viable epidermis into the systemic circulation requires both lipid and water solubility. DBDPO is severely limited in this respect. With measured and estimated octanol water partition coefficients > 6, DBDPO is often assumed to be highly soluble in lipid (e.g. that DBDPO is "lipophilic"). However, DBDPO's high K_{ow} is likely more reflective of its very low water solubility (hydrophobicity) than its absolute affinity for lipid (lipophilicity). DBDPO is only sparingly soluble in common organic solvents: < 0.01 wt % at 25 degrees C in acetone and methanol, and only 0.76 wt % in toluene. In fact, DBDPO is soluble to any extent in only a limited number of organic solvents.

Using polyhalogenated aromatic hydrocarbons as an example of lipophilic compounds, a main determinant of their dermal absorption is the partitioning of the highly lipophilic members of this class between the lipid-rich SC intercellular space and the relatively aqueous viable epidermis. Quantitative structure activity relationships between dermal absorption and octanol-water partition coefficient (K_{ow}) have shown that within structurally related groups of compounds, absorption increases with the K_{ow} up to a maximum since diffusion through the lipid matrix of the SC is rate-limiting. Dermal absorption then decreases with further increases in K_{ow} because diffusion out of the SC and into and through the viable epidermis becomes the rate-limiting step for highly hydrophobic penetrants (Jackson et al. 1993). Table 5-2 compares DBDPO's molecular weight and volume with two halogenated aromatic hydrocarbons, 2,3,7,8-TCDD and 2,3,7,8-TBDD, having measured dermal absorption data. TBDD has a larger molecular volume and weight than TCDD due to the presence of 4 bromine atoms versus 4 chlorine atoms. Even though both have K_{ow}'s > 6, their dermal absorption differs greatly. TBDD is poorly absorbed (~12%) while about 40% of a dermally applied TCDD dose was absorbed by the rat. In

comparison, DBDPO has a significantly greater molecular weight and molecular volume than either TCDD or TBDD. DBDPO's molecular weight is 49% greater than TBDD. Therefore, DBDPO's dermal absorption is expected to be correspondingly lower than that of TBDD, e.g. DBDPO's dermal absorption is expected to be < 12% of the dose based on this data.

TABLE 5-2. DBDPO: comparison of molecular volume and weight with 2,3,7,8-TCDD and 2,3,7,8- TBDD. Effect of molecular weight and volume on dermal absorption.

PROPERTY	TCDD[1]	TBDD[1]	DBDPO[2]
Molecular Weight (g/m)	316	492	959
Molecular Weight (vs. TCDD)	X	40% >X	67%>X
Molecular Volume (vs. TCDD)	Y	13% >Y	43%>Y
Dermal Absorption (%)	40	~12	N.M.
Water Solubility (ug/L)	N.R.	N.R.	< 0.1
K_{ow}	6.01	6.56	6.26

[1]Dilberto J et al., Toxicol. Appl. Pharmacol. 120, 315-326, 1993.
[2]Hardy, M. Proceedings of FRMP '97. Lille, France, Sept 1997.
N.M.= Not Measured
N.R.= Not Reported

Oral pharmacokinetic studies in the rat have shown DBDPO is sparingly absorbed from the GI tract (NTP 1986; El Dareer et al. 1987). Results of these studies demonstrate that after ^{14}C-DBDPO exposure, at all doses tested (250 - 50,000 ppm in the diet), greater than 99% of the radioactivity recovered was excreted in the feces within 72 hours. Concentrations of the radiolabel in all major organs and tissues were near the detection limits. Estimates of DBDPO absorption from the GI tract were calculated by comparing tissue levels after oral exposure versus intravenous administration. Absorption from the GI tract was calculated to be 0.33% $\pm$ 0.19% of the 50,000 ppm dose. Given that the GI tract has a greater absorptive surface and is more permeable than the skin, it is reasonable to conclude the amount of DBDPO absorbed from the GI tract is greater than that which could be absorbed through the skin. Skin absorption of DBDPO, if it occurs at all, should be significantly less than that absorbed orally. Therefore, DBDPO skin absorption is expected to be << 0.33% of a dermally applied dose. Thus, skin absorption is not expected to be a source of DBDPO exposure in the workplace.

DBDPO's no adverse effect level (NOAEL) in repeated dose studies is $\geq$ 1000 mg/kg/d. This NOAEL encompasses studies of prenatal developmental toxicity and assessment of the reproductive organs in subchronic/chronic studies. This high NOAEL, negligible skin absorption, the small amount of total skin surface area exposed in the workplace and the possible use of personal protective equipment indicate a high margin of safety with respect to dermal exposure to DBDPO in the workplace.

5.1.2 Inhalation

AIHA established a WEEL of 5 mg/m^3 for DBDPO. This WEEL is essentially that of a nuisance dust. Occupational exposure to dusts containing DBDPO may occur at the manufacturing site

during bagging operations or when the bags are emptied into hoppers at the processing site. The particle size used resin applications is ~5 microns, whereas that used in textile applications is finely ground to ease its dispersion in latex coatings. Any DBDPO particles present in air are likely to be associated with larger dust particles due to adsorption (estimated $K_{oc} = 1.796 \times 10^6$). DBDPO is a large molecule of high molecular weight (959.17) with negligible water solubility (<0.1 ug/L), and is likely to diffuse through biological membranes only with great difficulty based on oral pharmacokinetic studies. This, coupled with DBDPO's high no-adverse-effect level of 1,000 mg/kg/d in chronic studies, indicates the worker is not at risk of adverse effects due to dust exposure.

DBDPO oral absorption is minimal (<0.3 to 2% of an oral dose), but no data on its pulmonary absorption is available. Although the absorptive processes in the lung and gastrointestinal (GI) tract are similar, DBDPO absorption from the respiratory tract is expected to be less than from the GI tract. The respiratory membrane has a surface area of 160 m^2 versus 250 m^2 for the intestinal mucosal villi (Ritschel 1982), and the lung's absorptive surface is therefore ~64% of that of the small intestine. DBDPO has negligible solubility, and thus inhaled particle-bound DBDPO can be expected to behave similar to other inert insoluble particles deposited in the respiratory tract. Insoluble particles deposited within the ciliated airways of the respiratory tract (e.g., the nasal passages and tracheobronchial tree) undergo passive transport via the mucuciliary escalator to the pharynx and are subsequently swallowed (Lippman 1980). Insoluble particles reaching the alveoli are predominantly cleared by alveolar macrophages that phagocytize the particles and transport them proximally on the bronchial tree to be swallowed. Absorption of insoluble particles from the alveoli directly into the bloodstream is low and exceedingly slow. Thus, it appears unlikely that absorption of DBDPO from the respiratory tract is greater than that of the gastrointestinal tract.

5.1.2.1 Electronics Recycling or Computer Repair

Recent publications report detection of DBDPO in the blood of Swedish workers engaged in electronics recycling or computer repair (Sjodin et al. 1999; Sjodin 2000; Hagmar et al. 2000; Thuresson et al. 2002a) and in rubber manufacturing (Thuresson et al. 2002b). The studies in electronic recycling workers are the best documented of these papers and is discussed further in the following paragraphs.

The mean DBDPO blood levels reported were 5 pmol/g lipid in the Swedish electronics recycling workers, and 1.6 pmol/g lipid in the Swedish computer technicians. DBDPO air levels in the recycling workplace were 0.0002 mg/m^3. The PCB 153 blood levels measured in the same workers was 760 pmol/g lipid in the dismantlers and 290 pmol/g lipid in the technicians. Greater than or equal to 99% of the DBDPO detected in air at the electronics dismantling plant was associated with particulate matter (Sjodin 2000).

The amount of a substance absorbed (A_{dose}) through the respiratory tract over a given period of exposure can be calculated (Patty 1994) using the concentration in air in mg/m^3 (A_c), the duration of exposure in hours (T), the ventilation rate in m^3/hour (V), and the absorption rate (A_{bs}):

$$A_{dose} = A_c TVA_{bs.}$$

A theoretical DBDPO blood concentration can be calculated using the percent oral absorption as an indicator of respiratory uptake and the equation above. Using a maximum absorption of 2% of the dose, a ventilation rate of 10 m^3/8 hr work shift and an exposure equivalent to the AIHA WEEL (5 mg/m^3), the amount of DBDPO absorbed would be 1 mg/70 kg man or 0.014 mg/kg body weight. This is orders of magnitude less than DBDPO's reference dose (RfD) of 4 mg/kg-d calculated by NAS (see Appendix V). In the event that DBDPO's absorption was equal to 100%, the absorbed dose would still remain less than NAS's RfD. At 100% absorption and an exposure concentration of 5 mg/m^3, the internal dose would be 0.71 mg/kg body weight.

Using the equation $A_{dose} = A_c TVA_{bs,}$ a maximum absorption of 2% of the dose, a ventilation rate of 10 m^3/8 hr work shift and at maximum measured DBDPO air concentration of 0.2 ug/m^3 in the electronics dismantling plant (Sjodin et al. 1999), the absorbed dose would be 0.04 ug DBDPO/70 kg man or 0.57 ng DBDPO/kg body weight.

At a measured DBDPO serum lipid level of 4.8 ng/g lipid in the electronics dismantling workers (Sjodin et al. 1999), the DBDPO plasma level would be 0.0288 ng/ml plasma. Assuming 3,000 ml plasma in a 70 kg man and a normal plasma lipid concentration of 0.6% (Guyton 1986), the 0.0288 ng DBDPO/ml plasma represents a total blood volume content of 86.4 ng DBDPO/70 kg man or 1.2 ng/kg body weight. Thus, the theoretical DBDPO internal dose (0.57 ng/kg body weight) due to a measured air concentration of 0.2 ug/m^3 compares favorably with the actual dose of 1.2 ng/kg body weight in the electronics dismantling workers calculated from their measured blood values. The theoretical and measured values are well within the variation expected due to the assumptions used in calculating the expected values and the collection and analytical methods.

The measured DBDPO air level at the electronic recycling plant was 0.0002 mg/m (Sjodin et al. 1999). The American Industrial Hygiene Association (AIHA) evaluated DBDPO's toxicology and set a Workplace Environmental Exposure Level (WEEL) of 5 mg/m^3, e.g. that of a nuisance dust (AIHA 1996). Thus, the measured DBDPO air level at the electronics dismantling plant was 25,000 times below the AIHA level to which workers could be exposed every day with the expectation of no adverse effects. Further, using the equation $A_{dose} = A_c TVA_{bs}$ and a maximum absorption of 2%, the estimated internal DBDPO dose from an 8-hr exposure at the AIHA WEEL of 5 mg/m^3 would be 0.014 mg/kg body weight. The internal dose of the electronic recycling workers was 1.2 ng/kg or 0.01% of the internal dose that could be received at a DBDPO exposure equal to the AIHA WEEL. Finally, in the event that DBDPO absorption from the respiratory tract was greater than 2%, the internal dose of the electronic recycling workers at a measured DBDPO air level of 0.0002 mg/m^3 would remain substantially below that achievable at the AIHA WEEL. For example, if DBDPO absorption equaled 100%, the internal dose due to a workplace air level of 0.0002 mg/m^3 would be 0.004% of that dose which could be received at a DBDPO exposure equal to the AIHA WEEL.

5.1.2.2 Discussion of Blood and Air Levels

The DBDPO blood levels reported in Swedish electronics dismantling workers (5 pmol/g lipid) and computer technicians (1.6 pmol/g lipid) were extremely small and are representative of our increasing ability to detect minute amounts of chemicals in various media. Further, these values should be viewed as tentative given the difficulty of DBDPO analysis, the extremely low levels reported, and the problem of laboratory contamination contributing to measured values. The DBDPO blood levels were far below those of PCB 153 (dismantlers, 760 pmol/g lipid; technicians, 290 pmol/g lipid) measured in the same workers. Further, the electronics dismantling workers' internal DBDPO dose (1.2 ng/kg body weight) based on their measured blood level was comparable to the level expected (0.57 ng/kg body weight) calculated from the measured air levels. A similar comparison was not possible for the computer technicians because air values were not reported for that workplace. In addition, the DBDPO measured air level (0.2 ug/m^3) in the electronics recycling plant was approximately 25,000 times below the acceptable DBDPO workplace exposure level of 5 mg/m^3. This acceptable workplace exposure level, set by the AIHA, was based on an evaluation of DBDPO toxicology data. Thus, no impact on human health from DBDPO is expected in either the electronics dismantlers or computer technicians.

5.1.3 Occupational Exposure Conclusions

DBDPO is used to flame retard synthetic polymers used in electrical and electronic equipment and upholstery. Once encapsulated in a polymer matrix, DBDPO will be essentially unavailable. Therefore, reasonable exposure routes/scenarios are as follows: a) inhalation of dust and/or dermal contact at manufacture and b) at formulation prior to encapsulation in polymer or inclusion in the textile dispersion.

The most likely point at which exposure could occur during manufacture is when the flame retardant is transferred into bags for shipping. Likewise, the point at which worker exposure is most likely during formulation into the polymer dispersion is when the bags of DBDPO are emptied into a hopper prior to mixing the dispersion. Once formulated into the polymer dispersion, DBDPO is encased in the polymer matrix and the potential for worker exposure is negligible.

Theoretically, workplace exposure could occur via the dermal or inhalation routes. DBDPO's low vapor pressure makes vapor inhalation an unrealistic exposure scenario. DBDPO's potential for dermal absorption is low based on its physical and chemical properties and the known requirements for absorption of any compound through the skin. DBDPO's very low water solubility and very high molecular weight effectively precludes any significant skin absorption, and DBDPO's skin absorption is estimated at <<0.03% of a dermally applied dose. Occupational exposures to dusts may occur; however, DBDPO is a very large poorly absorbed molecule that exhibits little toxicity, and for which AIHA has assigned a WEEL of 5 mg/kg/d. The combined effects of poor absorption and minimal toxicity (NOAEL μ 1,000 mg/kg/d) indicate adverse effects should not occur as a results of occupational exposure. Nonetheless, workplace controls should focus on points where fine-particle-size-DBDPO may become airborne to limit inhalation exposure. This would be during bagging at manufacture and at formulation prior to inclusion in the resin or polymer dispersion.

5.2 General Population

DBDPO is not sold directly to the public, but may be present in various consumer goods; e.g. electrical and electronic equipment (primary use) and upholstery textiles (secondary use). A typical U.S. example is in the cabinet backs of television sets where DBDPO is used at a level of approximately 12%. Upholstered furniture in commercial settings in the U.S. is required to met federal flammability standards and may utilize upholstery textiles that are flame retarded with a backcoating containing DBDPO at ~5 mg/m^2. Residential furnishings, except in the state of California, are not required to met a comparable standard, although the Consumer Product Safety Committee (CPSC) is considering implementing such a standard. CPSC is also considering a standard for mattresses.

DBDPO exposure to a child could potentially occur via direct contact with consumer products containing DBDPO found in the typical U.S. home. Such exposures include direct dermal contact with fabric, inhalation of vapors and particles that are derived from fabric and electronic equipment, and ingestion following oral contact with both types of products. DBDPO's physical/chemical properties make these unlikely exposure scenarios. In infants or young children, another route could be oral through chewing or sucking on the upholstery textile.

5.2.1. Upholstery Textiles

The U.S. National Academy of Sciences (NAS) was asked by the Congress to evaluate the consumer risk of flame retardants that could be used to meet CPSC's proposed standard for upholstered furniture. The evaluation was published in the document "Toxicological Risks of Selected Flame-Retardant Chemicals" which is available on-line at www.nap.edu (NAS, 2000). DBDPO was one of the flame retardants evaluated (See pages 72-98 of that report), and the NAS's quantitative toxicity assessment of DBDPO is provided in Appendix V.

5.2.2 Electrical and Electronic Equipment

DBDPO has an extremely low vapor pressure, thus vaporization with subsequent inhalation will not occur to any significant extent once incorporated in a polymer matrix such as HIPS or a latex fabric backcoatings. Once encapsulated in a polymer matrix, DBDPO will be essentially unavailable. This prediction is borne out by the barely detectable DBDPO air level, 0.0002 mg/m^3, reported in the Swedish electronics recycling plant (Sjodin et al 1999).

Because of the reasons cited here and in the earlier discussion of dermal absorption, dermal absorption of DBDPO in this context is not anticipated.

5.3 U.S. Monitoring Data

A third potential exposure source is via environmental media (foods, water, air, soil, sediment, dust, etc.). Exposures among the general population are considered to be insignificant (WHO 1994). Nonetheless, for the purposes of this VCCEP program, this potential exposure source is evaluated using the available data. To supplement the monitoring data, DBDPO's predicted

behavior in the environment is also briefly reviewed. DBDPO is expected to partition to soil and sediment (~99%) if released to the environment. DBDPO is expected to bind to particulate matter in soil and sediment and be essentially immobile. DBPDO is not expected to volatilize from water. Waste-water treatment plants are predicted to remove the majority of the DBDPO in the effluent and to do so via sludge adsorption.

Concentrations of polybrominated diphenyl oxides/ethers (PBDPO, PBDEs) have been reported in many environmental and biological samples. However, the majority of studies reported only total PBDPOs or measured only the lower brominated congeners. DBDPO, specifically, has been measured in a smaller subset of studies, most of which were conducted in Europe and Japan. The European Union included a comprehensive compilation of the European and Japanese data (ECB 2002), and these data are also summarized in papers by Hardy (2000) and de Wit (2002). The available data for the U.S. are discussed below.

5.3.1 Sediment

Zweidinger et al. (1979) analyzed sediment near a DBDPO manufacturing site. Levels ranged from N.D. to 14,000 ug/kg. The detection limit was ~ 100 ug/kg. DBDPO was detected at 13 μg/kg in a sample of surface sediment from a sediment core collected from the western basin of Lake Ontario (Alaee 2001).

5.3.2 Sewage Sludge

Hale et al. (2001) reported detectable levels of DBDPO in some sewage sludge samples collected from four different regions in the U.S. DBDPO concentrations ranged from < 75 to 9,160 ug/kg dry wt. DBDPO was also detected in sewage sludge (1,470 ug/kg dry wt) collected from a sewage treatment plant located in a region of the U.S. where DBDPO-treated upholstery textiles are manufactured (Hale et al. 2002).

In some parts of the U.S., sewage sludge undergoes further treatment and is then applied to agricultural soils as a fertilizer. Thus, DBDPO could be present in soils used for agricultural purposes and the potential for its uptake into food crops or by grazing farm animals is considered. No studies have evaluated the potential for uptake of DBDPO by plants, but studies have demonstrated that DBDPO is not toxic to 6 species of terrestrial plants (Porch and Krueger 2001) or to earthworm survival or reproduction (Aufderheide et al. 2001). DBDPO's potential for uptake by plants can be evaluated based on its physical/chemical properties, data on related compounds, and plant physiology.

Although DBDPO data is not available, information is available on polybrominated biphenyl (PBB) plant uptake and translocation. No detectable PBB was found in plants collected from the 10 most highly contaminated fields in Michigan, U.S. (Jacobs et al. 1978). Autoradiograms of corn and soybean seedlings grown in the presence of ^{14}C-PBB showed no translocation (Chou et al. 1976). PBB was found associated with the roots of these plants, but due to the insolubility of PBB in water, the PBB was primarily associated with the root surface (e.g. physically adsorbed to the root's surface). The amount of PBB associated with (not absorbed by) three root crops

(onions, radishes, carrots) grown in two PBB-contaminated soils of differing organic matter and clay content ranged from 0 to a maximum of 0.5% of the soil concentration (Chou et al. 1976).

Three root crops, radishes, carrots, and onions, were grown in two PBB-contaminated soils of differing organic matter and clay content (Chou et al. 1976). No PBB uptake was found, but trace amounts of PBB were associated with the edible portions of each crop (Table 5-3). No PBB were associated with the roots of radishes, carrots or onions grown in high organic carbon soil contaminated with 100 ppb PBB. A maximum of 0.5% of the soil concentration was found in carrots grown on low organic carbon soils contaminated with 100,000 ppb PBB; high organic soil reduced the association to 0.1% of soil concentration. The authors concluded these trace amounts were probably associated with root surfaces, because Iwata et al. (1974) found 97% of polychlorinated biphenyl (PCB) residues in carrot roots in the peel and similar results were reported previously for DDT and other organochlorine pesticides in the soil in which carrots were grown.

Radishes grown in a garden (estimated PBB concentration = 500-1000 ppb) located in a heavily contaminated field (500-1000 ppb) did not contain PBB. Chou et al. concluded: "From these results plus our previous results of greenhouse and field studies in which we found no PBB in plant tops, we conclude that little if any PBB will be transferred from contaminated soil to plant tops. Thus, recontamination of animals from feeds grown in contaminated soil will likely not occur. Although some root crops from very highly contaminated soil might contain traces of PBB, much of this PBB could probably be removed by peeling."

TABLE 5-3. PBB found associated with radish, carrot, and onion roots after 6, 9, and 10 weeks, respectively, of growth in PBB contaminated soil. Detection limit = 0.3 ppb.

Soil Type	PBB Added to Soil	PBB in plant roots (ppb)		
	(ppb)	Radishes	Carrots	Onions
Loamy Sand	100	7	20	ND
(Low Carbon)	100,000	49	535	63
Clay Loam	100	ND	ND	ND
(High Carbon)	100,000	44	117	34

Plants may be a source of exogenous chemicals via retention by root surfaces, root uptake and translocation, and foliar uptake. Transfer to animal tissues can occur via soil and herbage ingestion (Wild and Jones 1992). "Assuming degradation of the compound does not occur within the plant, and plant root uptake and translocation of organic chemicals from the soil is passive, plant uptake can be described as a series of consecutive partition reactions. Partitioning occurs between soil solids and soil water, soil water and plant roots, plant roots and transpiration stream, and transpiration stream and plant stem. This partitioning can be related to the octanol:water partition coefficient, such that compounds with high log K_{ow} values (e.g. PAHs, PCBs, PCDD/Fs) are most likely to be sorbed by the soil and/or plant root. Chemicals with lower Kow values are likely to be translocated within the plant and may reach the above ground portions of the plant."

Wild and Jones (1992) go on to state "Relatively few studies have investigated the plant uptake of organic compounds from sludge-amended soils. However, some general comments can be made from the studies: (a) to date studies have been confined to relatively few groups of compounds, namely PCB, PAHs and some other organochlorines; (b) these compounds are generally not taken up into the above-ground portion of crop plants; (c) there is some evidence of slight enrichment of some compounds in some root crops, but the transfers are very inefficient, and consequently the BCFs are very low. Generally enrichments are confined to the root peels which are normally removed before consumption; (d) it is worth noting that the studies to date have focused on compounds which, because of their physico-chemical properties, are thought less likely to be transferred efficiently into crop plants. Future studies should focus on semi-volatile compounds of intermediate log Kow, and some polar compounds."

Based on the screening approach of Wild and Jones (1992), which uses log K_{ow} to predict plant uptake, DBDPO is predicted to have high adsorption to soil, low volatilization from soil, low degradation in soil, low potential for leaching, high retention by root surfaces, low potential for root uptake and translocation, low potential for foliar uptake, high potential for transfer to animal tissues by soil ingestion and low potential for transfer to animal tissues by foliage ingestion.

This screening approach identifies two possible routes of exposure to DBDPO following application of sewage sludge to agricultural soil: retention on root surfaces and transfer to animal tissues by soil ingestion. Based on DBDPO's log K_{ow}, adsorption to root surfaces appears likely. Although it seems likely that DBDPO could adsorb to root surfaces and thereby be ingested, DBDPO's known poor absorption from the gastrointestinal tract (<0.3-2% of the oral dose), makes potential for systemic exposure very low. Similarly, the potential for transfer to animal tissues by soil ingestion is based on the soil half life and log K_{ow}, and does not does not take into account actual animal absorption data. Since DBDPO is known to poorly absorbed from the gastrointestinal tract (<0.3-2% of the oral dose), the potential transfer of DBDPO to animal tissues by soil ingestion is therefore low.

In summary, based on the screening approach of Wild and Jones (1992) and PBB plant uptake data (Chou et al. 1976; Jacobs et al. 1978; Iwata et al. 1974) DBDPO is expected to sorb to root surfaces if present in soil, but not to be transferred into the interior of the root. The amount of DBDPO available for adsorption to roots is expected to be some fraction of the total soil content due to extensive binding to soil particles (K_{oc} = 1.796 x 10^6). DBDPO is not expected to be absorbed into the root nor is it expected to be transferred to foliage. Based on pharmacokinetic data, mammalian uptake of DBDPO after ingesting root crops would be < 0.3-2% of the oral dose. Thus, exposure to DBDPO as a result of its presence in agricultural soils due to the application of sewage sludge is expected to be insignificant.

5.3.3 Air

Sampling over a 3 year period (1997-1999) at 4 locations on the shores of the Great Lakes detected DBDPO only at trace levels in the Chicago filter samples. The average concentration over the three years in the Chicago area was 0.3 pg/m^3 and ranged from 2.0×10^{-7} μg/m^3 to

3.5×10^{-7} μg/m³ (Strandberg et al. 2001). DBDPO was not detected in any of the three years in samples collected from the shores of Lake Superior and Lake Erie, and a site on Lake Michigan farther north than Chicago (D.L. = 0.1 pg/m^3).

Samples of dust and smoke aerosols that settled east of the World Trade Center (WTC) in lower Manhattan after the collapse of the WTC were collected 5 or 6 days after September 11, 2001 were analyzed for a wide variety of components including volatile/semivolatile organic compounds, metals, polychlorinated dioxins and furans, polychlorinated biphenyls and PBDEs. DBDPO was detected in all three samples ranging in concentrations from 1,330 to 2,660 ug/kg dry weight (Lioy et al 2002).

5.3.4 Poultry, Meat and Dairy Products

Due to its poor bioavailability, poultry, meat and dairy products are not expected to be a human exposure source of DBDPO. Only limited monitoring data is available. DBDPO was not elevated above background levels (0.87 ng) in most samples of chicken fat (n=13) collected from four different areas of the U.S.; matrix and laboratory blanks contained low, but detectable, levels of DBDPO. Tetra- (0.56-10.58 ng/g), penta- (0.42-16.97 ng/g), and hexaBDE (0.02-4.63 ng/g) congeners were generally present at 3-100 times the background. Mono- to deca-brominated congeners were not detected in chicken feed or its ball clay additive (Huwe et al. 2002).

5.3.5 Fish

Fish consumption is not expected to be a source of human exposure to DBDPO. DBDPO has not been detected in fish collected in the U.S. (Table 5-4). DBDPO has negligible water solubility (<0.1 ug/L) and will preferentially partition to soil and sediment in the environment. Thus, any exposure to fish via water will be low. Further, DBDPO has been shown not to bioconcentrate in fish (CITI 1992; Kierkegaard et al. 1997, 1999). Bottom feeding species could conceivably be exposed to DBDPO-containing sediment. However, limited uptake by these species is expected due to DBDPO-sediment binding and DBDPO's large molecular weight and size. Thus, any exposure to humans would be extremely limited.

TABLE 5-4. Analytical results of freshwater fish collected in U.S. waters for DBDPO content.

Species	Location & Year Collected	DBDPO Level	Number of Samples	Reference
Various Fish spp.	3 Lakes, US, 2000	N.D. (D.L. = 1.5 ng/g wet wt)	20	Dodder et al. 2001. Environ. Sci. Technol., 36:146-151.
Carp	River, US, 1991	N.D. (D.L. = 0.1 ug/kg wet wt)	48	Loganathan, B et al. 1995. Environ. Sci. Technol., 29:1832-1838.
Salmon	Alaska, 2000*	N.D. (D.L. = 0.65 pg/g wet wt)	2	Easton et al. 2002. Chemosphere, 46:1053-1074.

*DBDPO was also not detected in 6 samples of wild or farmed salmon or fish-food collected in Canada in 2000. D.L. = 0.65 pg/g wet wt.

5.3.6 Human Tissues

A few studies have analyzed U.S. human adipose tissue, serum, and hair for the presence of DBDPO.

Responses were noted that corresponded to qualitative criteria for hexa- through octabromodiphenyl oxide congeners in adipose tissue collected from the general U.S. population in fiscal year 1987. This adipose tissues was collected as a part of the National Human Adipose Tissue Survey (NHATS 1990). A subsequent study analyzed selected composites from the 1987 NHATS repository (Cramer et al. 1990; Stanley et al. 1991). The presence of hexa- through octabromo congeners was confirmed, and nonabromo- and DBPDO were also identified. DBDPO was detected in 3 of the five extracts analyzed. The concentrations ranged from N.D. to 700 pg/g adipose.

Twelve samples collected in 1988 from a general population of U.S. blood donors in the Midwest were analyzed approximately 10 years later for DBDPO content. DBDPO concentrations in the serum ranged from <1 pmol/g lipid to 35 pmol/g lipid (equivalent to < 0.96 ng/g lipid to 33.6 ng/g lipid) (Sjödin et al. 2001b). Only five of the twelve samples were above the limit of quantification (LOQ = 1 pmol/g lipid).

Out of three composite hair samples collected in a barbershop located in the vicinity of DBDPO manufacture, one composite had a DBDPO concentration of 5 μg/kg, and a second had a low level of DBDPO detected, but not quantified (DeCarlo 1979).

5.3.7 Breast Milk

As discussed in Section 1, DBDPO has not been reported in breast milk. DBDPO is not expected to be transferred to breast milk based on its physical/chemical properties, pharmacokinetics and the physiology of milk production. These factors, along with a summary of polybrominated diphenyl oxide/ether (PBDPO; PBDE) isomers/congeners reported in breast milk are discussed below.

5.3.7.1 Transfer into Breast Milk

Published information on the physiology of xenobiotic excretion into breast milk is generally limited to pharmaceuticals; however, this information is relevant to all xenobiotics (Anderson 1991; Pons et al. 1994; Loebstein et al. 1997; Bailey and Ito 1997; Wilson 1983). Excretion into breast milk depends mainly on the passive diffusion of the unionized unbound drug from the bloodstream into milk along a concentration gradient. Although active or facilitated transport has been described for some endogenous substances across some membranes in the body, no drugs are known to enter human milk by these mechanisms. Because most drugs are excreted into milk by passive diffusion, the drug concentration in milk is directly proportional to the corresponding concentration in maternal plasma. Diffusion into milk is a minor route of drug elimination (usually <1% of a maternal dose), and, generally, drugs given to nursing mothers

reach infants in much smaller amounts than drugs given to pregnant women. For most drugs the amount ingested by the infant rarely attains therapeutic levels.

Drugs pass across the mammary epithelium by passive diffusion down a concentration gradient formed by the nonionized free drug on each side of the cell membrane. The membrane acts as a semipermeable lipid barrier, similar to other membranes in the body. Transit through membranes is via the lipid portion (for unionized drugs with high lipid solubility) or via water filled pores surrounded by proteins (for water soluble presumably low molecular weight drugs). Once inside the mammary alveolar cell, a drug may be metabolized. Drug in the alveolar cell may be expelled into the milk-containing lumen concomitantly with secretion of fat droplets and protein granules. Drug reuptake from the milk into plasma occurs and there is rapid bi-directional diffusion and rapid equilibration of drug between plasma and milk for the majority of drugs.

Passive diffusion of xenobiotics into breast milk is affected mainly by the drug's disposition in lactating mothers, by the physicochemical properties of the molecule and by the protein and lipid contents of breast milk. Drugs with molecular weights (< 200 D) diffuse more readily than drugs with larger molecular weights. Small, e.g. <200 D, highly lipid-soluble, unionized drugs are expected to diffuse more rapidly than other drugs. Lipid soluble drugs concentrate in milk lipids, and their milk to plasma concentration ratio is dependent on the lipid concentration of milk. Protein content is lower in milk (8-9 g/L) than in plasma (75 g/L), and protein binding in milk is thus lower than protein binding in plasma.

The complexity of the fluids on both sides of the mammary epithelium results in several simultaneous equilibration processes: ion trapping, protein binding, and lipid partitioning.

5.3.7.2 Ion Trapping

The most important equilibration process occurs across the mammary epithelium between the unbound, nonionized drug in the bloodstream and the aqueous phase of the milk. Because the pH of milk is typically slightly acid relative to that of plasma, the pH partition theory (Henderson-Haslebach equation) predicts that the ionized form of a weak base concentrates in milk in a process commonly called "ion trapping". Conversely, a weak acid is "trapped" in plasma because of the relatively greater concentration of the ionized form there. Ion trapping affects weak acids with a pKa of ~ 8 or less and weak bases with a pKa of 6 or greater. Weaker acids and bases act as noneletrolytes and do not undergo ion trapping.

Ion trapping will not affect DBDPO concentrations since it has no ionizable groups.

5.3.7.3 Protein Binding

Both plasma and milk contain proteins that can bind drugs. The total plasma protein concentration is ~ 75 g/L, whereas milk contains ~ 8-9 g/L. Of the plasma proteins, 45 g/L is albumin, a major drug-binding protein. In contrast, the albumin concentration in milk is only ~0.4 mg/L, and the major proteins in milk are casein, alpha-lactalbumin, lactoferrin, and

immunoglobulin A. Casein is apparently the major drug-binding protein, but none of these proteins binds drugs well and quantitatively important binding of drugs to milk proteins does not occur except in the case of drugs that are also extensively bound to plasma proteins. The net effect of protein binding is that highly protein-bound drugs tend to remain in the plasma and pass into the milk in low concentrations.

Protein binding is not expected to affect DBDPO concentrations. DBDPO is not known to be protein bound, but protein binding would serve to decrease DBDPO available for transfer into milk.

5.3.7.4 Lipid Partitioning

Unlike plasma, milk contains emulsified fat, ranging from 3-5%. Milk fat has the potential to concentrate lipid-soluble drugs, causing the total amount of drug in milk to increase. For highly lipid-soluble drugs such as diazepam and chlorpromazine well over half of the total amount of drug in milk is found in milk fat. Nevertheless, because the amount of fat in milk is low compared with the total volume of milk, the net effect of lipid partitioning on the total amount of drug reaching the infant is usually relatively small.

Lipid partitioning is not expected to affect DBDPO concentrations. DBDPO does not show an appreciable affinity for lipids.

5.3.7.5 Non-Steady State Conditions

The previous discussion relates to constant, steady state conditions in which plasma and milk drug concentrations have come to equilibrium. Because constant plasma concentrations are the exception, other factors must be taken into account during intermittent drug administration to the mother. The shorter the half-life of a drug, the greater the fluctuations in plasma concentrations during intermittent administration. A drug that enters the milk rapidly will achieve a greater initial concentration in milk relative to the plasma concentration than a drug that enters slowly. Because milk is produced and periodically emptied from the breast during nursing, slowly equilibrating drugs may never achieve high concentrations in milk. The physicochemical factors that determine the rate of passage into milk are the drug's lipid solubility and its molecular weight. Lipid solubility is important because the drug must dissolve in the lipid mammary epithelial cell membrane (on both entering and exiting the cell), whereas low molecular weight favors rapid diffusion across the aqueous interior of the cell. Another factor that comes into play during intermittent drug administration is retrograde diffusion of drugs from the milk back into plasma. The rate and extent of retrograde diffusion are determined by the same physicochemical factors governing passage from the plasma into milk. Many have the impression that once a drug has passed into milk, it will remain until the breast is emptied. However, because of retrograde diffusion, this is not the case.

5.3.7.6 Impact of Disposition on PBDE, PBB, PCB Content in Milk

DBDPO has not been reported in breast milk. Other brominated aromatics have been detected in milk, and include polybrominated diphenyl oxides/ethers (PBDPO, PBDE), polybrominated biphenyls (PBB) and polychlorinated biphenyls (PCB). Information on the pharmacokinetics and milk concentrations of these compounds can be of value in understanding the potential for DBDPO to be eliminated in milk.

Passive diffusion of substances into breast milk is affected by the substance's disposition in the lactating mother. Halogen content affects the absorption of PBDE/PBDPO, PBB and PCB congeners from the maternal gut and their subsequent transfer from plasma to depot fat. Studies with PCB have shown that the number of chlorines on the biphenyl molecule generally affects absorption, excretion, and toxicity. In addition, the behavior and toxicity of some chlorinated biphenyls is influenced by the chlorine atoms' position on the biphenyl molecule. Similar differences have been observed with the commercial PBDE/PBDPO products, individual PBDE/PBDPO isomers, and individual PBB congeners.

Maternal Oral Absorption. As a general rule, the percent absorption of PBBs and PBDE/PBDPOs declines with increasing halogenation (Fig 5.1). DBDPO, with 10 bromine atoms, is very poorly absorbed (<0.3-2% of an oral dose) (El Dareer et al. 1987). Only ~ 35% of octabromobiphenyl (OBB; 8 bromine atoms/molecules) was absorbed (Norris et al. 1973). In contrast, approximately 90% of an oral dose of 2,2',4,4',5,5'-HexaBB (the major component of the former PBB product known as FireMaster BP-6) was absorbed from the intestine (Matthews et al. 1977). When FireMaster BP-6 was fed to dairy cattle, a large proportion of its HeptaBB content was apparently excreted in feces without absorption (Willet and Durst 1978). The opposite occurred with the PentaBB component of FireMaster BP-6. PentaBB was more efficiently absorbed, and obtained equilibrium between plasma and tissues at a higher relative concentration than its concentration in the FireMaster BP-6 test article. A high absorption of ^{14}C-2,2',4,4'-TetraBDE and ^{14}C-2,2',4,4',5-PentaBDE was also reported (Orn and Klassen-Wheler, 1998; Hakk et al., 1999).

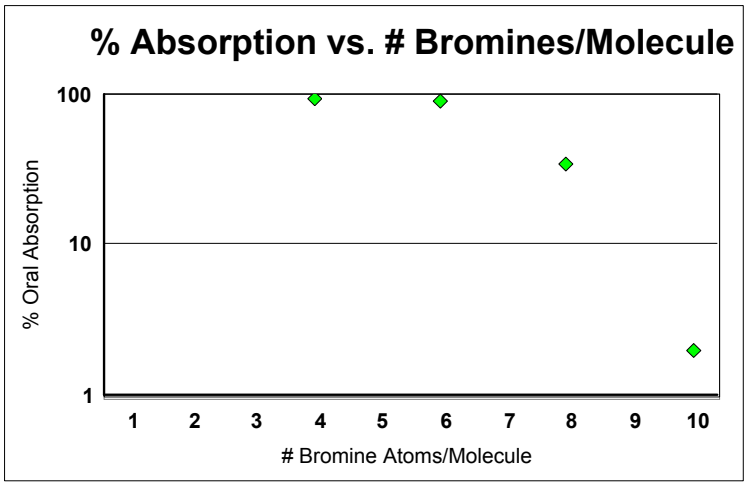

Figure 5-1. Decline in the percent of the oral absorption of PBB or PBDE/PBDPO congeners with increasing bromine content in the molecule.

Maternal Fecal Elimination. Elimination is influenced by both the degree and position of halogenation on the biphenyl or diphenyl oxide molecule, and as a general rule, increases as the number of bromines increases on the biphenyl or diphenyl oxide molecule (Figure 5.2). DBDPO was rapidly eliminated in the feces (>99% of the dose in 72 hr) with a half-life of ~ 24 hours (NTP 1986; El Dareer et al. 1987). Rats also eliminated OBB rapidly. After a single oral dose of ^{14}C-OBB, 65% of the isotope appeared in the feces in 1 day and a total of 73% was excreted in feces in 16 days (Norris et al. 1973 as cited by Di Carlo et al. 1978). In contrast, excretion of ^{14}C-2,2',4,4',5,'5-HexaBB by rats was extremely slow. After intravenous administration of a single dose, only 6.6% of the label was excreted in feces over a period of 6 weeks and the total urinary excretion was less than 0.1%. Mathematical extrapolation of the excretion data "indicates that only 9.5% of the total PBB dose would ever be excreted in the feces." Thus, elimination of 2,2'4,4',5,5'-HexaBB appeared to depend both on the number of bromines and their position (Matthews 1977 as cited by Di Carlo et al. 1978). A similar pattern was found for 2,2'4,4',5',5-HexaCB: only 2% of this hexa-chlorinated biphenyl was eliminated in the feces in 21 days. In contrast, 2,2',3,3',6,6'-HexaCB was readily metabolized and cleared (~93% of the dose). Thus, for hexa-halogenated biphenyls, the position of the halogens appears to be a very important determinant of clearance. 2,2',4,4',5-PentaBDE was poorly metabolized in the rat, but 43% of the oral dose was excreted within 3 days (Hakk et al. 1999). 2,2',4,4'-TetraBDE was readily absorbed, poorly metabolized and slowly eliminated by the rat with less than 0.5% of the oral dose eliminated in 5 days (Orn and Klassen-Wheler 1998).

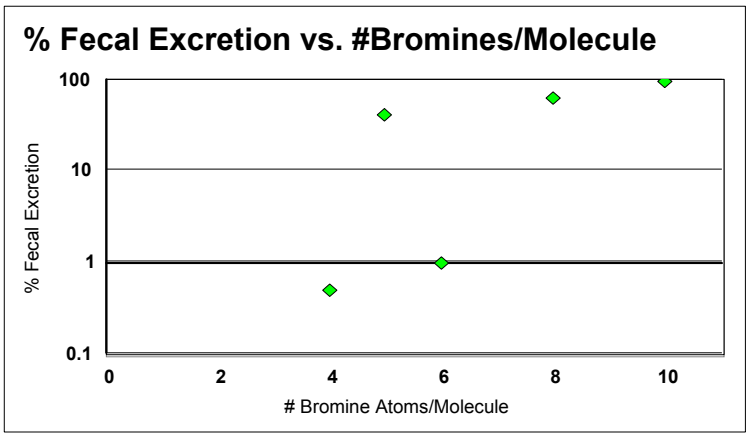

Figure 5-2. Increase in the percent excretion of PBB or PBDE/PBDPO congeners in the feces within 24-72 hr of dosing with increasing bromine content in the molecule.

Elimination in Milk. Following feeding FireMaster BP-6 (250 mg/kg/day for 60 days) to dairy cattle, fecal clearance of the HexaBB component was 0.7 mg/day in non-lactating cows whereas 2 mg/day were cleared in milk by lactating dairy cows. Thus, 2,2',4,4',5,5'-HexaBB was eliminated via milk at 3 times the rate in feces, although its total elimination was very low. Further, high relative concentrations of the PentaBB component present in the FireMaster product were detected in milk fat, but its HeptaBB component was virtually undetectable in milk

(Willet and Durst 1978). Relative to intake, five times more HexaBB than HeptaBB was transferred to milk when their concentrations were normalized to equal intakes of each. A similar relationship was found with hen eggs for PBB and milk for PCB: the more highly halogenated components were less efficiently transferred to milk and eggs. The less halogenated components of PBB and PCB more readily diffuse across biological membranes than the more halogenated compounds (Fries et al. 1978).

Thus, halogen content influences the absorption of PBDE/PBDPOs, PBBs and PCBs from the gut and their subsequent elimination. With the brominated compounds, a breakpoint in absorption and elimination (via feces and/or milk) occurs at 5-6 bromines/molecule. Congeners containing 4 to 5-6 bromines appear relatively well absorbed and slowly eliminated from the body. The major excretory route for these congeners is via the feces, with an added route being milk in lactating females. Congeners containing $\geq$7 bromines appear poorly absorbed and rapidly eliminated via the feces. Excretion in milk is not an important elimination pathway for these congeners.

5.3.7.7 Potential for Transfer of DBDPO into Breast Milk

Prior to transfer to breast milk, a substance must first be absorbed into the mother's bloodstream and presented to the mammary epithelium. DBDPO is very poorly absorbed (< 0.3-2% of an oral dose) and rapidly eliminated (> 99% of the dose within 72 hr). Low absorption coupled with rapid elimination will effectively limit the amount of DBDPO in the mother's bloodstream and available for transfer to breast milk.

Further, DBDPO is a large bulky molecule so that transfer to breast milk is likely to be slow and limited, if at all. Its concentration in breast milk is not expected to be affected by ion trapping, protein binding or lipid partitioning in the milk. DBDPO has no ionizable groups, is not known to undergo protein binding, and shows no preferential partitioning to lipids. Build-up of concentrations in breast milk over extended periods of time is not expected due to DBDPO's predicted slow diffusion into milk and periodic emptying of breast milk. This combination of low absorption from the maternal gut, rapid elimination in the maternal feces, and poor and/or slow diffusion into breast milk will effectively preclude DBDPO in breast milk. Thus, a risk to the nursing infant is not anticipated.

5.3.7.8 Measured PBDPO/PBDE Levels in Breast Milk

DBDPO has not been reported in breast milk. Other polybrominated diphenyl oxide/ether (PBDPO/PBDE) congeners have been reported, and to avoid confusion, publications (through 2001) are summarized here.

The congeners reported in human breast milk include tetrabromodiphenyl ether (TetraBDE), pentabromodiphenyl ether (PentaBDE) and hexabromodiphenyl ether (HexaBDE). Most of the data is derived from Europe, and only limited U.S. data is available. Unfortunately, problems with sampling and analysis methodology, incomplete reporting, non-representative sampling, sampling duration, and small sample size typically limit the value of these studies. The results

are generally reported as the total PBDE content derived as the sum of the congeners/isomers detected.

Analytical results of breast milk collected from Swedish, German, Finnish, Japanese, Canadian, and American women have been reported. The PBDE congeners detected in breast milk include the tri- to HeptaBDEs (Figure 5.3). PBDE congeners with higher levels of bromination (e.g. $\geq$ 7 bromine atoms) have not been reported, and are not expected based on their high molecular weights and their limited potential for absorption into the body and subsequent diffusion into breast milk. The predominant isomer reported in breast milk is 2,2',4,4'-TetraBDE, and generally accounts for 50-70% of the total PBDE content. The next most common isomer detected is 2,2',4,4',5-PentaBDE, followed by 2,2',4,4',6-PentaBDE or 2,2'4,4',5,5'/6-HexaBDE.

Mean levels in breast milk, reported as the total of all PBDEs detected as of 2000, are variable (Table 5.5). Mean levels reported in Canada (Ryan and Patry 2001), Germany (Furst 2001), Finland (Strandman et al. 2001), Sweden (Lind et al. 2001; Meironyte et al. 1998; Darnerud et al. 1998)

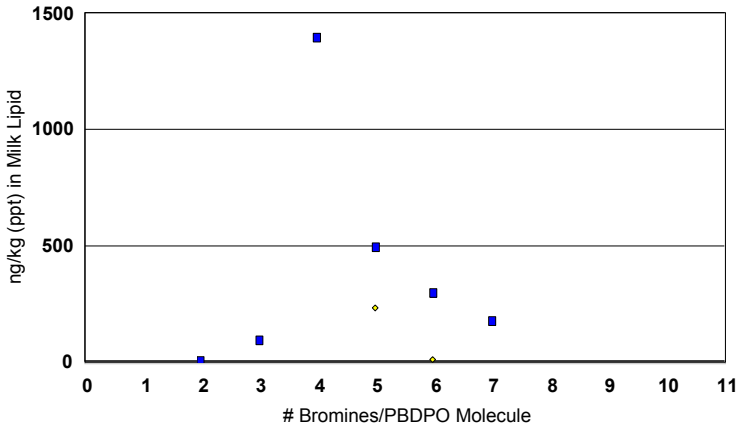

Figure 5-3. PBDE/PBDPO congener content in Canadian breast milk samples collected in 1992 (n=72). The congener content in milk declines with increasing bromine content in the congener.

and Japan (Ohta et al. 1998) range from 1.1-4.4 ng/g lipid (ppb). Levels recently reported for breast milk collected in Austin, TX and Denver, CO in 2000 are 204 ng/g lipid (Papke 2001), and is obviously outside the range of that reported in other countries. The cause of this outlier is unknown but could be related to exposure, diet, age, analytical methodology, unequal sample size, sample contamination or other factors. These breast milk samples were collected for a PCB survey and a subsample analyzed as an afterthought for PBDE content.

Recent results from Sweden (Table 5.5) indicate total PBDE concentrations in breast milk are declining (Lind et al. 2001). This is a reversal of the trend seen from 1975-1997 in which a

doubling of the levels every 5 years was reported (Meironyte et al. 1998; Darnerud et al. 1998). Levels in breast milk collected in Germany in 1992 and 2000 were similar (e.g. did not increase with time) and represent the lowest level reported in these 6 countries (Furst 2001). Thus, based on this very limited sample, total PBDE levels in breast milk in Europe do not appear to be increasing.

In Swedish breast milk, the highest concentration of PBDEs, reported for the year 1997, was approximately 0.36 % of that of the highest PCB level ever measured in Swedish milk samples (Meironyte et al. 1998; Darnerud et al. 1998). The 1997 total PBDE content in breast milk was ~100 times less than that of PCB. The authors concluded the PBDE content was unlikely to alter the sum of the toxicity equivalents (TEQs) represented in milk by the PCDDs, PCDFs, and PCBs. The authors initially found no correlation between the levels in Swedish breast milk and the mother's age, computer usage frequency, consumption of fish (total or specifically fatty Baltic fish), consumption of alcohol, place of residence during the mother's childhood and adolescence (in fishing village or not) or the birth weight of the child (Darnerud et al. 1998). A correlation was found between the total PBDPO levels in breast milk and the mothers' smoking habits and body mass - an increase in smoking correlated with an increase in total amount of PBDE. An update indicated that the major source of PBDE was from fish consumption with a weak association to smoking (Lind et al. 2001). Age, body mass index and alcohol showed no correlation with PBDE levels in breast milk. In contrast, Ryan and Patry (2001) calculated that most of the exposure to PBDEs (~80%) subsequently detected in Canadian breast milk was through meat consumption. Whether these differences are due to patterns of food consumption in Sweden versus Canada or some other factor is not known.

TABLE 5-5. Mean total PBDE/PBDPO content in breast milk (ng/g (ppb) milk fat).

Year Collected	Canada (n=72)	US (n=?)	Germany (n=?)	Finland (n=11)	Sweden (n=20)*	Japan (n=6)
1981-2						
1992	2.4		1.1			
1997					4.4+	
1998				2.25	3.88	
1999					3.46	
2000		205	1.1		2.79	
?						1.12

*1998, 1999, 2000
+n = 39

In summary, analytical results of breast milk collected from Swedish, German, Finnish, Japanese, Canadian, and American women have been reported. The PBDE congeners detected in breast milk include the tri- to HeptaBDEs. The predominant isomer reported in breast milk is 2,2',4,4'-TetraBDE, and generally accounts for 50-70% of the total PBDE content. Levels of total "PBDE" content in breast are generally far below that of total PCB content measured in the same samples. DBDPO, which makes up approximately 82% of "PBDEs" sold worldwide, has not been reported in breast milk, and is not expected to be present based on its physical/chemical

properties and limited potential for absorption into the body and subsequent diffusion into breast milk.

Except in unusual situations, breast feeding remains the preferred nutrition for the infant and a better understanding of the levels of environmental chemicals in breast milk, particularly in the United States, would be of value in predicting infant exposures (LaKind and Berlin 2001). A carefully planned and executed program of breast milk sampling and analysis would provide such information. An Expert Panel on Breast Milk Monitoring for Chemicals in Human Milk was convened in 2002 to develop harmonized guidelines for the surveillance and study of human milk for environmental chemicals in the U.S. The results are reported in a special issue of the Journal of Toxicology and Environmental Health ("Technical Workshop on Human Milk Surveillance and Research on Environmental Chemicals in the United States", Volume 65, Number 22, November 22, 2002). BFRIP contributed financial support to this panel.

5.3.8 Occupational

The American Industrial Hygiene Association (AIHA) set a Workplace Environmental Exposure Level (WEEL) for DBDPO of 5 mg/m³. The U.S. Occupational Safety and Health Administration (OSHA) has not set a Permissible Exposure Level (PEL) for this specific chemical, but has a "nuisance dust" limit of 5 mg/m³. Most industrial hygiene surveys determined employee 8-hour time-weighted average (TWA) exposures to DBDPO to be in the 1–4 mg/m³ range, with possible excursions as high as 42 mg/m³ during certain tasks (AIHA 1981). During operations involving dumping the material into hoppers, airborne concentrations reached as high as 400 mg/m³ (AIHA 1981). During these operations, workers were required to wear respirators.

5.4 U.S. Toxic Inventory Release Data

The Toxics Release Inventory (TRI) is a publicly available EPA database that contains information on chemical releases and other waste management activities reported annually by certain covered industry groups as well as federal facilities (http://www.epa.gov.tri). This inventory was established under the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) and expanded by the Pollution Prevention Act of 1990. TRI stores the information that is self-reported annually from industries that conduct manufacturing operations within certain specified standard industrial classification codes (SIC Codes 20-39) until the 1998 reports when additional sectors were added. In addition to industrial classification, facilities are only required to report if they manufacture or process more than 25,000 pounds of a listed chemical during a year, or otherwise used more than 10,000 pounds, and have the equivalent of more than 10 full-time employees. They must report the on-site releases of toxic chemicals into the air, water, and land; and quantities treated, combusted for energy recovery, and recycled on-site. They also report on transfers of wastes that are disposed, treated, combusted for energy recovery, or recycled at a separate facility. Approximately 650 chemicals have been designated for reports under TRI. In all about 73,000 reports are submitted annually by 21,000 manufacturing facilities and 200 Federal facilities in 1996.

According to the U.S. EPA, TRI data have certain limitations. TRI data reflect releases and other waste management of chemicals, and not exposures of the public to those chemicals. TRI data alone are not sufficient to determine exposure or to calculate potential adverse effects on human health and the environment. TRI data, in conjunction with other information, can be used as a starting point in evaluating exposures that may result from release and other waste management activities, which involve toxic chemicals.

Definitions provided by EPA for the terms used in describing releases are:

- Total Air Emissions: This is the sum of fugitive air and stack air release amounts (in pounds for all chemicals other than Dioxin and Dioxin-like compounds. The data for Dioxin and Dioxin-like compounds is in grams).
- Surface Water Discharges: Releases to water include discharges to streams, rivers, lakes, oceans, and other bodies of water. This includes releases from contained sources, such as industrial process outflow pipes or open trenches. Releases due to runoff, including storm water runoff are also reportable to TRI.
- Underground Injections: Underground injection is the subsurface emplacement of fluids through wells. TRI chemicals associated with manufacturing, the petroleum industry, mining, commercial and service industries, and Federal and municipal government related activities may be injected into class I, II, III, IV, or V wells, if they do not endanger underground sources of drinking water (USDW), public health or the environment. Class I wells are industrial, municipal, and manufacturing related wells which inject fluids into deep, confined and isolated formations below potable water supplies.
- Releases to Land: Disposal to land on site is the release of a chemical to land within the boundaries of the reporting facility. Releases to land include disposal of toxic chemicals in landfills (in which wastes are buried), land treatment/application farming (in which a waste containing a listed chemical is applied to or incorporated into soil), surface impoundments (which are uncovered holding areas used to volatilize and/or settle materials), and other land disposal methods (such as waste piles) or releases to land (such as spills or leaks).
- Total On-site Releases: This field is the sum of total air emissions, surface water discharges, underground injections, and releases to land.
- Total Off-site Releases: Off-site releases are from Section 6 (transfers off-site to disposal) of the Form R. Off-site releases include metals and metal compounds transferred off-site for solidification/stabilization and for waste water treatment, including to POTWs.
- Total On- and Off-site Releases: This field is the sum of total on-site release and total off-site release amounts (in pounds).

DBDPO was included on the original inventory created under TRI. Annual DBDPO releases reported from1988 through 2000 or for the year 2000 are shown in Tables 5-6, 5-7, and 5-8. Annual total on- and off-site releases for DBDPO's manufacture and use throughout the U.S. are ~1% of DBDPO's manufactured volume. As expected, air emissions make up only a small fraction of the total in any given year and are largely associated with DBDPO's manufacture (Chemical, SIC 29). On-site surface water discharges also make up only a small fraction of the total, and are nearly all associated with operations (Textiles, SIC 28) that apply DBDPO to

upholstery textiles. Again, this is as expected because textile operations utilize water in their processes whereas DBDPO manufacturing and plastics applications (Plastics, SIC 30) do not. Releases to land dominate on-site releases and are predominantly associated with disposal of DBDPO in either a manufacturer's on-site landfill or in a commercial chemical landfill. The manufacturer's landfill is built to hazardous waste standards with a double liner and leachate collection system. Off-site releases for disposal typically exceed on-site releases.

TABLE 5-6. TRI On-site and Off-site Reported Releases (in pounds), Trend Report for facilities in Original Industries (SIC codes 20-39), DBDPO, U.S., 1988-2000.

Year	Air Emissions	Surface Water Discharges	Underground Injections	Releases to Land	Total On-Site Releases	Total Off-Site Releases	Total On- and Off-Site Releases
1988	29,604	500	292	21,450	51,846	555,181	607,027
1989	50,207	3,450	52	9,394	63,103	749,567	812,670
1990	64,601	2,577	43	24,844	92,065	710,187	802,252
1991	50,235	3,817	38	220,075	274,165	839,031	1,113,196
1992	37,217	3,873	285	529,340	570,715	721,583	1,292,298
1993	203,168	2,176	39	506,785	712,168	856,809	1,568,977
1994	170,122	1,958	40	298,191	470,311	998,628	1,468,939
1995	39,283	3,846	11	204,248	247,388	716,245	963,633
1996	45,608	3,680	0	196,688	245,976	707,498	953,474
1997	29,549	2,499	.	869,294	901,342	726,500	1,627,842
1998	31,114	3,168	0	191,253	225,535	773,136	998,671
1999	116,241	2,701	0	396,169	515,111	916,182	1,431,293
2000	106,219	9,006	0	487,409	602,634	1,006,690	1,609,324

TABLE 5-7. TRI On-site and Off-site Reported Releases (in pounds), Trend Report for facilities in New Industries (SIC codes 10, 12, 4911, 4931, 4939, 5169, 5171, 4953, 7389), DBDPO, U.S., 1998-2000.

Year	Air Emissions	Surface Water Discharges	Underground Injections	Releases to Land	Total On-Site Releases	Total Off-Site Releases	Total On- and Off-Site Releases
1998	0	.	.	310,000	310,000	.	310,000
1999	0	.	0	350,000	350,000	.	350,000
2000	0	.	0	400,837	400,837	.	400,837

TABLE 5-8. TRI On-site and Off-site Reported Releases (in pounds), DBDPO, By Industry, U.S., 2000.

SIC-Industry	Air Emissions	Surface Water Discharges	Underground Injections	Releases to Land	Total On-Site Releases	Total Off-Site Releases	Total On- and Off-Site Releases
28 Chemicals	88,811	5	0	370,578	459,394	102,540	561,934
30 Plastics	8,417	34	.	15,653	24,104	470,632	494,736
4953/7389 RCRA/Solvent Recovery	0	.	0	400,837	400,837	.	400,837
22 Textiles	4,314	8,933	.	90,496	103,743	136,489	240,232
26 Paper	.	5	.	1,100	1,105	116,326	117,431
33 Primary Metals	59	0	.	.	59	68,948	69,007
34 Fabricated Metals	41	0	.	.	41	60,960	61,001
36 Electrical Equip.	27	.	.	.	27	17,798	17,825
35 Machinery	.	.	.	7,982	7,982	7,983	15,965
Multiple Codes 20-39	3,800	2	.	1,600	5,402	8,904	14,306
37 Transportation Equip.	.	.	.	.	.	13,000	13,000
32 Stone/Clay/Glass	750	27	.	.	777	3,110	3,887
Total	106,219	9,006	0	888,246	1,003,471	1,006,690	2,010,161

In 2000, total on- and off-site DBDPO releases in the 50 states were dominated in descending order by Arkansas, Louisiana, North Carolina, Pennsylvania, California and Ohio (data not shown). These 6 states reported ~ 76% of the total releases in the U.S. Arkansas, home to the 2 DBDPO manufacturing facilities in the U.S., reported the highest total releases with the majority going to land in one manufacturer's on-site landfill. Releases in Louisiana consisted of land releases to a commercial chemical landfill for disposal. Releases in Pennsylvania, California and Ohio were primarily off-site for disposal, a category that includes discharges to publicly owned treatment works (POTWs). North and South Carolina accounted for 92.5% of the nation's discharges to surface waters. These trends are generally applicable to previous years (data not shown).

EPA defines transfers off-site for further waste management as follows:

- Transfers to Recycling: The total amount (in pounds) of the chemical transferred from the facility to a off-site location during the calendar year (January 1 - December 31) for recycling. This refers to the ultimate disposition of the chemical, not the intermediate activities used for the waste stream.
- Transfers to Energy Recovery: The total amount (in pounds) of the chemical transferred from the facility to a off-site location during the calendar year (January 1 - December 31) for energy recovery. This refers to the ultimate disposition of the chemical, not the intermediate activities used for the waste stream.
- Transfers to Treatment: The total amount (in pounds) of the chemical transferred from the facility to a off-site location during the calendar year (January 1 - December 31) for treatment. This refers to the ultimate disposition of the chemical, not the intermediate activities used for the waste stream.
- Transfers to POTWs: The total amount (in pounds) of the chemical transferred from the facility to all Publicly Owned Treatment Works (POTWs) during the calendar year (January1 - December 31). POTW refers to a municipal sewage treatment plant. The most common transfers will be conveyances of the chemical in facility wastewater through underground sewage pipes, however, trucked or other direct shipments to a POTW are also included in this estimate.
- Other Off-site Transfers: In TRI Explorer, chemicals in waste that were reported as transferred off-site but for which the off-site activity (i.e., recycling, energy recovery, treatment, or disposal) was not specified or was not an accepted code has been classified as "other off-site transfers."
- Total Transfers Off-site for Further Waste Management: This field is the sum of transfers to recycling, transfers to energy recovery, transfers to treatment, transfers to POTWs, and other off-site transfers amounts (in pound).

Total waste transfers of DBDPO off-site for further waste management are generally dominated by transfers to POTWs (Table 5-9). Between 1991 and 2000, waste transferred off-site to POTWs ranged from 22-63% of the aggregate waste transfers. However, in 2000, a significant rise in transfers going to recycling occurred and these recycling transfers were slightly over twice that to POTWs. Connecticut, North Carolina and Washington accounted for 79% of this recycling, and of Chemicals (SIC 29), Textiles (SIC 28) and Plastics (SIC 30), Textiles

accounted for the largest share of the growth in recycling with a corresponding drop in that sent to POTWs. Transfers from New Industries between 1998 and 2000 were solely to treatment and did not account for a significant portion of each year's total. Textiles were responsible for the bulk of the waste transfer to POTWs between 1991-2000 (Tables 5-10, 5-11, 5-13), whereas Plastics released minimal amounts to POTWs (Tables 5-10 and 5-12). The amounts sent to POTWs by Textiles have declined over the past 3 years. The states with the largest amounts of DBDPO waste transferred to POTWs in 2000 were Maryland, South Carolina and North Carolina, in descending order. These three states accounted for ~71% of all DBDPO-waste transfers to POTWs in 2000.

In summary, land releases dominate DBDPO releases on-site from its manufacture and use, and are predominantly associated with disposal of DBDPO in either a manufacturer's on-site landfill in Arkansas or in a commercial chemical landfill in Louisiana. Air and water releases make up only a small fraction of on-site releases. DBDPO releases off-site for disposal from its manufacture and use are typically larger than that on-site. DBDPO-waste transfers for further waste management are dominated by transfers to POTWs. The largest releases of DBDPO or DBDPO-waste to water occur in North and South Carolina and result from its use in textile applications. These water releases occur as a result of discharge of DBDPO to surface water and DBDPO-waste to POTWs. DBDPO is expected to settle out of surface water or in a POTW to sediment or sludge, respectively, and bind extensively to organic carbon (see Section 4.2).

TABLE 5-9. TRI Transfers Off-site for Further Waste Management (in pounds), Trend Report for facilities in Original Industries (SIC codes 20-39), DBDPO, U.S., 1991-2000.

Year	Transfers to Recycling	Transfers to Energy Recovery	Transfers to Treatment	Transfers to POTWs	Other Off-site Transfers	Total Transfers Off-site for Further Waste Management
1991	68,313	8,551	71,567	44,914	0	193,345
1992	31,032	7,406	93,759	127,772	.	259,969
1993	35,105	8,129	73,725	203,871	.	320,830
1994	169,003	30,860	64,923	396,137	.	660,923
1995	141,971	18,826	64,977	249,108	.	474,882
1996	117,679	4,881	67,422	265,565	.	455,547
1997	61,842	6,338	75,079	313,967	.	457,226
1998	87,794	3,473	38,271	246,375	.	375,913
1999	95,188	6,040	71,478	162,496	.	335,202
2000	320,844	6,637	43,107	152,881	.	523,469

TABLE 5-10. TRI Transfers Off-site for Further Waste Management (in pounds), DBDPO, By Industry, U.S., 2000.

SIC – Industry	Tranfers to Recycling	Transfers to Energy Recovery	Transfers to Treatment	Transfers to POTWs	Other Off-site Transfers	Total Transfers Off-site for Further Waste Management
22 Textiles	91,496	3,000	5,139	144,376	.	244,011
26 Paper	.	.	6,084	.	.	6,084
28 Chemicals	.	.	2,273	2,865	.	5,138
30 Plastics	26,096	1,231	28,393	273	.	55,993
32 Stone/Clay/Glass	.	.	.	.	.	.
33 Primary Metals	117,867	.	.	10	.	117,877
34 Fabricated Metals	.	270	.	250	.	520
35 Machinery	.	.	.	4,822	.	4,822
36 Electrical Equip.	59,143	.	837	0	.	59,980
37 Transportation Equip.	.	.	.	.	.	.
Multiple Codes 20-39	26,242	2,136	381	285	.	29,044
Original industry subtotal:	320,844	6,637	43,107	152,881	.	523,469
4953/7389 RCRA/Solvent Recovery	.	.	19,500	.	.	19,500
New industry subtotal:	.	.	19,500	.	.	19,500
Total	320,844	6,637	62,607	152,881	.	542,969

TABLE 5-11. TRI Transfers Off-site for Further Waste Management (in pounds), Trend Report for facilities in Chemicals (SIC 28), DBDPO, U.S., 1991-2000.

Year	Tranfers to Recycling	Transfers to Energy Recovery	Transfers to Treatment	Transfers to POTWs	Other Off-site Transfers	Total Transfers Off-site for Further Waste Management
1991	999	.	12,241	4,846	0	18,086
1992	0	250	14,610	5,401	.	20,261
1993	.	250	10,555	6,986	.	17,791
1994	.	250	905	7,808	.	8,963
1995	.	.	4,490	1,445	.	5,935
1996	.	.	3,233	5,620	.	8,853
1997	.	.	2,481	3,532	.	6,013
1998	.	.	2,815	3,426	.	6,241
1999	.	.	2,319	2,466	.	4,785
2000	.	.	2,273	2,865	.	5,138

TABLE 5-12. TRI Transfers Off-site for Further Waste Management (in pounds), Trend Report for facilities in Plastics (SIC 30), DBDPO, U.S., 1991-2000.

Year	Transfers to Recycling	Transfers to Energy Recovery	Transfers to Treatment	Transfers to POTWs	Other Off-site Transfers	Total Transfers Off-site for Further Waste Management
1991	.	1	56,025	4,960	.	60,986
1992	4,235	2,606	62,660	355	.	69,856
1993	6,905	2,729	54,072	515	.	64,221
1994	81,711	3,450	41,000	601	.	126,762
1995	32,216	5,973	35,947	301	.	74,437
1996	19,042	890	31,055	284	.	51,271
1997	15,620	1,838	37,001	255	.	54,714
1998	7,448	1,120	28,512	520	.	37,600
1999	2,630	1,180	54,742	520	.	59,072
2000	26,096	1,231	28,393	273	.	55,993

TABLE 5-13. TRI Transfers Off-site for Further Waste Management (in pounds), Trend Report for facilities in Textiles (SIC 22), DBDPO, U.S., 1991-2000.

Year	Tranfers to Recycling	Transfers to Energy Recovery	Transfers to Treatment	Transfers to POTWs	Other Off-site Transfers	Total Transfers Off-site for Further Waste Management
1991	.	8,500	2,557	17,045	.	28,102
1992	.	4,500	1,016	112,656	.	118,172
1993	.	5,100	2,335	191,381	.	198,816
1994	.	25,010	6,773	385,436	.	417,219
1995	1,993	3,300	5,434	243,056	.	253,783
1996	5	3,741	3,337	257,651	.	264,734
1997	.	3,750	9,547	308,920	.	322,217
1998	250	505	3,738	240,839	.	245,332
1999	71,768	3,755	6,826	152,924	.	235,273
2000	91,496	3,000	5,139	144,376	.	244,011

5.5 Human Exposure Estimation (Developed by Exponent, Boulder, CO)

The studies regarding DBDPO in U.S. environmental media and human tissues, discussed above, preclude a direct assessment of children's exposure. Therefore, exposures were estimated based on hypothetical contact that might reasonably be expected to occur. These exposure estimates were derived in a manner that biases the derived values high, likely overestimating actual exposures. Therefore, this assessment provides upper-bound estimates of exposure, and thus risk, and actual risk would be expected to be lower. The following section presents the approach we used to calculate these hypothetical exposures.

5.5.1 Potential Exposure Scenarios

Exposures that can affect children are defined in the VCCEP guidance as, "those which would occur prior to conception (to either parent), during prenatal development, and postnatally to the age of sexual maturation, which is completed around 18–21 years of age" (U.S. EPA 2000a). As mentioned above in section 4.1.3, DBDPO has not caused any reproductive or developmental effects in any animals tested at doses up to 1,000 mg/kg/day (the highest dose tested). Because of this lack of reproductive and developmental effects associated with DBDPO exposures, there is no need to conduct exposure assessments for pregnant women or prospective parents (male or female). Therefore, the only exposures considered in this evaluation for DBDPO are for children exposed postnatally.

The exposure scenarios that are the most relevant to children's exposure to DBDPO are:

- Infant ingestion of breast milk from a mother who manufactures DBDPO or works in a formulation or molding facility
- Infant ingestion of breast milk from a mother who disassembles computer monitors

- Infant ingestion from mouthing DBDPO-containing plastic electronic products
- Children inhaling DBDPO particulates released from plastic electronic products
- Infants mouthing DBDPO-containing fabric
- Adult and child dermal exposure to DBDPO-containing fabric
- Exposure to DBDPO via the general environment (e.g., eating food, incidental ingestion of soil and dust, breathing ambient air, and drinking water).

Due to the lack of available information, the typical exposure calculation—in which a contact rate (consumption, drinking, mouthing, and inhalation rate) is multiplied by an exposure-point concentration (DBDPO concentration in food, water, air, consumer product, etc.)—is not currently possible for every possible pathway. However, the published literature does provide sufficient data to allow calculation of some hypothetical exposures. A large degree of uncertainty is associated with these estimates due to the paucity of reliable scientific information on levels of DBDPO. However, in each scenario, sufficient conservatism is built into the calculations such that these exposure estimates represent potential upper bounds.

Throughout these calculations, the approach used a plausible, yet conservative, estimate of potential exposure to DBDPO. These calculations are termed the Reasonable Estimate (RE) for the purposes of this report. A higher exposure value was also calculated for each scenario. These calculations are termed the Upper Estimate (UE) and should be viewed as so conservative that they represent the absolute worst-case exposures. This approach—calculating a "bounding estimate" of exposure that is probably beyond the realm of plausible exposures—was undertaken to determine whether any hypothetical exposure would warrant further evaluation. Using this approach, our analysis indicates that a significant health risk is not expected for children under any of the scenarios evaluated, even using extremely conservative assumptions. Therefore, no further, more detailed evaluation of DBDPO is warranted to ensure adequate health protection for young children.

The various scenarios and the exposure assumptions used for quantitative analysis of exposures are described in the sections below. For each scenario, a separate section is included describing the results of the analysis and uncertainties associated with the calculated values.

5.5.2 Infant Ingestion of Breast Milk from a Mother Who Manufactures DBDPO

Workplace exposure to DBDPO could potentially occur during manufacturing or formulation into resins or a liquid polymer dispersion. DBDPO is manufactured in a closed system by the reaction of bromine with diphenyl oxide, and the highest potential worker exposures are associated with the activities of packaging DBDPO for shipping, or in emptying bags of flame

retardant into a hopper for product formulation. Once formulated, DBDPO is encased in a polymer matrix, significantly reducing the potential for worker exposure.

This assessment evaluates the potential exposures that might be incurred by a nursing infant of a working mother, and assumes that the mother packages DBDPO at its manufacturing site or empties bags of DBDPO into hoppers at formulating/compounding site.

Assumptions

It is assumed that the mother works at this task for 8 hours a day, 5 days per week. It is also assumed that during this task, the mother inhales DBDPO-containing dust from the workplace air, and the DBDPO that she inhales partitions into her breast milk. For the reasonable estimate (RE), an infant is assumed to breast feed from the exposed mother daily from birth through 3 months of age (Collaborative Group on Hormonal Factors in Breast Cancer 2002). For the upper estimate (UE), an infant was assumed to breast feed from the exposed mother daily from birth for 2 years based on professional judgment.

Ideally, a calculation to estimate intake from breast milk would begin with a measured concentration of the chemical of interest in breast milk. However, DBDPO has never been measured in breast milk in any country, and may not actually partition into breast milk, so a hypothetical intake is estimated indirectly. Because of DBDPO-specific data is not available, several steps were taken to estimate this intake, using the best available data. The concentrations of DBDPO that might be found in breast milk were estimated based on information regarding the relation between air concentrations of DBDPO and associated serum concentrations and on limited data regarding the partitioning of lower brominated DPO congeners to breast milk. Specifically, published measured workplace air concentrations and associated blood levels for Swedish workers were used to estimate an air-to-serum relation, which was then combined with estimates of air concentrations for a U.S. worker to derive a hypothetical serum level for a U.S. worker. Then, data regarding the partitioning of lower brominated DPO congeners from serum to breast milk were used to set an upper bound for the partitioning behavior of DBDPO, yielding an estimate of DBDPO in breast milk. The assumptions used almost certainly overestimate the possible intake of DBDPO through this pathway. The specific assumptions for this scenario are discussed below and shown in Table 5-5.

DBDPO concentration in workplace air (respirable). Upper Estimate (UE): Because workplace air data in the U.S. is not available, an upper value of 5 mg/m^3 was selected based on the Workplace Environmental Exposure Level (WEEL) (AIHA 1996). The WEEL is the level at which workers could be exposed every day for an 8-hour shift with the expectation of no adverse effects.

Reasonable Estimate (RE): An air concentration of 1 mg/m^3 was selected, because the EU risk assessment notes that the majority of workplace air levels (TWA) are below 1 mg/m^3 (ECB 2002).

Air-to-serum conversion factor. To yield a breast-milk concentration of DBDPO for a given inhalation exposure concentration, it was necessary to develop an estimate of internal dose/body

burden or serum concentration for a given workplace exposure. Sjödin et al. (1999) measured workplace air concentration and serum levels of DBDPO for Swedish workers disassembling and shredding used computer monitors and other plastic components containing DBDPO. Mean levels (mean of two samples) in the air were 175 ng/m³ (Hagmar et al. 2000), and the median serum concentration of DBDPO (n=19) among the workers was 4.8 ng/g lipid (Sjödin et al. 1999). This yields a ratio factor of 27.4 (μg DBDPO/g serum lipid)/(mg DBDPO/m³). This ratio of serum levels to workplace exposures is the best available. There are many simplifying assumptions in this approach that collectively make it quite conservative. It assumes that all the measured DBDPO in the serum of the workers is attributed to the workplace exposures. This is conservative, because food and ambient exposures may contribute to the body burden of DBDPO. Sjödin and coworkers did not provide enough detailed information to develop a reasonable range of estimates for this parameter. Only two air concentrations were reported in the study (Hagmar et al. 2000). Therefore, this single value is used for both the UE and the RE.

Breast-milk to blood-serum ratio. To yield an estimate of breast-milk concentrations of DBDPO associated with occupational exposure, the correlation between serum levels and breast-milk levels must be established. DBDPO has never been documented as being present in breast milk, so a transfer ratio was estimated based on information from other compounds. Efforts by Exponent, Judy LaKind, and Jake Ryan to determine this ratio for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) resulted in a rapid communication that is in press in the *Journal of Toxicology and Environmental Health*. The available data indicate that the ratios of breast milk to serum levels for TCDD and related dioxins, furans, and polychlorinated biphenyls (PCBs) are near 1.0 when calculated on the basis of lipid weight. For these highly lipophilic compounds, lipid partitioning is the key to their disposition in serum and breast milk. These molecules are one-half to one-third the molecular weight of DBDPO; thus, there is no size limitation on their passage into breast milk.

To establish a ratio between serum and breast milk levels for DBDPO, we calculated the ratios of breast-milk levels reported for various PBDPOs (in Ryan et al. 2001) to levels in serum for the same PBDPOs (in Sjödin et al. 2001b). We found that the ratio of breast milk to serum levels (both were reported on a lipid weight basis) was less than 1.0 for all congeners, and decreased with increasing molecular weight/bromination. The ratio of breast milk to serum levels for HeptaBDPO, the highest molecular weight congener in the series, was 0.54. There is some uncertainty in using this analysis. First, these were not paired samples: the PBDPO levels in breast milk were determined in samples collected in Canada in the late 1990s, whereas the serum levels were derived from U.S. donors whose blood was collected in the late 1980s. Second, they are from different countries. Thirdly, and most importantly, they are from different time periods. However, because the breast-milk levels are from later time points, and because levels of PBDPOs in humans have reportedly increased between the 1980s and late 1990s, the levels in breast milk in the late 1990s could be expected to be higher than that in the late 1980s. Therefore, this analysis would be expected to produce an overestimate of the ratio of breast milk to serum for these congeners. Further, the ratio for DBDPO would be lower than for HeptaBDPO. How much lower (if not zero) is uncertain. Because of this uncertainty, we used the following reasoning for the values used for these parameters.

- UE: A breast-milk to blood-serum ratio of 0.5 was selected (i.e., the concentration in breast milk is one-half the concentration in serum on a lipid weight basis), because this was the ratio observed for HeptaBDPO. Because the higher brominated congeners appear to have a lower transfer rate to breast milk, using the ratio derived for HeptaBDPO is a conservative estimate that is likely to overestimate the actual relation.

- RE: A breast-milk to blood-serum ratio of 0.1 was selected, because it is likely that the larger molecular size and greater bromination of DBDPO would limit its ability to enter breast milk, and toxicologists have predicted that it would not transfer into breast milk at all, thereby eliminating breast milk as a route of exposure for infants (Hardy 2001). A prudent estimate is approximately 0.1 for the ratio of DBDPO in serum lipids that can partition into breast-milk lipids.

Fraction of breast milk that is lipid. UE and RE: A value of 4% was selected based on the value recommended in the *Child-Specific Exposure Factors Handbook* (U.S. EPA 2000).

Ingestion rate. UE: A UE ingestion rate of 980 mL/day was selected based on the upper percentile value for a 12-month average breast-milk ingestion rate for a child less than 1 year old (U.S. EPA 2000). The EPA does not present any ingestion rates for children between 12 and 24 months, but they do show that ingestion rates decrease after the age of 9 months (U.S. EPA 2000). Therefore, using the 12-month average value to represent the entire 2-year period is a conservative assumption that is likely to overestimate actual exposures.

RE: An RE ingestion rate of 742 mL/day was used, based on the mean value for children ages 1–6 months (U.S. EPA 2000).

Absorption. Although the gastrointestinal absorption of DBDPO is estimated to be less than 2% (Hardy 2002, NTP 1986, El Dareer et al. 1987), an absorption factor of 100% was used in these intake calculations, because the toxicity values are based on an ingested dose rather than an absorbed dose. This same parameter and value were used in the intake calculations shown in Tables 5-5 through 5-8.

Body weight. UE: As an upper estimate, it was assumed that the maximum duration over which an infant would be breast fed in the U.S. would be two years. Therefore, a UE body weight of 7.84 kg was derived from the 50th-percentile weights for children ages birth through 24 months, presented in Table 11-1 of the *Child-Specific Exposure Factors Handbook* (U.S. EPA 2000). This value was used in the intake calculations presented in Tables 5-2 through 5-5.

RE: Because the majority of children are breast fed only through the first three months of life (Collaborative Group on Hormonal Factors in Breast Cancer 2002), an RE body weight of 4.36 kg was derived from the 50th-percentile weights for children ages birth through 3 months, presented in Table 11-1 of the *Child-Specific Exposure Factors Handbook* (U.S. EPA 2000). This value was used in the intake calculations presented in Tables 5-5 and 5-6.

Results

In this scenario, the mother of a breast-feeding infant was assumed to work in the bagging operation at a DBDPO manufacturing site. The calculated daily intake for an infant exposed via breast milk ranged from 1.9×10^{-2} to 3.4×10^{-1} mg/kg-day for the RE and UE, respectively (Table 5-14). As discussed in previous sections, DBDPO has not been reported in breast milk in any country, and is not expected to partition into breast milk, so a hypothetical intake was estimated indirectly.

There is a great deal of uncertainty surrounding the methods employed to calculate serum levels, as well as the percentage of DBDPO in the serum that would partition into the breast milk. Even for the RE value, a large degree of conservatism is built into these values. It is also unlikely that a worker would be exposed at the WEEL for an entire 8-hour shift. It should be noted that 5 mg/m³ is the PEL for nuisance dust, suggesting that AIHA's WEEL for DBDPO assumes no intrinsic toxicity to the inhalation of this compound. If DBDPO does not, in fact, partition into breast milk, then the true exposure from this scenario would be zero.

Table 5-14. Infant ingestion of breast milk from a mother who manufactures DBDPO.

Exposure Parameters	Reasonable Estimate (birth to 3 months) Value	Source/Comment	Upper Estimate (birth to 2 years) Value	Source/Comment
C_a: DBDPO concentration in workplace air (respirable) (mg/m3)	1	BFRIP	5	WEEL (AIHA 1996)
CF_{a-s}: Air-to-serum conversion factor; (μg DBDPO/g lipid serum) per (mg DBDPO/m^3 air)	27.4	Based on working 8 hour/day and 5 day/week (Sjödin et al. 1999). See text for details.	27.4	Based on working 8 hour/day and 5 day/week (Sjödin et al. 1999). See text for details.
R_{b-m}: Breast milk to serum ratio (unitless)	0.1	Based on the fact that higher brominated DPO do not partition into milk as effectively as lower brominated DPO (see text)	0.5	Conservative assumption that DBDPO partitions into breast milk and serum on a lipid weight basis at the ratio that hepta-DPO does (BDE-183) (see text)
$F_{l:bm}$: Fraction of breast milk that is lipid (g/mL)	0.04	4% expressed as g/mL (CS-EFH Table 2-12; U.S. EPA 2000)	0.04	4% expressed as g/mL (CS-EFH Table 2-12; U.S. EPA 2000)
CF: Conversion factor (mg/μg)	1E-03		1E-03	
IR: Ingestion rate (mL/day)	742	Mean for ages 1–6 months (CS-EFH, Table 2-12, p. 2-19, U.S. EPA 2000)	980	12-month average, upper percentile (CS-EFH, Table 2-12, p. 2-19, U.S. EPA 2000)
ABS: Absorption (percent)	100[a]	Necessary to use with toxicity value	100%[a]	Necessary to use with toxicity value
BW: Body weight (kg) 0–3 months (RE) and 0–2 years (UE)	4.36	Average of 50th percentile weights, birth through 3 months (CS-EFH, Table 11-1, U.S. EPA 2000)	7.84	Average of 50th percentile weights, birth through 24 months (CS-EFH, Table 11-1, U.S. EPA 2000)
Daily Intake (mg/kg-day)	1.9E-02	Calculated	3.4E-01	Calculated

$$\text{Intake} = \frac{C_a \times CF_{a-s} \times R_{b-m} \times F_{l:bm} \times CF \times IR \times ABS}{BW}$$

[a] Although the absorption of DBDPO is estimated to be less than 2%, an absorption of 100% is necessary in the intake calculations because the toxicity values are based on an ingested dose rather than an absorbed dose. See text for details.

5.5.3. Infant Ingestion of Breast Milk from a Mother Who Disassembles Electronics

In this scenario, the mother of a breast-feeding infant was assumed to be an electronics disassembly worker. DBDPO has not been reported in breast milk in any country, and is not expected to partition into breast milk, so a hypothetical intake was estimated indirectly. There are no U.S. data for either workplace air concentrations or serum levels for a disassembly worker. However, DBDPO and other polybrominated diphenyl ether isomers were detected in serum of Swedish workers engaged in dismantling electronic equipment (Sjödin et al. 1999, Sjödin 2000) and in Swedish computer technicians (Hagmar et al. 2000). Therefore, DBDPO serum concentrations for a U.S. worker were assumed to be the same as the levels measured in the computer disassembly workers in Sweden (Sjödin et al. 1999). Additionally, DBDPO in the serum was assumed to partition into breast milk, as discussed above, and consumed by an infant daily from birth through 3 months (RE) and from birth through 2 years (UE).

Assumptions

The assumptions made for this scenario are described below and shown in Table 5-6.

DBDPO concentration in mother's blood. UE: Based on the study by Sjödin et al. (1999), Swedish workers who disassembled computer monitors and worked near the shredding devices had detectable levels of DBDPO in their blood. As a conservative assumption, the maximum level reported by Sjödin was used for the UE (9.9 ng/g serum lipid).

RE: For the RE, the median level reported by Sjödin (1999) was used (4.8 ng/g serum lipid). The values used for the ratio of breast milk to serum, fraction of breast milk that is lipid, ingestion rate, absorption, and body weight are the same as in the previous scenario.

All other assumptions are identical to the assumptions used in the previous scenario.

Results

In this scenario, the mother of a breast-feeding infant was assumed to be a computer monitor disassembly worker. The calculated daily intake for the infant ranged from 3.3×10^{-6} to 2.5×10^{-5} mg/kg-day for the RE and UE, respectively (Table 5-15). For this pathway, there was less uncertainty regarding serum concentration than in the previous scenario, because the values were taken directly from the published literature for workers performing this activity. However, there is still a great deal of uncertainty and conservatism in the percentage of DBDPO in the serum that would partition into the breast milk. Even for the RE value, a large degree of conservatism is built into these values.

Table 5-15. Estimated intake of DBDPO by an Infant ingesting breast milk from a mother who disassembles electronics.

Exposure Parameters	Reasonable Estimate (birth to 3 months)		Upper Estimate (birth to 2 years)	
	Value	Source/Comment	Value	Source/Comment
$C_{b:}$ DBDPO concentration in mother's blood (ng/g lipid)	4.8	Median for computer disassembly workers in Sweden (Sjödin et al. 1999)	9.9	Highest level reported for computer disassembly workers in Sweden (Sjödin et al. 1999)
$R_{b\text{-}m:}$ Breast milk to serum ratio (unitless)	0.1	Based on the fact that higher brominated DPO do not partition into milk as effectively as lower brominated DPO (see text)	0.5	Conservative assumption that DBDPO partitions into breast milk and serum on a lipid weight basis at the ratio that hepta-DPO does (BDE-183) (see text)
$F_{l:bm:}$ Fraction of breast milk that is lipid (g/mL)	0.04	4% expressed as g/mL (CS-EFH Table 2-12; U.S. EPA 2000)	0.04	4% expressed as g/mL (CS-EFH Table 2-12; U.S. EPA 2000)
CF: Conversion factor (mg/ng)	1E-06		1E-06	
IR: Ingestion rate, breast milk (mL/day)	742	Mean for ages 1–6 months (CS-EFH, Table 2-12, p. 2-19, U.S. EPA 2000)	980	12-month average, upper percentile (CS-EFH, Table 2-12, p. 2-19, U.S. EPA 2000)
ABS: Absorption (percent)	100[a]	Necessary to use with toxicity value	100[a]	Necessary to use with toxicity value
BW: Body weight, (Kg) 0–3 months (RE) 0–2 years (UE)	4.36	Average of 50th percentile weights, birth through 3 months (CS-EFH, Table 11-1, U.S. EPA 2000)	7.84	Average of 50th percentile weights, birth through 24 months (CS-EFH, Table 11-1, U.S. EPA 2000)
Daily Intake (mg/kg-day)	3.3E-06	Calculated	2.5E-05	Calculated

$$\text{Intake} = \frac{C_b \times R_{b\text{-}m} \times F_{l:bm} \times CF \times IR \times ABS}{BW}$$

[a] Although the absorption of DBDPO is estimated to be less than 2%, an absorption of 100% is necessary in the intake calculations because the toxicity values are based on an ingested dose rather than an absorbed dose. See text for details.

5.5.4 Infant Ingestion from Mouthing DBDPO-Containing Electronics

DBDPO is used to flame-retard synthetic polymers used in electrical and electronic equipment. A typical example of DBDPO's use in the United States is in the cabinet backs of television sets, where DBDPO is used at a level of approximately 12% (WHO 1994). In this exposure scenario, an infant is assumed to mouth consumer electronic products (e.g., television, computer monitor) that contain DBDPO. The DBDPO is assumed to leach from the surface of the electronic product into the saliva of the infant. The infant is exposed via swallowing the DBDPO-containing saliva. This scenario is not likely to represent typical exposures, because children are unlikely to be mouthing television sets or computer monitors. However, to be conservative, it is assumed that the possibility exists.

Assumptions

The assumptions made for this scenario are described below and shown in Table 5-16.

DBDPO concentration leached from surface into liquid. DBDPO is unlikely to leach from electronic equipment based on its physical/chemical properties, the types of plastics it is used in (e.g. dense, hard high impact polystyrene), and laboratory study results (Norris et al. 1974).

Norris et al. (1974) demonstrated that a pellet of acrylonitrile butadiene-styrene (ABS) terpolymer containing 4.25% DBDPO, placed in 2 L of water for a full day at 120 °F, did not leach DBDPO into the water at levels that could be detected (detection limit of 0.075 mg/L). Similarly, a 3% acetic acid solution at 120 ^{o}F for 1 or 7 days also did not leach DBDPO from the ABS pellets. The only conditions in this experiment under which DBDPO leached into the solution were pellets being put into a solution of cottonseed oil for seven days at 135 ^{o}F, with a resulting DBDPO concentration of 1 mg/L (Norris et al. 1974).

For the calculations involved in estimating intake from this exposure pathway, the concentrations obtained in the experiment described above were converted into a mass-per-time value. The first step in doing this conversion entailed calculating the total mass leached from the pellet by multiplying the concentration (i.e., 1 mg/L) by the total volume used in the experiment (i.e., 2 L). Then, to obtain a mass-per-time rate, the total mass leached was divided by the total number of days in the experiment (i.e., 7 days).

Step 1: (1 mg/L) × (2 L) = 2 mg

Step 2: (2 mg) / 7 days = 0.29 mg/day

This conversion assumes that the rate of leaching would be constant over the entire 7-day period. It also assumes that a smaller volume of liquid would have leached a smaller mass of DBDPO. Either assumption may be incorrect; however, because DBDPO was not extracted by either water or acetic acid (at high temperatures and over a 7 day period), and may not leach from plastic at all when mouthed by an infant; these assumptions are likely to have a negligible impact on the final calculations.

UE: A value of 0.29 mg/day was used based on DBDPO leached by cottonseed oil at 135 ^{o}F in seven days in the Norris et al. (1974) experiment, and the conversions described above.

RE: For a more reasonable estimate, the limit of detection (0.075 mg/L) over a 1-day period was used in the conversion described above to derive a value of 0.15 mg/day. Because no DBDPO was actually detected in the water, this value is likely to overestimate actual exposures.

Mouthing time per day – all objects. UE: A value of 97.2 minutes per day of total mouthing time was selected based on an average of the maximum mouthing times for children ages 3–18 months presented in Table 6-1 of the *Child-Specific Exposure Factors Handbook* (U.S. EPA 2000). This mouthing time encompasses all objects mouthed, including fingers and toys.

RE: A value of 32.4 minutes per day of mouthing time was selected based on an average of mean mouthing times presented in the table described above for children ages 3–18 months (U.S. EPA 2000), again for all objects mouthed.

Fraction of objects with DBDPO. UE: A value of 10% was selected based on professional judgment. It is not known for certain what percentage of items in the normal household contain DBDPO flame retarded polymer casings. Tulve et al. (2002) reported that 90% of the time, items mouthed by children less than 24 months were hands, other areas of their body or toys. The items mouthed in the remaining 10% were not provided, but it is unlikely that this consisted entirely of electronic equipment or textiles containing DBDPO. To be conservative, however, 10% was assumed as an upper estimate of the fraction of items that contain DBDPO and are mouthed by a child.

RE: A value of 1% was chosen as a more reasonable estimate based on professional judgment. Again, it is unlikely children will mouth hard plastic electronic items, such as television set cabinets, that might contain DBDPO.

Results

The calculated daily intake for a child exposed via mouthing DBDPO-containing electronic products ranged from 4.3×10^{-6} to 2.5×10^{-4} mg/kg-day for the RE and UE, respectively (Table 5-16). There is a significant amount of uncertainty surrounding the amount of DBDPO that may actually leach out of treated plastics. Both values used in these calculations were produced by a method (i.e., Norris et al. 1974, see discussion above) of which the relevance to actual human contact is debatable. Other values with considerable variability are the total mouthing time and fraction of objects mouthed that contain DBDPO. Even with this level of uncertainty, a large degree of conservatism is built into both the UE and RE values. Despite this conservatism, the calculated exposures for this hypothetical scenario are very small.

Table 5-16. Estimated DBDPO intake by an infant mouthing DBDPO-containing electronics.

Exposure Parameters	Reasonable Estimate		Upper Estimate	
	Value	Source/Comment	Value	Source/Comment
C_L: Mass of DBDPO leached from surface into liquid per day (mg/day)	0.15	Norris et al. 1974. No DBDPO was extracted from ABS terpolymer in water for 1 day at 120 °F. This value is the limit of detection (0.075 mg/L) multiplied by the total volume (2 L) divided by the total number of days (1 day).	0.29	Norris et al. 1974. Extraction of DBDPO from ABS terpolymers in cottonseed oil at 135 °F for 7 days. This value is the concentration of DBDPO leached (1 mg/L) multiplied by the total volume (2 L) divided by the total number of days (7 days).
CF: Conversion factor (day/min)	6.9E-04	1 day has 1,440 minutes	6.9E-04	1 day has 1,440 minutes
MT: Mouthing time (min/day)	32.4	Total mouthing time, average of means for ages 3–18 months (CS-EFH, Table 6-1, p. 6-12, U.S. EPA 2000)	97.2	Total mouthing time, average of maximums for ages 3–18 months (CS-EFH, Table 6-1, p. 6-12, U.S. EPA 2000)
FS: Fraction of objects with DBDPO (percent)	1	Professional judgment (see text)	10	Professional judgment (see text)
ABS: Absorption (percent)	100[a]	Necessary to use with toxicity value	100[a]	Necessary to use with toxicity value
BW: Body weight, 0–2 years (kg)	7.84	Average of 50th percentile weights, birth through 24 months (CS-EFH, Table 11-1, U.S. EPA 2000)	7.84	Average of 50th percentile weights, birth through 24 months (CS-EFH, Table 11-1, U.S. EPA 2000)
Daily Intake (mg/kg-day)	4.3E-06	Calculated	2.5E-04	Calculated

$$\text{Intake} = \frac{C_L \times CF \times MT \times FS \times ABS}{BW}$$

[a]Although the absorption of DBDPO is estimated to be less than 2%, an absorption of 100% is necessary in the intake calculations because the toxicity values are based on an ingested dose rather than an absorbed dose. See text for details.

5.5.5 Child's Inhalation of DBDPO-containing Dust Originating from Electronics

In addition to the low likelihood of leaching from a hard plastic into a liquid, DBDPO's negligible vapor pressure indicates that it also would not volatilize out of the plastic components. DBDPO has been measured in air in a room full of computers, and therefore we calculated the exposures that a child might experience when exposed to DBDPO in indoor air.

Assumptions

The assumptions made for this scenario are outlined below and shown in Table 5-17.

DBDPO concentration in air (respirable); vapor attaches to dust particulates in air. UE: A respirable air concentration of 0.087 ng/m³ was selected as an upper estimate based on the highest value reported for an office with computers (Sjödin et al. 2001a). Sjödin et al. (2001a) reported that DBDPO in air was associated with particulates.

RE: An air concentration of 0.052 ng/m³ was selected, based on the mean of all samples reported for an office with computers, using one-half the detection limit for non-detected concentrations (Sjödin et al. 2001a).

Fraction of time spent in room with TV or computer. UE: As an upper estimate, it was assumed that an infant spends all of his or her time indoors, in a room with a TV or computer, yielding a fraction of 1.

RE: A fraction of 0.833 was selected based on the assumption that 20 hours in a 24-hour period were spent indoors in a room with a TV or computer monitor. There are no guidance values for this parameter from the EPA *Child-Specific Exposure Factors Handbook*, but it is reasonable to assume that infants spend a large portion of a day indoors, and that most of their time might be spent in a room that also contains a television or computer monitor.

Inhalation rate. UE and RE: An inhalation rate of 5.65 m³/day was used based on the average of the mean value for children less than 1 year old (4.5 m³/day) and the mean for children aged 1–2 years old (6.8 m³/day). No medians or high-end values were presented for this parameter, so the same value was used as both the UE and the RE (U.S. EPA 2000).

Results

The calculated daily intake for a child exposed via the inhalation of particulates from plastic electronic products ranges from 3.1×10^{-8} mg/kg-day to 6.3×10^{-8} mg/kg-day for the RE and UE, respectively (Table 5-17). Even using the conservative assumptions discussed above, the calculated intakes via this pathway are orders of magnitude less than the intakes estimated via other pathways. Therefore, inhalation of DBDPO in the household is estimated to contribute only minimally to total exposure.

Table 5-17. Estimated DBDPO intake of young children inhaling particulates released from electronics.

Exposure Parameters	Reasonable Estimate		Upper Estimate	
	Value	Source/Comment	Value	Source/Comment
C_a: DBDPO concentration in air (respirable); vapor attaches to dust particulates in air (ng/m3)	0.052	Office w/computers (mean of all samples, using one-half the detection limit for non-detects) Sjödin et al. 2001a	0.087	Office w/computers (highest value reported) Sjödin et al. 2001a
CF: Conversion factor (mg/ng)	1.0E-06		1.0E-06	
FI: Fraction of time spent in room w/TV or computer (unitless)	0.83	20 hrs in 24-hr period; professional judgment	1	24 hrs in 24-hr period; professional judgment
IhR: Inhalation rate (m3/day)	5.65	Average of <1 yr (4.5) & 1–2 yrs (6.8), means [CS-EFH, Table 7-13, p. 7-20, U.S. EPA 2000][a]	5.65	Average of <1 yr (4.5) & 1–2 yrs (6.8), means [CS-EFH, Table 7-13, p. 7-20, U.S. EPA 2000][a]
ABS: Absorption (percent)	100[b]	Necessary to use with toxicity value	100[b]	Necessary to use with toxicity value
BW: Body weight, 0–2 years (kg)	7.84	Average of 50th percentile weights, birth through 24 months (CS-EFH, Table 11-1, U.S. EPA 2000)	7.84	Average of 50th percentile weights, birth through 24 months (CS-EFH, Table 11-1, U.S. EPA 2000)
Daily Intake (mg/kg-day)	3.1E-08	Calculated	6.3E-08	Calculated

$$\text{Intake} = \frac{C_a \times CF \times FI\ IhR \times ABS}{BW}$$

[a] Only means are reported

[b] Although the absorption of DBDPO is estimated to be less than 2%, an absorption of 100% is necessary in the intake calculations because the toxicity values are based on an ingested dose rather than an absorbed dose. See text for details.

5.5.6 Exposure via Mouthing, Dermal Contact with DBDPO-Containing Textiles, and Inhalation of DBDPO-Containing Dust Originating from the Textiles

The National Academy of Sciences (NAS) recently conducted a consumer exposure and risk assessment for flame retardants that may be used to flame retard upholstery textiles (see Table 5-18 for a summary of the NAS calculations, and Appendix V). The results from the NAS are reported in Table 5-6 without modifications.

Assumptions

A number of very conservative assumptions were used in NAS's exposure assessment calculations, including the following.

For dermal exposure:

- An adult spends one-fourth of every day sitting on furniture upholstery that is back-coated with DBDPO.
- One quarter of the receptor's upper torso is in contact with the upholstery.
- Receptor's skin and clothing, and the upholstery fabric, present no barrier to DBDPO movement.
- Sufficient water (e.g., from sweat) is present to allow dissolution of DBDPO in the water and transfer to the skin and into the body of the receptor.
- All of the DBDPO that dissolves is absorbed immediately by the receptor. An alternative iteration of dermal exposure assumed that DBDPO dissolves up to its solubility limit in water.
- Estimated upholstery application rate for DBDPO is 5 mg/cm^2.
- Estimated extraction rate by water for DBDPO (0.025/day) is based on extraction data for hexabromocyclododecane in polyester fiber (McIntyre et al. 1995).

For inhalation exposure:

- An adult spends one-fourth of a lifetime in a room with a low air-exchange rate (0.25/hour).
- The room contains a relatively large amount of fabric upholstery (30 m^2 in a 30-m^3 room) treated with DBDPO.
- The DBDPO treatment is gradually wearing away over 25% of its surface, to 50% of its initial quantity over the 15-year lifetime of the fabric.
- One percent of the worn-off DBDPO is released into indoor air as respirable particulates.
- For vapor inhalation, release of DBDPO by evaporation from the upholstery is assumed.

For oral exposure:

- A child, 0–2 years, mouths 50 cm^2 of fabric back-coated with DBDPO for 1 hour per day, daily, for 2 years.

- Extraction rate by saliva for DBDPO (0.025/day) is based on extraction data for hexabromocyclododecane in polyester fiber (McIntyre et al. 1995).

NAS noted uncertainty in these exposure estimates because dermal absorption data for DBDPO was available, the minimal solubility of DBDPO in water, the low vapor pressure of DBDPO, and the encapsulation of DBDPO in a polymer matrix.

Results

NAS's exposure estimates indicated that potential consumer exposure to DBDPO as a result of its use in upholstery fabrics, reported as a single-value for each exposure route, was minimal. The estimated exposures that NAS derived are higher than some of the intake estimates calculated here for other types of exposures. NAS stated that its results were extremely conservative, and that the estimated exposures did not warrant concern from a human health risk perspective. NAS also concluded that no further data was needed.

Table 5-18. Summary of NAS (2000) results re DBDPO exposures from upholstery textiles.

Exposure Pathway	Noncancer Intake	Noncancer Hazard Quotient	Comment/Assumptions
Dermal-Adult (mg/kg-day)	9.8E-01	0.25	▪ Adult spends 1/4 of every day sitting on furniture upholstery backcoated with DBDPO ▪ 1/4 of the adult's upper torso is in contact with upholstery ▪ Adult's skin and clothing and upholstery fabric present no barrier to DBDPO movement ▪ Sufficient sweat is present to allow dissolution of DBDPO and transfer to the skin and into the body ▪ All DBDPO that dissolves is absorbed immediately
Dermal-Adult (mg/kg-day)	1.33E-09	3.34E-10	Same as dermal scenario above except assumes that DBDPO only dissolves up to its solubility limit in water
Inhalation of Particulates-Adult (mg/m3)	4.8E-04	0.000034	▪ Adult spends 1/4 of life in a room with low air-exchange rates ▪ Room contains relatively large amount of fabric upholstery treated with DBDPO ▪ DBDPO treatment is gradually wearing away over 25% of its surface to 50% of its initial quantity over the 15-year lifetime of the fabric ▪ 1% of the worn-off DBDPO is released into indoor air as small particles that may be inhaled
Inhalation of Vapors-Adult (mg/m3)	3.8E-04	0.0000271	Same as particulate scenario above except assumes that DBDPO is released by evaporation
Oral-Child, 0-2 yrs (mg/kg-day)	2.6E-02	0.0065	Child mouths fabric backcoated with DBDPO for 1 hour per day, daily, for 2 years

5.5.7 Exposure to Children via the Environment

There are limited data on measured DBDPO concentrations in the U.S. environment or food items. Fish, chicken, air, sewage, sewage treatment plant (STP) sludge, and sediment have been sampled to quantify DBDPO in the U.S. (see Table 5-1), but the data are insufficient to calculate a reasonable exposure for the general population that might be exposed to DBDPO via food, water, air, and soil.

DBDPO has been detected in U.S. citizens, albeit at very low levels, with the majority of the results being non-detects. These detections indicate that at least some persons in the U.S. were exposed in some way to DBDPO. Quantifying exposures based on levels measured in humans is a reasonable approach, given the lack of alternative data on levels of DBDPO in the environment.

This intake calculation was assumed to represent the total amount of DBDPO that a child living in the U.S. might absorb via pathways other than breast milk ingestion or direct ingestion from electronic products or fabrics, including inhalation of ambient outside air; inhalation of indoor air; ingestion from food; incidental ingestion and dermal contact with soils or sediments; and ingestion, dermal contact, and inhalation from water.

Calculating the absorbed dose of DBDPO that would result in the measured serum DBDPO in humans requires information on the half-life of DBDPO in humans, and the volume distribution of DBDPO in humans. To calculate the ingested dose (which is required to compare to the reference dose, or RfD), requires knowledge of the bioavailability of DBDPO in humans (via all routes).

Assumptions

The following describes what is known about each of these parameters, and this information is summarized in Table 5-19.

Concentration of DBDPO in Humans. Sjodin et al. (2001) reported measuring DBDPO in the blood of U.S. blood donors collected in 1988. The median serum concentration of DBDPO in these blood donors was < 1 pmol/g lipid weight. The range was <1 – 35 pmol/g lipid weight.

UE: The highest level reported was 35 pmol/g lipid weight or 33.6 ng/g serum lipid.

RE: The median level was < 1 pmol/g lipid weight or < 0.96 ng/g serum lipid. For the purposes of this assessment, a median = 0.96 ng/g will be used.

Half-life. A study of workers who had detectable DBDPO levels in their serum showed that the levels of DBDPO declined rapidly when the workers went on vacation for an extended period of time (at least 30 days). Sjödin et al. (2000) reported that the average half-life of DBDPO in these workers was 6.8 days, with a confidence interval of 3–12 days.

UE: A half-life in the body of 3 days was used, based on lower bound value of the confidence interval report by Sjödin et al. (2000)[1]. This value may underestimate the half-life, because the confidence interval represents a statistical calculation (i.e., mean minus two times the standard deviation), rather than the lowest observed half-life, which was not reported. In another study, a half-life of approximately 15 days was observed in a worker who had detectable serum levels (Thuresson 2002a). However, because additional data regarding the possible lower-end values is unavailable, the conservative estimate of 3 days was used.

RE: A half-life in the body of 6.8 days was used, based on the median value reported by Sjödin et al. (2000).

Volume of distribution. This parameter represents the volume of the tissues in the body into which a chemical will distribute. Measures of DBDPO in serum report the compound in the lipid fraction of serum. When rats were exposed to DBDPO via oral ingestion, concentrations of DBDPO were higher in the liver than in adipose tissue, and levels in other tissues and muscle were much lower (El Dareer et al. 1987). Therefore, the following reasoning was used for the volume of distribution values.

UE: A value of 50% was used as an upper-bound estimate, because DBDPO does not partition in the lipid fraction exclusively. DBDPO does not partition into muscle (which accounts for approximately 50% of the body's volume) to any appreciable amount. In rats dosed with DBDPO, the concentration of DBDPO in the muscle tissue was one to two orders of magnitude lower than that in the adipose tissue. However, the lack of more detailed information precludes us from refining this estimate any further.

RE: A value of 25% adipose tissue in humans was used based on EPA's value used to calculate 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) body burdens. EPA reported this value to be on the high end of the range for the general population. It is probably a reasonable figure to use for DBDPO, which does not partition in the lipid fraction to the extent and affinity that TCDD does.

Absorption (bioavailability). The bioavailability of DBDPO in rats has been found to be less than 2% when administered in feed (El Dareer et al. 1987). Data on the bioavailability of DBDPO via the inhalation route is not available, and only limited data is available (via an *in vitro* assay) on the bioavailability via the dermal route (Hughes et al. 2001). An assessment of the DBDPO blood levels in Swedish workers suggests bioavailability via inhalation may be similar to that of oral (Hardy 2001).

UE: A value of 1% absorption was used. Intake is calculated from an "absorbed dose," so a lower absorption factor provides a higher intake estimate (i.e., more conservative assumption), because the absorption factor is in the denominator of the equation.

[1] In this equation, a lower half-life was chosen for the UE because a lower value will yield a higher estimate of intake since the half-life is in the denominator of the equation.

RE: A value of 2% absorption (bioavailability) was used based on the highest value report by El Dareer et al. (1987).

Results

The calculated intakes for exposures via the general environment were 1.2×10^{-3} and 3.9×10^{-1} mg/kg-day for the RE and UE, respectively (Table 5.19). These values are probably higher than the true intake. Given that the majority of serum samples tested had non-detectable levels of DBDPO, it is most likely that the majority of the U.S. population has very low, if not zero, exposure.

Table 5-19. Estimated children's exposures to DBDPO via the general environment.

Input Parameters	Reasonable Estimate		Upper Estimate	
	Value	Source/Comment	Value	Source/Comment
C_{ss}: Concentration in body, steady state (ng/g lipid)	0.96 [a]	Median (Sjödin et al. 2001b)	33.6[a]	Maximum (Sjödin et al. 2001b)
V_d: Volume of distribution = {BW × FL}				
BW: Body weight (3–6 yrs) (kg)[b]	18.7	Average of means (CS-EFH, Tables 11-3 & 11-4, U.S. EPA 2000)[b]	18.7	Average of means (CS-EFH, Table 11-3 & 11-4, U.S. EPA 2000)[b]
FL: Fraction of lipid per body weight (kg lipid/kg BW)	0.25	Used by U.S. EPA Dioxin Reassessment	0.5	Upper-end estimate
CF_1: Conversion factor 1 (g lipid/kg lipid)	1E+03		1E+03	
k: First order rate constant = {Ln(2) / $t_{1/2}$}				
Ln(2): Natural log of 2 (unitless)	0.693		0.693	
$t_{1/2}$: Half life of chemical (days)	6.8	Mean (Sjödin 2000)	3	Lower bound on calculated confidence interval (Sjödin 2000)
CF_2: Conversion factor 2 (mg/ng)	1E-06		1E-06	
ADD: Average daily dose (absorbed) (mg/day)	0.0005	Calculated	0.073	Calculated
BW: Body weight (3–6 yrs) (kg)	18.7	Average of means (CS-EFH, Tables 11-3 & 11-4, U.S. EPA 2000)	18.7	Average of means (CS-EFH, Tables 11-3 & 11-4, U.S. EPA 2000)
ABS: Absorption (percent)	2	El Dareer et al. 1987	1	In this equation, use of a lower ABS will result in a higer intake estimate.
Daily Intake (mg/kg-day)	1.2E-03	Calculated	3.9E-01	Calculated

ADD = $C_{ss} \times V_d \times CF_1 \times k \times CF_2$
ADD = $C_{ss} \times \{BW \times FL\} \times CF_1 \times \{Ln(2) / t_{1/2}\} \times CF_2$
Daily Intake = ADD / (BW × ABS)
Note: The daily intake must be converted from an absorbed dose to an ingested dose because the toxicity value (RfD) is calculated based on an ingested dose.
[a] Values converted from pmol/g lipid to ng/g lipid using the formula:
(pmol/g lipid) × (959 g/mol) × (1 mol/10^{12} pmol) × (10^9 ng/1 g) = ng/g lipid
[b] In this equation for daily intake, the value for body weight is in both the numerator and the denominator, and thus, will cancel out. Therefore, these calculated intakes are applicable to a receptor of any age.

5.5.8 Aggregate Exposure Estimate and Discussion of Uncertainties

The calculations presented here suggest that the potential exposures for each scenario evaluated are very small. Furthermore, the upper estimates (UEs) for each scenario are considerably larger than the reasonable estimates (REs)—several orders of magnitude larger for some of the scenarios. For each of the scenarios, it must be stressed that the RE is very likely to be an estimate of exposure that is greater than the actual exposure experienced by the mean of the U.S. population. For example, the prevailing opinion of experts in the field is that DBDPO does not partition into breast milk. However, given the uncertainties that still exist for this pathway (because of the lack of definitive proof that DBDPO does not exist in breast milk), a conservative assumption was made to calculate exposure. As can be seen from Figures 5-1 and 5-2, the breast-milk exposures calculated for the worker scenarios are among the highest exposure potentials calculated, if not the highest. If DBDPO is not present in breast milk, then exposure via this pathway would be zero for all populations.

The UE estimates of exposure almost certainly represent levels that no one would actually receive, and no exposures would be expected to be above that level. This approach of calculating an exposure that is unlikely to occur for anyone was undertaken to develop an upper bound on potential exposures. The actual upper bound may be less than that calculated here. Barring evidence that the U.S. general population has serum levels on the order of 100–300 ng/g lw DBDPO, this conclusion would not change. Preliminary results from recent surveys conducted by the Centers for Disease Control (CDC) indicate that DBDPO serum levels in U.S. citizens have not changed appreciably compared to the levels measured in the late 1980s (Patterson 2002, personal communication). Therefore, it is not likely that the results presented herein would need to be adjusted upward for the early 2000s, as opposed to the late 1980s.

These UEs for the general environment scenario should be placed into appropriate perspective. Assuming that all U.S. citizens are exposed to DBDPO in the environment at the UE levels, then humans in the U.S. ingest over 13% of the total volume of DBDPO produced in the U.S. each year. This is obviously not the case; therefore, the UE estimates should be considered upper bounds that are not likely to occur.

Table 5-20 summarizes the aggregate exposures experienced by the three populations evaluated in this exposure assessment—the infant of a mother working in the bagging operations at a DBDPO manufacturing site (infant, manufacturer), infant of a mother who disassembles computer monitors (infant, disassembler), and a child's average exposures associated with DBDPO in the environment. The infant of a mother in the bagging operation would experience exposures from drinking the mother's milk, ingesting DBDPO while mouthing electronic consumer products, ingesting DBDPO while mouthing furniture fabric, and from general environmental exposures. The infant of a mother who disassembles computer monitors would have the same exposures, except that the mother's breast milk would contain a different amount of DBDPO. Children through age 18 who do not breast feed would be exposed only via the general environment.

There is up to an order-of-magnitude difference between the RE and UE for the two infant scenarios, and a two order-of-magnitude difference between the RE and UE for the general environment scenario (Table 5-20). The highest estimated exposure (UE for the infant, manufacturer scenario) is 0.76 mg DBDPO/kg-day. The lowest estimated exposure (RE for the general environment scenario) is 0.0012 mg DBDPO/kg-day.

Table 5-20. Summary: Estimated pathway-specific and aggregate U.S. children's exposures to DBDPO.

Daily Intakes	Exposure Duration (yrs)	Reasonable Estimate	Upper Estimate
Pathway-specific			
Ingestion, breast milk (manufacturer); mg/kg-day	0–2	1.9E-02[a]	3.4E-01
Ingestion, breast milk (disassembler); mg/kg-day	0–2	3.3E-06[a]	2.5E-05
Ingestion, consumer electronic products; mg/kg-day	0–2	4.3E-06	2.5E-04
Ingestion, mouthing fabric (NAS); mg/kg-day	0–2	2.6E-02	2.6E-02
General exposures; mg/kg-day	0–18	1.2E-03	3.9E-01
Aggregate			
Infant, manufacturer[b]; mg/kg-day	--	0.046[b]	0.76[b]
Infant, disassembler[c]; mg/kg-day	--	0.027[c]	0.41[c]
Lifetime (0–70)[d]; mg/kg-day	--	0.0012[d]	0.39[d]

[a] Assumes a shorter duration for nursing (0–3 months), based on Collaborative Group on Hormonal Factors in Breast Cancer 2002.
[b] This value incorporates the intakes for ingestion of breast milk from a mother who is a manufacturer, plus ingestion from consumer electronic products, ingestion from mouthing fabric, and general exposures.
[c] This value incorporates the intakes for ingestion of breast milk from a mother who is a disassembler, plus ingestion from consumer electronic products, ingestion from mouthing fabric, and general exposures.
[d] This value incorporates the intake from general exposures. See text for details.

Some of the highest estimated exposures for both the RE and UE scenarios are associated with breast-milk ingestion by an infant whose mother works in the bagging operation at a DBDPO manufacturing site. There are only two facilities in the U.S. that manufacture DBDPO, the number of employees who might be exposed at these levels is less than 50, and no women are employed in the bagging operation (Personal communication, BFRIP). (Women are not excluded from this task, but the type of work does not attract female employees.) It is less certain how many employees might be involved in compounding operations where DBDPO bags are emptied into hoppers prior to incorporating into a polymer matrix. It is likely that fewer than 1,000 employees are engaged in this type of work. Of these potential 1,000 employees, very few, at any point in time, would be lactating mothers. Therefore, fewer than 10 infants would be estimated to be exposed to the highest levels predicted for the infant, manufacturing scenario.

The number of infants that might be exposed to breast milk from a mother who disassembles computer monitors, molds plastic casings, or handles flame-retarded upholstery textiles in the

workplace might be larger—perhaps several thousands. Therefore, the corresponding number of nursing infants that might have this exposure potential might number in the hundreds.

The remaining evaluations are for exposures that all U.S. infants have the potential to experience. Because residential furniture is required to meet fire safety standards (and thus might utilize DBDPO in the textiles) only in California, the number of infants that actually might be exposed to DBDPO via upholstery textiles is likely a fraction of the U.S. population. The calculations for the general-population exposures (child through age 18) also reflect the exposures experienced by the entire U.S. population, even though, again, only a fraction of the population might incur such exposures.

For all of these scenarios, it must be stressed that the exposures predicted in this evaluation are meant to be highly conservative (as a screening estimate), and the actual exposures experienced by nursing infants, infants that mouth fabrics, and the general population are very likely to be below the levels predicted for the RE, and far below the UE estimates.

6.0 RISK ASSESSMENT

DBDPO is used solely as a flame retardant, and in all applications is encapsulated in a polymer matrix with no direct consumer exposure. Its primary application is in electrical and electronic equipment with a secondary application in upholstery textiles. A typical U.S. application for DBDPO is in television cabinets composed of high impact polystyrene. DBDPO is not sold directly to the public.

DBDPO is a data rich chemical with virtually all VCCEP Tier I, II and III hazard endpoints fulfilled. It is a large poorly absorbed molecule that exhibits little toxicity. Testing has shown that DBDPO is not acutely toxic or mutagenic, and is not a developmental or reproductive toxicant. The NOAEL for DBDPO in subchronic and/or chronic studies in the rat or mouse is at least 1,000 mg/kg/d. DBDPO's low toxicity is likely related to its poor absorption and rapid elimination (NTP 1986). Pharmacokinetic studies have shown that DBDPO is poorly absorbed (0.3 -2% of an oral dose), has a short half-life (24 hr in rats) compared to PCB 153 (<2% of an oral dose was eliminated by rats in 21 days), and is rapidly eliminated in the feces (>99% in 72 hr in rats) (NTP 1986; Norris et al. 1973, 1975; El Dareer et al. 1987; Moreck and Klassen-Wheler 2001).

These features coupled with DBDPO’s low potential for migration out of plastic resin are indicative of low risk. The U.S. National Academy of Sciences (NAS) evaluated the potential risk to the consumer posed by DBDPO-treated upholstery textiles. In all scenarios evaluated by NAS, dermal, oral or inhalation exposure to DBDPO was determined not to present a risk of adverse health effects to the consumer, including children mouthing upholstery textiles. A similar conclusion was reached in the current assessment with respect to exposures resulting from DBDPO’s use in electrical and electronic applications. The WHO and the European Union also concluded the general population is at negligible risk from DBDPO.

Exposure to DBDPO could potentially occur through food or breast milk. However, DBDPO has not been detected in limited sampling of fish and poultry in the U.S., and based on its properties, is not anticipated to be present in these food items or in meat or dairy products. Likewise, leafy vegetables and root crops are not expected to be a source of DBDPO exposure to the general public, and a risk of adverse health effects is not anticipated.

DBDPO transfer to breast milk is likely to be slow and very limited, if at all. Protein binding, ion trapping and lipid partitioning are not expected to alter DBDPO concentrations in breast milk due to DBDPO's physical/chemical properties. Build-up of DBDPO concentrations in breast milk is not expected due to its anticipated slow diffusion into milk and periodic emptying of breast milk. This combination of low absorption from the gut, rapid elimination in the feces, poor and/or slow diffusion into breast milk should effectively preclude DBDPO in milk. Thus, a risk to the nursing infant is not anticipated.

Highly conservative estimates of U.S. DBDPO pathway-specific and aggregate exposures (Table 5-11) are substantially lower than DBDPO's NOAEL of 1,000 mg/kg/d and the reference dose (RfD), 4 mg/kg/d, calculated by NAS[2] (NAS 2000). These estimated exposures are intentionally biased to generate worst-case exposures; actual exposures in the U.S. are expected to be substantially lower. For noncancer health effects, quantitative risk estimates are typically provided in the form of Hazard Quotients (HQs). The HQ represents the estimated exposure for a specific chemical divided by the reference dose (RfD), expressed in mg/kg-day. As such, HQs indicate the calculated exposure estimates in comparison to an exposure level that is unlikely to result in adverse health effects. If an HQ value is less than one, then it can reasonably be assumed that the chemical exposure will not be associated with toxicity. As HQ values increase above one, the potential for toxicity increases. As shown in Table 6-1, all calculated HQs for DBDPO are significantly less than one, with the highest aggregate HQ of 0.2 being five-fold lower than one. Thus, these HQs indicate that even when using conservative, worst-case estimates of exposure to DBDPO, adverse health effects are not expected.

The protection provided by DBDPO in terms of enhanced fire safety reduces the very real risk of death or injury that consumers face in the home from fires. In the applications in which DBDPO is used, an estimated 280 lives are saved each year in the U.S. through the use of a brominated flame retardant. These estimated lives-saved are particularly relevant to the VCCEP program, because children are especially vulnerable to fire deaths and injuries. The benefits derived from the use of DBDPO in consumer products, particularly for children, far outweigh the insignificant potential for harm.

[2] NAS derived an oral RfD for DBDPO by using the chronic NOAEL of 1,120 mg/kg-d, based on liver thrombosis and degeneration observed in rats at the next higher dose (NTP 1986), and a composite uncertainty factor of 300, resulting in an RfD of 4 mg/kg-d (RfD = NOEL + 300). In the IRIS Database, EPA provides a reference dose (RfD) of 1 x 10-2 mg/kg-d for DBDPO based on the 1 mg/kg-d NOAEL for histopathology and other toxicity endpoints in rats exposed via diet for 2 yr (Kociba et al. 1975). Doses higher than 1 mg/kg-d were not tested in this study, precluding identification of a LOAEL. The reason the NTP (1986) 2-yr toxicology/carcinogenesis bioassay for DBDPO was not considered in the current Risk summary in IRIS (EPA 1999) is because the NTP results were not available at the time of the Risk derivation (1984-1985).

TABLE 6-1. DBDPO exposure estimates and hazard quotient based on a RfD of 4 mg/kg/day.

Daily Intakes	Exposure Duration (yrs)	Exposure Estimate (mg/kg/d)		Hazard Quotient (RfD = 4 mg/kg/d[e])	
		Reasonable	Upper	Reasonable Estimate	Upper Estimate
Pathway-specific					
Ingestion, breast milk-manufacturer	0–2	1.9E-02[a]	3.4E-01	0.005	0.09
Ingestion, breast milk-disassembler	0–2	3.3E-06[a]	2.5E-05	8E-07	6E-06
Ingestion, consumer electronics	0–2	4.3E-06	2.5E-04	1E-06	6E-05
Ingestion, mouthing fabric (NAS)	0–2	2.6E-02	2.6E-02	0.007	0.007
General exposures	0–70	1.2E-03	3.9E-01	0.0003	0.1
Aggregate					
Infant, manufacturer[b]	--	0.046[b]	0.76[b]	0.01	0.2
Infant, disassembler[c]	--	0.027[c]	0.41[c]	0.007	0.1
Lifetime (0–70)[d]	--	0.0012[d]	0.39[d]	0.0003	0.1

[a] Assumes a shorter duration for nursing (0–3 months), based on Collaborative Group on Hormonal Factors in Breast Cancer 2002.
[b] This value incorporates the intakes for ingestion of breast milk from a mother who is a manufacturer, plus ingestion from consumer electronic products, ingestion from mouthing fabric, and general exposures.
[c] This value incorporates the intakes for ingestion of breast milk from a mother who is a disassembler, plus ingestion from consumer electronic products, ingestion from mouthing fabric, and general exposures.
[d] This value incorporates the intake from general exposures. See text for details.
[e] The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data. The RfD for DBDPO, 4 mg/kg/d, was calculated by the U.S. National Academy of Sciences instead of using the current 1999 IRIS Rfd (0.01 mg/kg/d). NAS calculated a revised RfD for DBDPO using the NTP 2 year bioassay results, which were not available at the time of the IRIS derivation (1984-1985).

7.0 DATA NEEDS ASSESSMENT

Data is available on DBDPO for essentially all Tier I, II and III hazard endpoints (Table 7-1). The U.S. National Academy of Sciences concluded its review of DBDPO with a finding that no additional information was needed to evaluate its risk to the consumer through the use of flame-retarded upholstery textiles. BFRIP concurs with the findings of that assessment, and believe they also apply to DBDPO's use in electrical and electronic equipment and for exposures from the diet and ambient environment.

While available data do not provide for an accurate estimation of children's actual exposures to DBDPO, the exposure assessment conducted as part of this VCCEP submission is so conservative in nature that it most likely vastly overestimates actual exposures that might be encountered by children. Despite their overly conservative nature, the exposure estimates are

below the lifetime daily dose expected to result in no harmful effects (RfD). Therefore, additional data to help refine our estimates of children's exposures to DBDPO appear unnecessary.

TABLE 7-1. A comparison of the data available on DBPDO to the studies listed in the VCCEP's Tiers I, II and III.

TESTS	DATA AVAILABLE?
Tier I	
Acute Oral	Yes
Acute Inhalation	Yes
In vitro Gene Mutation – Bacterial Reverse Mutation	Yes
Repeated Dose Oral Toxicity	Yes: In Two Species
Reproductive Toxicity (1-Generation)	Yes
In vitro Chromosome Aberrations	Yes. Additional mutagenicity results are available from mouse lymphoma and sister chromatid exchange studies
Tier II	
90-Day Subchronic Toxicity in Rodents	Yes: In Two Species
Reproduction and fertility effects (2-Generation)	Data is not available from a 2-generation study. Data from repeated dose, developmental and reproduction studies do not indicate effects on reproduction or fertility.
Prenatal Developmental Toxicity (Two Species)	Yes: One Species
In vivo mammalian bone marrow chromosome aberrations	Evaluated as a part of a 1-Generation study
Immunotoxicity	Data is not available from studies performed via the listed guideline. No indication of immunotoxicity was observed in two species tested at high dose levels administered over a two year time period.
Metabolism and Pharmacokinetics	Yes
Tier III	
Carcinogenicity	Yes: Two Species
Neurotoxicity Screening Battery	Data is not available from a study performed via the listed guideline. Data from repeated dose studies at very high dose levels in two species do not indicate an effect on the nervous system.
Developmental Neurotoxicity	Data is not available from a study performed via the listed guideline.

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