Technical Pentabromodiphenyl Ether (32534-81-9)
Technical Octabromodiphenyl Ether (32536-52-0)
2,2«,4,4«-Tetrabromodiphenyl Ether (5436-43-1)
2,2«,4,4«,5-Pentabromodiphenyl Ether (60348-60-9)
2,2«,4,4«,5,5«-Hexabromodiphenyl Ether (68631-49-2)

Review of Toxicological Literature

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Review of Toxicological Literature

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EXECUTIVE SUMMARY

The nomination of 2,2«,4,4«-tetrabromodiphenyl ether, 2,2«,4,4«,5-pentabromodiphenyl ether, and 2,2«,4,4«,5,5«-hexabromodiphenyl for toxicology and carcinogenicity testing is based on their structural similarity to PCBs, potential toxicity, and pervasiveness in the environment and human tissues. The nomination of technical octabromodiphenyl ether and pentabromodiphenyl ether is as a source for these compounds. There is some evidence to support the carcinogenicity of a related congener, decabromodiphenyl ether (CASRN 1163-19-5), in male and female rats dosed orally in a two-year study (NTP, 1986).

Two technical mixtures and three selected congeners are included in a class of compounds known as PBDEs. PBDEs are structurally related to polybrominated biphenyls (PBBs) with 209 possible congeners. Although commonly called commercial mixtures in some references, we will use the term technical since even small amounts sold as analytical standards may be deemed commercial.

Analysis

Extraction and clean-up methods used to identify and quantify PBDEs in various media are similar to methods used for PCBs and PBBs. Solvent extraction is used to isolate PBDEs from biological and environmental media (sediment and air). Fat is removed with concentrated sulfuric acid or over alumina columns and clean up or fractionation of samples is accomplished with a silica column. Gas chromatography/mass spectrometry (GC/MS) or GC coupled with some other detection method is most frequently used to characterize and quantify PBDEs in environmental media with limits ranging from <5 to 60 g/kg. GC/MS, HPLC, and high-resolution gas chromatography (HRGC) have been used to determine PBDEs in biological media with limits of detection ranging from 0.73 ng/kg to 0.10 mg/kg. The lack of certified reference standards for individual PBDEs poses a problem for analysis, since comparative analysis of data from different studies is impaired by the determination of compounds on the basis of technical mixture equivalents instead of by comparison with individual congeners. Methods have been described for the synthesis of some congeners.

Production

The production of organobromine compounds in the United Sates is limited geographically to sites containing underground bromide deposits located in Michigan and Arkansas; however, no production is presently occurring in Michigan. According to the U.S. Bureau of Mines, these deposits are likely to satisfy the United States demand for brominated chemicals for another 55 years. The two commercial mixtures, OBDE and PeBDE, reviewed in this draft are produced by two companies in the United States, Albemarle Corporation, located in Magnolia, AR, and the Great Lakes Chemical Corporation, in El Dorado, AR. The majority of brominated compounds currently produced at these facilities are for use as flame retardants in polymers. Technical OBDE is produced commercially in the United States as DE-79, FR-1208, and Saytex 111. Technical PeBDE is produced commercially in the United States as Bromkal 70-5DE, DE-71, Tardex 50, and Tardex 50 L.

The brominated diphenyl ethers comprise the largest volume of brominated flame retardants used in the world today. In, 1992, technical OBDE and DeBDE were 75% and 15% respectively, of the world production of PBDEs (40,000 metric tons), while technical PeBDE accounted for 10% of world production. In 1990, the production and import of technical OBDE

in the United States was reportedly between 6,498,521 and 13,415,800 lb (2,948-6085 metric tons) and the production and import of technical PeBDE, between 5,330,389 and 11,436,800 lb (2418-5188 metric tons).

PBDEs are produced by the bromination of diphenyl ether. Technical OBDE may be produced by the reaction of diphenyl ether with eight equivalents of bromine in the presence of Al_2Cl_6/Al_2Br_6 first at 35 ¡C and then at 120 ¡C. Technical PeBDE is synthesized by treating diphenyl ether with five equivalents of bromine at 30-65 ¡C in the presence of powdered iron.

Composition of Technical Products

These technical mixtures are comprised of lesser and higher brominated congeners other than those specified in the name. For example, technical PeBDE typically contains 50-60% pentabrominated diphenyl ethers (PeBDE), 24-38% tetrabrominated diphenyl ethers (TeBDE), and 4-8% HxBDE. The technical PeBDE mixture Bromkal 70-5DE was analyzed in one study and found to contain 37% 2,2«,4,4«-tetrabromodiphenyl ether (BDE-47), 35% % 2,2«,4,4«,5-pentabromodiphenyl ether (BDE-99), 6.8% 2,2«,4,4«,6-pentabromodiphenyl ether (BDE-100), and 2.5% 2,2«,4,4«,5,5«-hexabromodiphenyl ether (BDE-153). Technical OBDE product DE-79 is a mixture of 11% PeBDE/HxBDE, 44% heptabromodiphenyl ethers (HpBDE), 31% OBDE, 10% nonabromodiphenyl ethers, and 0.5% decabromodiphenyl ether (DeBDE). Another source reported that OBDE contains 10-12% BDE-153. Toxicology studies submitted to EPA found different concentrations of constituents in the mixtures than is reported by other sources. Either the mixtures may vary in content of congeners from one batch to the next from the same producer or standardization of analytical techniques is needed to accurately determine the congener profile for each mixture.

Use

PBDEs are a class of additive flame retardants used since the 1960s in thermoplastics to suppress or delay combustion. These additive flame retardants are added to the polymer material, but are not chemically incorporated into the polymer matrix. Because the PBDEs are not chemically bound to the polymer product, they may migrate out of the product during its lifetime. The use of flame retardants has increased during the last 10 years due to stricter fire regulations in many countries and increased use of plastic materials and synthetic fibers.

Determining which products contain PBDEs and how much is difficult because many manufacturers do not report this and some may not even know if their products contain PBDEs or some other flame retardant. Much of the information about use of PBDEs in products has been gathered by the European Community and is expected to be similar to products used in the United States since most European polymer products and U.S. products that would contain flame retardants come from the United States or Southeast Asia. Currently, technical DeBDE is the most widely used PBDE flame retardant worldwide, with technical OBDE being the second most widely used. Seventy percent of technical OBDE produced worldwide and 95% of technical OBDE supplied to Europe is used as a flame retardant in acrylonitrile-butadiene-styrene (ABS) plastic (12-18% by weight) for computers and business machine cabinets and casings. However, its use in ABS plastic is being replaced by other brominated flame retardants, primarily tetrabromobisphenol A (TBBP-A), due to ultraviolet light instability of OBDE. In Europe, the remaining 5% of OBDE is used as an additive in high-impact polystyrene (HIPS), polybutylene terephthalate (PBT), and polyamide polymers (12-15% by weight).

The PBDEs are used in paint, high-impact plastic, foam, and textiles, as well as in electronic, building, automotive, furniture, and household plastic products. The concentration of PBDEs incorporated into the polymer material can range from 5 to 30% of the product by weight. In computers, PBDEs can be used in printed circuit boards, connectors, plastic covers, and cables. Technical OBDE is used in casings for television sets and other electronic equipment, while technical DeBDE is used in different plastics (e.g. epoxy resins for circuit boards and polyethylene terephthalate for electrical components). PeBDE is used primarily as an additive in epoxy resins, phenol resins, polyesters, and polyurethanes. PeBDE can occur in the in the phenolic resin coating of printed circuit boards and may occur in the upholstery of furniture. PeBDE is also sold commercially as a blend with triaryl phosphate for use in polyurethane foams. PeBDE has been used in the past in Germany as a hydraulic fluid by the mining and oil industries. PBDEs can be used in the upholstery, seats and doors, floor mats, and wiring of automobiles. The polyurethane foam in car seats probably accounts for the largest share of PBDEs in an automobile and the average amount of total PBDEs per vehicle is estimated to be <250 g. The European Union and several European countries are now calling for the phasing-out of PBDE flame retardants in Europe, specifically technical PeBDE, in favor of using alternatives such as TBBP-A.

Environmental Occurrence

Environmental occurrence of PBDEs has been determined in many European studies; however, relatively few have been performed in the United States. It is apparent from these studies and non-occupational human tissue studies that several PBDE congeners are now ubiquitous in the environment. The PBDEs have a high affinity for sediment and soils. Concentrations of PBDE congeners in soils and sediments closely match those found in technical mixtures from point sources near locations where samples were collected. Concentrations of PBDE congeners in sewage sludge also closely matched congeners found in technical mixtures. A study of sediment cores in the Netherlands revealed a time-dependent increase of PBDEs in soil that corresponded to the appearance of technical PeBDE in the last 30 years and the appearance of DeBDE about 20 years ago. The ratios of BDE-47, BDE-99, and BDE-100 found in sediment cores were similar to those of the technical PeBDE product.

A study of sewage sludge from Mid-Atlantic publicly owned treatment works (POTWs) found that all samples contained BDE-47 (499-1049 g/kg dry weight), BDE-99 (377-851 g/kg dry weight), and BDE-100 (71-134 g/kg dry weight). One sample from a POTW using heat-treatment of sludge found decabromodiphenyl ether (BDE-209) (588 mg/kg dry weight). In a study of sewage sludge in Sweden, it was determined that the presence of PBDEs in sewage sludge was from residential waste and not from atmospheric washout. Debromination of PBDEs has been demonstrated in an anaerobic environment, which may occur at POTWs. The EPA has assumed that the upper bound leachate concentration of technical OBDE is 0.2 mg/L, based on water solubility. More studies on the leaching behavior of PBDEs is recommended due to high accumulation in soil and sediments and lack of information on leaching.

PBDEs may be released to the environment in wastes from their production, by degradation of products containing PBDEs, or possibly by the migration and volatilization of PBDEs from products that contain them.

Moderately brominated PBDEs, such as PeBDEs and HxBDEs, will be found in air relatively close to a PBDE source; however, TeBDE may travel greater distances in air from a source. Highly brominated PBDEs (deca- and octa-) are unlikely to be transported in air due to

their relatively low vapor pressure. BDE-47, BDE-99, and BDE-153 were detected in air samples from urban, rural, and remote areas along the shoreline of the Great Lakes with the highest levels found in Chicago, IL (48, 25, and 0.66 pg/m^3, respectively). TeBDEs were the predominant congeners detected in air samples collected near recycling plants in Japan and Taiwan. PBDEs have the potential for long-range airborne transport and highly brominated PBDEs in organic solutions have been shown to degrade in the laboratory to lower brominated PBDEs in the presence of UV light and sunlight.

PBDE concentrations in water are expected to be minimal due to low solubility. In 222 samples collected in Japan, no PBDEs were detected (limit of detection = 0.1 g/L).

PBDEs have been found in aquatic biota in the Atlantic, Great Lakes, Baltic Sea and rivers throughout Europe and Japan. The predominant PBDE congeners found in all biota are BDE-47 and BDE-99, with BDE-47 comprising more than 50% of all PBDE congeners determined in tissues. Studies conducted in Europe have shown that the concentration of PBDEs in aquatic animals is positively correlated with the trophic levels in which they reside and with age. The highest concentrations of PBDEs as single isomers found in the United States (up to 57 mg BDE-47/kg lipid weight) occurred in bottom-feeding fish (e.g. carp, catfish) from rivers of Virginia. Lower concentrations of BDE-47, BDE-99, and BDE-100 in biota were found in harbor seals in San Francisco Bay, fish from the Great Lakes, dolphins in the Gulf of Mexico, and carp from the Buffalo River in New York. In aquatic species of the U.S. and Europe, the concentration of total PBDEs equals or has surpassed the concentrations of total PCBs.

Bioaccumulation and Environmental Degradation

The bioconcentration profile in all species does not match that of any technical mixture. This may be due to the higher bioaccumulation of lower brominated diphenyl ethers (tetra- through hexa-congeners) when compared to more highly brominated diphenyl ethers (octa- through deca-congeners). The biological concentration factors of TeBDEs and PeBDEs (5,000-35,000) are much higher than the factors for OBDE and DeBDE (5 to <50). Much of the difference in bioaccumulation of BDE congeners has been attributed to the size of these hydrophobic PBDE molecules. The ability of hydrophobic molecules to pass through biological membranes is reportedly limited by the size of the molecule. The bioaccumulation of PBDE congeners is much higher in aquatic organisms, such as fish and mussels, than it is in rats and mice dosed orally with PBDEs. Perhaps fish are more capable of absorbing large hydrophobic molecules than are terrestrial mammals. The rate of bioaccumulation of PBDEs in mussels is faster than that of several PCBs. The concentration of PBDEs in biological tissues is expected to rapidly decline upon depuration. The concentration of BDE-47 in blue mussels was >500 ng/g dry weight at the beginning of depuration and decreased to <100 ng/g dry weight after 26 days. The depuration rate for most hydrophobic compounds, including PCBs, is inversely related to the octanol/water partition coefficient; however, the PBDEs do not appear to follow this general rule.

There is evidence for the debromination of highly brominated diphenyl ethers to lower brominated diphenyl ethers. There are indications that metabolic debromination may occur in fish. Debromination due to photodegradation has been shown in many experiments involving DeBDE. Most experiments have used an organic solvent instead of water, due to the low solubility of PBDEs in water. Debromination of PBDEs in water alone is not expected to occur. Photohydroxylation is the expected route of transformation and the resulting hydroxylated products would then be degraded rapidly due to increased UV absorption. The half-life of

decabromodiphenyl ether (BDE-209) in sand exposed to UV radiation and sunlight was between 12 and 37 hours, with lower PBDEs and other compounds (not specified) detected after UV radiation.

Human Exposure

Human exposure to PBDEs may occur by inhalation as an indoor or occupational air pollutant, by dermal absorption as an occupational hazard, by contact with products containing PBDEs, or by oral ingestion in foods. The release of PBDEs from polymers is dependent on the migration of PBDE molecules through the polymer matrix to the surface where emission takes place. Since PBDEs are large molecules, migration is expected to proceed slowly. Although no studies were located that determined the rate of migration in polymers, estimates have been made. Estimated evaporation of deca-, octa-, and penta-BDEs from plastic are 0.038%, 0.054, and 0.39% per year, respectively, based on worst case emission factors for organic flame retardants.

Potential point sources may lead to increased concentrations of PBDEs in indoor air. OBDE has been found in indoor areas containing electronic products that are flame retarded with PBDEs (televisions and computers). Among the PBDEs, BDE-209 is the least volatile, but even BDE-209 has been found in blood collected in 1988 (0-35 pmol/g lipid) from normal human subjects in the United States. More studies are needed to determine emissions of PBDEs from various products and absorption of PBDE vapor and PBDE containing particulates by inhalation.

No information was found concerning occupational exposure to PBDEs during formulation or incorporation in polymers. Studies of workers that grind polymer parts of dismantled electronic equipment indicate that concentrations of higher brominated PBDEs (hepta- through deca-BDE) in adipose tissue were significantly more than workers in other occupations (automobile drivers, farmers, cleaners, and monitor repair personnel). The concentration of hepta-BDE, the major constituent of technical OBDE, was found to be 65 times higher in the blood of individuals that disassembled electronic parts when compared to hospital workers that had little or no occupational exposure to PBDEs. This could mean that higher congeners are effectively absorbed in the lungs after inhalation of particulates containing PBDEs. This should be considered since the generation of electronic waste is expected to result in a dramatic increase in the disassembly of electronic equipment in the future. Today 2% of TV sets are disassembled after use; however, as much as 89% of all TV sets are expected be disassembled by 2010. Further studies are needed to determine if absorption after inhalation of particulates containing PBDEs is actually greater than absorption after inhalation of PBDE vapors.

In the United, widespread exposure is evident by the levels of PBDEs found in the tissues of individuals from all areas of the country and in all age groups. OBDE ranged from not detected to 8000 ng/kg lipid in adipose tissue collected in 1987 as part of the National Human Adipose Tissue Survey. HpBDE was also found in adipose tissues from the same study. Serum from 12 blood donors in the United States showed detectable concentrations of BDE-47 (0-48 pmol/g lipid), BDE-153 (0-3 pmol/g lipid), 2,2«,3,4,4«,5«,6-heptabromodiphenyl ether (BDE-183), and BDE-209 (0-35 pmol/g lipid). Analysis of adipose tissue samples from these subjects showed that levels of HxBDEs and HpBDEs were generally higher in middle-age (15-44 years) and older individuals (45+ years); whereas, concentrations of OBDE were generally higher in younger (0-14 years) and middle-age individuals. In breast adipose tissue collected from five female subjects from the United States in the late 1990s, the concentrations of HxBDE (2-1000

pg/g lipid), HpBDE (1-2000 pg/g lipid), and OBDE (70-8000 pg/g lipid) congeners showed that PBDEs in breast tissues could result in neonatal exposure of PBDEs in breast milk.

In studies of the general population of countries other than the United States it has been shown that the exposure to PBDEs is widespread. In the U.S. and other countries, exposure does not appear to follow the general pattern of persistent organohalogen exposure. General organohalogen exposure results in tissue concentrations that are positively correlated with age. This is what has been seen in bioaccumulation studies of aquatic species. Many studies have shown that this is not the case for PBDE accumulation in humans. In one study the lowest and the highest concentrations of PBDE congeners were found in the oldest individuals. Because of the poor correlation of age and exposure levels, it has been suggested that there may be unidentified point sources of occupational exposure or other sources unrelated to food consumption. Studies also found a difference in the concentrations of congeners found in women when compared to men. PBDEs do not appear to be as persistent as PCBs in human tissue, unlike PBDEs in fish that may equal PCB concentrations.

Consumption of food is considered the major route of PBDE exposure in humans. Consumption of fish has been linked to higher concentrations of PBDEs in Swedish individuals. The fish of greatest concern to humans are the bottom feeders, such as carp and catfish. An increased risk to Arctic Native Americans that consume the blubber of animals should be considered. Commercially available fish oils sold as dietary supplements were found to contain PBDE congeners (0.2-28.1 ng/g lipid) and methoxylated PBDEs (0.4-29.7 ng/g lipid). Some of these oils were reportedly purified to eliminate contaminants. PBDEs have been detected in cow s milk and dairy products such as cheese and butter.

The presence of PBDEs in human breast milk from Europe and Japan also indicate the possible widespread exposure to PBDEs in women and in neonates. PBDEs detected in breast milk are the tri- to hexabrominated diphenyl ethers. Levels of PBDEs in the breast milk of Swedish women shows an exponentially increasing trend in exposure since the 1970s, with perinatal exposure doubling every fifth year. While breast milk concentrations of DDT and toxic equivalents of TCDD/PCDF/PCB are decreasing, the concentrations of PBDEs are increasing exponentially from about 300 pg/g lipid in 1976 to about 4000 pg/g lipid in 1997. PBDEs have not been produced in Sweden, but they are imported for flame retardant applications. The concentrations of PBDEs in breast milk of European women are still below concentrations of PCBs reported to cause adverse behavioral effects in mice. The sum of all PCB congeners detected in breast milk comprised 67% (323.61 ng/g lipid) of all halogenated contaminants while total PBDEs comprised 1% (4.83 ng/g lipid). PBDEs have been detected and quantified in the placental tissue of 11 Finnish women and found to be between 1.00 and 4.40 ng/g lipid. If concentrations in the placenta represent actual concentrations in the fetus, then fetal exposure may occur during development. Additional studies are needed to assess the extent of human exposure to PBDEs in the United States.

Regulations

The technical PeBDE, OBDE, and DeBDE mixtures are regulated by the U.S. Environmental Protection Agency (EPA) under the authority of the Toxic Substances Control Act (TSCA). Producers of these mixtures must submit health and safety data to the EPA upon request. Any new and significant uses of these brominated compounds must be submitted to the U.S. EPA. Other than general provisions in the Federal Code of Regulations the EPA has proposed, or made final, rules that apply to production of technical PBDE mixtures.

In 1987, the U.S. EPA promulgated a testing and reporting rule for compounds that may be contaminated with halogenated dibenzo-*p*-dioxins and dibenzofurans. Eight submissions of information relating to the presence of polybrominated dibenzo-*p*-dioxins (PBDDs) and polybrominated dibenzofurans (PBDFs) were received by the EPA and reviewed. It was then determined that the testing procedures employed in those studies were not adequate due to the lack of standard reference materials, analyte lability, insolubility, and removal of interferences, particularly PBDEs. As a result of those shortfalls in testing, an industry consortium was organized to develop more suitable analytical methods for the determination of PBDDs and PBDFs in technical formulations. As of 1991, no adequate testing methods had been developed that satisfied all of the EPA s criteria. No further information was located on this subject.

In 1989, the U.S. EPA Interagency Testing Committee (ITC) designated technical PeBDE, OBDE, and DeBDE for further studies involving chemical and environmental fate, health effects (acute and chronic), and ecological effects. The risk of exposure to PBDDs and PBDFs was also a factor for priority testing. In 1994, the U.S. EPA concluded that waste streams from the production of technical OBDE and DeBDE should not be listed as hazardous. This was based on data that indicated a one-in-a-million health risk level and oral reference dose of 0.1 mg/L and 0.003 mg/kg/day, respectively for technical OBDE extrapolated from a single rat study using the induction of liver enzymes and liver histopathology as end-points. It was concluded that human exposure to OBDE would be less than the one-in-a-million health risk level.

TOXICOLOGY

Toxicology testing continues on technical PeBDE and OBDE per industry's commitments under the Organization for Economic Cooperation and Development (OECD) Voluntary Industry Committee (VIC) and European Union (EU) risk assessment programs.

There are no human studies of technical PeBDE and OBDE or specific TeBDE, PeBDE, or HxBDE congeners. Preliminary results of a medical examination program of workers in a resin-compounding operation have shown a potential adverse trend of thyroid stimulating hormone (TSH) results, where values were in the borderline hypothyroid range. The possibility of a workplace association was related to the use of brominated flame retardants such as OBDE. Test results of the same samples from the Mayo Clinic reference laboratory, however, did not support the elevated TSH screening trend. In two male employees who worked as extruder operators during production of resins containing PBDEs and a technician who performed analyses in support of the production operation, digestive tract neoplasms were reported. A Swedish study of cancer patients has reported an association between adipose tissue levels of TeBDE and the risk of non-Hodgkin's lymphoma.

Chemical Disposition, Metabolism and Excretion

Absorption and Distribution

The absorption of BDE-47 is very high in aquatic organisms (e.g. fish, mussels), but not as high in mice and rats. The uptake of more highly brominated compounds is lower in all species tested (rats, mice, fish, invertebrate). In pike that were fed trout injected with ^{14}C-labelled BDE-47, 99% of the dose was absorbed. In rats gavaged with ^{14}C-labelled BDE-47 (30 mol/kg), 14% of the administered dose measured as radioactivity was found in the feces and <0.5% in the urine 5 days after the single administration. Absorption of BDE-99 was less than absorption of BDE-47 in rats gavaged with ^{14}C-labelled BDE-99 (2.2 mg/rat) as shown by the

greater amount of radioactivity excreted in 72-hour collections of feces (43% of the dose) and urine (1%). The rates of absorption of BDE-47, BDE-99, and BDE-153 were more rapid than those of PCBs with similar K_{ow}. In pike, the uptake efficiencies of BDE-47, BDE-99, and BDE-153 after oral administration were 90%, 60%, and 40%, respectively.

An effective molecular cross section greater than 9.5 is expected to limit the diffusion of hydrophobic substances through the intestine. The effective molecular cross sections of BDE-47, BDE-99, and BDE-153 are 8.1, 9.6, and 9.6 , respectively. This may help to explain why the absorption of BDE-99 and BDE-153 is considerably less than that of BDE-47, but it does not explain how absorption of BDE-99 and BDE-153 occurs. This rule is only true for passive diffusion and does not account for protein-mediated active transport in the intestines of hydrophobic substances that may be greater than once expected. The absorption of PBDEs could be associated with bile acids.

After absorption to the blood, the lipophilic PBDEs are preferentially deposited in lipophilic tissue and the liver. In male rats gavaged with ^{14}C-labelled BDE-47, the concentration of radioactivity in adipose tissue was 70 times greater than in other tissues on a fresh weight basis five days after a single exposure. However, mice dosed under the same conditions had only a 10-fold increase of radioactivity in adipose tissue when compared to other tissues. On a lipid weight basis, the amounts in adipose tissue were similar, possibly indicating a saturation point of PBDEs in lipophilic tissues. The concentration of PBDEs in blood is much lower than that found in tissues. It is believed that the PBDEs are sequestered in tissues according to lipid content, until some point of saturation is reached. Muscle concentrations of PBDEs in Baltic Salmon were similar to blood concentrations. PBDEs metabolites may irreversibly bind to macromolecules in tissue as DDT metabolites do, but this has not been proven conclusively.

Metabolism

Methoxy and hydroxy derivatives of PBDEs have been detected in aquatic and mammalian species. The large amounts found in marine organisms (algae, sponges, and some fish) indicate that these organisms are efficient metabolizers of exogenous PBDEs or biosynthesizers of these methoxylated (MeO-BDE) and hydroxylated (OH-BDE) PBDEs. As far as is known MeO-BDEs and OH-BDEs are not commercially produced. It is possible that OH-PBDE could be formed as a contaminant of polybromophenol production, but this has not been established. MeO-BDEs may be formed by microbial methylation, and specifically by symbiotic microorganisms that inhabit marine sponges.

Fish appear to be efficient metabolizers of PBDEs judging from the high ratio of PBDE metabolites to parent congeners (total MeO-TeBDE/total TeBDE = 1.1-2.5). Mice and rats appear to be less efficient metabolizers of PBDEs when dosed orally (total MeO-TeBDE/total TeBDE = <<1). In one 70-year-old human subject, no metabolites of PBDEs were found in adipose tissue but two tetra- and penta-BDE congeners were found (9.1 and 2.9 ng/g lipid, respectively). In all studies reviewed except one, hydroxy- and methoxy-substitution on the PBDE moiety occurs on the carbon adjacent to the ether linkage (ortho-position). In one study of metabolism in rats, hydroxy substitution was found to take place meta, para, as well as ortho to the ether linkage. More studies are needed to determine if the MeO-BDEs and OH-BDEs found in sponges are really naturally produced or metabolites of PBDEs present in the environment. Future studies of natural occurrence in sponges and algae should also seek to determine the presence of PBDE congeners in water or sediment in the vicinity of the organism.

Elimination

Hydrophobic compounds are normally rapidly eliminated, negatively correlated with the octanol/water partition coefficient. The elimination of BDE-47 was significantly higher in mice than it was in rats. Rats dosed orally with ^{14}C-labelled BDE-47 (30 mol/kg) eliminated 14% of the dose in feces and <0.5% of the dose in urine in a 5-day collection period, while mice eliminated 20% of the dose in feces and 33% of the dose in a 5-day collection period. In pike, only 1% of the dose was eliminated. Species differences in the ability to eliminate PBDEs is evident. Excretion of higher brominated PBDEs is much greater than of lower brominated compounds. Fecal excretion of BDE-99 in the rat after oral administration was 43% of the dose in 72-hour collections, but fecal elimination of BDE-209 was 99% of the dose in 72-hour collections.

The half-life of 95% pure BDE-209 is less than 24 hours in rats dosed orally; however, male and female rats dosed orally with technical PeBDE mixture showed half-lives of two hexaBDE congeners of 44.6 and 90.0 days in female rats and 55.1 and 119.1 days, respectively, in male rats. Judging from elimination rates, it would be expected that the half-life for TeBDEs after administration of a technical mixture would be even longer. Perhaps there is a difference in the absorption and elimination of congeners after the administration of technical mixtures when compared to administration of purified or synthesized congeners.

Acute Toxicity

No studies were identified for TeBDE or HxBDE.

Acute toxicity values for technical PeBDE and technical OBDE have been reported. In rats, an LC_{50} value >200 mg/L was calculated, and oral LD_{50} values of 7400 mg/kg bw in males and 5800 mg/kg bw in females were calculated for technical PeBDE. As Tardex 50 and 50L, the oral LD_{50} values were 2640 and 3350 mg/kg, respectively, in both males and females. Additionally, a percutaneous LD_{50} >11,000 mg/kg has been reported for Tardex 50L in rats. For technical OBDE, the LC_{50} value was >50 mg/L, while oral LD_{50} values were >5 and >28 g/kg bw in rats. In rabbits, a dermal LD_{50} value >2g/kg bw was reported.

In rats, inhalation of technical PeBDE (2 or 200 mg/L or emission products of Tardex 50 heated at 200 ¡C) or technical OBDE (2 or 60 mg/L) resulted in decreased motor activity, erythema, eye squint, salivation, and tachypnea. PeBDE also produced lacrimation and respiratory irritation and discomfort (e.g., occasional sneezing attacks and slight dyspnea); all animals were normal after the test period.

Topical application of technical PeBDE as Tardex 50 or 50L (1.25-11.0 g/kg as an 11.4-50% v/v dispersion in cottonseed oil) to the occluded skin of rats caused weight loss, piloerection, lethargy, slight tremors, diarrhea, hyperesthesia, staining, and chromodacryorrhea; survivors were asymptomatic by day 7 with Tardex 50 and by day 12 with Tardex 50L. In rabbits, the latter was classified as a mild primary irritant. Technical PeBDE (200 or 2000 mg/kg bw or 0.5 mL) resulted in no change or a slight decrease in growth and no or a very slight erythema. When applied into the conjunctival sac of the eye of the rabbit, technical PeBDE (0.1 mL) produced slight to moderate irritation. Technical OBDE was also not toxic or irritant in rabbits. A single application (100 mg) in the eye caused a slight discharge and slight redness but no ocular irritation or corneal damage.

Oral administration of technical PeBDE as DE-71 (500 mg/kg bw) significantly increased liver weight/body weight ratios in mice. In rats, decreased growth, diarrhea, piloerection, reduced activity, forelimb clonic persistent tremors (50-9600 mg/kg bw), as well as death at

doses ≥2400 mg/kg were seen. Administered as Tardex 50 or 50L (1.2-8.8 g/kg as a 20% v/v dispersion in cottonseed oil), most of the same signs of toxicity as with topical application of the chemical were observed; survivors were asymptomatic by day 10. In contrast, oral administration of technical OBDE (50, 500, or 5000 mg/kg bw) had no toxic effects.

Short-term or Subchronic Studies

No studies were identified for TeBDE or HxBDE.

In mice, DE-71 (18, 36, or 72 mg/kg/day *per os* for 14 days) caused dose-dependent increases in liver weight/body weight ratios. In rats, oral administration of technical PeBDE (2, 10, 100, or 1000 mg/kg/day in the diet for up to 90 days) increased relative liver weights. Microscopically, cytoplasm had areas of finely granular appearance, and enlarged hepatocytes contained eosinophilic "round bodies". Compound-related increases in tissue total bromine levels were also observed, and at the highest dose, relative weights of the pituitary and adrenal glands were decreased. Repeated topical application of technical PeBDE as 2.5% v/v Tardex 50 to the inner surface of the pinna in rabbits for six hours per day for 28 days produced slight to moderate epithelial hyperplasia.

Inhalation of micronized dust of technical OBDE (1.2, 12, 120, or 1200 mg/m^3 for eight hours per day for 14 days) resulted in significantly increased total lung, liver, and fat bromine levels and relative liver weights in rats. Histopathological lesions consisted of focal to multifocal cytoplasmic enlargement of the hepatocytes and focal acidophilic degeneration of cells. Oral exposure to technical OBDE (100, 1000, or 10,000 mg/kg diet for up to 91 days) also produced an increase in liver weights as well as dose-related increases in liver total bromine content. Other findings included increased kidney and splenic weights, kidney lesions, and significant decreases in packed cell volume, total erythrocyte count, and in hemoglobin, hematocrit, and blood glucose levels. A rat study using diets formulated with mixed lower brominated diphenyl oxides containing 37.4% OBDE (8, 80, or 800 mg/kg bw/day for four weeks) showed that in males only, serum glutamic pyruvic transaminase and serum glutamic oxaloacetic transaminase were significantly increased along with relative kidney and testicular weights. In females, only blood urea nitrogen was significantly increased.

Chronic Exposure

No studies were identified.

Synergistic/Antagonistic Activity

No studies were identified.

Reproductive, Developmental, and Teratogenic Effects

No studies were identified for TeBDE or HxBDE.

Adult mice receiving the BDE-99 congener (8.0 mg/kg) on postnatal day 3 or 10 exhibited behavioral aberration. In rats, oral exposure to technical PeBDE (10-5000 mg/kg) on gestation days 6-15 produced weight gain at doses of ≥100 mg/kg, while levels of ≥500 mg/kg were maternally lethal. No developmental adverse effects were seen, except for a slight effect on implantation frequency with 500 mg/kg. In three-spined sticklebacks (*Gasterosteus aculeatus*), oral doses of Bromkal 70-5DE (0.45-10.39 mg) caused a reduction in spawning at the high doses and a significantly higher 6β-progesterone hydroxylase activity in the ovaries. Fry had lower frequencies of defects.

Oral administration of technical OBDE (2.5-50.0 mg/kg bw) to rats on gestation days 6-15 or days 5-16 produced no adverse maternal effects but did increase serum bromide levels (at 25 mg/kg) and cholesterol levels (at 50 mg/kg). Additionally, at the highest dose, mean maternal and fetal body weights were reduced and postimplantation loss was increased. The observed fetal malformation and developmental variation were associated with maternal toxicity. In rabbits, significantly increased liver weight and decreased body weight gain were observed with Saytex 111(2, 5, or 15 mg/kg bw). Slight fetal toxicity was seen at the maternally toxic dose.

Carcinogenicity

No carcinogenicity, initiation/promotion, or anticarcinogenicity studies were identified.

Genotoxicity

No studies were identified for HxBDE.

TeBDE (10-40 g/mL; 21-82 M) was found to be weakly recombinogenic in the Chinese hamster SPD8 cell line.

In the presence and absence of metabolic activation, technical PeBDE (100-10,000 g/plate) was nonmutagenic in *Salmonella typhimurium* and *Saccharomyces cerevisiae*. However, in the absence of metabolic activation, PeBDE as Tardex 50 was positive for mutagenicity in *S. typhimurium* strains TA1535 and TA1536 at a dose of 10 mg/plate. In human peripheral blood lymphocytes, technical PeBDE (0.25-2500 g/mL) was negative for the induction of chromosome aberration in both the presence and absence of metabolic activation.

Technical OBDE (dose not provided) also failed to show any mutagenic activity in assays using *S. typhimurium* and *S. cerevisiae*, in the presence and absence of metabolic activation. The compound (7.5-750 g/mL) did not induce unscheduled DNA synthesis in monolayers of WI-38 human fibroblast cells or sister chromatid exchange in Chinese hamster ovary cells.

Immunotoxicity

In mice, acute oral exposures to DE-71 (0.8-500 mg/kg bw) were not immunotoxic, but subchronic oral exposures to the technical PeBDE (18, 36, or 72 mg/kg for 14 days) produced a moderately suppressed plaque-forming cell response to sheep erythrocytes at the highest dose. Thymus weight was significantly decreased and corticosterone levels were increased. Excluding the 100 mg/kg acute dose, total serum thyroxine (T4) levels were significantly suppressed following all doses of DE-71 given acutely and subchronically.

In guinea pigs, Tardex 50L was classified as a mild contact allergen. Technical PeBDE (5% in corn oil or 50:50 corn oil/Freund's adjuvant solution) and technical OBDE (2.5% in corn oil or 50:50 corn oil/Freund's adjuvant solution) both failed to produce any erythema or edema in the animals.

In human peripheral lymphocytes, BDE-47 (TeBDE) and BDE-85 (PeBDE) (concentrations up to 0.01 mM) did not affect mitogen-induced proliferation or immunoglobulin synthesis.

Other Data

TeBDE increased 2- and 4-hydroxylation activity of estradiol in male rat liver microsomes, but decreased 2-hydroxylation activity and did not change 4-hydroxylation activity in microsomes from female rats. In rainbow trout (*Oncorhynchus mykiss*), ethoxyresorufin-*O*-deethylase (EROD) activity was decreased.

Studies conducted in mice, rats, fish, and chick embryos found that technical PeBDE and technical OBDE were both effective inducers of hepatic enzymes (e.g., EROD activity, pentoxyresorufin-*O*-deethylase [PROD] activity, NADPH cytochrome c reductase, *p*-nitroanisole demethylation, and UDP-glucuronyl transferase activity). The induction of EROD activity and mechanistic studies show that some congeners of polybrominated diphenyl ethers have significant Ah receptor-mediated (e.g., dioxin-like) effects, with the activity of PeBDE being greater than that of TeBDE. Additionally, polybrominated diphenyl ethers and phenols and their metabolites (e.g., BDE-47, BDE-108, and BDE-123) from *Dysidea* sponges were found to inhibit 15-lipoxygenase, inosine monophosphate dehydrogenase, and guanosine monophosphate synthetase.

In endocrine modulation studies, subchronic oral exposure to technical PeBDE or technical OBDE produced slight to moderate hyperplasia of the thyroid in rats; however, whether this was compound-related was unclear. Additionally, TeBDE reduced thyroid hormone levels in female rats. In mice, PeBDE significantly suppressed total serum T4 levels.

In an *in vitro* assay, incubation of β-naphthoflavone (NF)-induced microsomes enriched with CYP1A or with phenobarbital (PB)-induced microsomes enriched with CYP2B with pure BDE-99 in the presence of NADPH resulted in the formation of hydroxylated metabolites that inhibited 3,3«-diiodothyronine (T2) sulfotransferase. With BDE-47, only the CYP2B-enriched microsomes catalyzed the formation of metabolites active against T2 sulfotransferase. Incubation of BDE-99 or BDE-47 with PB-induced microsomes in the presence of NADPH yielded metabolites capable of competing with T4 binding to transthyretin (TTR). BDE-47 showed a greater than 60% competition compared to controls. Both compounds and BDE-153, however, failed to compete with T4 binding in NF- and clofibrate (CYP4A3-enriched)-induced microsomes. Binding potency was found to depend on the degree of bromine substitution and the nature of the halogen substitution.

Structure-Activity Relationships

TeBDE, PeBDE, HxBDE, and OBDE are structurally related to decabromodiphenyl ether (BDE-209), PCBs, PBBs, DDTs, PBDDs/PBDFs, PCDDs/PCDFs, the herbicide nitrofen, and T4.

BDE-209 is not acutely toxic, irritating, a sensitizer, a reproductive toxicant, teratogenic, mutagenic, or an inducer of chloracne or liver enzymes. In chronic studies, it produced slight toxic effects. There is some evidence of carcinogenicity for male and female F344/N rats, an equivocal evidence of carcinogenicity for male $B6C3F_1$ mice, and no evidence of carcinogenicity for female $B6C3F_1$ mice.

The structurally similar compounds Tris(*p*-chlorophenyl)methanol, 3,4,5-trichloroguaiacol, and 3,3«,4,4«,5-pentachlorobiphenyl induced 4-hydroxylation activity in rat liver microsomes. In rats, three congeners of PCDEs reduced T4 levels in dams and in offspring exposed *in utero*, while hydroxylated metabolites of PCBs, PCDDs, and PCDFs were potent inhibitors of T2 sulfotransferase activity *in vitro*. Incubation of NF- or PB-induced microsomes with 2,2«,4,4«-TCDE in the presence of NADPH resulted in the formation of metabolites that inhibited T2 sulfotransferase more than 60% compared to controls. With nitrofen and 3,3«,4,4«-TCDE, only the latter microsomes caused formation of the metabolites.

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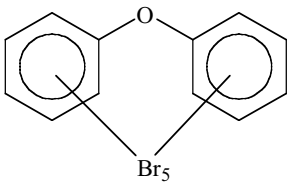
1.0 BASIS FOR NOMINATION

The nomination of 2,2«,4,4«-tetrabromodiphenyl ether, 2,2«,4,4«,5-pentabromodiphenyl ether, and 2,2«,4,4«,5,5«-hexabromodiphenyl for toxicology and carcinogenicity testing is based on their structural similarity to PCBs, potential toxicity, and pervasiveness in the environment and human tissues. The nomination of technical octabromodiphenyl ether and pentabromodiphenyl ether is as a source for these compounds. There is some evidence to support the carcinogenicity of a related congener, decabromodiphenyl ether (CASRN 1163-19-5), in male and female rats dosed orally in a two-year study (NTP, 1986).

2.0 INTRODUCTION

2.1 Chemical Identification

2.1.1 Technical Pentabromodiphenyl Ether

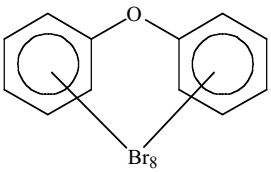


Technical pentabromodiphenyl ether (CASRN: 32534-81-9; $C_{12}H_5Br_5O$; mol. wt. = 564.75) is also called:

Benzene, 1,1«-oxybis-, pentabromo deriv. (9CI)	PeBDE
Bromkal 70	Pentabromodiphenyl ether
Bromkal 70-5 DE	Pentabromodiphenyl oxide
Bromkal G1	Pentabromprop
DE 60FTM	Planetron PB501
DE 71	Saytex 125
FR 1205/1215	

On the basis of chemical structure, there are 46 possible isomers of pentabromodiphenyl ether.

2.1.2 Technical Octabromodiphenyl Ether



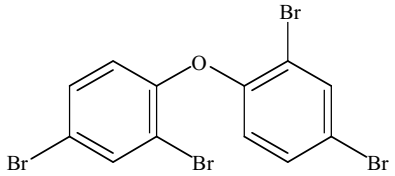
Technical octabromodiphenyl ether (CASRN: 32536-52-0; $C_{12}H_2Br_8O$; mol. wt. = 801.47) is also called:

Benzene, 1,1«-oxybis-,octabromo deriv. (9CI)	Adine 404
	Bromkal 79-8DE

CD 79
DE 71
DE 79
EB 8
FR 1208
FR 143
Octabromodiphenyl ether
Octabromodiphenyl oxide
Phenyl ether, octabromo deriv.
Saytex 111
Tardex 80

On the basis of chemical structure, there are 12 possible isomers of OBDE (Danish EPA, 1999).

2.1.3 2,2«,4,4«-Tetrabromodiphenyl Ether

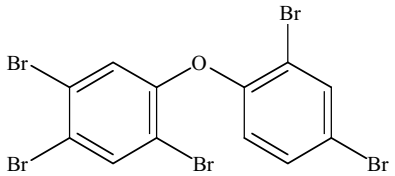


2,2«,4,4«-Tetrabromodiphenyl ether (CASRN: 5436-43-1; $C_{12}H_6Br_4O$; mol. wt. = 485.82) is also called:

Benzene, 1,1«-oxybis [2,4-dibromo- (9CI)
2,4,2«,4«-Tetrabromodiphenyl ether
BDE 47
PBDE 47
Tetrabromodiphenyl ether
Tetrabromodiphenyl oxide

There are 41 other possible tetra-BDE congeners.

2.1.4 2,2«,4,4«,5-Pentabromodiphenyl Ether

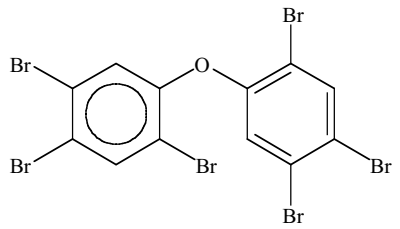


2,2«,4,4«,5-Pentabromodiphenyl ether (CASRN: 60348-60-9; $C_{12}H_5Br_5O$; mol. wt. = 564.75) is also called:

Benzene, 1,2,4-tribromo-5-(2,4-dibromo-phenoxy)- (9CI)
BDE 99
Bromkal 70
Bromkal 70-5 DE
Bromkal G1
DE 71
FR 1205/1215
Pentabromodiphenyl ether
2,2«,4,4«,5-Pentabromodiphenyl oxide
PBDE 99
Pentabromprop
Tardex 50
Tardex 50L

There are 45 other possible penta-BDE congeners.

2.1.5 2,2«,4,4«,5,5«-Hexabromodiphenyl Ether



2,2«,4,4«,5,5«-Hexabromodiphenyl ether (CASRN: 68631-49-2; $C_{12}H_4Br_6O$; mol. wt. = 643.62) is also called:

Benzene, 1,1«-oxybis[2,4,5-tribromo- (9 CI)	Hexabromodiphenyl oxide
BDE 153	Hexabromodiphenyl ether
BR 33N	PBDE 153

There are 41 other possible hexa-BDE congeners.

In this report, the chemical class called polybrominated diphenyl ethers will be referred to as PBDEs in accordance with abbreviations used in IPCS (1994). Like polychlorinated biphenyls there are 209 possible congeners. Octabromodiphenyl ether, tetrabromodiphenyl ether, pentabromodiphenyl ether, and hexabromodiphenyl ether will be referred to as OBDE, TeBDE, PeBDE, and HxBDE, respectively, when the specific isomer is not known. These are also in accordance to abbreviations used in IPCS (1994). When specific compounds and not the general class are discussed, the compounds will be referred to by the same numbering scheme as the PCB congeners (Erickson, 1997), but will have a prefix of BDE (for brominated diphenyl ether; e.g., BDE-47 = 2,2«,4,4«-tetrabromodiphenyl ether) for all.

2.1.6 Analytical Techniques

Extraction and cleanup methods used to identify and quantify PBDEs in various media are similar to methods used to determine PCBs and PBBs (de Boer et al., 1999a,b; Pijnenburg et al., 1995). Sample separation for determination in fish and sediment may be performed by solvent extraction (e.g., with acetone/hexane, hexane/diethylether, or pentane/dichloromethane), fat removal with concentrated sulfuric acid or over alumina columns, and cleanup or fractionation over a silica column.

GC/MS and GC/ECD (electron capture detector) with electron impact (EI), electron capture negative ionization (ECNI), or negative chemical ionization (NCI) usually employed in the characterization and quantification of PBDEs in environmental media with limits of detection ranging from <5 to 60 µg/kg. On nonpolar or moderately polar capillary GC columns, BDE-47 and BDE-99 elute late in the chromatogram of the second silica fraction between *p,p*«-DDT and

octachloronaphthalene. The plasticizer, bis(2-ethylhexyl) phthalate may co-elute with BDE-47 (Pijnenburg et al., 1995).

GC/MS, HPLC, and high-resolution gas chromatography (HRGC) have been used to determine BDEs in biological media with limits of detection of 0.73 ng/kg — 0.10 mg/kg. Analysis with HRGC can identify different congeners at the lowest concentration (0.73 ng/kg). Other detector methods coupled with GC to identify or quantify PBDEs are ECD, LRMS, and HRMS. GC-LRMS (CI) and GC-HRMS (EI) were successfully employed to separate and determine 5 PBDE congeners (BDE-47, BDE-85, BDE-99, BDE-138, and BDE-153) in spiked plasma and technical mixtures. The GC-HRMS (EI) method offered higher selectivity and greater ease of obtaining suitable internal standards; however, one drawback of HRMS/HRGC is its high cost and troublesome maintenance (Hori et al., 2000). NC1-GC/MS is cheaper and was shown to be equally reliable to GC/HRMS when analyzing biological samples for multiple PBDE congeners (Thomsen et al., 2000).

The technical PeBDE mixture Bromkal 70-5DE is most often used as an external reference standard (Pijnenburg et al., 1995). The lack of certified reference materials for individual BDEs can pose a problem for analysis, since comparative analysis of data from different studies is impaired by the determination of compounds on the basis of technical mixture equivalents instead of by individual congeners. However, synthesis of individual congeners has been described for BDE-47 (Wolf and Rimkus, 1985; cited by Pijnenburg et al., 1995). An external standard method was employed to determine the BDEs present in the mono-ortho fraction of a PCDD/PCDF/Dioxin-like PCBs sample analysis (MacPherson et al., 2000). Some studies reviewed were not able to confirm estimated concentrations of PBDEs in biological samples derived from mass spectrometric results due to the unavailability of individual PBDE standards (Stanley et al., 1991).

Hori et al. (2000) described a method for determining the concentration of PBDEs in seafood. Extraction of the homogenized sample with 30% acetone/cyclohexane instead of sulfuric acid or dichloromethane could allow PBDE analysis to become more routine. Cleanup was performed by gel permeation chromatography followed by a mini-column cleanup. The use of this extraction and cleanup procedure efficiently removed obstacles to analysis, such as fat. Analysis with GC/MS; NCI-GC/MS was used because of its highly sensitive analysis of halogenated organic compounds, which was found to be about 10 times more sensitive than GC/MS (EI).

Methods used to determine congeners of PBDEs will be useful in determining the most reactive or toxic species of PBDEs.

X-ray microanalysis coupled with cryofixation techniques was used to determine the bromine content of tissue of the sponge (*Aplysina aerophoba*) (Turon et al., 2000). Although the method may have methodological problems when quantifying elements, the use of reference peaks (like Cl) allow for the comparison between tissues or structures (Roomans, 1988; cited by Turon et al., 2000).

Sensitive methods are recommended for the determination of general and elevated background levels of PBDEs in air and in air particles at a minimum detection level (MDL) of picograms per cubic meter (Lindstr m, 1999).

Sj din et al. (1998) described a high-resolution capillary GC method, using 31 BDE standards, to identify BDE congeners in a technical PeBDE mixture (Bromkal 70-5DE).

2.2 Physical-Chemical Properties

Property	Information	Reference
Technical Pentabromodiphenyl ether:		
Physical State:	clear, amber to pale yellow, highly viscous liquid	IPCS (1994)
Odor:	organic smell	IPCS (1994)
Melting point (¡C):	-7 to —3	IPCS (1994)
Density (g/mL):	2.28 at 25 °C; 1.78 at 40 °C	IPCS (1994)
Solubility in		IPCS (1994)
water:	9.0×10^{-7} mg/L at 22 °C	IPCS (1994)
methanol:	10 g/L at 25 °C	IPCS (1994)
acetone:	Soluble	IPCS (1994)
toluene:	Soluble	IPCS (1994)
benzene:	Soluble	IPCS (1994)
Vapor Pressure	$<10^{-7}$ mm Hg	IPCS (1994)
n-Octanol/water partition coefficient	6.58 6.64-6.97	Hardy (1999) IPCS (1994)
Technical Octabromodiphenyl ether:		
Physical State:	off-white powder	IPCS (1994)
Odor:	Faint	IPCS (1994)
Melting point (¡C):	75-220	IPCS (1994)
Density (g/mL):	2.76 at 25 °C	IPCS (1994)
Solubility (g/L) in		IPCS (1994)
water:	<1	IPCS (1994)
methanol:	2 [7]	IPCS (1994)
acetone:	20 [122]	IPCS (1994)
toluene:	190 [353]	IPCS (1994)
benzene:	200	IPCS (1994)
n-Octanol/water partition coefficient	6.29 5.5 [8.35-8.90]	Hardy (2000a,b) IPCS (1994)
2,2«,4,4«-Tetrabromodiphenyl ether:		
n-Octanol/water partition coefficient	5.87-6.16	IPCS (1994)
2,2«,4,4«,5-Pentabromodiphenyl ether:		
Vapor Pressure	$-5.11 \log P^{0}_{L,exp}$ (25 °C, Pa)	Tittlemier and Tomy (2000)

Property	Information	Reference
n-Octanol/water partition coefficient	6.64-6.97	IPCS (1994)
2,2«,4,4«,5,5«-Hexabromodiphenyl ether:		
Vapor Pressure	0.95-0.99 kPa at 25 °C	IPCS (1994)
n-Octanol/water partition coefficient	6.86-7.92	IPCS (1994)

2.3 Commercial Availability

Polybrominated diphenyl ether (PBDE) flame retardants are produced by two companies in the U.S., Albemarle Corporation (formerly Ethyl Corporation) and Great Lakes Chemical Company (SRI, 1999). A list of several brominated diphenyl ether technical flame retardant mixtures and their composition is provided in **Tables 1** and **2**.

Three BDEs are commercially available as technical mixtures of brominated diphenyl ethers: penta-, octa-, and decabromodiphenyl ether (Danish EPA, 1999; Hardy, 2000b). These technical mixtures are not only mixtures of the single penta-, octa, or deca-congeners, as the name implies, but each mixture will include lesser or higher brominated congeners as well. Although commonly called commercial mixtures in some references, we will use the term technical since even small amounts sold as standards may be deemed commercial .

Technical TeBDE is a mixture of 41% 2,2«,4,4«-tetra-; 45% 2,2«,4,4«,5-penta-; 7% hexa-, and 7-8% unspecified polybrominated diphenyl ethers (IPCS, 1994). Although it was produced in Japan in 1987 (1000 Mg), there is no known current commercial production under the name pentabromodiphenyl.

The technical PeBDE product DE-71 is a mixture of brominated biphenyl ethers containing 50-60% PeBDE, 24-38% TeBDE, and 4-8% HxBDE (IPCS, 1994). In an analysis of DE-71 collected near a point source in the vicinity of Hadley Lake, in West Lafayette, IN (Dodder et al., 2000), the peak area profile consisted of 27% 2,2«,4,4«-TeBDE; 43% 2,2«,4,4«,5-PeBDE, 10% 2,2«,4,4«,6-PeBDE, 9% 2,2«,4,4«,5,6«-HxBDE, and 8% 2,2«,4,4«,5,5«-HxBDE. The technical pentabromodiphenyl ether mixture Bromkal 70-5DE was analyzed in one study and found to contain BDE-47 (37%), BDE-99 (35%), BDE-100 (6.8%), and BDE-153 (2.5%) along with other congeners (see **Table 1**) (Sj din et al., 1998). Bromkal 70-5DE has been reported to contain 41.7% BDE-47, 44.4% BDE-99, 7.6% other PBDE isomers, and 6% HxBDE isomers (DeKok et al., 1979; Sundstrom and Hutzinger, 1976; both cited by Stanley et al, 1991). It appears that there may be some variation in the composition of decabromodiphenyl ether commercial mixtures.

Technical OBDE product DE-79 is a mixture of 11% PeBDE/HxBDE, 44% HpBDE, 31-35% OBDE; 10% NBDE, and 0.5% DeBDE (IPCS, 1994). The technical mixture DE-79 contains 10-12% 2,2«,4,4«,5,5«-HxBDE (Dodder et al., 2000). See **Table 2**.

HxBDE is not known to be produced commercially, but is an impurity in technical tetra-, penta, and octabromodiphenyl ether (IPCS, 1994).

3.0 PRODUCTION PROCESSES

Brominated diphenyl ethers (BDEs) are produced by the bromination of diphenyl oxide (Pettigrew, 1993). Bromine content can range from three to ten atoms of bromine (Danish EPA, 1999).

OBDE congeners may be synthesized by the reaction of diphenyl ether with eight equivalents of Br_2 in the presence of Al_2Cl_6/Al_2Br_6 first at 35 ¡C and then at 120 ¡C (US EPA, 1986; cited by IPCS, 1994).

Pentabromodiphenyl ether is synthesized by treating diphenyl ether with five equivalents of Br at 30-65 ¡C in the presence of powdered iron (U.S. EPA, 1986; cited by IPCS, 1994).

Two studies characterized the transformation of OBDE to PBDFs and PBDDs during the processing of polymers (IPCS, 1994). One study showed that no transformation of OBDE occurred, while the other showed that there were increases in post-extrusion concentrations of PBDFs and PBDDs when compared to pre-extrusion concentrations. Extrusion processes may be used to blend additives such as flame retardants with polymers and to produce pelletized products. Extrusion may also be used when finished products are manufactured.

4.0 PRODUCTION AND IMPORT VOLUMES

The production of organobromine compounds in the United States is geographically limited to sites where underground bromide bearing deposits are located (U.S. EPA, 1994, 59 FR 24530). The primary deposits of this type are located in Michigan and Arkansas; however, no production is currently occurring in Michigan. These bromide deposits are expected to satisfy the domestic demand for brominated chemicals for another 55 years according to the U.S. Bureau of Mines. Two firms in Arkansas are responsible for 95% of the organobromine chemical production in the United States. The EPA does not expect any other bromine producing companies to enter the market during this time. The majority of organobromine compounds currently produced at these plants are flame retardants for incorporation in polymers.

Commercial production of technical OBDE and technical PeBDE occurs at the Albemarle Corporation (Magnolia, AR) and at Great Lakes Chemical Corporation (El Dorado, AR) (SRI, 1999). The reported production and import of technical OBDE and technical PeBDE in the United States is greater than one million pounds according to the 1990 TSCA Inventory Update Rule (US EPA OPPT, 1998).

Brominated diphenyl ethers comprise the largest volume of brominated flame retardants used in the world today (Pettigrew, 1993). In 1992, technical deca- and octa-BDE were 75% and 15%, respectively, of the world production of PBDEs (40,000 Mg), while technical penta-BDE accounted for 10% of world production (Hale et al., 2000; Hooper and MacDonald, 2000).

Table 1. Constituents of Technical Pentabromodiphenyl Ether

Trade Name	Manuf.[b]	Substituents and Their Percentage in Commercial Mixtures														Reference
		Tri	Tetra	BDE 47	Penta	BDE 99	BDE 100	Penta & Hexa	Hexa	BDE 153	Hept	Octa	Nona	Deca	Other PBDEs	
Typical		0-1	24-38		50-62				4-8							Arias (1992) [c]
Pentabrom-prop			39		61				9							IPCS (1994)
Bromkal 70-5DE	GL?		35.2		59.8				5.8		0.2					Nylund et al. (1992) [c]
Bromkal 70-5DE	GL?		41.7		45										7% of another TeBDE	Nylund et al. (1992) [c]
Bromkal 70-5DE	GL?			37		35	6.8			3.9					Others[a]	Sj din et al. (1998)
Trade Name n.p.			35		58										4 higher Br compounds	IPCS (1994)
Bromkal 70			36		74											IPCS (1994)
DE-71	GL	<1									<2					McAllister and Ariano (1982) [c]
Tardex 50			38.3		61.2										0.5, mainly HXBDE	Dow Chemical Co. (1977); ISC Chemicals Ltd. (1977)
Tardex 50L			33.3		65										1.2, mainly HxBDE	Dow Chemical Co. (1977); ISC Chemicals Ltd. (1977)

Some information was supplemented by Ash and Ash (1997).
[a] The other quantified congeners were BDE-17=0.022%; BDE-28=0.11%; BDE-66=0.22%; BDE-85=1.6%; BDE-138=0.41%; BDE-154=2.5%; and BDE-183=not detected
[b] The abbreviations used to identify manufacturers are: AL = Albemarle Chemicals; DSB = Dead Sea Bromine (Israel); GL = Great Lakes Chemicals
[c] Cited by IPCS (1994)

Table 2. Constituents of Technical Octabromodiphenyl Ether

Trade Name	Manuf.[a]	Substituents and Their Percentage in Commercial Mixtures														Reference
		Tri	Tetra	47	Penta	99	100	Penta & Hexa	Hexa	153	Hept	Octa	Nona	Deca	Other PBDEs	
Typical								10.5-12.0			43.7-44.5	31.3-35.3	9.5-11.3	0-0.7		IPCS (1994)
Trade Name n.p.									4		62	34				De Kok et al. (1979) [b]
FR-1208	DSB				0.1				8.2		58.8	25.3	6.7	0.9	0.12	Life Sci. Res. Israel (1987)
Saytex 111	AL				0.2				8.6		45.0	33.5	11.2	1.4		Breslin et al. (1994); cited by IPCS, 1994)

Some information was supplemented by Ash and Ash (1997).
[a] The abbreviations used to identify manufacturers are: AL = Albemarle Chemicals; DSB = Dead Sea Bromine (Israel); GL = Great Lakes Chemicals
[b] Cited by IPCS (1994)

5.0 USES

In this section all references to PeBDE, OBDE, and DeBDE are for the technical mixtures only since that is the only form incorporated into products worldwide.

PBDEs are a class of additive flame retardants used since the 1960s in thermoplastics to suppress or delay combustion (SVTC, 1999; Hooper and McDonald, 2000). Additive flame retardants are added to the plastic, but are not chemically incorporated into the polymer matrix. Since the additive flame retardants are not bound to the polymer, they may migrate out of the product during its lifetime (de Boer et al., 1999a). Reactive flame retardants, on the other hand, are chemically modified and bound to the polymer, thereby resisting migration. Both reactive and additive flame retardants start to decompose when heated. The PBDEs are used in paint, high-impact plastic, foam, and textiles, as well as in electronic, building, automotive, furniture, and household plastic products (Luross et al., 2000; Hooper and McDonald, 2000). The use of PBDE flame retardants have increased in the last 10 years due to stricter fire regulations in many countries and increased use of plastic materials and synthetic fibers (Alcock et al., 1999). The concentration of the PBDEs incorporated in the materials can vary from between 5 to 30% of the product by weight (IPCS, 1994; Dodder et al, 2000). A list of some products that contain PBDEs, as well as their amounts, is provided in **Table 3**.

In computers, PBDEs can be used in printed circuit boards, connectors, plastic covers, and cables (SVTC, 1999). Although the PBDEs have been used in cables, large cable manufacturers in Europe have discontinued use or have set dates for the discontinuation of PBDE addition to electrical cables (KemI, 1999). In Sweden, technical OBDE is used in casings for television sets and other electronic equipment, while technical DeBDE is used in different plastics. Tests conducted on new Swedish household plastic products such as toasters, tea kettles, and coffee makers showed that they did not contain PBDEs (KemI, 1999). PBDEs can be added to the plastic capsule surrounding electronic components (e.g., circuit boards). The encapsulation of circuit boards is primarily performed in Southeast Asia by a small number of firms. Although the amount of PBDEs added to components is insignificant, the number of components in electronic products far outweighs the number of casings or covers.

OBDE is the second most widely used brominated flame retardant in the world. DecaBDE is the leading additive PBDE flame retardant incorporated into most plastics (KemI, 1999). Seventy percent of the OBDE produced worldwide and 95% of the total OBDE supplied to Europe is used as a flame retardant in acrylonitrile-butadiene-styrene (ABS) plastic (12-18% by weight) for computers and business cabinets and casings; however, its use in ABS plastic is being replaced by other brominated flame retardants, primarily tetrabromobisphenol-A (TBBPA), due to the ultraviolet light instability of OBDE (Pettigrew, 1993; IPCS, 1994; Danish EPA, 1999; KemI, 1999). In Europe, the remaining 5% of OBDEs is used as an additive in high impact polystyrene (HIPS), polybutylene terephthalate (PBT), and polyamide polymers (12-15% by weight). OBDE is usually used in combination with antimony trioxide (Danish EPA, 1999).

PeBDE is used primarily as an additive in epoxy resins, phenol resins, polyesters, and polyurethanes (IPCS, 1994). PeBDE is one of the major commercial brominated diphenyl ether flame retardants and is sold commercially as a blend with triaryl phosphate for use in polyurethane foams (Pettigrew, 1993). PeBDE can occur in the phenolic resin coating of printed circuit boards and may occur in the upholstery of furniture (KemI, 1999).

Table 3. Use of PBDEs in Products

Resin/Polymers/ Substrate	Technical Mixture[a]			Applications	Representative Products
	DeBDE	OBDE	PeBDE		
ABS		X		Molded parts	TV-sets/business machines, computer housings, household appliances (hairdryer, curler), automotive parts, electronics, and telecommunications
Epoxy resins	X			Circuit boards, protective coating	Computers, ship interiors, electronic parts
Phenolic resins	X		X	Printed circuit boards	Paper laminates/glass prepregs for printed circuit boards
PAN	X			Panels, electrical components	Lighting panels for elevators and rooms, housing of electrical appliances
PA	X	X		Electrical connectors, automotive interior parts	Computers, connectors, housing in electrical industry, board, electrical connectors, automotive industry, transportation
PBT	X	X		Electrical connectors and components	Switches, fuse, switch box, computer housing, switchboard electrical connectors, stereos, business machines, military electronics
PE/XPE	X			Cross-linked wire and cable, foam tubing, weather protection and moisture barriers	Major application: power cable with cross-linked low density PE; also used for conduit for building with high density PE; Final uses: portable apparatus building control, instrument shipboard, automotive, marine appliances, insulation of heating tubes
PET	X			Electrical components	Boxes, relays, coils, bobbins
PP	X			Conduits, electronic devices	TV and electronic devices, such as yoke, housings, circuit board hangers, conduits; Final uses: electro-mechanical parts TV, hot wastewater pipes, underground junction boxes
PS/HIPS	X	X		TV cabinets and back covers, electrical appliance housings	TV back panels, computer covers and housings of electrical appliances, office machines, smoke detectors
PVC	X		X	Cable sheets	Wire and cables, floor mats, industrial sheets
PUR			X	Cushioning materials, packaging, padding	Furniture, sound insulation panels, wood imitations, transportation
UPE	X		X	Circuit boards, coatings	Electrical equipment, coating for chemical processing plants, molding, military and marine applications: construction panels

Table 3. Use of PBDEs in Products (Continued)

Resin/Polymers/ Substrate	Technical Mixture[a]			Applications	Representative Products
	DeBDE	OBDE	PeBDE		
Rubber	X		X	Transportation	Conveyer belts, foam insulation for pipes
Paints/Lacquers	X		X		
Textiles	X		X	Coatings	Back coatings, impregnation: carpets, automotive seating, furniture in homes and official buildings, aircraft, undergrounds, tents, trains, and military safety clothing

Source: IPCS (1994)
Abbreviations: ABS = acrylonitrile-butadiene-styrene; HIPS = high impact polystyrene; PA = polyamide; PAN = polyacrylonitrile; PBT = polybutylene terephthalate; PE = polyethylene; PET = polyethylene terephthalate; PP = polypropylene; PS = polystyrene; PUR = polyurethane; PVC = polyvinylchloride; UPE = unsaturated polyesters; XPE = cross-linked polyethylene

Technical PeBDE has been used in the past as a hydraulic fluid by the mining and oil industries (BSEF, 2000). Currently there appears to be a phasing-out of PBDEs in Europe in favor of using TBBPA where possible, mostly because of environmental concerns. Use of PBDE-containing ABS plastics in home electronics and medical equipment in Europe is being phased out due to the carcinogenicity of antimony trioxide, a compound incorporated into several technical mixtures.

PBDEs can be found in the cars produced in Asian countries and the United States (KemI, 1999). They are used in upholstery, seats and doors, floor mats, and wiring. The polyurethane foam found in seats accounts for the largest share of PBDEs in vehicles. The average amount of PBDEs per vehicle has been reported to be <250 g.

Gathering information on the use of brominated flame retardants in products can prove difficult because vendors and importers seldom know if their products contain brominated flame retardants or are reluctant to submit the information (Danish EPA, 1999). Due to the lack of information on the use of brominated flame retardants in the United States, much of the information on use of brominated flame retardants in specific products has been taken from use information in European countries and Japan. It is assumed that the formulation of the PBDEs in U.S. products would be similar to that found in those developed nations.

The Swedish National Chemical Inspectorate has called for a gradual phase-out of the use of PBDEs as flame retardants (KemI, 1999). Only the technical PeBDE mixture, and not the technical OBDE and Deca-BDE mixtures, was determined to pose a risk to the environment in a recent European Union risk assessment of PBDEs (Bjerregaard, 1999).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

This section will cover the occurrence and persistence of specific selected polybrominated diphenyl ethers in the environment, including biota. Two of the compounds of concern in this report have undesignated positions for the attachment of bromine atoms to the benzene rings. When the positions of the bromine atoms are specified in studies or reviews, the discussion will reflect this by including the positions of the bromine atoms prior to the name; however, if the positions of the bromine atoms are not specified, the text will use the name of the congener group designated by the number of bromine atoms per molecule.

The European community has been aware of persistent concentrations of PBDEs in the environment and human tissues for many years. European countries such as Sweden have seen a gradual rise in the concentrations of PBDEs in the environment and in human breast milk. For this reason the environmental occurrence of PBDEs in Europe has been well documented; however, there have been relatively few studies performed in the United States. This section will concentrate only on the occurrence of specific PBDEs in the United States environment with some comparisons to levels detected in other countries.

Although IPCS (1994) stated that PBDEs are not produced naturally, several recent studies have provided evidence for the natural production of hydroxy-substituted brominated diphenyl ethers and methoxy brominated diphenyl ethers. These types of brominated compounds have been isolated in sponges worldwide and in green algae from Japan (Cameron et al., 2000; Gribble et al., 1998; Fu et al., 1995; Fu and Schmitz, 1996; Turon et al., 2000;

Kierkegaard et al., 1999a). By the early 1990s, brominated compounds had been identified in more than 25 sponge species (Gribble, 1992; cited by Turon et al., 2000). These compounds may comprise as much as 12% of the dry weight of the sponge (Unson et al., 1994). Although the authors of these studies call these brominated compounds metabolites, it still has not been shown that the sponges themselves are transforming brominated compounds from the environment or producing them endogenously. Many of these sponges are known to contain symbiotic cyanobacteria and bacteria that may produce these compounds and deposit them in the sponge s tissue (Turon et al., 2000). One brominated biphenyl ether, 2-(2,4-dibromo-phenyl)-4,6-dibromophenol, was found in symbiotic filamentous cyanobacteria (*Oscillatoria spongeliae*) of the sponge *Dysidea herbacae*, but was not found in the sponge tissue itself or other symbiotic heterotrophic bacteria (Unson et al., 1994). Until the PBDE content of the water and sediment around the sponges and the identity of possible precursors in the sponge environment and in the sponge are determined and reported, the natural production of these brominated compounds by aquatic organisms may be doubtful.

Organohalogens appear to be more widespread in the environment than previously thought (Grimvall, 1995). Man-made organohalogens may represent only a small part of a natural cycling of organohalogen compounds in the environment. The organohalogens detected in species from unpolluted waters may be formed by the halogenation of humic substances; however, there is still much uncertainty about the mechanisms of natural halogenation.

Because of the low water solubility and low vapor pressure of the PBDEs, they are expected to persist in the environment and bioaccumulate (Hakk et al., 1999; She et al., 2000). Concentrations of PBDEs in the environment have been a concern ever since the 1981 publication of the first bioaccumulation article that detected PBDEs in pike, eel, and sea trout from a river in Western Sweden (Andersson and Blomquist, 1981; cited by Dodder et al., 2000). Since then, PBDEs have been detected in air, sediment, sewage sludge, aquatic species, terrestrial species, and humans from Europe and aquatic species and humans in the United States. Approximately 70% of the PBDEs found in the environment are related to 2,2«,4,4«-TeBDE (BDE-47) and the next most frequently detected PBDE is 2,2«,4,4«,5-PeBDE (BDE-99) (Hardy, 2000b).

During the 1970s, the concentrations of BDE-47, BDE-99, and BDE-100 in the North American environment were relatively low, as determined by accumulation in Great Lakes trout; however, after the ban on PBBs in the early 1980s, the increased reliance on PBDEs has resulted in greater environmental accumulation (Luross et al., 2000). Today, penta- to hexa-BDEs are probably widely distributed in the U.S. environment judging from results of the few environmental persistence studies. In one study, concentrations of PBDEs in edible fish in Virginia rivaled concentrations of organochlorine pesticides and PCBs, contaminants which usually predominate in U.S. fish (Hale et al., 2000). To accurately determine the extent of PBDE persistence in the United States environment, more studies are needed.

During the 1980s, the concentrations of BDE-47 in the environment were calculated as doubling every two years, but now the rate has slowed to every five years as determined by breast milk concentrations detected in women from Sweden (de Wit, 1999). European studies have shown that PBDE concentrations in the environment are beginning to level off or decrease in selected areas (Renner, 2000; cited by Luross et al., 2000).

The Swedish National Chemical Inspectorate has called for a gradual phase-out of the use of PBDEs as flame retardants (KemI, 1999). Only the technical PeBDE mixture, and not the technical OBDE and DeBDE mixtures, was determined to pose a risk to the environment in a recent European Union risk assessment of PBDEs (Bjerregaard, 1999).

There are some theories about the increased prevalence of the lower brominated congeners when compared to the higher brominated congeners. If environmental concentrations of PBDEs are based on amounts from production, then the deca-form should be the most prevalent in the environment since it is the most prevalent in products. This is what is seen in sediment, soil, and sewage sludge. However, the observable trend is for the preferential accumulation of tetra and penta-BDEs in biota, which is due to the higher bioaccumulation of the penta- and tetrabrominated diphenyl ethers when compared to DeBDE.

An alternative theory is that the congeners currently found in the environment are the result of past environmental releases due to short use as an off-shore oil drilling lubricant in the early 1990s and the use in Germany as hydraulic fluid in the coal mining industry (Renner, 2000).

Details of studies that determined the environmental persistence of PBDEs in the United States environment and biota are detailed in **Table 4** and **Table 5**, respectively. The occurrence of PBDEs in biota of other countries is detailed in **Table 6**.

6.1 PBDEs in Air

PBDEs may be released to the air from PBDE production plants, thermal degradation of products containing PBDEs, and possibly by the release of PBDEs from products during normal use. From a study in the United States, it has been shown that moderately brominated PBDEs (PeBDE and HxBDEs) will be found in air relatively close to a PBDE source; however, TeBDE may travel greater distances from a source (Dodder et al., 2000). Highly brominated diphenyl ethers, such as deca- and octabromodiphenyl ethers are unlikely candidates for atmospheric transport due to their relatively low vapor pressure (Hardy and Smith, 1999 abstr.).

BDE-47, BDE-99, and BDE-153 were detected in air samples from urban, rural, and remote areas along the shoreline of the Great Lakes in the United States (Dodder et al., 2000). The urban area (Chicago, IL) showed a significantly higher concentration (5 times that of the rural and remote areas) of all PBDE congeners determined.

Concentrations of PBDEs have been detected in air samples collected from or near recycling plants in Japan and Taiwan (Watanabe et al., 1992; cited by IPCS, 1994), with TeBDEs predominating. In Japan, DeBDE appears to be the dominant PBDE contaminant in air (83-3060 pg/m^3), but TeBDEs, PeBDEs, and HxBDEs were also detected (Watanabe et al., 1995; cited by de Boer et al., 1999a).

PeBDEs are persistent in air and have the potential for long-range airborne transport (KemI, 1999). Highly brominated PBDEs (e.g., decabromodiphenyl ether) can photolytically degrade to lower brominated PBDEs in the presence of UV light and sunlight (Kierkegaard et al., 1999b; EU, 1998; cited by KemI, 1999).

6.2 PBDEs in Water

Concentrations of PBDEs in water are expected to be low due to their low solubility in water. No studies of PBDE concentrations in U.S. waters were found; however, in a study of waste streams from the production of technical OBDE and technical DeBDE in the United States, the U.S. EPA concluded that concentrations of these mixtures would be minimal in water subject to releases.

In Japan, OBDE was not detected in 75 water samples (limit of detection = 0.1 µg/L) in 1987 and also not detected in 147 samples from 49 areas (limit of detection = 0.07 µg/L) in 1988-89 (EAJ, 1989; cited by IPCS, 1994). The location, type of water, and exposure conditions were not provided.

6.3 PBDEs in Soil, Sediment, and Sewage Sludge

The PBDEs are more strongly absorbed to sediments than are the PCBs and are therefore more likely to persist in the environmental compartment (de Boer and Dao, 1993; cited by Allchin et al., 1999).

Concentrations of PBDE congeners in soil, sediment, and sewage sludge reportedly closely agree with concentrations in commercial mixtures. High concentrations of BDE-209 were detected in river sediment in Great Britain and Ireland (34-1800 ng/g wet weight). A study of sediment cores in the Netherlands from a fjord and two fresh water lakes revealed a time-dependent increase in the concentrations of PBDEs that corresponded to the first appearance of technical PeBDE (Bromkal 70-5DE) in the last 30 years and the appearance of technical DeBDE about 20 years ago (Zegers et al., 2000). The ratios of BDE-47, BDE-99, and BDE-100 congeners found in the commercial PeBDE product, were highly similar over the 30-year period. The congener BDE-209 appeared in the soils around the late 1970s while commercial PeBDE congeners had leveled off in the soil, again corresponding to the increased used of DeBDE.

A recent study of sewage sludge biosolids from publicly owned treatment works (POTWs) in the United States revealed that the composition of PBDEs in the biosolids closely matched the DE-71 commercial formulation (La Guardia et al., 2000). On a dry weight basis, the samples contained 499-1049 g BDE-47/kg, 377-851 g BDE-99/kg, and 70.8-134 g BDE-100/kg. Three of the four samples originated from Mid-Atlantic POTWs had been lime stabilized or composted before distribution. A heat-treated POTW sample of biosolids from an international distributor also contained BDE-209 (588 mg/kg) and OBDE (not quantified). All samples analyzed contained BDE-47 and BDE-99 together being >1 mg/kg dry weight. All of the sewage sludge biosolids were intended for land application as fertilizer.

The concentration of PBDEs in sewage sludge from Sweden and Japan appear to represent the composition of technical mixtures (mostly Bromkal 70-5DE and TBBP-A) better than concentrations found in biota. Studies have shown that concentrations of specific PBDE congeners and TBBP-A in river sediment and sewage sludge are higher downstream from plants where flame retardants are used than upstream from the plants (Sellstr m and Jansson, 1995; Sellstr m, 1996; Sellstr m et al., 1998a; all cited by de Wit, 1999). In a study of river sediments in England, it was shown that levels were significantly higher downstream from manufacturing facilities when compared to sediment upstream (Allchin et al., 1999). When analyzed as

equivalents to DE-71, DE-79, and DE-83 formulations, the highest concentrations were found to be 366, 1405, and 3190 g/kg dry weight downstream from the plants. One plant produced technical OBDE and PeBDE while three other manufacturers used technical PeBDE in such products as polyurethane foams and rubber and tires.

The same has been shown in sewage sludge samples with inputs from plants using brominated flame retardants for plastics (Sellstr m and Jansson, 1995; cited by de Wit, 1999). These studies detected BDE-47, BDE-99, BDE-100, and BDE-209 in samples from plants using TBBP-A.

In a study of sewage sludge from a treatment plant in Sweden, concentrations of PBDEs in the sludge were similar during a rainy period (21 ng/g dry weight) and during a period of little rain (25 ng/g dry weight), indicating that PBDEs present in sewage sludge were from households and industrial effluent and not due to washout from the atmosphere (Sellstr m, 1996; IPCS, 1994; both cited by de Boer et al., 1999a). Another study reported that sewage sludge in Sweden contained 15 and 19 g/kg of TeBDE and PeBDE, respectively (Sellstrom et al., 1993; cited by Alcock et al, 1999).

Microbial debromination of PBDEs is expected to occur in an anaerobic environment.

The EPA assumed that the upper bound leachate concentration of technical OBDE was 0.2 mg/L (U.S. EPA, 1994, 59 FR24530). More studies on the leaching of technical OBDE and PBDE are recommended due to accumulation in soil and sediments and lack of information on leaching to the water table.

6.4 PBDEs in Biota

The persistence of PBDEs has been extensively studied in aquatic species and several terrestrial species in Europe, but only a few recent studies are available to determine bioaccumulation in the United States. One U.S. study showed that concentrations of PBDEs equaled or have surpassed the concentration of some PCB congeners in certain species (Asplund et al., 1999a). The bioaccumulation of PBDEs in aquatic species is especially important in countries that rely on fish for food, such as Japan and Scandinavian countries, but should be a concern worldwide since PBDEs have been detected in the deepest depths of the ocean and in Antarctica. PBDEs may be transferred through food webs like other hydrophobic organic halogen compounds, leading to biomagnification (Burreau et al., 2000a,b; Haglund et al., 1997). Monitoring data in the Baltic and elsewhere show that levels of penta- and tetra-BDEs increased up the food chain (EU, 1998; cited by KemI, 1999).

The biomagnification of PBDEs in aquatic food is inversely related to the degree of bromination (Jansson et al., 1993; cited by Burreau et al., 2000a). In fish samples worldwide, highly brominated congeners of PBDEs are seldom detected, probably due to their low bioavailability (Hardy, 2000b). In contrast, PBDEs containing 4 to 6 bromine atoms are found most frequently in biological samples (Burreau et al., 1997). In fish consumers, the relative abundance of the slightly brominated PBDEs when compared to highly brominated PBDEs was even greater than in fish. The bioconcentration profile of specific PBDEs in fish and fish consumers does not match that of Bromkal 70-5DE, the most widely used PBDE flame retardant. This is probably due to the fact that lower brominated diphenyl ethers (tetra- through hexa-) have

a higher bioaccumulation in fish due to better absorption (Burreau et al., 1997 and 2000a). However, concentrations of PBDEs in herbivorous mammals in Sweden and in sediments are similar to concentrations in the commercial product (Jansson et al., 1993; cited by Pijnenburg et al., 1995).

Concentrations of PBDEs in biota are correlated with the trophic levels in which they reside. A study of herring, salmon muscle, and gray and ringed seal samples collected from 1981-1988 along the Swedish coastline of the Baltic found that PBDE concentrations increased with the trophic level (Haglund et al., 1997).

In studies conducted in the United States, concentrations of PBDEs (as single isomers) found in freshwater fish ranged from undetectable to 57,000 µg PBDE/kg lipid (Hale et al., 2000; Dodder et al., 2000; Luross et al., 2000). The BDE-47 congener of TetraBDE predominated in all studies, followed by BDE-99, BDE-100, BDE-153, BDE-154, and BDE-77. All of these compounds contain 2,2«,4,4« bromine substitution, which may be important for bioaccumulation (Luross et al., 2000). In food fish from Virginia rivers, the concentration of BDE-47 was about 62-85% of all congeners detected (Hale et al., 2000). BDE-47, BDE-99, and BDE-153 were found in harbor seals in the San Francisco Bay at mean concentrations of 1124, 107, and 49.7 ng/g lipid, respectively.

The concentration of PBDEs in trout from the Great Lakes differed according to the lake in which they were found (Luross et al., 2000), which could help to elucidate sources that contribute to environmental exposure.

The PBDE exposure to aquatic mammals can be greatly enhanced by transfer through breast milk to newborns (Lindstr m, 1999).

6.5 Bioaccumulation Factors

Details of several bioaccumulation studies are provided in **Table 7.**

The biological concentration factors for the TeBDEs and PeBDEs (5,000-35,000) are much higher than the factors for OBDE and deca-BDE (5 to <50) (KemI, 1999).

Much of this difference in bioaccumulation has been attributed to the size of the PBDE molecules. The ability of hydrophobic compounds to pass through biological membranes is reportedly limited by the size of the compound (Burreau et al., 1997). Hydrophobic compounds greater than 9.5 theoretically will not pass through biological membranes. The sizes of the PBDE congeners BDE-47, BDE-99, and BDE-153 are 8.1, 9.6, and 9.6 , respectively (Burreau et al., 1997). It would be assumed that only BDE-47 would be available for absorption in biological systems, and no BDE-99 and BDE-153 would be absorbed; however, this is not the case. Even BDE-209 (decaBDE) has been found in humans due to occupational exposure.

Several studies, as well as the previously mentioned persistence data, indicate that BDE-47, BDE-99, and BDE-153 are effectively absorbed in mussels, fish, mice, and rats (Gustafsson et al., 1999; Burreau et al., 2000a; rn and Klasson-Wehler, 1998). The bioaccumulation of the three PBDE congeners is much higher in aquatic organisms such as fish and mussels than it appeared to be in rats and mice dosed orally with PBDEs. This could be due to the greater bioavailability of the substances absorbed from the aqueous environment than their availability

from food. However, when pike were fed trout injected with ^{14}C-labelled BDE-47, 96% of the radioactivity in the trout was absorbed by the pike (Burreau et al., 2000a). Perhaps fish are better able to absorb large hydrophobic molecules than mammals.

The rate of bioaccumulation of the PBDEs is faster than that of several PCBs in mussels (Gustafsson et al., 1999). The reason for this is unknown.

The concentration of PBDEs in biological tissues is expected to rapidly decline upon depuration. This has been observed in mussels in which the concentration of BDE-47 was >500 ng/g dry weight at the beginning of depuration and decreased to <100 ng/g dry weight after 26 days (Gustafsson et al., 1999). The theoretical half-lives of BDE-47, BDE-99, and BDE-153 in blue mussels (*Mytilus edulis*) are 7.7, 5.6 and 8.1 days, respectively. The depuration rate for most hydrophobic compounds, including the PCBs, are inversely related to the octanol/water partitioning coefficient; however, the PBDEs do not appear to follow this general rule.

6.6 Environmental Degradation

It is conceivable that debromination of higher brominated PBDEs (DeBDE and OBDE) could lead to formation of tetra- and penta-BDEs. Debromination of higher brominated PBDEs has been demonstrated in the laboratory (Renner et al., 2000; Sellstr m and Jansson, 1995; cited by Haglund et al., 1997). There are indications that debromination may occur in fish during metabolism (Hakk et al., 1999; Kierkegaard et al., 1999a); however, this is still inconclusive. Di- and tribrominated diphenyl ethers have been identified but not quantified in black skimmer tissues and eggs in the U.S. (Stafford, 1983; cited by de Wit, 1999).

Experiments have been performed to determine if lower brominated diphenyl ethers are formed by the photodegradation of DeBDE. Most of these experiments have used an organic solvent instead of, or in addition to, water since the solubility of DeBDE in water is extremely low. Photodegradation of technical DeBDE in a hexane and water solution exposed to ultraviolet radiation or sunlight resulted in a mixture of tri- through octa- congeners, a large number of PBDFs containing 1-6 bromine atoms, and a small amount of bromobenzenes (Watanabe and Tatsukawa, 1987; cited by IPCS, 1994). In xylene, DeBDE was rapidly degraded by reductive debromination with a half-life of 15 hours (Norris et al., 1973, 1975; cited by IPCS). The lower brominated products formed in xylene may be more resistant to UV photolysis. In toluene, DeBDE was rapidly degraded with a half-life of 15 minutes after exposure to UV radiation (Sellstr m et al., 1998b; cited by de Boer et al., 1999a). This degradation in the presence of toluene is important since toluene along with PBDEs are found in waste materials from the production of PBDEs and are dumped into public landfills in the United States.

The photodegradation of PBDEs in water alone does not lead to the formation of lower brominated PBDEs or PBDFs (Norris et al., 1973, 1975; cited by IPCS, 1994). In water, photohydroxylation of PBDEs is the expected route of transformation and the resulting hydroxylated products would then be degraded rapidly due to increased UV absorption.

The half-life of DeBDE in sand exposed to UV radiation or sunlight was between 12 and 37 hours (Sellstrom et al., 1998b; cited by de Boer et al., 1999a). Lower PBDEs and other compounds (not specified) were found after radiation.

6.7 Formation of Polybrominated Dibenzo-*p*-dioxins (PBDDs) and Polybromodibenzofurans (PBDFs) During Processing, Use, and Disposal of Products Containing PBDEs

In 1987, the U.S. EPA promulgated a testing and reporting rule for compounds that may be contaminated with polychlorinated and polybrominated dibenzo-p-dioxins (PCDDs and PBDDs) and dibenzofurans (PCDFs and PBDFs) (U.S. EPA, 1987; cited by Johnson et al., 1990), due to the severe toxicity of the 2,3,7,8-substituted congeners at trace levels. Many studies have shown that PBDDs and PBDFs are formed during the extrusion of plastics and during their combustion. Also, PBDDs and PBDFs have been found in finished products containing PBDEs. This could pose a risk to humans and the environment due to occupational exposure, industrial release, and combustion in waste facilities. However, careful monitoring of temperatures and the reduction of oxygen concentrations during combustion of wastes, combined with proper scrubbing techniques, would significantly reduce emissions of PBDDs and PBDFs to the environment. The use of approved safety equipment would be expected to reduce the risk of occupational exposure.

PBDDs and PBDFs are formed by the heating of polymers during extrusion, which may occur during blending with additives or during product manufacture. Post-extrusion samples of poly(butylene terephthalate) (PBT) at 255 to 275 ¡C showed concentrations of PBDD/PBDFs below 0.35 g/kg (Scheinert et al., 2000). PBDFs were found in air at the workplace and the machine extractor where PBT was processed and finished with PeBDE at 300 ¡C (CEM, 1989; cited by IPCS, 1994). PBDFs were also found in the air of a vessel where granulate was stored. However, indications are that most PBDFs formed during processing of polymers remain in the polymer products.

Very little 2,3,7,8-TCDD, if any at all, was formed as a result of pyrolysis of PBDEs (BFRIP, 1990; Thoma et al., 1987a,b; Thoma and Hutzinger, 1987; Dumler et al., 1989; all cited by IPCS, 1994). The pyrolysis of technical mixtures containing OBDE and antimony trioxide at 600 ¡C resulted in very little to significant amounts of 2,3,7,8-isomers (Neupert et al., 1989; Fresenius Institute, 1990; both cited by IPCS, 1994).

The combustion or thermal degradation of PBDEs and products containing them could be a potential source of environmental and occupational exposure and possibly a health concern because of the possible formation of toxic PBDDs and PBDFs (WHO, 1998; cited by Sakai, 2000). Many studies determined concentrations of PBDFs and PBDDs formed during the degradation of products containing PBDEs. Some studies have shown that large amounts of PBDDs and PBDFs were formed as a result of the model combustion of plastics containing PBDEs (Clausen et al., 1987; Thoma et al., 1987a; both cited by Zelinski et al., 1993). Combustion studies performed on products containing PBDEs and on PBDEs themselves have shown that the PBDFs are the predominant species formed and usually result in very low concentrations of PBDDs. When waste TV casings and circuit boards containing between 2.1 and 11.0 mg PBDEs/g were combusted in a primary and secondary combustion chamber at 900 ¡C in both, PBDEs were 99.9% destroyed (Sakai, 2000) and concentrations of total PBDEs in incinerated residues were between 2.9 and 180 g PBDEs/g. The concentrations of PBDDs and PBDFs in flue gas decreased when compared to original PBDD concentrations in the products while the concentrations of PCDDs and PCDFs increased. Both of these results were thought to be caused by the reaction of chlorine contained in the products with the PBDDs and PBDFs.

When heavy metals were also included in the combustion system, the concentration of PBDDs and PBDFs were higher than if no metals were included. The Fresenius Institute study found total PBDDs and PBDFs to be 31.5 and 1631 mg/kg, respectively, but formation of PBDDs and PBDFs was lower when combustion occurred at 200 ¡C (1.75 and 110.8 mg/kg, respectively) and at 250 ¡C (0.75 and 666 mg/kg, respectively) (Fresenius Institute, 1990; cited by IPCS, 1994).

The analysis of residues from one accidental apartment fire in England revealed that most prevalent PBDE congeners were tetra- through hepta-BDEs, with PBDE-isomers ranging from 0.24 to 51,870 mg/kg (most were between 0.5 and 150 mg/kg) (Zelinski et al., 1993). The highest concentrations were found in residues from TV cases (16-51,870 mg/kg), followed by wallfacing (262 mg/kg), plastic veneer of dresser drawers (146 mg/kg), fitted carpet (20.1 mg/kg), loudspeakers (16.6 mg/kg), and radio/cable/cabinet (11.6 mg/kg). The PBDE concentration in 20 samples, which normally would contain 5 to 15% flame retardants by weight, actually represented 5.2% of plastic by weight. The distribution of isomers detected in the TV set corresponded to the Bromkal 70-5DE technical mixture. The mono- through tri-BDFs were also prevalent (not detected-18,914 µg/kg), followed by tetra- through octa-BDFs (0.4-14,910 µg/kg). The PBDD concentrations in all samples were very low (not detected to 50.5 µg/kg), showing that formation of PBDFs was favored upon combustion of plastics. It was assumed that the TV was the source for all PBDD levels in the flat, which may have been true for other contaminants as well. However, this was difficult to ascertain because the differences in the temperatures of each fire would have caused differences in the degradation of the PBDEs in products.

It is believed by some that the benefits of reduction of house fires and fatalities from them may outweigh the hazard from the environmental persistence of PBDEs. In a study of fires caused by TV sets, it was observed that 16 people die each year and 197 are injured in European fires caused by TV sets with HB (conforming to European horizontal burn test specifications) enclosures and in the United States there is no record of individuals dying from TV fires with V0 (conforming to Underwriters Laboratory Class 94 vertical burn test specifications) enclosures (UK Department of Trade and Industry, 1996; Simonson et al., 2000). However, this may have been an underestimate of European statistics and the true estimate may be as much as 10 times this number (Simonson et al., 2000).

Environmental persistence of PBDDs along with PBDFs has been measured in a few studies. The levels of tetra-BDD/BDF, penta-BDD/BDF, and hexa-BDD/BDF in carp from the Buffalo River in New York were below the detection limit of 2, 3, and 8 pg/g (Loganathan et al., 1995). In a Swedish study, PBDDs and PBDFs were not found in salmon and osprey (Wilberg et al., 1992; cited by Loganathan et al., 1995). In both of these studies PCDDs and PCDFs were present at significantly higher concentrations.

PBDFs, mostly hepta- isomers, were detected in waste solids (4.4 ppb) from technical OBDE production (U.S. EPA, 1994, 59 FR 24530). The EPA considered these to be the least toxic of the PBDF isomers. When evaluated in terms of the risk of exposure to 2,3,7,8-TCDD, the EPA concluded that the risk posed by this constituent was below one in a million.

6.8 Disposal of Commercial and Residential Waste Items Containing PBDEs

Solid waste from commercial production of OBDE, such as filter cakes, is typically disposed of in landfills (U.S. EPA, 1994, 59 FR24530). In 1994, this production waste was shipped to Subtitle C hazardous waste facilities. These wastes are known to contain toluene. No toluene was detected in landfill leachate and estimated toluene concentrations in a hypothetical receptor well were expected to be an order of magnitude lower than the Maximum Concentration Level (MCL) for toluene under the Safe Drinking Water Act.

The disposal of computers in landfills, in incinerators, or by transport as hazardous waste exports is likely to increase worldwide due to their rapid obsolescence. In the United States, only 6% of computers were recycled in 1998 compared to the numbers of new computers put on the market that year, and the number of obsolete computers is projected to be 315 million between 1997 and 2004 (NSC, 1999; cited by SVTC, 1999). Based on a monitor weight of 30 pounds, this is estimated to be over 350 million pounds of brominated flame retardants (Atlantic Consultancy and IPU, 1998; NSC, 1999; both cited by SVTC, 1999). The European community is currently developing a plan to make producers responsible for taking back their old products as well as phasing out toxic compounds used in computers. This is expected to encourage clean product design with less waste generation.

Table 4. Environmental Occurrence Studies of Selected Polybrominated Diphenyl Ethers in the United States

Medium	Location	Compound	Concentration	Sample Preparation and Analytical Method	Limit of Detection	Comments	Reference
In Sewage Sludge:							
Sewage Sludge	Four sets of samples from publicly owned treatment works (POTWs)	BDE-47	499-1049 g/kg dry weight	Enhanced solvent extraction for biosolids; clean-up by size exclusion chromatography; separation in a silica column; GC-ELCD analysis	n.p.	Two sets came from POTWs using lime or composting before distribution. The third came from a local retail nursery. A fourth set of samples was heat-treated and came from an international distributor. The composition in the biosolids closely resembled the DE-71 commercial formulation. The sum of tetra- and penta- congeners was >1 mg/kg in all samples.	La Guardia et al. (2000)
		BDE-99	377-851 g/kg dry weight				
		BDE-100	70.8-134 g/kg dry weight				
		BDE-209	Not quantified				
In Air:							
Air samples from the Great Lakes Region of the U.S. as part of the Integrated Atmospheric Deposition Network (IADN)	Chicago, IL (on Lake Michigan; urban)	BDE-47 BDE-99 BDE-153	48 pg/m^3 25 pg/m^3 0.66 pg/m^3	Air samples taken every 12 d for 24 hr at each site in a high volume sampler containing a quartz fiber filter and an absorbent to collect particle and gas phase compounds, respectively; filters and absorbent were Soxhlet extracted for 24 hr with acetone/hexane; silica column chromatography clean-up; GC/MS analysis	n.p.	This highly populated area of Chicago had levels 5 times higher than other the areas consisting of predominantly 2,2«,4,4«-TeBDE and 2,2«,4,4«,5-PeBDE. Separate measurements of the particle and vapor phase concentrations of PBDE were conducted. 2,2«,4,4«-TeBDE was found mostly in the vapor phase while 2,2«,4,4«,5-PeBDE and 2,2«,4,4«,5,5«-HxBDE were found in the particle phase. Less brominated compounds in vapor tend to travel farther from a point source than more highly brominated compounds (in particle phase).	Dodder et al. (2000)
	Sleeping Bear Dunes, IL (on Lake Michigan; rural)	BDE-47 BDE-99 BDE-153	9.2 pg/m^3 5.0 pg/m^3 0.28 pg/m^3				
	Sturgeon Point, NY (on Lake Erie; rural)	BDE-47 BDE-99 BDE-153	6.2 pg/m^3 4.3 pg/m^3 0.27 pg/m^3				
	Eagle Harbor, MI (near Lake Superior; remote)	BDE-47 BDE-99 BDE-153	3.7 pg/m^3 2.6 pg/m^3 0.21 pg/m^3				

Table 5. Environmental Occurrence Studies of Selected Polybrominated Diphenyl Ethers in United States Biota

Species/Animal	Location	Tissue	Compound	Mean Concentration	Method	Limit of Detection	Comments	Reference
29 common and white-sided dolphins (*Delphinus delphis* and *Lagenorhychus acutus*) at various stages of development	Gulf of Mexico	Blubber	PBDEs (n.s.)	2260 ng/g lipid (range: 35-16,300 ng/g lipid)	GC/MS (separation by gel permeation chromatography)	n.p.	Concentrations of PBDEs increased in the order of fetus, adult female, suckling, immature, and adult male. The concentration of PBDEs in dolphins also varied according to the regions where they were found. Concentrations of PBDEs in the blubber of male dolphins decreased from the early 1990s to late 1990s.	Kuehl and Haebler (1995)
11 harbor seals (*Phoca vitulina*) samples (collected from 1989-1998)	San Francisco Bay Shoreline	Blubber	BDE-47	1124 ng/g lipid (range: 46-6682)	separation with gel permeation and Florisil chromatography; Analysis by GC/ECNI	n.p.		She et al. (2000)
			BDE-99	107 ng/g lipid (range: 17-303)				
			BDE-153	49.7 ng/g lipid (range: 4-160)				
40 lake trout from four Great Lakes (only the lakes with the lowest [Erie] and highest [Ontario] concentrations are tabulated)	Lake Ontario	Whole Fish	TeBDE	~75 ng/g lipid	separation of lipid by GPC; fractionation with silica gel column; analysis with GC/MS	n.p.	The highly industrialized Lake Ontario had the highest concentrations of all PBDE congeners (604 ng/g lipid), followed by Superior (392 ng/g), Huron (247 ng/g), and Erie (117 ng/g). The most predominant congener detected in all fish was BDE-47 (55% of total), followed by BDE-99 (15%), and BDE-153 (4%).	Luross et al. (2000)
			PeBDE	~30 ng/g lipid				
			HxBDE	<10 ng/g lipid				
	Lake Erie	Whole Fish	TeBDE	~390 ng/g lipid				
			PeBDE	~170 ng/g lipid				
			HxBDE	<10 ng/g lipid				

Table 5. Environmental Occurrence Studies of Selected Polybrominated Diphenyl Ethers in United States Biota (Continued)

Species/Animal	Location	Tissue	Compound	Mean Concentration	Method	Limit of Detection	Comments	Reference
Crappie and bluegill from the Great Lakes Region	Hadley Lake (HL), Indiana (1.3 km from a PBDE plant that may emit DE-71, DE-79, and DE-81)	Whole fish (crappie)	BDE-47 BDE-99 BDE-153	250 ng/g lipid 430 ng/g lipid 340 ng/g lipid	Homogenation of whole fish (including skin, bones, and intestine); $NaSO_4$ added to homogenate; Soxhlet extracted with acetone/hexane; clean-up with GPC, analyzed with HRGC/MS (EI)	n.p.	The profile of congeners detected in the fish from HL was similar to that in DE-71, especially the increased concentrations of PBDE-47 and BDE-99 compared to PBDE-100, which was lowest in HL. The high concentrations of PBDE-153 and PBDE-154 may be due to higher bioaccumulation in fish. Another source of PBDE-153 could be DE-79. Fish from LO had a different congener profile than those in HL. PBDE-47 was more than twice the concentration of the other congeners and the total PBDE concentration in fish from HL was four times that of fish from LO. Fish from LO were heavier (older) and had greater lipid content than fish from HL, which could have led to higher concentrations of PBDE in LO fish.	Dodder et al. (2000)
		Whole fish (bluegill)	BDE-47 BDE-99 BDE-153	420 ng/g lipid 320 ng/g lipid 450 ng/g lipid				
	Lake of the Ozarks (LO), Missouri (distant from any point source)	Whole fish (crappie)	BDE-47 BDE-99 BDE-153	190 ng/g lipid 78 ng/g lipid 7.7 ng/g lipid				
		Whole fish (bluegill)	BDE-47 BDE-99 BDE-153	200 ng/g lipid 91 ng/g lipid 23 ng/g lipid				
45 young, middle-age and old carp (*Cyprinus carpio*) (24F, 17M, and 4 n.d.)	Buffalo River, New York, USA	Muscle tissue	TeBDE	17.6 ng/g wet wt	Homogenization of muscle tissue; sample dehydrated and digested with KOH/ethanol; separation with GC-ECD); analysis by GC/MS	0.1 ng/g wet wt.	Concentrations of all PBDEs were positively correlated with the age of the fish. Tetra-, penta-, and hexa-BDEs were 94-96%, 3-4%, and 1% of total PBDEs recovered from fish, respectively. No BDE-209 was detected in the samples. Concluded that PBDEs may be widespread in the Buffalo River ecosystem	Loganathan et al. (1995)
			PeBDE	0.81 ng/g wet wt				
			HxBDE	0.24 ng/g wet wt				

Table 5. Environmental Occurrence Studies of Selected Polybrominated Diphenyl Ethers in United States Biota (Continued)

Species/Animal	Location	Tissue	Compound	Mean Concentration	Method	Limit of Detection	Comments	Reference
253 samples from 30 species with an emphasis on species eaten by humans (e.g., catfish, walleye, striped bass, perch, and carp)	50 freshwater sites in Virginia, U.S.A.	Edible muscle tissues	BDE-47; BDE-99; BDE-153	See Comments	Enhanced solvent extraction of samples; purified by size exclusion and SGC; analysis by ELCD or MS (EI)	5 µg/kg lipid	About 85% of samples contained >5 µg/kg BDE-47. Concentrations of BDE-47 were >2000 µg/kg lipid in 9% of samples and 32% of samples were between 100 and 500 µg BDE-47/kg lipid. The highest total PBDE concentrations were seen in carp from the Dan/Hyco River (up to 57,000 µg/kg lipid) . Textile and furniture facilities are located in areas that feed into the rivers where fish were sampled. One reservoir, dammed on both ends, contained fish with very low concentrations of PBDEs that may be due to the fish s inability to migrate.	Hale et al. (2000)

Table 5. Environmental Occurrence Studies of Selected Polybrominated Diphenyl Ethers in United States Biota (Continued)

Species/Animal	Location	Tissue	Compound	Mean Concentration	Method	Limit of Detection	Comments	Reference
6 Female steelhead trout (*Oncorhynchus mykiss*)	Lake Michigan, Kewaunee, WI	Muscle tissue	BDE-28	110 ± 35 ng/g lipid	Muscle samples extracted and treated with sulfuric acid; separation by HPLC; analysis by GC/MS using (ECNI) for detection of bromine atoms		Fish collected prior to spawning and had low lipid content when compared to non-reproducing fish. PBDE concentrations in Michigan fish were compared to those in Baltic salmon (Ballschmitter et al., 1993). The concentrations of all congeners detected were significantly higher in Lake Michigan trout. The total concentration of PBDEs (fresh weight basis) in Michigan fish was about six times the levels found in Baltic salmon. This difference was even higher (almost 17 times) when concentrations were compared on a lipid weight basis	Asplund et al. (1999a)
			BDE-47	1700 ± 760 ng/g lipid				
			BDE-99	600 ± 350 ng/g lipid				
			BDE-100	360 ± 150 ng/g lipid				
			BDE-153	110 ± 49 ng/g lipid				
			BDE-154	200 ± 120 ng/g lipid				

Abbreviations: BDE-28 = 2,4,4«-tribromodiphenyl ether; BDE-47 = 2,2«,4,4«-TeBDE; BDE-99 = 2,2«,4,4«,5-PeBDE; BDE-100 = 2,2«,4,4«,6-PeBDE; BDE-153 = 2,2«,4,4«,5,5«-HxBDE; BDE-154 = 2,2«,4,4«,5,6«-hexabromodiphenyl ether; ; ECNI = electron capture negative ionization; EI = electron impact mode with selected ion monitoring; ELCD = electrolytic conductivity detector; F = female; GPC = gel permeation chromatography; M = male; MS = mass spectroscopy; n.d. = not detected; n.p. = not provided; n.s. = not specified; SGC = silica gel chromatography

Table 6. Occurrence of Selected Polybrominated Diphenyl Ethers in Aquatic and Terrestrial Animals in Countries Other Than the United States

Species/Animal	Location	Tissue	Compound	Mean Concentration Detected	Method of Quantification	Limit of Detection	Comments	Reference
31 female sea-run Baltic salmon (*Salmo salar*)	Dal lven, Baltic Sea	Muscle	BDE-47	100-410 ng/g lipid	GC-ECD	n.p.		Asplund et al. (1999b)
			BDE-99	26-73 ng/g lipid				
		Egg	BDE-47	40-110 ng/g lipid				
			BDE-99	8-22 ng/g lipid				
		Blood	BDE-47	76-410 ng/g lipid				
			BDE-99	20-160 ng/g lipid				
Pike (*Esox lucius*)	Lake Bolman (Sweden)	Muscle tissue	2,2«,4,4«-TeBDE (BDE47)	<10 ng/g lipid in 1968; ~75 ng/g lipid in 1997	GC/MS	n.p.	Lake Bolman is a mesotropic lake situated in woodland with agricultural and industrial activities. There was a trend for increasing concentrations of BDE-47 from 1968 to 1997 with fluctuations. There was a trend for decreasing concentrations of MeO-BDE-47 in muscle from 1968 to 1997also with fluctuations	Kierkegaard et al. (1999a)
		Muscle tissue	Methoxy-2,2«,4,4«-TeBDE	>400 ng/g lipid in 1967; ~125 ng/g lipid in 1997				
Roach (*Rutilus rutilis*)	Lake Krankesj n (Sweden)	Muscle tissue	2,2«,4,4«-TeBDE (BDE-47) and Methoxy-2,2«,4,4«-TeBDE	5 ng/g lipid in 1980; <5 ng/g lipid in 1996 (BDE-47 only)	GC/MS	n.p.	Lake Krankesj n is eutrophied and situated in an agricultural region. Bell shaped curve. Highest levels detected in 1987. No MeO-BDE-47 was detected in the roach samples	Kierkegaard et al. (1999a)

Table 6. Occurrence of Selected Polybrominated Diphenyl Ethers in Aquatic and Terrestrial Animals in Countries Other Than the United States (Continued)

Species/Animal	Location	Tissue	Compound	Mean Concentration Detected	Method of Quantification	Limit of Detection	Comments	Reference
3 Baltic herring (*Clupea harengus*) and 9 sprat (*Sprattus sprattus*)	Baltic Sea	Whole herring homogenates (n=3)	BDE-47	13.94 ng/g lipid	GC/MS	0.5 ng/g lipid	There was a positive correlation between the age of the fish and the concentration of PBDEs in tissue	Strandman et al. (1999)
			BDE-99	4.14 ng/g lipid				
			BDE-153	0.76 ng/g lipid				
		Whole sprat homogenates (n=9)	BDE-47	64.98 ng/g lipid				
			BDE-99	4.53 ng/g lipid				
			BDE-153	1.12 ng/g lipid				
53 long-finned pilot whales (taken in 1994 and 1996)	Faroe Islands	Blubber	BDE-47	411.9-1782.1 ng/g lipid (Mean: 1062.6 ng/g lipid)	HRGC/MS (clean-up by column chromatography)	0.1-1.0 ng/g lipid	The lowest concentrations of all congeners was found in the samples taken in 1994. Higher total concentrations of PBDE congeners was found in young males (3,160 ng/g lipid) and females (3,038 ng/g lipid) when compared to older males (1,610 ng/g lipid) and females (843 ng/g lipid). This is contradictory to bioconcentrations of other persistent organohalogens such as PCBs, which generally show an increase in tissue concentrations that are positively related to age.	Lindstr m et al. (1999)
		Blubber	BDE-99	164.1-603.6 ng/g lipid (Mean: 372.8 ng/g lipid)				
		Blubber	BDE-153	32.0-90.0 ng/g lipid (Mean: 57.6 ng/g lipid)				

Table 6. Occurrence of Selected Polybrominated Diphenyl Ethers in Aquatic and Terrestrial Animals in Countries Other Than the United States (Continued)

Species/Animal	Location	Tissue	Compound	Mean Concentration Detected	Method of Quantification	Limit of Detection	Comments	Reference
12 long-finned pilot whales (taken in 1997)	Torshavn, Faroe Islands	Blubber	BDE-47	379.2 ng/g lipid (range: 66-864.2)	HRGC/MS-SIR		The sum of total PBDEs in the blubber of each whale ranged from 125 to 1246 ng/g lipid. BDE-47 BDE-99, and BDE-153 were the most prevalent in samples. Following them were undetermined congeners of PeBDE (12.4-97.7 ng/g lipid) and HxBDE (6.9-42.4 ng/g lipid).	Van Bavel et al. (1999)
			BDE-99	81.4 ng/g lipid (range: 23.9-169.3)				
			BDE-153	7.23 ng/g lipid (range: 2.1-13.5)				

Abbreviations: BDE-47 = 2,2«,4,4«-TeBDE; BDE-99 = 2,2«,4,4«,5-PeBDE; BDE-100 = 2,2«,4,4«,6-PeBDE; BDE-153 = 2,2«,4,4«,5,5«-HxBDE; ECD = electrolytic conductivity detector; F = female; GPC = gel permeation chromatography; MS = mass spectroscopy;

Table 7. Bioaccumulation Studies of Selected Polybrominated Diphenyl Ethers

Subjects	Compound (Dose)	Exposure Parameters	Analytical Method	Limit of Detection	Results	Reference
Blue mussels (*Mytilus edulis*) collected in Northern Baltic Sea, Sweden	BDE-47 (1.58 mg); BDE-99 (1.72 mg); BDE-153 (1.33 mg)	Fish were exposed to mixture of 5 PCBs and the three PBDEs in a flow-through tank for 44 d with a 26 d depuration period for some fish in natural brackish water. The flow rate of water into the tanks was 1.6 L/h	GC/MS	0.6, 1.4, and 2.7 pg for BDE-47, BDE-99, and BDE-153, respectively	The water concentration of BDE-47, BDE-99, and BDE-153 during the exposure period were 0.31 – 0.2 ng/L, 0.070 – 0.05 ng/L, and 0.086 – 0.11 ng/L, respectively. The bioaccumulation factors for BDE-47 and were 6-8 times higher than for PCBs 52 and 77, and the bioaccumulation factor for BDE-99 was 5-7 times higher than for PCBs 118 and 153.	Gustafsson et al. (1999)
5 pike (*Esox lucius* L.), sex n.p.	^{14}C-labelled BDE-47 injected into dorsal muscle of live brown trout and immediately fed to pike every 18 days (between 0.21 and 0.24 µCi/g fresh wt	Pike were housed separately in aquaria (flow type n.p.). Pike were sacrificed at 9, 18, 36, and 65 d	Scintillation counting		The radioactivity in the exposed pike was 96% of the dose given in the food.	Burreau et al. (2000a)
Carp	Mixed PBDEs (HxBDE through DeBDE)	Exposure for 8 wk	n.p.		Little bioaccumulation of hexa- through decaBDEs (<7)	CBC (1982); cited by IPCS (1994)
Carp	Technical PeBDE (trade name not specified) at 10 or 100 g/L	Exposure for 8 wk	n.p.		Bioconcentration factors of more than 10,000	CBC (1982); cited by IPCS, 1994

Abbreviations: BDE-47 = 2,2«,4,4«-TeBDE; BDE-99 = 2,2«,4,4«,5-PeBDE; BDE-153 = 2,2«,4,4«,5,5«-HxBDE; d = day(s); MS = mass spectroscopy; n.p. = not provided

Table 8. Summary of PBDE Environmental Occurrence Data in Locations Other Than the United States

Samples/Location	Units	Concentrations of Congeners Detected											Reference
Air		**28**	**35**	**47**	**49 + 51**	**99**	**100**	**153**	**154**	**155**	**183**	**209**	
outdoor air	pmol/m^3			0.2		0.1		0.006			0.0009	0.04	Bergman et al. (1999)
Sediment		**28**	**35**	**47**	**TeBDE**	**99**	**PeBDE**	**153**	**154**	**155**	**185**	**OBDE**	
river sediment/Japan	µg/kg dry wt				12-31								IPCS (1994)
river sediment/Japan, 1987-89	µg/kg dry wt											8-22	
river sediment/Sweden					<840 ign. loss								
sewage sludge/Sweden	g/kg				15		19						
sewage sludge/Sweden					15								
Water		**28**	**35**	**47**	**49 + 51**	**99**	**100**	**153**	**154**	**155**	**185**	**OBDE**	
Japan 1987-89	µg/L											<1 (ND)	IPCS (1994)
Aquatic Species													
Rivers		**28**	**35**	**47**	**49 + 51**	**99**	**100**	**153**	**154**	**155**	**185**	**209**	
Diff fish/Sweden	µg/kg wet wt.			<0.1-110									IPCS (1994)
Diff fish/Sweden, 1986-87	µg/kg lipid			15-450									
Fish/Germany	mg/kg lipid			≤1									

Table 8. Summary of PBDE Environmental Occurrence Data in Locations Other Than the United States (Continued)

Samples/Location	Units	Concentrations of Congeners Detected											Reference
Herring/North Sea 1983-89	µg/kg lipid			8.4-100									IPCS (1994)
Atlantic Ocean		**28**	**35**	**47**	**49 + 51**	**99**	**100**	**153**	**154**	**155**	**185**	**209**	
zoo plankton/Iceland	ng/g lipid	0	0	2.0	0.1	1.4	0.5		0	0			Burreau et al. (2000b)
small herring/Iceland	ng/g lipid	0.3	0.2	2.2	0.5	0.4	0.3		0.1	0			
large herring/Iceland	ng/g lipid	0.8	0.4	4.1	1.6	0.4	0.7		0.3	0.2			
salmon/Iceland	ng/g lipid	1.2	0.4	7.6	0.9	1.5	1.8		1.1	0.5			
sperm whale	g/kg wet wt			58-95		17-40		<5					
Baltic Sea		**28**	**35**	**47**	**49 + 51**	**99**	**100**	**153**	**154**	**155**	**185**	**209**	
sprat/central, northern	ng/g lipid	0.3	0.4	6.8	2.6	1.7	2.5		0.3	0			Burreau et al. (2000b)
herring/central, northern	ng/g lipid	0.7	0.4	19.1	4.3	2.8	5.3		0.8	0			
salmon/central, northern	ng/g lipid	1.0	1.8	45.8	11.7	10.0	13.0		1.6	0.4			
ringed seal blubber	ng/g lipid			256		33		9.6					Haglund et al. (1997)
ringed seal liver	ng/g lipid			33		3.0		2.5					
gray seal blubber	ng/g lipid			308		54		11					
gray seal liver	ng/g lipid			16		1.3		nd (<0.1)					
2 yr old herring	ng/g lipid			3.2		nd (<0.1)		nd (<0.1)					
3 yr old herring	ng/g lipid			10		1.0		nd (<0.1)					
5 yr old herring	ng/g lipid			27		2.9		nd (<0.1)					
ringed and gray seals/Sweden, 1979-1985	µg/kg lipid			47(1979) 650(1985)									IPCS (1994)

Table 8. Summary of PBDE Environmental Occurrence Data in Locations Other Than the United States (Continued)

Samples/Location	Units	Concentrations of Congeners Detected											Reference
Japan		**28**	**35**	**47**	**49 + 51**	**99**	**100**	**153**	**154**	**155**	**185**	**OBDE**	
mussels and fish/diff. locations	µg/kg wet wt			<0.1-14.6									IPCS (1994)
fish, 1987-89	µg/kg wet wt											<5 (ND)	
Birds		**28**	**35**	**47**	**49 + 51**	**99**	**100**	**153**	**154**	**155**	**185**	**209**	
muscle tissue/Baltic, North Sea, Spitzbergen	µg/kg lipid			80-370									IPCS (1994)
osprey/Sweden 1982-86	µg/kg lipid			1800 avg.									
cormorant liver	µg/kg wet wt			1.69-69.3		0.49-14.57	0.45	0.18-13.78	0.14-9				Allchin et al. (2000)
Other Terrestrial Species		**28**	**35**	**47**	**49 + 51**	**99**	**100**	**153**	**154**	**155**	**185**	Total PBDEs	
rabbit pooled muscle/Sweden	µg/kg lipid			<2 avg.									IPCS (1994)
moose pooled muscle/Sweden	µg/kg lipid			0.82 avg.									
reindeer pooled muscle/Sweden	µg/kg lipid			0.18 avg.									
cow s milk/Germany	µg/kg lipid											2.5-4.5	
cow s milk/Germany	µg/kg lipid											3	Kruger (1988) [b]

Abbreviations: nd = not determined

[a] Concentrations are recorded as ng/g lipid unless otherwise noted.
[b] Cited by IPCS (1994)

7.0 HUMAN EXPOSURE

Human exposure to PBDEs may occur by inhalation as an indoor or occupational air pollutant, dermal absorption as an occupational hazard, or oral ingestion in foods (Lindstr m, 1999).

Indoor air concentrations of PBDEs in lecture halls, computerized indoor environments, and rooms with other electronic devices, such as television sets, have revealed relatively low levels of PBDEs compared to other exposure pathways (Lindstr m, 1999). Potential point sources may lead to increased concentrations of PBDEs in indoor air. OBDE has been found in indoor areas that contain electronic products containing PBDEs (televisions and computers) (Bergman et al., 1997; cited by KemI, 1999). Among the PBDEs, BDE-209 is the least volatile; however, even deca-BDE has been found in adipose tissue from normal subjects in the United States.

The release of PBDEs from polymers is dependent on the migration of PBDE molecules through the polymer matrix to the surface where emission takes place (Danish EPA, 1999). Migration is predominantly determined by the size of the molecule. PBDEs are large molecules and migration would be expected to proceed slowly. Although no studies were located that determined the rate of evaporation of PBDEs from plastics, estimates have been made. Estimated evaporation of deca-, octa-, and penta-BDEs from plastics are 0.038%, 0.054%, and 0.39% per year, respectively, based on worst case emission factors for organic flame retardants (Danish EPA, 1999).

Dermal exposure during production and by contact with products containing PBDEs could occur. Exposure by dermal contact with fabrics or polymers (e.g., clothes, foam cushions) could be another route, but little is known about the incorporation of PBDEs in textiles.

The details of several studies that determined the concentration of PBDEs in the tissues of non-occupationally exposed individuals are provided in **Table 9**.

Occupational exposure of individuals to technical formulations containing PBDEs have been recorded at plants that dismantle electronic equipment, as well as exposure to automobile drivers, farmers, cleaners, actors, and monitor repairers (Lindstr m, 1999). The details of several studies that determined the concentration of PBDEs in tissues of occupationally exposed workers are provided in **Table 10**. The greatest risk from occupational exposure is through the inhalation of PBDEs. Inhalation exposure to PBDEs is expected to be low due to their low vapor pressure (10^{-7} mm Hg); however, inhalation of particulates is possible during grinding or shredding of solids during reprocessing. In studies of workers involved in the grinding of post-use polymers for reclamation, levels of BDE-209 in the workers were much higher than concentrations found in the general population. Since the absorption of BDE-209 after oral administration is very low in rats (<1%) and probably in man, this could indicate that inhalation of particulate containing PBDEs could lead to considerably greater absorption when compared to oral exposure. The number of TV sets being disassembled is expected to rise in the future. In a scenario presented to estimate emissions of PBDD/PBDFs and polyaromatic halogens from flame-retarded and non-flame retarded TV sets, 2% of TV sets presently go to disassembly after use and in the future 89% was expected to be disassembled, with the disassembled cases being incinerated (Simonson et al., 2000). The use of dust masks and preferentially respirators is recommended in areas of potential exposure (IPCS, 1994). Dermal exposure can occur during

production and processing of the polymer materials and during product formation. The concentration of hepta-BDE, the most common ingredient in technical OBDE, was found to be 65 times higher in the blood of individuals that dismantled electronic parts when compared to hospital housekeepers that had little or no occupational exposure to PBDEs (KemI, 1999). These studies show an association between the handling of products that contain PBDEs and tissue concentrations of PBDEs.

In the United States, widespread exposure is evident by the levels of PBDEs found in the tissues from individuals from all areas of the country and in all age groups. OBDE ranged from not detected to 8000 ng/kg in adipose tissue samples collected for the National Human Adipose Tissue Survey (NHATS) in 1987, with limits of detection of 10-40 ng OBDE/kg lipid (Cramer et al., 1990a,b; Stanley et al., 1991). HeptaBDE (1-2000 ng/kg) was also found in the adipose tissue (Stanley et al., 1991). No PBDDs or PBDFs were found in the tissues (Cramer et al., 1990a,b). The majority of studies that were available on human exposure in the United States involved samples that were taken in the late 1980s and the early 1990s. Three studies were based on PBDE concentrations detected in adipose tissue studies from the 1987 NHATS. It is evident in fish that PBDEs accumulate over time since older fish have much higher concentrations of PBDEs in their tissues when compared to younger fish. Analysis of adipose tissue samples from subjects of various ages and geographic locations within the U.S. showed that levels of HxBDE and HpBDE were generally higher in middle-age (15-44 years) and older individuals (45+ years); whereas, levels of OBDE was generally higher in younger (0-14 years) and middle-age individuals. Human exposure patterns are certainly different from those in other species.

In studies of the general population of countries other than the United States it has also been shown that exposure to the general population is widespread. In 13 individuals of various ages in Spain, exposure to PBDEs did not appear to follow the general pattern of persistent organohalogen exposure (Meneses et al., 1999). General organohalogen exposure results in tissue concentrations that are positively correlated with age; however, in this study the highest as well as the lowest concentrations of PBDEs in adipose tissue were found in older individuals. Also, the pattern of exposure was different in men and women, as evident by the different concentrations in adipose tissue. The concentrations of BDE-47 were lower (1.4 ng/g lipid) than concentrations found in the adipose tissue of Swedish subjects (3.6-8.8 ng/g lipid) (Lindstrom et al., 1998; Nordstrom et al., 1999; both cited by Meneses et al., 1999; Haglund et al., 1997). The higher levels reported in Sweden could be due to many factors such as different lifestyles, climate conditions, and dietary habits. Although the Spanish and Swedish consume large amounts of fish, the higher fat content of Baltic Sea fish when compared to that of the lean fish from the Mediterranean could account for the lower adipose tissue concentrations in Spain (Meneses et al., 1999). Two factors should be considered if exposure is due to the use of electronic equipment. The Swedish population spends more time indoors than the Spanish population due to climate and the Swedish have imported and used more electronic products than the Spanish.

Consumption of food is expected to be the major route of exposure in humans (Lindstr m, 1999). Consumption of fish has been linked to higher levels of PBDEs in Swedish individuals (Bergman et al., 1999). Fish consumption in the Great Lakes region is approximately 15.7 g/day, according to fish-consumption surveys (Loganathan et al., 1995). In Sweden where

fish consumption is reported to be about 30 g/day, an estimated 0.1 µg of PeBDE and 0.3 µg of total PBDEs is ingested in fish by humans (Jansson, personal communication; cited by IPCS, 1994). The fish of greatest concern to humans, as far as TCDD exposure and presumably PBDEs, are bottom feeders like carp and catfish. Like PCBs, there may be a higher risk of exposure to PBDEs in Native Americans that reside in the Arctic region who consume whale and seal blubber (Jaret, 2000).

Four types of commercial fish oils (three from deep sea fish oils and one cod liver oil) were found to contain PBDEs (0.2-28.1 ng/g lipid weight) and methoxylated PBDEs (0.4-29.7 ng/g lipid weight), indicating that both PBDEs and MeO-PBDEs may be ubiquitous in the environment (Haglund et al., 1997). The highest concentration of PBDEs was found in the cod liver oil, while the highest concentration of methoxylated PBDEs was found in one of the deep sea fish oils followed by cod liver oil. All of these oils were from four products marketed as dietary supplements for humans. The country where these supplements were produced or sold was not stated, although it could be assumed that they are available in Sweden, since this was a study conducted in Sweden. The two products that contained the highest concentrations of PBDEs and methoxylated PBDEs, the cod liver and one deep sea fish oil, are reportedly purified to reduce contaminants.

Exposure of adult females and neonates is evident due to the presence of PBDEs in breast milk of women from around the world as well as one study indicating the presence of PBDEs in placental tissue. The PBDEs detected in breast milk are the tri- to hexabrominated diphenyl ethers, but not the hepta- to decabrominated diphenyl ethers (LaKind and Berlin, 2000), which are the same congeners found in bioaccumulation studies with fish and other mammals. Levels of PBDEs in the breast milk of Swedish women shows an exponentially increasing trend in exposure since the 1970s, with concentrations of PBDEs in breast milk doubling every fifth year (Lindstr m, 1999). While DDT and TCDD/PCDF/PCB in breast milk are decreasing exponentially in Swedish women, the concentrations of PBDEs in breast milk are increasing exponentially from about 300 pg/g lipid in 1976 to about 4000 pg/g lipid in 1997 in Swedish women (Nor n and Meironyt , 2000). PBDEs have not been produced in Sweden, but they are imported for flame retardant applications. A concentration of 28.4 g/kg was found in the adipose tissue of one subject by Swedish researchers (Renner, 2000). One study from the United States indicated that the mean concentration of PBDEs in the breast adipose tissue collected from 5 women in the late 1990s was 18, 4.9, and 2.2 ng/g lipid for BDE-47, BDE-99, and BDE-153, respectively. This indicates that levels of PBDEs may be equal to or higher than concentrations found in European women. The levels of PBDEs detected in breast milk of European women are still far below levels of PCBs and lower than levels found to cause adverse behavioral effects in mice (KemI, 1999; Renner, 2000; Nor n and Meironyt , 2000). The sum of all PCB congeners detected in breast milk represented 67% of all halogenated contaminants (323.61 ng/g lipid) while total PBDEs represented 1% (4.83 ng/g lipid) (Nor n and Meironyt , 2000). This is in contrast to levels of PBDEs in fish, which have equaled or surpassed tissue concentrations of PCBs. The sum of four PBDE congeners (BDE-28, BDE-47, BDE-99, and BDE-209) was between 0.88 and 5.89 ng/g lipid in breast milk and between 1.00 and 4.40 ng/g lipid in placental tissue of 11 Finnish women (Strandman et al., 2000). The four highest concentrations of PBDEs were found in nulliparous women. If concentrations of PBDEs in the placenta represent actual concentration in the fetus, then fetal exposure may occur during development with possible undesirable effects.

Because of the poor correlation of age and exposure levels, it has been suggested that there may be unidentified point sources of occupational exposure or other sources unrelated to food consumption (Lindstr m, 1999).

Table 9. Concentrations of PBDEs Found in the Tissues of Non-Occupationally Exposed Individuals

Subjects	Location	Tissue	PBDE	Mean Concentration or Range	Comments	Analysis	Reference
U.S. Studies							
5 human females (samples collected in late 1990s)	Northern California	Breast adipose tissue	BDE-47	18 ng/g lipid (range: 7.0-28)		gel permeation and Florisil chromato-graphy; Analysis by GC/ECNI	She et al. (2000)
			BDE-99	4.9 ng/g lipid (range: 3.1-7.3)			
			BDE-153	2.2 ng/g lipid (range: 1.5-3.2)			
12 blood donors in 1988 (no demographic information)	Illinois	Blood serum	BDE-47	~1.5 pmol/g lipid (range: 0-48)	The concentrations of compounds in the serum of U.S. blood donors was compared to that of non-occupationally exposed female cleaners in Sweden and found to be in the same range.	Analysis by GC/MS (ECNI)	Patterson et al. (2000)
			BDE-153	~0.5 pmol/g lipid (range: 0-3)			
			BDE-183	minute (range: 0-1.5 pmol/g lipid)			
			BDE-209	1 pmol/g lipid (range: 0-35)			
Human adipose tissue samples	U.S.A.	Adipose tissue	HxBDE/HCDE through DeBDE/ DeCDE in tissues	Amounts not provided (**See next row**)	Detected the presence of HxBDE/HCDE through DeBDE/DeCDE in tissues	n.p.	Remmers et al. (1990); cited by IPCS (1994)

Table 9. Concentrations of PBDEs Found in the Tissues of Non-Occupationally Exposed Individuals (Continued)

Subjects	Location	Tissue	PBDE	Mean Concentration or Range	Comments	Analysis	Reference
Adipose samples from 47 U.S. residents (from 1987 National Human Adipose Tissue Survey [NHATS])	All regions of the United States	Adipose tissue	HxBDE	2-1000 pg/g lipid (mean: 209)	Concentrations were estimated from mass spectrometry results. All three PBDEs were detected in samples representing all regions of the U.S and all ages. There was a trend for higher concentrations of HxBDE and HpBDE in individuals over 45 years of age, except for OBDE, which appeared to be higher in samples from middle age (15-44) and younger (0-14) subjects.	HRGC/HRMS-SIM	Stanley et al. (1991); Cramer et al. (1990a,b)
			HpBDE	1-2000 pg/g lipid (mean: 180)			
			OBDE	70-8000 pg/g lipid (mean: 646)			
Non-U.S. Studies							
10 Human subjects (sex n.p.)	Finland	Adipose tissue	BDE-47	7.28 ng/g lipid (range: 3.07-16.75)		GC/MS (ECNI)	Strandman et al. (1999)
			BDE-99	2.07 ng/g lipid (range: 0.74-5.51)			
			BDE-153	2.33 ng/g lipid (range: 1.26-3.74)			
Human samples from 1991	Sweden	Blood serum (No fish intake)	BDE-47	0.83 ± 1.9 pmol/g lipid		GC/MS; LOD=<0.3 pmol/g lipid; LOQ=<0.7 pmol/g lipid	Bergman et al. (1999)
		Blood serum (High fish intake)	BDE-47	4.4 ± 4.4 pmol/g lipid			

Table 9. Concentrations of PBDEs Found in the Tissues of Non-Occupationally Exposed Individuals (Continued)

Subjects	Location	Tissue	PBDE	Mean Concentration or Range	Comments	Analysis	Reference
13 adipose tissue samples (10M, 3F)	Tarragona, Spain	Adipose tissue	BDE-47	Men: 1.58 ± 1.60 ng/g lipid	The subjects in this study ranged from 23 to 72 years old. Unlike other studies of human persistence of PBDEs in adipose tissue which showed that the predominant congener was BDE-47, the predominant congener in this study was BDE-153 in both men and women. The concentrations of BDE-47 and BDE-99 were not significantly higher in men than in women. The highest and lowest concentrations of PBDEs were found in men between the age of 60 and 70. Generally for persistent organohalogens, the concentrations increase with age. Even though the men s average age was lower than the women s, the concentration of PBDEs was higher in men.	GC/MS (EI), LOD: 0.05 ng/g	Meneses et al. (1999)
				Women: 0.59 ± 0.24 ng/g lipid			
			BDE-99	Men: 0.50 ± 0.61 ng/g lipid			
				Women: 0.17 ± 0.05 ng/g lipid			
			BDE-153	Men: 1.82 ± 1.05 ng/g lipid			
				Women: 1.84 ± 1.30 ng/g lipid			
			PeBDE-1 (an unidentified penta-congener)	Men: 0.59 ± 0.33 ng/g lipid			
				Women: 0.24 ± 0.04 ng/g lipid			
Healthy 74-yr-old male (collected in 1994)	Sweden	Adipose tissue	BDE-47	8.8 ng/g lipid	Total TeBDE congener (2 detected) and PeBDE congener (2 detected) concentrations were 9.1 and 2.9 ng/g lipid, respectively.	GC/MS (ECNI)	Haglund et al. (1997)
			BDE-99	1.1 ng/g lipid			
			BDE-153	1.7 ng/g lipid			

Table 9. Concentrations of PBDEs Found in the Tissues of Non-Occupationally Exposed Individuals (Continued)

Subjects	Location	Tissue	PBDE	Mean Concentration or Range	Comments	Analysis	Reference
Human breast milk and placenta samples from 11 donors	Finland	Breast Milk	BDE-28	0.16 ± 0.15 ng/g lipid	The sum of the four PBDE congeners was between 0.88 and 5.89 ng/g lipid in breast milk and between 1.00 and 4.40 ng/g lipid in placental tissue. If concentrations of PBDEs in the placenta represent actual concentration in the fetus then fetal exposure may occur during development with possible undesirable effects.	GC/MS (SIR)	Strandman et al. (2000)
			BDE-47	1.31 ± 1.15 ng/g lipid			
			BDE-99	0.39 ± 0.23 ng/g lipid			
			BDE-153	0.39 ± 0.20 ng/g lipid			
		Placenta	BDE-28	0.14 ± 0.08 ng/g lipid			
			BDE-47	1.09 ± 0.83 ng/g lipid			
			BDE-99	0.42 ± 0.18 ng/g lipid			
			BDE-153	0.42 ± 0.17 ng/g lipid			
2 human subjects that suffered sudden death (66 and 78 yr old)	Sweden	Adipose and (liver) tissues of Subject A only	BDE-28	<0.1 and (0.1) ng/g lipid	The ratio of PBDE congeners found in the adipose tissue of both subjects was similar while the ratio of PBDE congeners in the liver of both subjects was not similar. The concentration of all PBDEs in the liver of Subject A (shown) was considerably higher than in Subject B (not shown). Subject B s concentrations of the congeners were similar in both adipose and liver tissue and similar to adipose concentrations found in subject A.	GC/MS (EI)	Guvenius and Nor n (1999)
			BDE-47	2.4 and (3.8) ng/g lipid			
			BDE-85	1.0 and (2.0) ng/g lipid			
			BDE-99	1.8 and (5.4) ng/g lipid			
			BDE-100	0.25 and (0.6) ng/g lipid			
			BDE-153	1.2 and (3.2) ng/g lipid			
			BDE-154	<0.1 and (0.3) ng/g lipid			

Table 9. Concentrations of PBDEs Found in the Tissues of Non-Occupationally Exposed Individuals (Continued)

Subjects	Location	Tissue	PBDE	Mean Concentration or Range	Comments	Analysis	Reference
Pooled milk samples from mothers	Stockholm, Sweden	Breast milk	BDE-28	nd[a]; 0.19 ng/g lipid[b]	A continuous increase in all BDE congeners was detected between 1972 and 1997. The sum of all BDE congeners detected rose from 0.07 ng/g lipid in 1972 to 4.02 ng/g lipid in 1997. BDE-17 was not found in any sample.	GC/MS (EI); LOD = 5 pg/g lipid	Meironyte et al. (1999)
			BDE-47	0.06[a]; 2.28 ng/g lipid[b]			
			BDE-66	nd[a]; 0.07 ng/g lipid[b]			
			BDE-85	nd[a]; 0.07 ng/g lipid[b]			
			BDE-99	nd[a]; 0.48 ng/g lipid[b]			
			BDE-100	nd[a]; 0.42 ng/g lipid[b]			
			BDE-153	0.01[a]; 0.46 ng/g lipid[b]			
			BDE-154	nd[a]; 0.05 ng/g lipid[b]			

Abbreviations: BDE-28 = 2,4,4«-tribromodiphenyl ether; BDE-47 = 2,2«,4,4«-TeBDE; BDE-66 = 2,3«,4,4«-TeBDE; BDE-85 = 2,2«,3,4,4«-PeBDE; BDE-99 = 2,2«,4,4«,5-PeBDE; BDE-100 = 2,2«,4,4«,6-PeBDE; BDE-153 = 2,2«,4,4«5,5«-HxBDE; BDE-154 = 2,2«,4,4«5,6«-HxBDE; BDE-209 = 2,2«,3,3«,4,4«5,5«,6,6«-DecaBDE; CB-153 = 2,2«,4,4«5,5«-Hexaclorobiphenyl; GPC = gel permeation chromatography; n.d. = not detected; n.p. = not provided; n.s. = not specified; SGC = silica gel chromatography; SIM = selective ion monitoring

[a] Results are from pooled milk samples collected from 75 mothers in 1972.

[b] Results are from pooled milk samples collected from 40 mothers in 1996/1997.

Table 10. Occupational Exposure to PBDEs in Non-U.S. Workers

Subjects	Location	Samples	PBDE	Mean Concentration or Range	Comments	Analysis	Reference
Tissue Concentrations							
19 workers at an electronics disassembly plant (15M, 4F)	Sweden	Air	BDE-47	~5 pmol/m^3	The concentration of all PBDEs in air was higher in the grinding area (where plastics are shredded) than in the dismantling area. Determined that the point source for PBDE exposure was at the grinding area when plastics containing PBDEs are processed. When grinding plastics that do not contain PBDEs, concentrations in the air are similar to those in the dismantling area. Concentrations of BDE-183 and BDE-209 in air were 6 and 9 times higher than those of BDE-153, respectively. Levels of BDE-183 and BDE-209 in serum were 10 and 5 pmol/g lipid, respectively.	GC/MS (ECNI)	Sj din et al. (1999)
			BDE-153	~20 pmol/m^3			
		Blood Serum	BDE-47	~6 pmol/g lipid			
			BDE-153	~7 pmol/g lipid			
20 hospital cleaners (all F)	Sweden	Blood Serum	BDE-47	~3 pmol/g lipid	Concentrations of BDE-183 and BDE-209 were below 1 pmol/g lipid.	GC/MS (ECNI)	Sj din et al. (1999)
			BDE-153	~1 pmol/g lipid			
Cleaners at a hospital	Sweden	Blood Serum	BDE-47	3.2 ± 8.0 pmol/g lipid		GC/MS; LOD: <0.3 pmol/g lipid; LOQ: <0.7 pmol/g lipid	Bergman et al. (1999)
			BDE-153	0.89 ± 1.6 pmol/g lipid			
			BDE-183	0.16 ± 0.10 pmol/g lipid			
			BDE-209	<0.70 ± 0.10 pmol/g lipid			
Clerks at the same hospital as the cleaners above	Sweden	Blood Serum	BDE-47	3.0 ± 2.7 pmol/g lipid		GC/MS; LOD: <0.3 pmol/g lipid; LOQ: <0.7 pmol/g lipid	Bergman et al. (1999)
			BDE-153	1.3 ± 1.0 pmol/g lipid			
			BDE-183	0.24 ± 0.29 pmol/g lipid			
			BDE-209	<0.7 ± 1.8 pmol/g lipid			

Table 10. Occupational Exposure to PBDEs in Non-U.S. Workers (Continued)

Subjects	Location	Samples	PBDE	Mean Concentration or Range	Comments	Analysis	Reference
Employees dismantling electronic parts	Sweden	Blood Serum	BDE-47	5.9 ± 13 pmol/g lipid		GC/MS; LOD: <0.3 pmol/g lipid; LOQ: <0.7 pmol/g lipid	Bergman et al. (1999)
			BDE-153	7.0 ± 4.1 pmol/g lipid			
			BDE-183	11 ± 7.4 pmol/g lipid			
			BDE-209	5.0 ± 2.7 pmol/g lipid			
In Air:							
Plant for recycling of electronics, dismantling of electronics (n=12)	Sweden	Air	BDE-47	0.73-4.3 pmol/m^3		GC/MS	Bergman et al. (1999)
			BDE-99	1.0-9.8 pmol/m^3			
			BDE153	1.4-17 pmol/m^3			
			BDE-183	8.7-60 pmol/m^3			
			BDE-209	12-73 pmol/m^3			
Office with computers (n=4)	Sweden	Air	BDE-183	0.0063-0.016 pmol/m^3		GC/MS	Bergman et al. (1999)
			BDE-209	0.083-0.090 pmol/m^3			

Abbreviations: BDE-47 = 2,2«,4,4«-TeBDE; BDE-99 = 2,2«,4,4«,5-PeBDE; BDE-153 = 2,2«,4,4«5,5«-HxBDE; BDE-154 = 2,2«,4,4«5,6«-HxBDE; BDE-183 = 2,2«,3,4,4«,5«,6-HpBDE; BDE-209 = 2,2«,3,3«,4,4«5,5«,6,6«-DecaBDE; LOD = limit of detection; LOQ = limit of quantification; SIR = selective ion recording

8.0 REGULATORY STATUS

U.S. government regulations pertaining to the penta-, octa-, and decabrominated diphenyl ether commercial technical mixtures are summarized in the table and text below. There are no regulations for individual congeners.

Table 11. Regulations Relevant to PeBDE, OBDE, and DeBDE

	Regulation	Summary of Regulation
E P A	40 CFR 712.30	Any manufacturer of any of the three technical mixtures was required to submit production, use, and exposure data for the compound by March 12, 1990 or upon request of the TSCA Interagency Testing Committee under the authority of 15 USC 2607(a).
	40 CFR 716.120	Any manufacturers of a technical mixture must submit lists and copies of studies related to the health and safety of the compounds upon request of the EPA under the Authority of 15 U.S.C. 2607(d)
	40 CFR 721.775	Producers of brominated aromatic compounds are required to report any new compounds or significantly new uses for existing compounds, which also includes protection in the workplace, hazard communication programs, releases to water, and industrial, commercial, and consumer activities.

The technical mixtures of penta- (32534-81-9), octa- (32536-52-0), and deca-BDE (1163-19-5) are regulated by the United States Environmental Protection Agency under the authority of the Toxic Substances Control Act (TSCA). Any manufacturers of a technical mixture must submit lists and copies of studies related to the health and safety of the compounds upon request of the EPA under the Authority of 15 U.S.C. 2607(d) (40 CFR 716.120). Any manufacturer of any of the three technical mixtures was required to submit production, use, and exposure data for the compound by March 12, 1990 or upon request of the TSCA Interagency Testing Committee under the authority of 15 USC 2607(a) (40 CFR 712.30). Producers of brominated aromatic compounds are required to report any new compounds or significantly new uses for existing compounds, which also includes protection in the workplace, hazard communication programs releases to water, and industrial, commercial, and consumer activities (40 CFR 721.775).

Other than these general provisions, rules and proposed rules have been set forth by the EPA in the *Federal Register* over the last 13 years, which have included one or both of the three technical brominated diphenyl ether flame retardant mixtures currently produced (OBDE and PeBDE) or imported (DeBDE) in the United States.

In 1987, the U.S. EPA promulgated a testing and reporting rule under sections 4 and 8 of TSCA for compounds that may be contaminated with polybrominated dibenzo-p-dioxins (PBDDs) or polybrominated dibenzofurans (PBDFs) (U.S. EPA, 1987; cited by Johnson et al., 1990). This was based on the fact that the PBDDs and PBDFs are highly toxic at trace levels and

that there are insufficient data to determine the risk of exposure to human health and the environment. The testing required quantitation to the parts-per-billion level. Eight analytical method submissions were submitted for PeBDE, OBDE, and DeBDE and the EPA judged the testing procedures used to be inadequate due to the lack of standard reference materials, analyte lability, insolubility, and removal of interferences, particularly brominated diphenyl ethers (U.S. EPA, 1989; cited by Johnson et al., 1990). As a result of the shortfalls in testing, an industry consortium (Brominated Flame Retardants Industry Panel or BFRIP) was formed to share methods development and analytical costs associated with responding to the Rule (Remmers et al., 1991). As of 1991, analytical methods had not been established to comply with the EPA Rule.

In 1989, the TSCA Interagency Testing Committee (ITC) designated technical penta-, octa-, and decabromodiphenyl ether along with two other brominated flame retardants, hexabromocyclododecane (CASRN 3194-55-6) and 1,2-bis(2,4,6-tribromophenoxy)ethane (CASRN 37853-59-1) for priority consideration for proposing test rules under section 4(e) of TSCA (U.S. EPA ITC, 1989). They were recommended because of substantial production and environmental persistence or for the potential to cause adverse health effects. Further studies proposed included chemical and environmental fate, health effects (acute and chronic), and ecological effects.

In 1994, the EPA issued a Proposed Rule on the management of wastes generated from the production of technical OBDE and DeBDE. At that time the EPA proposed not to list waste streams from the production of OBDE and DeBDE as hazardous (U.S. EPA, 1994, 59 FR24530). This would allow for the disposal of solid wastes that contained low levels of toluene and PBDFs (~4.4 ppb) into Class D landfills (those not regulated as hazardous under RCRA). Also, wastewaters could be deep well injected as in the past. This decision was based on estimated one-in-a-million health risk level and oral reference dose (RfD) of 0.1 mg/L and 0.003 mg/kg/day, respectively, for technical OBDE extrapolated from a single rat study (Carlson, 1980) using the induction of liver enzymes and liver histopathology as endpoints. Assuming an upper bound leachate concentration of 0.2 mg/L based on the solubility of technical OBDE and a dilution factor of 100 to the nearest well, the concentration of technical OBDE would be below levels of concern. Due to the low expected solubility of OBDE (0.2 mg/L) and low 2,3,7,8-TCDD equivalent of brominated dibenzofurans detected in wastewater streams from OBDE production, it was decided not to list waste streams from OBDE production as hazardous. However, in the Integrated Risk Information System (IRIS) database maintained by the EPA the confidence in the RfD based on this single study was listed as low (U.S. EPA, IRIS, 1990). This Proposed Rule was made final and made effective on November 4, 1998 (U.S. EPA, 1998).

9.0 TOXICOLOGICAL DATA

9.1 General Toxicology

Toxicological summaries for technical OBDE and PeBDE have been prepared in recent reviews, which cite the majority of the studies appearing in the following sections (Hardy, 1999a,b, 2000c; Hooper and McDonald, 2000). Toxicology testing by the Chemical Manufacturers Association (CMA) Brominated Flame Retardant Industry Panel (BFRIP) continues on the two technical polybrominated diphenyl ethers per industry's commitments under

the Organization for Economic Cooperation and Development (OECD) Voluntary Industry Committee (VIC) and European Union (EU) risk assessment programs (Hardy, 1999a). The potential for toxicity is inversely related to the degree of bromination the greater the degree, the lesser the toxicity (Hardy, 1999b, 2000c). DeBDE, which has both aromatic rings fully brominated (thus preventing the two rings from rotating into or occupying a coplanar configuration due to steric hindrance by the bromine atoms in the ortho positions), had very slight adverse effects in chronic studies using high doses (Hardy, 1999b, 2000a,c). (See also Section 10.0, Decabromodiphenyl Ether.)

9.1.1 Human Data

No human studies of the effects of technical PeBDE or OBDE or specific TeBDE, PeBDE, or HxBDE congeners are available (IPCS, 1994).

Preliminary results of a medical examination program involving company workers in a resin-compounding operation showed a potential adverse trend of thyroid stimulating hormone (TSH) results exceeding the upper limit of the reference range (0.4-4) in nine (TSH results range: 3.1-7.6) of 42 individuals exposed to the processing environment and in one employee (TSH: 5.2) from a workforce of 15 not exposed to the processing environment (General Electric Co., 1990). Test results were in the borderline hypothyroid range. The possibility of a workplace association was related to the use of brominated flame retardants such as OBDE. Test results for the same samples from the Mayo Clinic reference laboratory, however, did not support the elevated TSH screening trend. Only two employees with a TSH greater than the upper limits of the reference range (0.4-5.5) were identified one in the exposed group with a TSH of 7.3 and one in the control group with a TSH of 9.5.

In a study of 34 male production workers (29 of whom were extruder operators) and eight technical support personnel potentially exposed to polybrominated dibenzo-*p*-dioxins (PBDDs) and furans (PBDFs) during production of resins containing PBDEs, no definitive associations between liver, blood lipid, thyroid, or immunological variables and exposure to brominated dioxins or blood lipid concentrations of 2,3,7,8-TBDD (ND to 475 parts per trillion [ppt]) were found (Ott and Zober, 1996). Five years later, however, two cases of digestive tract neoplasms were reported within this group and an additional case of digestive tract neoplasm in a technician who performed analyses in support of the production operation (Zober and Ott, 1997). The two who worked as extruder operators throughout the period of PBDE use had squamous cell carcinoma of the esophagus or tubular adenoma of the rectum. Their 2,3,7,8-TBDD blood lipid concentrations in 1989 were 527 and 425 ppt, respectively. The technician had an adenocarcinoma of the duodenum; postmortem measurements found no detectable 2,3,7,8-TBDD concentration in blood lipids.

In a Swedish study of female and male cancer patients, an association between adipose tissue levels of TeBDE and the risk of non-Hodgkin's lymphoma was reported (Hardell et al., 1998).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

9.1.2.1 Absorption of Selected PBDEs

The uptake of BDE-47 is very high in aquatic organisms (e.g., fish and mussels), but is not as high in rats and mice. The uptake of more highly brominated compounds is much lower. When pike were fed trout injected with ^{14}C-labelled BDE-47, 96% of the dose was initially absorbed. In rats gavaged with ^{14}C-labelled BDE-47 (30 µmol/kg), 14% of the administered dose of radioactivity was found in the feces and <0.5% was found in the urine; but absorption of ^{14}C-labelled BDE-99 was much lower as made evident by the higher percentage of the radioactive dose excreted in the feces (43%) and the urine (1%) (rn and Klasson-Wehler; 1998; Hakk et al., 1999).

The uptake rates of BDE-47, BDE-99, and BDE-153 were compared to the uptake rates of PCBs with similar octanol-water partition co-efficient (K_{ow}) (Gustafsson et al., 1999). The BDE-47 uptake rates in mussels were 6-8 times higher than for PCBs 52 and 77, and the uptake rate of BDE-99 was 5-7 times higher than for PCBs 118 and 153.

An effective molecular cross section greater than 9.5 is expected to limit the diffusion of hydrophobic substances absorbed through the intestine (Opperhuizen et al., 1990; cited by Kierkegaard et al., 1999b). The effective molecular cross-sections for BDE-47, BDE-99, and BDE-153 are 8.1, 9.6, and 9.6 , respectively. This may help explain why the absorption of BDE-99 and BDE-153 is considerably less than absorption of BDE-47; however, it does not explain why absorption of BDE-99 and BDE-153 occurs. The above model is only true for passive diffusion and does not take into account active membrane protein-mediated transport of PBDEs in the intestine, which may be higher than once expected (Burreau et al., 1997).

It was thought that the absorption of BDE-47 may be associated with bile acids since the amount of radioactivity in the 72-hour fecal collection of bile duct-cannulated rats was twice as much as the radioactivity recovered in the feces of normal rats (Hakk et al., 1999).

9.1.2.2 Distribution of Selected PBDEs

After absorption, the lipophilic PBDEs are distributed by the blood and preferentially deposited in lipophilic tissue and the liver. In male rats gavaged with ^{14}C-labelled BDE-47 (30 µmol/kg), the concentration of radioactivity in adipose tissue was 70 times greater than in other tissues on a fresh-weight basis 5 days after a single exposure; however, mice dosed under the same conditions had only a 10-fold increase in adipose tissue radioactivity on a fresh-weight basis compared to other tissues (rn and Klasson-Wehler, 1998). Interestingly, on a lipid-weight basis the amounts in adipose tissue of rats and mice were similar, possibly indicating a saturation point of the PBDEs in lipophilic tissues. BDE-47 is the predominant congener detected in all tissue samples of rats in studies reviewed, followed by BDE-99, BDE-153, and BDE-154. The highest concentrations of BDE-47 in fish are also found in the lipid rich tissues (Burreau et al., 1997, 2000a).

Plasma concentrations of radioactivity were very low in rats and undetectable in mice 5 days after an initial oral dose (rn and Klasson-Wehler, 1998). Ninety-eight percent of the detected radioactivity was found in the organic phase and only 2% was found in the phenolic phase, indicating relatively small amounts of metabolites present in the blood. Because of the

higher concentrations found in tissue when compared to blood, it appears that the PBDEs are sequestered in the tissues according to their lipid content, until some point of saturation is reached.

In Baltic salmon (*Salmo salar*), mean muscle concentrations of BDE-47 (~200 ng/g lipid) were the same as mean blood concentrations (Asplund et al., 1999b).

It is possible that irreversible binding of PBDE metabolites to macromolecules in tissue may occur as it does with DDT metabolites; however, this has not been shown conclusively. In one distribution study, pike dosed with ^{14}C-labelled BDE-47 still contained radioactivity in some tissues after extraction, which could have been radioactivity irreversibly bound to macromolecules (Burreau et al., 2000a).

9.1.2.3 Metabolism of Selected PBDEs

Methoxy- and hydroxy-derivatives of PBDEs have been detected in several aquatic and mammalian species (Asplund et al., 1999b). Their presence in relatively high concentrations in biota (mostly sponges and algae) and their similarity to the PBDEs indicate that large quantities may be present in the environment. In herring collected between 1981 and 1988 off the Swedish coast, concentrations of methoxylated TeBDE (MeO-TeBDE) were higher than the concentrations of unmethoxylated TeBDE (Haglund et al., 1997). This could mean that fish are efficient metabolizers of PBDEs or perhaps there is another source of MeO-PBDEs in the environment. As far as is known, MeO-BDE and OH-BDE are not commercially produced. It is possible that OH-BDE could be formed as a contaminant of polybromophenol production, but this has not yet been proven. MeO-PBDEs may be formed by microbial methylation in the environment and they have been found in sponges and algae.

Aquatic organisms appear to have a higher ratio of MeO-TeBDEs and MeO-PeBDEs to PBDEs when compared to rats, mice, and humans. The ratio of total MeO-TeBDE/total TeBDE in whole herring, salmon muscle, ringed seal blubber, and gray seal blubber collected from the Baltic was 0.94, 0.15, 0.57, and 0.25. The rat was less capable of metabolizing BDE-47 after oral ingestion than the mouse (rn and Klasson-Wehler, 1998). In a study of one 70-year-old Swedish man, no MeO-TeBDE or MeO-PeBDE was found (LOD = 0.1 ng/g lipid weight), but TeBDE and PeBDE were found (9.1 and 2.9 ng/g lipid weight, respectively) (Haglund et al., 1997).

MeO-BDEs were present in the neutral fraction of blood plasma in Baltic salmon that were comparable to those of the PBDE congeners (Asplund et al., 1999b). In addition to MeO-PBDEs, OH-PBDEs with 4 or 5 bromine atoms/molecule were also present in blood plasma. The MeO-PBDEs have the same chromatographic properties as the OH-PBDEs, which may indicate that the two classes of compounds are interconvertible by methylation/demethylation reactions.

Several OH-PBDEs have been determined as metabolites of mice and rats *in vivo* (Hakk et al., 1999; rn and Klasson-Wehler, 1998). These consisted of mono- and dihydroxylated congeners. MeO-PBDE was determined to be a natural product of algae (*Cladophora fascicularis*) collected from Miyako Island, Japan (Kuniyoshi et al., 1985; cited by Asplund et al., 1999b). It is interesting that one compound found in *C. fascicularis*, 2-(2«,4«-

dibromophenoxy)-4,6-dibromo-anisole, has also been found in Baltic salmon (Asplund et al., 1999b).

All hydroxylated and methoxylated PBDEs found in all aquatic species examined show hydroxylation/methoxy substitution on either one or both rings on the carbon(s) ortho to the diphenyl ether linkage on either one or both rings. For a list of these compounds and their structures see **Table 12**.

The polybrominated phenoxyphenols formed from the hydroxylation of the PBDEs have been found to compete with thyroxine for binding to the thyroxine-transporting protein transthyretin (TTR) (Meerts et al., 1998a). Pentabromophenol has been shown to competitively inhibit the binding of thyroxine to TTR, with a relative binding potency 20 times that of thyroxine (Brouwer and Meerts, 2000; cited by Bergman, 2000).

The biological debromination of the PBDEs may be possible. The dehalogenation of organic brominated compounds can be expected to proceed more easily than for chlorinated compounds since the carbon-bromine bond is weaker than the carbon-chlorine bond (Wakefield, 1989; cited by Burreau et al., 2000a). The debromination of hexabromobenzene by the rat after oral exposure has been shown (Yamaguchi et al., 1988; cited by Burreau et al., 2000b). Two debrominated monomethoxy metabolites were reported after oral dosing of 6 Sprague-Dawley rats with ^{14}C-labelled BDE-99 (Hakk et al., 1999). Fish undergoing depuration for 71 days after receiving technical decabromodiphenyl ether (7.5-10 mg/day) for 49 days, exhibited higher ratios of BDE-154 to technical DeBDE over time which could have been due to debromination (Kierkegaard et al., 1999b). The biotransformation of PBDEs by reductive dehalogenation could be mediated by the cytochrome P-450 system (Sipes and Gandolfi, 1986; cited by Burreau et al., 2000a).

Two brominated dioxins were tentatively characterized in the sponge *Tedania ignis* that may have resulted from the conversion of 3,5-dibromo-2-(2«,4«-dibromophenoxy)phenol, a PBDE derivative found in sponges (Gribble, 1999).

9.1.2.4 Elimination of Selected PBDEs

The depuration rates of hydrophobic compounds, such as the PCBs, are negatively correlated with the log K_{ow}; however, the depuration rates of PBDEs do not follow this pattern. and appear to be independent of the log K_{ow} (Gustafsson et al., 2000). The theoretical half-lives of BDE-47, BDE-99, and BDE-153 in mussels are 7.7, 5.6, and 8.1 days, respectively (Gustafsson et al., 1999). The rate of elimination of BDE-99 and BDE-153 was higher than expected in mussels based on the K_{ow}.

The half-life of 95% pure DeBDE was found to be less than 24 hours in a 103-week study of rats dosed orally in feed, with more than 99% of the dose being excreted in the feces in 72 hours (El Dareer et al., 1987; cited by Hardy, 2000a; NTP, 1986). DeBDE (BDE-209, purity not provided) has been reported to have a half-life in human serum of 6.8 days (95% CI), ranging from 3 to 26 days (Patterson et al., 2000). Male and female Wistar rats dosed with a single oral administration (300 mg/kg) of a technical PeBDE mixture (Bromkal 70) had mean half-lives for two HxBDE congeners of 44.6 and 90.0 days in female rats and 55.1 and 119.1 days, respectively, in male rats (Von Meyerinck et al., 1990; cited by IPCS, 1990).

The majority of the ^{14}C-labelled doses of BDE-47 and BDE-99 dose was excreted unchanged in the feces of rats and mice, with BDE-99 having higher fecal elimination. Fecal excretion of BDE-47 was greater in mice than in rats. Sprague-Dawley rats dosed with ^{14}C-labelled BDE-47 eliminated 14% of the dose in the feces during 120-hour fecal collection, while 33% of a similar dose was found in feces of mice (rn and Klasson-Wehler, 1998). More radioactivity (43% of the dose) was found in the feces of rats after administration of ^{14}C-labelled BDE-99 (Hakk et al., 1999).

Urinary excretion of radioactivity after gavage with ^{14}C-labelled BDE-99 in Sprague-Dawley rats was 0.2 ± 0.01% of the dose (Hakk et al., 1999). In rats, administration of [^{14}C]-labelled BDE-47 resulted in the urinary excretion of 0.5 ± 0.02% of the dose after collection for 120 hours (rn and Klasson-Wehler, 1998). This is in contrast to the increased urinary excretion of radiation after administration of ^{14}C-labelled BDE-47 to mice (33 ± 0.4% of the dose in 120 hours). This shows that there are interspecies variations in the urinary excretion of PBDEs.

The fact that the fecal elimination of BDE-99 in rats is more than twice that of BDE-47, while urinary excretion is the same for both compounds, provides evidence for the greater bioavailability of BDE-47 compared to BDE-99.

The binding of ^{14}C-labelled BDE-99 and its metabolites to urinary and biliary proteins was studied in six conventional Sprague-Dawley rats and 10 bile-duct-cannulated Sprague-Dawley rats after a single oral dose of 2.2 mg/rat in peanut oil.

Table 12. Possible Metabolites from Aquatic Organisms That Are Derivatives of PBDEs[a]

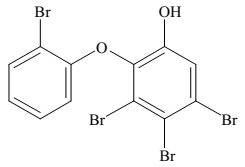
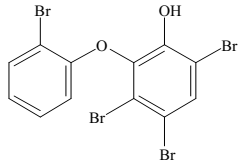
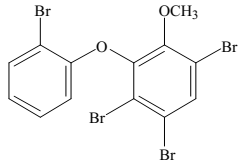
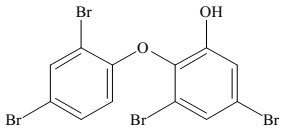
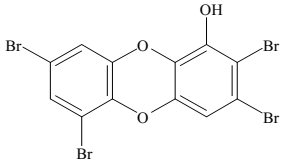
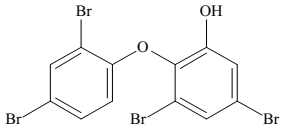
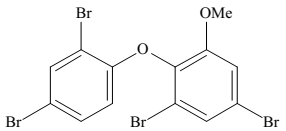
Species/Location	Structure	Corresponding PBDE	Reference
Marine sponge (*Dysidea herbacea*)/ West Sumatra, Indonesia		BDE-41	Handayani et al. (1997)
Marine sponge (*Dysidea herbacea*)/ West Sumatra, Indonesia		BDE-43	Handayani et al. (1997)
Marine sponge (*Dysidea herbacea*)/ West Sumatra, Indonesia		BDE-43	Handayani et al. (1997)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-47	Fu and Schmitz (1996); Fu et al. (1995)
Marine Sponge (*Tedania ignis*)/ location n.p.		BDE-47	Gribble (1999)
Baltic salmon (*Salmo salar*); collected near Dal lven in 1995		BDE-47	Asplund et al. (1999b)
Baltic salmon (*Salmo salar*); collected near Dal lven in 1995		BDE-47	Asplund et al. (1999b)

Table 12. Possible Metabolites from Aquatic Organisms That Are Derivatives of PBDEs[a] (Continued)

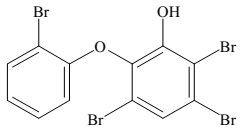
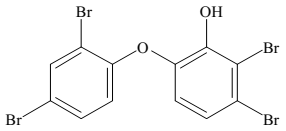
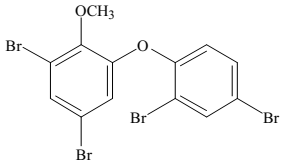
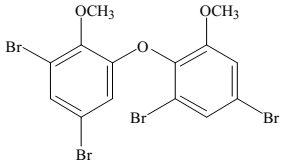
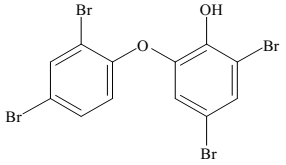
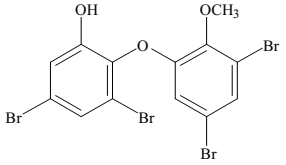
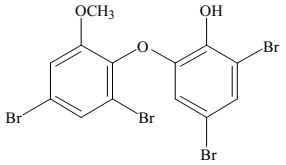
Species/Location	Structure	Corresponding PBDE	Reference
Marine sponge (*Dysidea herbacea*)/West Sumatra, Indonesia		BDE-48	Handayani et al. (1997)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-66	Fu and Schmitz (1996)
Marine sponge (*Dysidea* sp.)/Queensland and n.p.		BDE-68	Cameron et al. (2000); Gribble (1998)
Marine sponge (*Dysidea* sp.)/Queensland and Chuuk State, Micronesia		BDE-68	Cameron et al. (2000)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia; Symbiotic Sponge Cyanobacteria isolated from *Dysidea herbacea*		BDE-68	Fu and Schmitz (1996); Fu et al. (1995); Handayani et al. (1997); Unson et al. (1994)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-68	Fu et al. (1995)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-68	Fu et al. (1995)

Table 12. Possible Metabolites from Aquatic Organisms That Are Derivatives of PBDEs[a] (Continued)

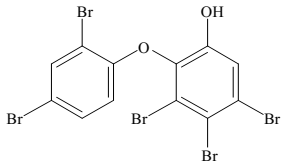
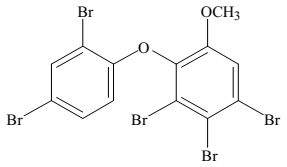
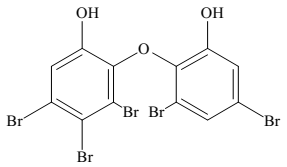
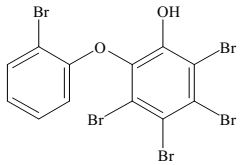
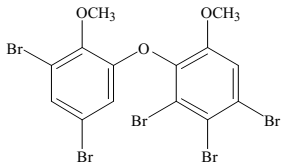
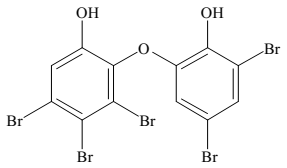
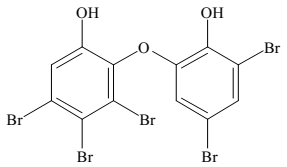
Species/Location	Structure	Corresponding PBDE	Reference
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-85	Fu and Schmitz (1996); Fu et al. (1995)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-85	Fu and Schmitz (1996)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-85	Fu et al. (1995)
Marine sponge (*Dysidea herbacea*)/West Sumatra, Indonesia		BDE-86	Handayani et al. (1997)
Marine sponge (*Dysidea* sp.)/Queensland and Chuuk State, Micronesia		BDE-108	Cameron et al. (2000); Fu et al. (1995)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-108	Fu et al. (1995)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-108	Fu et al. (1995)

Table 12. Possible Metabolites from Aquatic Organisms That Are Derivatives of PBDEs[a] (Continued)

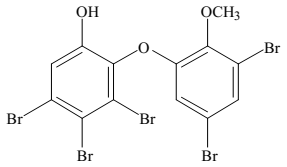
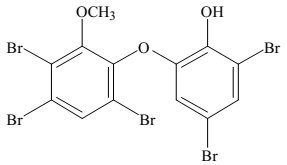
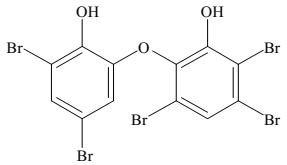
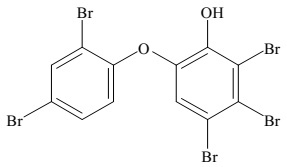
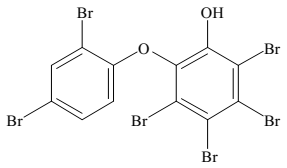
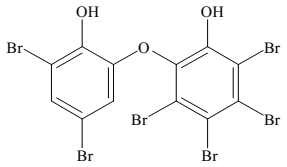
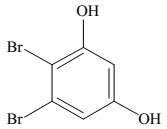
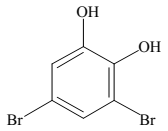
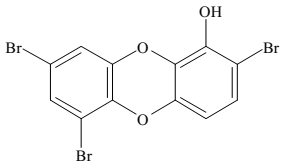
Species/Location	Structure	Corresponding PBDE	Reference
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-108	Fu et al. (1995)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-120	Fu et al. (1995)
Marine sponge (*Dysidea* sp.)/Queensland and Chuuk State, Micronesia		BDE-120	Cameron et al. (2000); Fu et al. (1995)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia		BDE-123	Fu and Schmitz (1996); Fu et al. (1995)
Marine sponge (*Dysidea herbacea*)/West Sumatra, Indonesia		BDE-137	Handayani et al. (1997)
Marine sponge (*Dysidea* sp.)/Queensland and Chuuk State, Micronesia		BDE-159	Cameron et al. (2000); Fu et al. (1995)
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia			Fu et al. (1995)

Table 12. Possible Metabolites from Aquatic Organisms That Are Derivatives of PBDEs[a] (Continued)

Species/Location	Structure	Corresponding PBDE	Reference
Marine sponge (*Dysidea* sp.)/Chuuk State, Micronesia			Fu et al. (1995)
Marine Sponge (*Tedania ignis*)/location n.p.			Gribble (1999)

[a] Although these compounds resemble the PBDE flame retardants there appears to be no clear evidence in the literature that these are metabolites from exposure to PBDEs. In all studies reviewed no one reported if the respective PBDE that corresponds to each congener was detected in the local environment. In all cases the authors appear to infer that these compounds are naturally produced by the organism. Abbreviations: n.d. = not determined; n.p. = not provided

Table 13. Metabolism of PBDEs in Experimental Animals and Humans

Subjects	Compound/Route	Dose	Exposure Period	Remarks	Analytical Techniques and Limit of Detection	References
6 conventional and bile duct cannulated male Sprague-Dawley rats	2,2«,4,4«,5-Pentabromo-[^{14}C]diphenyl ether (BDE-99)/gavage	2.2 mg/rat in peanut oil	72 hr	Feces was the major route of elimination in the rat (43% of dose in conventional rats and 86% in bile-duct cannulated rats). The authors concluded that bile salts are necessary for intestinal uptake of BDE-47. Cumulative urinary excretion was 1% in conventional rats and 0.3% in bile-duct cannulated rats. Only 76% of ^{14}C was recovered in the 72-hr feces of conventional rats. Less than 10% of the dose was detected in the feces as two monomethoxy and two debrominated monomethoxy metabolites. Most of the ^{14}C in fecal extracts was present as parent compound. Two monohydroxy- and dihydroxy-PeBDE metabolites were found in the bile, and two thio-substituted PeBDEs were suggested as metabolites. No glucuronide or sulfate conjugates were detected in the bile. BDE-47 was preferentially distributed (as ^{14}C) in adipose tissue, blood, carcass, and GI tract. The skin held the highest concentration of ^{14}C in the carcass. The majority of radioactivity was found in lipophilic tissues (adipose tissue, skin, and adrenals). This is in contrast to 2,3,7,8-TCDD, which is distributed to the liver (55% of dose), where specific dioxin-binding proteins exist. Apparently, BDE-47 does not induce or serve as a suitable ligand for hepatic proteins. On some occasions, the metabolites found in the feces reverted back to the parent BDE-47 compound.	Liquid scintillation counting performed on urine, bile, air dried feces, and blood. HPLC and TLC were performed on the feces. GC/MS was used to determine metabolites in fecal extracts and in bile.	Hakk et al. (1999)

Table 13. Metabolism of PBDEs in Experimental Animals and Humans (Continued)

Subjects	Compound/Route	Dose	Exposure Period	Remarks	Analytical Techniques and Limit of Detection	References
4 male Sprague-Dawley rats	^{14}C-labelled 2,2«,4,4«-TeBDE (BDE-47)/gavage	30 µmol/kg bw in corn oil	5 d	The metabolism and excretion of BDE-47 in the rat was much slower and incomplete when compared to that of the mouse. The percentage of the dose found in the feces was 14 – 3% and in the urine, <0.5 – 0.02%. In the feces, the majority of ^{14}C was found in the lipid fractions (GPC-LF). At day 3-5, less than 10% of the radioactivity in feces was water-soluble. After 5 days, 11% of the amount of radioactivity in the feces was associated with lipids, 3% was water-soluble, 7% was not extracted, and 79% was the parent compound and non-conjugated metabolites. Five hydroxylated metabolites were detected but not specifically identified. A sixth metabolite was tentatively identified as a methylthio-substituted BDE-47. The concentration of ^{14}C in adipose tissue was 70 times greater on a fresh-weight basis than in other tissues and 3 to 5 times more on a lipid-weight basis. All five of the hydroxylated BDE-47 metabolites were found in liver extract while only two were found in the lung. Levels of ^{14}C were low in plasma (0.76 nmol/g) with most being the parent compound in the lipid phase (98% of plasma ^{14}C). Two metabolites were found in the phenolic fraction (2% of plasma ^{14}C).	Feces, tissues, plasma, and urine were analyzed by GC/MS. Radioactivity measurements were performed by scintillation counting. Fecal samples were analyzed prior to and after derivatization with diazomethane.	rn and Klasson-Wehler (1998)

Table 13. Metabolism of PBDEs in Experimental Animals and Humans (Continued)

Subjects	Compound/Route	Dose	Exposure Period	Remarks	Analytical Techniques and Limit of Detection	References
6 conventional male Sprague-Dawley rats and 10 bile duct-cannulated rats	2,2«,4,4«,5-Pentabromo [^{14}C]-diphenyl ether (BDE-99); oral	2.2 mg/rat (1.0 µCi)	single dose	Urine and bile were collected every 24 hours for 3 days; however, due to low levels of radioactivity in daily samples all three 24-hour collections were pooled. Cumulative elimination of radioactivity into conventional and cannulated urine was less than 1% of the dose. Cumulative biliary elimination was slightly higher (3.7%). In the 72-hour urine collection from conventional rats, 6.3% of the radioactivity in the urine was bound to protein ($\alpha 2_u$-globulin exclusively). No radioactivity in the urine of cannulated rats was associated with proteins probably because most of the radioactivity in urine is in polar metabolites that do not require protein for transport. In cannulated rats, 28.4% of the radioactivity was associated with proteins in 24-hour bile collections and 46.9% was associated with proteins in 72-hour bile collections. The protein thought to be responsible for binding in bile is a 79-kDa protein that has been associated with polyhalogenated aromatic compounds (dioxins) and their metabolites in previous rat studies (Weiner and Larsen, 1997). Metabolism of BDE-99 into water-soluble metabolites is low, possibly being restricted by stereochemistry.	Excreta was separated with column chromatography; protein analysis by SDS-PAGE, Western Blot, and TLC analysis	Larsen et al. (1999)
16 male C57B$_l$ mice	^{14}C-labelled 2,2«,4,4«-TeBDE (BDE-47)/ oral	30 µmol/kg b.w. in corn oil	5 d	The mouse excreted approximately 20 – 4% of the TeBDE dose in feces and 33 – 0.4% in urine during the 5-day collection period. The non-extractable and water-soluble ^{14}C in feces was higher in the mouse when compared to the rat (see above study). The same 5 hydroxylated compounds that were identified in the rat were found in the mouse feces. The adipose tissue had a ten-fold higher concentration of ^{14}C-BDE-47 when compared to	Feces, tissues, plasma, and urine were analyzed by GC/MS. Radioactivity measurements were performed by scintillation counting. Fecal samples were analyzed prior to and after derivatization with diazomethane.	rn and Klasson-Wehler (1998)

Table 13. Metabolism of PBDEs in Experimental Animals and Humans (Continued)

Subjects	Compound/Route	Dose	Exposure Period	Remarks	Analytical Techniques and Limit of Detection	References
5 Pike (*Esox lucius* L.), sex n.p.	^{14}C-labelled BDE-47 injected into dorsal muscle of live brown trout and immediately fed to pike every 18 days	between 0.21 and 0.24 µCi/g (fresh weight) dissolved in lipid extract from rainbow trout	9, 18, 36 , and 65 days	Sagittal whole-body sections were taken from each fish. Radioactivity was present in all tissues of the pike except for the backbone. The fish exposed for 9 and 18 days exhibited the highest levels of radiation in the liver, perivisceral adipose tissue (PT), vertebrate-surrounding tissue (VT), and the eye capsule with lower levels seen in the gall bladder. Intermediate levels were seen in the brain, spinal cord, heart, and kidney. The lowest levels were present in muscle tissue, spleen, and gills. The fish exposed for 36 d showed high levels of radioactivity in liver, PT, and VST. All other tissues showed a decrease in radioactivity, most notably the gall bladder and eye capsule. The fish exposed for 65 days still had high radioactivity in the PT and VT that were almost unchanged from that seen in the fish exposed for 9 d. Liver radioactivity had declined considerably to levels between the PT and VT and the rest of the body. No good images of the spinal cord were obtained at 36 and 65 d. Levels of radioactivity in the liver were most likely due to metabolic action since pike have livers with relatively low lipid content when compared to other fish, such as carp, and also because concentrations had decreased by 65 d. The unexpected high amounts of radioactivity in the heart muscle was attributed to the high blood perfusion of the tissue. It appears that most of the BDE-47 dose resisted transformation in pike due to nondetectable clearance in the lipid-rich PT and VT and because of the uniform distribution of radioactivity along the length of the kidney. No hydrophilic metabolites were detected. Hydrophobic metabolites, less hydrophobic than BDE-47, are formed in the liver. Distribution is by hydrophobic carriers in the blood preferentially to lipid-rich tissues.	Autoradiography of saggital whole-body sections; scintillation counting for absorption of radioactivity; extraction of several sections with polar and non-polar solvents to determine covalent binding of BDE to macromolecules.	Burreau et al. (2000a)

Table 13. Metabolism of PBDEs in Experimental Animals and Humans (Continued)

Subjects	Compound/Route	Dose	Exposure Period	Remarks	Analytical Techniques and Limit of Detection	References
15 Pike (*Esox lucius* L.), sex n.p.	5 PCBs, 4 PCNs, and 3 PBDEs (BDE-47, BDE-99, and BDE-153) injected into dorsal muscle of live brown trout and immediately fed to pike every 18 days	900 ng of each substance	at least 9 days	The lipid content (wet weight) of the pike was about 1.5% and the trout was 3.0%. The gastrointestinal tract was removed to exclude unabsorbed substances. The mean amounts BDE-47, BDE-99, and BDE-153 determined in whole fish exposed to all compounds were 950 – 96 ng, 454 – 39 ng, and 294 – 3 ng, respectively. Two unexposed pike had a mean BDE-47 total body concentration of 3 ng and 3 trout had whole-body amount s of BDE-47 and BDE-99 equal to 52 – 8 ng and 5 – 0.4 ng, respectively. The uptake efficiency of the compounds was calculated by dividing the total amounts in the 15 pike by the total exposure amounts. The uptake efficiencies of BDE-47, BDE-99, and BDE-153 were approximately 90%, 60%, and 40%, respectively. Since halogenated organic compounds (HOC) can be expected to be associated with lipids and fatty acids, their absorption in the intestine may be mediated by proteins in the cell membrane of epithelial cells lining the intestine. Because of the association of lipids with HOC, the lipid content of the diet may influence the absorption of the PBDEs. The absorption of PBDEs is probably due to diffusion and cell membrane protein-mediated transport. When relying on an empirical model of dietary uptake of hydrophobic compounds, it was found that mediated absorption may be dependent on size, with compounds between 400 and 500 g/mol having higher mediated intestinal absorption; however, this has not yet been proven.	Pike were homogenized and extracted with acetone/hexane; clean-up with SGC; analysis with GC/MS	Burreau et al. (1997)

Table 13. Metabolism of PBDEs in Experimental Animals and Humans (Continued)

Subjects	Compound/Route	Dose	Exposure Period	Remarks	Analytical Techniques and Limit of Detection	References
Rainbow trout (number n.p.)	Technical decabromodiphenyl ether (DeBDE); oral in diet	7.5-10 mg/day	16, 49, and 120 d; one group was fed DeBDE for 49 d and control diet for 71 d	Concentration of PBDEs in liver and muscle were reported in a wet weight basis due to fluctuation in lipid content of tissues over the 120 d feeding period. Low amounts of DeBDE (~0.005%) were absorbed by the trout as determined by concentrations in tissue. This may have been due to the debromination of DBDE which may have occurred since fish undergoing depuration experienced higher ratios of BDE-154 to DeBDE over time. Nona-, Octa-, and hepta-BDE isomers that were impurities in the technical DeBDE were detected in muscle and liver extracts. Concentrations of HxBDE and nona-BDE in muscle and liver increased with longer exposure. Due to the lack of reference standards for specific congeners and large differences in response of PBDE congeners, only a rough estimation of unknown congeners could be made. Concentrations of BDE-44, -47, and-99 in muscle decreased with longer exposure time; but concentration of these isomers in liver increased after 120 days of exposure probably due to the decrease in muscle lipids over time. However, BDE-153 and -154 increased in muscle and liver as the length of exposure increased.	Tissues were homogenized, solvent extracted or centrifuged and solvent extracted; Analysis with GC/MS(ECNI); LOD in muscle = 0.6 ng/g fresh weight, LOD in liver = 5 ng/g fresh weight	Kierkegaard et al. (1999b)
Samples from 2- to 5-yr-old herring, salmon muscle, and gray and ringed seals (collected between 1981 and 1988)	Environmental exposure	na	na	This study revealed that fish and seals have high concentrations of methoxylated PBDEs when compared to PBDEs. The total concentrations of PBDEs and MeO-PBDEs in 5-yr-old herring, salmon muscle, ringed seal, and gray seal blubber were 36, 298, 380, 468 ng/g lipid and 34, 47, 220, 121 ng/g lipid, respectively, indicating biomagnification.	GC/MS (ECNI)	Haglund et al. (1997)

Table 13. Metabolism of PBDEs in Experimental Animals and Humans (Continued)

Subjects	Compound/Route	Dose	Exposure Period	Remarks	Analytical Techniques and Limit of Detection	References
70-yr-old human male from Sweden	Normal environmental exposure	na	na	No methoxylated TeBDEs or PeBDEs were detected in the adipose tissue sample, but two TeBDE and PeBDE congeners were found (9.1 and 2.9, respectively).	GC/MS (ECNI)	Haglund et al. (1997)

Abbreviations: BB-153 = 2,2«,4,4«5,5«-Hexabromobiphenyl; BDE-47 = 2,2«,4,4«-TeBDE; BDE-99 = 2,2«,4,4«,5-PeBDE; BDE-100 = 2,2«,4,4«,6-PeBDE; BDE-153 = 2,2«,4,4«5,5«-HxBDE; BDE-154 = 2,2«,4,4«5,6«-HxBDE; BDE-209 = 2,2«,3,3«,4,4«5,5«,6,6«-DecaBDE; CB-153 = 2,2«,4,4«5,5«-Hexaclorobiphenyl;ELCD = electrolytic conductivity; GPC = gel permeation chromatography; n.p. = not provided; n.s. = not specified; SGC = silica gel chromatography

9.1.3 Acute Exposure

Acute toxicity values for technical PeBDE and technical OBDE are presented in **Table 14**. The details of studies discussed in this section are presented in **Table 15**. [No acute exposure studies are available for TeBDE and HxBDE (IPCS, 1994).]

Table 14. Acute Toxicity Values for Polybrominated Diphenyl Ethers

Route	Species (sex and strain)	LD_{50}/LC_{50}	Reference
Technical PeBDE			
inhalation	rat (sex and strain n.p.)	LC_{50} >200 mg/L (>200 g/m^3)	Kopp (1990); cited by IPCS (1994)
oral	rat (M, Wistar)	LD_{50} = 7400 mg/kg bw	Great Lakes Chem. Corp. (undated a); cited by IPCS (1994)
	rat (F, Wistar)	LD_{50} = 5800 mg/kg bw	
	rat (M and F, Wistar)	LD_{50} = 2640 mg/kg (Tardex 50)	Dow Chem. Co (1977); ISC Chem. Ltd. (1977)
	rat (M and F, Wistar)	LD_{50} = 3350 mg/kg (Tardex 50L)	
percutaneous	rat (M and F, Wistar)	LD_{50} >11,000 mg/kg (Tardex 50L)	
Technical OBDE			
inhalation	rat (sex and strain n.p.)	LC_{50} >50 mg/L (>50 g/m^3)	US EPA (1986); cited by IPCS (1994)
oral	rat (sex and strain n.p.)	LD_{50} > 28 g/kg bw	Kalk (1982); cited by IPCS (1994)
		LD_{50} >5 g/kg bw	Kopp (1990); Great Lakes Chem. Corp. (1990a); both cited by IPCS (1994)
dermal	rabbit (sex and strain n.p.)	LD_{50} >2 g/kg bw	Great Lakes Chem. Corp. (1987, 1990a); cited by IPCS (1994)

Abbreviations: bw = body weight; F = female(s); LC_{50} = concentration lethal to 50% of test animals; LD_{50} = dose lethal to 50% of test animals; M = male(s); n.p. = not provided

Technical Pentabromodiphenyl Ether

In mice given DE-71 (500 mg/kg bw) orally, liver weight/body weight ratios were significantly increased (Fowles et al., 1994).

In rats, inhalation of technical PeBDE (2 mg/L) for one hour increased and then decreased motor activity, produced erythema, and caused eye squint (Great Lakes Chem. Corp., undated a; cited by IPCS, 1994). At a higher dose (200 mg/L), the same symptoms were seen plus lacrimation, salivation, and tachypnea (rapid breathing). Four days later, all animals were normal. Inhalation of emission products of technical PeBDE as Tardex 50 heated at 200 ¡C for up to four hours caused respiratory irritation and discomfort, such as occasional sneezing attacks and slight dyspnea, during exposure; behavior was normal after the test period (Dow Chem. Co.,

Table 15. Acute Exposure to Polybrominated Diphenyl Ethers

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration[a], and Observation Period	Results/Comments	Reference(s)
Technical Pentabromodiphenyl Ether (PeBDE)				
Mice, C57BL/6J, 8-wk-old, 6 F per dose group	DE-71, purity n.p.	oral; 0.8, 4.0, 20, 100, or 500 mg/kg bw in peanut oil; animals killed on day 8. Given i.p. injection of sheep erythrocytes 2 days after exposure.	Liver weight/body weight ratio was significantly increased at the highest dose.	Fowles et al. (1994)
Rats, Charles River CD, age n.p., 10 M and 10 F per dose group	technical PeBDE, purity n.p.	inhalation; 2 or 200 mg/L of aerosol mist for 1 h; observed for 14 days	At the low dose, increased and then decreased motor activity, erythema, and eye squint were observed during exposure and for the next 24 h; afterwards, animals were normal. At the high dose, the same symptoms were seen plus lacrimation, salivation, and tachypnea. At 24 and 48 h, 2 rats had nasal congestion, and after 72 h, 1 rat had respiratory congestion. From day 4 onwards, all animals were normal and showed normal body weight gain.	Great Lakes Chem. Corp. (undated a; cited by IPCS, 1994)
Rats, Wistar BK albino, age n.p., 1 M and 1 F per exposure period	Tardex 50, purity n.p.	inhalation; thermal emission products of test substance (386 g of warm [50 ¡C] mobile liquid heated to 200 ¡C) for 2.5, 4, or 6 h; observed daily for 7 days	Respiratory irritation and discomfort were observed in the rats during exposure. Afterwards, behavior of the animals was normal. During the period of 2.5 h, occasional sneezing attacks and slight dyspnea occurred in the male and female, and increased urinary secretion and periods of rapid scratching of the metal platform were exhibited by the male rat. During the exposure period of 4 h, slight dyspnea occurred in both animals, and occasional sneezing attacks and rapid scratching of the metal platform were exhibited by the male. Macroscopic examination showed many small red foci on the surface of the lungs in the female, but this was not considered toxicologically important. During the exposure period of 6 h, behavior was normal. Macroscopic examination showed slight congestion of the lungs of both rats, but this was not considered toxicologically important.	Dow Chem. Co. (1977); ISC Chem. Ltd. (1977)
Rats, Wistar, age n.p., 5 M and 5 F per dose group	Tardex 50, purity n.p.	topical application; 1.25 and 2.5 as an 11.4% and 22.8% v/v dispersion in cottonseed oil, respectively, to the occluded skin (not specified) for 24 h; observed daily for up to 14 days	Weight loss, piloerection, lethargy, slight tremors, diuresis, and chromodacryorrhea were observed by day 3. All animals were asymptomatic by day 7; one died at day 8.	Dow Chem. Co. (1977); ISC Chem. Ltd. (1977)

Table 15. Acute Exposure to Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference(s)
Rats, Wistar, age n.p., 5 M and 5 F per dose group	Tardex 50L, purity n.p.	topical application; 5.5 and 11.0 g/kg as a 50% v/v dispersion in cottonseed oil and as supplied, respectively, to the occluded shaved back and flanks for 24 h; observed daily for up to 14 days	At 5.5 g/kg, piloerection, staining around the mouth and nostrils, diarrhea, chromodacryorrhea, tremors, and hyperesthesia were observed within 3 to 4 days. At the higher dose, piloerection and slight staining were seen. Weight was reduced for all rats up to day 7. Survivors were asymptomatic by day 12.	Dow Chem. Co. (1977); ISC Chem. Ltd. (1977)
Rats, albino Charles River CD, age n.p., 5 M per dose group	technical PeBDE, purity n.p.	oral (by gavage); 50, 500, or 5000 mg/kg bw in corn oil; observed for 14 days	At the highest dose, 4 rats died within 5 days. Remaining animals showed normal body weight gain and growth.	Great Lakes Chem. Corp. (undated a; cited by IPCS, 1994)
Rats, Wistar, age n.p., 5 M and 5 F per dose group	technical PeBDE, purity n.p.	oral (by gavage); 2400, 4800, 6048, 7621, or 9600 mg/kg bw as an 80% w/v suspension in maize oil; observed for 44 days	Decreased growth, diarrhea, piloerection, reduced activity, clonic persistent tremors of the forelimbs, red staining around the eyes and nose, and continual chewing action of the jaws were observed. At autopsy, pale (mottled), enlarged, necrotic livers and multiple ulcerations of the gastric mucosa were found.	Great Lakes Chem. Corp. (undated a; cited by IPCS, 1994)
Rats, Wistar, age n.p., 5 M and 5 F per dose group	Tardex 50, purity n.p.	oral (intragastric intubation); 1.2, 2.2, 3.3, 4.4, or 8.8 g/kg as a 20% v/v dispersion in cottonseed oil; observed daily for up to 14 days	At 1.2 g/kg, only slight loss of activity was seen. At the mid and high doses, unsteady gait, tremors, convulsions, loss of activity, diarrhea, diuresis, hyperesthesia, blood staining around the mouth and nostrils, and piloerection were observed within 24 h; males were more susceptible than the females. Weight was reduced in all animals up to day 7. Survivors were asymptomatic by day 10. No gross abnormalities were observed, except one male from the 3.3 g/kg dose group had blood in the bladder and yellow patches in the lobes of the liver.	Dow Chem. Co. (1977); ISC Chem. Ltd. (1977)
Rats, Wistar, age n.p., 5 M and 5 F per dose group	Tardex 50L, purity n.p.	oral (intragastric intubation); 1.38, 1.98, 2.77, 3.89, 4.73, and 5.50 g/kg as a 20% v/v dispersion in cottonseed oil; observed daily for 14 days	At the mid and high doses, unsteady gait, tremors, convulsions, loss of activity, excessive salivation, chromodacryorrhea, diarrhea, diuresis, hyperesthesia, blood staining around the mouth and nostrils, and piloerection were observed within 24 h. Weight was reduced in these groups up to day 7. Survivors were asymptomatic by day 10.	Dow Chem. Co. (1977); ISC Chem. Ltd. (1977)

Table 15. Acute Exposure to Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference(s)
Rabbits, New Zealand white, age n.p., 2 M and 2 F per dose group	technical PeBDE, purity n.p.	topical application; 200 or 2000 mg/kg bw to the occluded and clipped intact or abraded skin for 24 h; observed for 14 days	Normal body weight gain or a slight decrease in growth was observed.	Great Lakes Chem. Corp. (undated a; cited by IPCS, 1994)
Rabbits, New Zealand white, age n.p., 3 M and 3 F per dose group	technical PeBDE, purity n.p.	topical application; 0.5 mL to the occluded and clipped intact or abraded skin for 24 h; examined at 24 and 72 h	No, or only very slight, erythema was observed.	Great Lakes Chem. Corp. (undated a; cited by IPCS, 1994)
Rabbits, New Zealand White, age n.p., 6, sex n.p.	Tardex 50L, purity n.p.	topical application; 0.5 mL to the occluded intact or abraded skin of the back for 24 h; examined at 24 and 72 h	Slight or well-defined erythema with occasional slight edema was observed.	Dow Chem. Co (1977); ISC Chem. Ltd. (1977)
Rabbits, New Zealand white, age n.p., 3 M and 3 F	technical PeBDE, purity n.p.	single application of 0.1 mL into the conjunctival sac of the eye; examined at 24, 48, and 72 h and at 7 days	At 24 h, slight redness, chemosis, and discharge of the conjunctivae, which all decreased during 7 days, were observed. At 72 h, 1 animals showed slight corneal damage. At 7 days, 2 animals had slight alopecia around the eyelid.	Great Lakes Chem. Corp. (undated a; cited by IPCS, 1994)
Rabbits, New Zealand White, "adult" (age not specified), 6, sex n.p.	Tardex 50L, purity n.p.	topical application; 0.1 mL of the test substance as a 25% v/v dispersion in Liquid Paraffin B.P. instilled into the eye; observed at 1, 2, 3, 4, and 7 days	Tardex 50L was irritating to the eyes in each test situation. The undiluted substance produced mild or moderate conjunctival responses within 24 h, which disappeared by the end of the test period. Some animals had hair loss around the eyes. Dispersion of the substance was less irritating; slight to mild conjunctival inflammation occurred in those whose treated eye was not washed, but all effects disappeared by day 7.	Dow Chem. Co. (1977); ISC Chem. Ltd. (1977)
Technical Octabromodiphenyl Ether (OBDE)				
Rats, Charles River CD, age n.p., number n.p., M and F	technical OBDE, purity n.p.	inhalation; 2 or 60 mg/L for 1 h; observed for 14 days	During exposure, decreased motor activity, erythema, and eye squint were observed at both doses. At the high dose, tachypnea was also seen in animals, and one rat showed salivation on days 5 and 7.	Great Lakes Chem. Corp. (1987; cited by IPCS, 1994)

Table 15. Acute Exposure to Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference(s)
Rats, Charles River CD, age n.p., number n.p., M	technical OBDE, purity n.p.	oral (by intubation); 50, 500, or 5000 mg/kg bw suspended in corn oil; observed for 14 days	No toxic effects or death was observed. Animals showed normal weight gain.	Great Lakes Chem. Corp. (1987, 1990a; cited by IPCS, 1994)
Rabbits, Albino, age n.p., number n.p., M and F	technical OBDE, purity n.p.	topical application; 200 or 2000 mg/kg bw to the clipped, abraded, or intact skin for 24 h; observed for 14 days	No toxic effects or death was observed. Animals showed normal weight gain.	Great Lakes Chem. Corp. (1987, 1990a; cited by IPCS, 1994)
Rabbits, Albino, age n.p., number n.p., M and F	technical OBDE, purity n.p.	topical application; 500 mg to the occluded and clipped intact or abraded skin; examined at 24 and 72 h	Only one rabbit had slight erythema at 72 h.	Great Lakes Chem. Corp. (1987; cited by IPCS, 1994)
Rabbits, New Zealand white, age n.p., 3 M and 3 F	technical OBDE, purity n.p.	single application of 100 mg into the conjunctival sac of the eye; examined at 24, 48, and 72 h and at 7 days	At 24 h, 2 rabbits had a slight discharge from their eyes. At 48 h, 1 rabbit had a slight redness. No ocular irritation or corneal damage was seen.	Great Lakes Chem. Corp. (1987; cited by IPCS, 1994)

Abbreviations: bw = body weight; F = female(s); h = hour(s); M = male(s); n.p. = not provided
[a] Dosing frequency and duration are only provided for studies involving repeated dosing by gavage or i.p. All studies with no frequency data are assumed to be single-dose studies.

1977; ISC Chem. Ltd., 1977). Topical application of Tardex 50/50L (1.25-11.0 g/kg as an 11.4-50% v/v dispersion in cottonseed oil) to the occluded skin of rats for 24 hours caused weight loss, piloerection, lethargy, slight tremors, diarrhea, hyperesthesia, staining, and chromodacryorrhea within 3-4 days (Dow Chem. Co., 1977; ISC Chem. Ltd., 1977). Survivors were asymptomatic by day 7 with Tardex 50 and by day 12 with Tardex 50L.

Administered orally, technical PeBDE (50-9600 mg/kg bw) caused decreased growth, diarrhea, piloerection, reduced activity, forelimb clonic persistent tremors, as well as death at doses of 2400 mg/kg or more (Great Lakes Chem. Corp., undated a; cited by IPCS, 1994). Gross lesions observed at necropsy included pale, enlarged, necrotic livers and multiple ulcerations of the gastric mucosa in rats. Tardex 50/50L (1.2-8.8 g/kg as a 20% v/v dispersion in cottonseed oil) given in mid to high doses resulted in unsteady gait, tremors, convulsions, loss of activity, excessive salivation, chromodacryorrhea, diarrhea, diuresis, hyperesthesia, blood staining around the mouth and nostrils, and piloerection within 24 hours (Dow Chem. Co., 1977; ISC Chem. Ltd., 1977). Weight was reduced up to day 7, and survivors were asymptomatic by day 10.

Topical application of Tardex 50/50L (1.25-11.0 g/kg as an 11.4-50% v/v dispersion in cottonseed oil) to the occluded skin of rats for 24 hours caused weight loss, piloerection, lethargy, slight tremors, diarrhea, hyperesthesia, staining, and chromodacryorrhea within 3-4 days (Dow Chem. Co., 1977; ISC Chem. Ltd., 1977). Survivors were asymptomatic by day 7 with Tardex 50 and by day 12 with Tardex 50L.

Administered orally, technical PeBDE (50-9600 mg/kg bw) caused decreased growth, diarrhea, piloerection, reduced activity, forelimb clonic persistent tremors, as well as death at doses of 2400 mg/kg or more (Great Lakes Chem. Corp., undated a; cited by IPCS, 1994). Gross lesions observed at necropsy included pale, enlarged, necrotic livers and multiple ulcerations of the gastric mucosa in rats. Tardex 50/50L (1.2-8.8 g/kg as a 20% v/v dispersion in cottonseed oil) given in mid to high doses resulted in unsteady gait, tremors, convulsions, loss of activity, excessive salivation, chromodacryorrhea, diarrhea, diuresis, hyperesthesia, blood staining around the mouth and nostrils, and piloerection within 24 hours (Dow Chem. Co., 1977; ISC Chem. Ltd., 1977). Weight was reduced up to day 7, and survivors were asymptomatic by day 10.

In rabbits, topical application of technical PeBDE (200 or 2000 mg/kg bw or 0.5 mL) to the occluded and clipped intact or abraded skin for 24 hours resulted in no change or a slight decrease in growth and no or a very slight erythema (Great Lakes Chem. Corp, undated a; cited by IPCS, 1994). Tardex 50L was classified as a mild primary irritant in the animals (Dow Chem. Corp., 1977; ISC Chem. Ltd., 1977). Application of 0.1 mL of technical PeBDE into the conjunctival sac of the eye produced slight to moderate irritation (Great Lakes Chem. Corp., undated a; cited by IPCS, 1994; Dow Chem. Co., 1977; ISC Chem. Ltd., 1977).

Technical Octabromodiphenyl Ether

In rats, inhalation of technical OBDE (2 or 60 mg/L) for one hour resulted in decreased motor activity, erythema, and eye squint during the exposure period (Great Lakes Chem. Corp., 1987; cited by IPCS, 1994). At the highest dose, tachypnea and salivation were also observed. Oral administration of the compound (50, 500, or 5000 mg/kg bw) in corn oil had no toxic effects (Great Lakes Chem. Corp., 1987, 1990a; cited by IPCS, 1994).

In rabbits, technical OBDE was also not toxic or irritant (topical application of 200 or 2000 mg/kg bw or 500 mg for 24 hours) (Great Lakes Chem. Corp, 1987, 1990a; cited by IPCS, 1994). A single application (100 mg) into the conjunctival sac of the eye caused a slight discharge and slight redness but no ocular irritation or corneal damage.

9.1.4 Short-Term and Subchronic Exposure

No short-term exposure studies are available for TeBDE or HxBDE (IPCS, 1994). For the former compound, the reader is referred to those for technical PeBDE, which contains 4% TeBDE.

The details of the following studies are presented in **Table 16**.

Technical Pentabromodiphenyl Ether

In mice, DE-71 (18, 36, or 72 mg/kg/day *per os*) for 14 days caused dose-dependent increases in liver weight/body weight ratios compared to controls (Fowles et al., 1994).

In rats, oral administration of technical PeBDE (2, 10, 100, or 1000 mg/kg/day in the diet for up to 90 days) resulted in increased relative liver weights (Great Lakes Chem. Corp., undated a; cited by IPCS, 1994). Microscopically, cytoplasm had areas of finely granular appearance, and enlarged hepatocytes contained eosinophilic "round bodies". Compound-related increases in tissue total bromine levels were also observed. At the highest dose, relative weights of the pituitary and adrenals glands were decreased.

In rabbits, repeated topical application of 2.5% v/v Tardex 50 to the inner surface of the pinna produced slight to moderate epithelial hyperplasia (Dow Chem. Co., 1977; ISC Chem. Ltd., 1977).

Table 16. Short-term and Subchronic Exposure to Polybrominated Diphenyl Ethers

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Technical Pentabromodiphenyl Ether (PeBDE)				
Mice, C57BL/6J, 8-wk-old, 6-8 F per dose group	DE-71, purity n.p.	oral; 18, 36, or 72 mg/kg bw/day for 14 days for total doses of 250, 500, or 1000 mg/kg; killed 5 days after immunization	Liver weight/body weight ratios were dose-dependently increased compared to controls.	Fowles et al. (1994)
Rats, Charles River CD, age n.p., 10 M and 10 F per dose group	technical PeBDE, purity n.p.	oral; 100 or 1000 mg/kg daily (dissolved in corn oil) in the diet for 28 days (unclear whether doses were weight/body weight or concentration in feed); observation period n.p.	At the LD, absolute and relative liver weights were significantly increased in females; at the HD, weights were increased in both males and females. Dose-dependent liver lesions were more common in males. At the HD, decreased relative weights of the pituitary and adrenal glands were observed. At both levels, enlargement of the centrolobular and midzonal liver parenchyma cells was seen. The cytoplasm had areas of finely granular appearance, and enlarged hepatocytes contained eosinophilic "round bodies". Several rats from both groups also had slight to moderate hyperplasia of the thyroid; it is not clear if this was compound-related. Total liver bromide levels from the treated rats were 6-12x higher than those in controls; increases were dose-dependent.	Great Lakes Chem. Corp. (undated a; cited by IPCS, 1994)
Rats, Sprague-Dawley, age n.p., 30 M and 30 F per dose group	DE-71, purity n.p.	oral; 2, 10, or 100 mg/kg daily in the diet for 90 days; 10 rats/sex sacrificed after 4 wk of exposure, 5 animals sacrificed after a 6-wk recovery period, and 5 animals after a 24-wk recovery period	In the LD and MD groups, tetraiodothyronine levels were decreased (not dose-related), while serum total bromide levels were increased after 4 and 13 wk. Relative liver weights were increased but returned to normal after a 24-wk recovery period. Microscopically, hepatocytomegaly and thyroid hyperplasia were seen; the latter was reversible in 24-wk recovery period. At the LD, liver cell degeneration and necrosis were still observed in females after the 24-wk recovery period. In the LD and HD groups (MD group not measured), compound-related increases in tissue total bromine levels in all tissues were observed, which slowly decreased during the recovery period (but did not reach control levels). At the HD, a decrease in food consumption was seen in females and a decrease in body weight in both males and females. An increase in cholesterol levels was also seen in both sexes. After 13 wk, compound-related increases in liver and urine porphyrins were seen (almost 400x and 8[males]-13[females]x than levels of the controls).	Great Lakes Chem. Corp. (undated a; cited by IPCS, 1994)

Table 16. Short-term and Subchronic Exposure to Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rabbits, New Zealand White, age n.p., 4 F	Tardex 50, purity n.p.	preliminary test: topical application; 0.25 mL of test substance at concentrations of 1.25, 2.5, 5.0, and 10.0% v/v in Maize Oil B.P. to the back for 6 h/day for 5 days bromacnegenic activity assay: topical application; 2.5% v/v in Maize Oil B.P. to the inner surface of the left pinna for 6 h/day for 28 days; ear examined 24 h after each application	The 10% v/v dispersion consistently caused slight irritation, becoming well-defined erythema and edema with each application. The 5% v/v dispersion caused well-defined reactions after the second application in 2 animals. The 1.25 and 2.5% v/v dispersions caused no initial irritation; well-defined effects were seen after day 3 or 4. The 2.5% v/v dispersion was selected for use in the bromacnegenic activity assay. Slight erythema was observed after the third application. More applications produced slight to moderate epithelial hyperplasia (slight to moderate hyperemia, extensive exfoliation and hair loss, enlargement of the hair follicles, and significant thickening of the ear).	Dow Chem. Co. (1977); ISC Chem. Ltd. (1977)
Technical Octabromodiphenyl Ether (OBDE)				
Rats, Charles River CD, age n.p., 5 M and 5 F per dose group	micronized dust of technical OBDE, purity n.p.	inhalation (whole-body); 1.2, 12, 120, and 1200 mg/m^3 (mean analytical concentrations of 0.58, 3.68, 23.9, and 165.2 mg/m^3, respectively) for 8 h/day for 14 days; observation period n.p. (Amounts ingested from grooming exposed fur were not estimated.)	After the 8-h exposure period, all animals in the 1200 mg/m^3 group and some in the 120 mg/m^3 group exhibited a fast breathing pattern, which disappeared by the next morning. Total lung, liver, and fat bromine concentrations were significantly higher than in controls. The average postmortem concentrations in the lung and fat were about 1.5-12.5x higher than in the liver. The relative liver weights of animals in the ≥12 mg/m^3 dose groups were significantly increased in a dose-related manner. Histopathological lesions consisted of focal to multifocal cytoplasmic enlargement of the hepatocytes, and focal acidophilic degeneration of individual and small groups of liver cells. At 120 and 1200 mg/m^3, the enlargement of the hepatocytes was multifocal to diffuse in distribution; small to large areas had necrosis in the centrolobular regions of the affected liver lobules, especially in the highest dose group.	Great Lakes Chem. Corp. (1987; cited by IPCS, 1994) Apparently, this is the same test submitted by Anonymous (1992b).

Table 16. Short-term and Subchronic Exposure to Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, Charles River CD, age n.p., 10 M and 10 F per dose group	technical OBDE, purity n.p.	oral; 100 or 1000 mg/kg diet daily for 28 days; observation period n.p.	At the low dose, absolute and relative liver weights were significantly increased in females. At the high dose, both males and females had increased liver weights. At both doses, the compound-related histopathological liver lesions observed consisted of enlarged centrolobular and midzonal liver parenchymal cells in which the cytoplasm had large areas of finely granular structures containing eosinophilic "round bodies". The changes were more frequent and more severe in males and were dose-related. It was not clear whether the slight to moderate hyperplasia of the thyroid observed at the high dose was compound-related. Dose-related increases in total bromine levels of the liver that were seen in both males and females ranged from about 6-137x the levels found in controls.	Great Lakes Chem. Corp. (1987; cited by IPCS, 1994)
Rats, Charles River CD, age n.p., 10 M and 10 F per dose group (Controls were 35 M and 35 F from the 90-day feeding study.)	technical OBDE, purity n.p.	oral; 100, 1000, or 10,000 mg/kg diet daily for 28 days; observed for ≥8 wk (5 rats of each sex/group were sacrificed at 28 days; remaining animals were maintained on normal diets for 4 wk [recovery period])	At the highest dose, serum urea nitrogen levels were slightly increased in some of the rats. At MD and HD, absolute and relative liver weights were increased in some rats. At all doses, livers from rats showed enlargement of the centrolobular and midzonal hepatocytes (cytoplasm had large areas of finely granular appearance and frequently contained eosinophilic "round bodies"). The livers of the HD group showed accentuated lobulization and discoloration, vacuolization of hepatocytes, and necrosis of scattered individual hepatocytes. Liver lesions were less severe in all groups allowed a 4-wk recovery. Additionally, a dose-related increase in liver total bromine content was seen in all treated rats after 4 wk, which decreased rapidly in the recovery period. In the LD group, the liver total bromine concentration approached control levels after a 4-wk withdrawal period.	Great Lakes Chem. Corp. (1987; cited by IPCS, 1994)

Table 16. Short-term and Subchronic Exposure to Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, Sprague-Dawley, age n.p., 5 M per dose group	technical OBDE SA-1902, purity n.p.	oral; dietary levels of 0.01, 0.1, and 1.0% (100, 1000, and 10,000 mg/kg or ppm diet equivalent to approximately 10, 100, and 1000 mg/kg/day [0.01, 0.125, and 1.248 mmol/kg/day]) for 30 days; observation period n.p.	All levels produced hepatic centrilobular cytoplasmic enlargement and vacuolation, renal tubular hydropic degeneration, and thyroid hyperplasia. Liver weights were also increased at all doses, kidney weights at the two high doses, and splenic weights only at the lowest dose. At the highest dose, a significant decrease in packed cell volume and total erythrocyte count was observed. Gross pathology showed significant liver enlargement and pale foci. Kidney changes consisted of cortical petechial hemorrhage, cortical cyst, enlargement, and mottling. Hepatic lesions included centrilobular cytoplasmic enlargement and vacuolation and minimal focal necrosis. Kidney lesions consisted of hyaline droplet degenerative cytoplasmic changes, focal proteinaceous tubular casts, and, at the higher doses, minimal focal tubular necrosis and regeneration and intratubular hemorrhage. At all doses, thyroid hyperplasia in the colon was observed. Rats in the control and test groups showed colonic infection with nematode parasites.	Dow Chem. Co. (1971) [authors: Sparschu et al.]

Table 16. Short-term and Subchronic Exposure to Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, Charles River CD, age n.p., 35 M and 35 F per dose group	technical OBDE, purity n.p.	oral; 100, 1000, or 10,000 mg/kg diet daily for ≤13 wk; observed for ≤1 yr after treatment: 5 rats/sex/group examined at 1 and 2 mo and at the end of the study; 5 rats/sex/group sacrificed after 13 and 21 wk and 6 mo after withdrawal	In the LD group, absolute and relative liver weights were increased. Microscopic changes, consisting of granular cytoplasmic changes, were seen in 4/10 rats. During exposure, liver total bromine content was increased but decreased during the recovery period. In the MD group, body weight gain was decreased. Absolute and relative liver and thyroid weights were increased during treatment. Microscopic lesions, which included vacuolization and hyaline intracytoplasmic inclusions, were seen in the cytoplasm of the centrolobular and midzonal hepatocytes. One rat each from the 1000 and 10,000 mg/kg groups had a hyperplastic nodule 6 mo after withdrawal. In the HD group, body weight gain was decreased even during the withdrawal period. Hemoglobin, hematocrit, and erythrocyte counts were also decreased. Hypochromia, polychromia, and anisocytosis of the erythrocytes was observed in one female. Blood glucose levels were slightly lower than in controls (no OBDE given), and orange coloration of the urine was observed during weeks 13-39 (up to 26 wk of withdrawal). Absolute and relative liver, kidney, and thyroid weights were significantly increased. At necropsy, accentuated lobulation, yellowish mottling of the livers, and brownish discoloration of the liver and kidneys were observed; however, after a year of recovery, there were no such gross changes. Histopathological liver changes in the HD group consisted of granular cytoplasmic changes, cytoplasmic vacuolization (possibly representing fatty degeneration), necrosis of scattered parenchymal cells or of centrolobular cells, centrolobular fibrosis, and pigmented Kupfer cells. In the kidneys, small to moderate numbers of cortical regenerative tubules occurred with one rat showing a severe tubular nephrosis. Thyroid cellular changes were probably compound-related. The histological changes decreased in severity and frequency during the recovery period. Total liver bromine increased during the 13-wk treatment, then decreased during the recovery period to levels not significantly higher than the control values after a year.	Great Lakes Chem. Corp. (1987; cited by IPCS, 1994) Presumably same study submitted by Anonymous (1992a).

Table 16. Short-term and Subchronic Exposure to Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, Sprague-Dawley (Spartan substrain), 6- to 7-wk-old, 5 M and 5 F per dose group	mixed lower brominated diphenyl oxides (MLBDO) containing 37.4% OBDE, 12.4% DeBDE, 37.9% NoBDE, and 12.2% HpBDE; purity n.p.	oral; diets formulated to provide 8, 80, or 800 mg MLBDO/kg bw/day for 4 wk; no observation period (post exposure)	No deaths occurred. At the highest dose, all rats had a statistically significant decrease in body weight. In males only, food consumption was significantly decreased at the highest dose, and SGPT and SGOT were statistically significantly increased. In females, only blood urea nitrogen was statistically significantly increased; SGPT, SGOT, and AP were slightly elevated. A trend of increased SGOT was seen in males at all dose levels and in females at 80 and 800 mg/kg/day. Gross examination showed a dose-related increase in liver size in males and females given 80 or 800 mg/kg/day. The livers were pale or darkened in appearance, and some had pale foci. At the highest dose, all or most rats had a diffuse darkening of the kidney. Other effects included gastric hemorrhage and foci, thymus atrophy, atrophy of accessory sex glands, decreased adipose reserves, and decreased body size; these were probably the result of the overall body condition associated with inanition. Male and female rats also showed statistically significantly decreased fasted body weights and increased absolute and relative liver weights. In males only, there was an increase in relative kidney and testicular weights but a decrease in absolute weights of the two.	Dow Chem. Co. (1982) [authors: Gorzinki et al.]; Ethyl Corp. (1982)
Rats, Sprague-Dawley (Spartan substrain), 6- to 7-wk-old, 15 M and 15 F	mixed lower brominated diphenyl oxides (MLBDO) containing 37.4% OBDE, 12.4% DeBDE, 37.9% NoBDE, and 12.2% HpBDE; purity n.p.	oral; diet formulated to provide 80 mg MLBDO/kg bw/day for 4 wk; observed for ≤18 wk after exposure	Males had an increased total bromine concentration in adipose tissue, which declined during the 18-wk recovery period. A half-life of ~13 wk was estimated.	Dow Chem. Co. (1982) [authors: Gorzinki et al.]; Ethyl Corp. (1982)

Abbreviations: AP = alkaline phosphatase activity; bw = body weight; F = female(s); h = hour(s); HD = high dose; LD = low dose; M = male(s); MD = mid dose; n.p. = not provided; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; wk = week(s)

Technical Octabromodiphenyl Ether

Rats inhaling micronized dust of technical OBDE (1.2, 12, 120, or 1200 mg/m^3) for eight hours daily for two weeks exhibited a fast breathing pattern during exposure to the two high doses (Great Lakes Chem. Corp., 1987; cited by IPCS, 1994). Total lung, liver, and fat bromine concentrations were significantly higher than in controls. At ≥12 mg/m^3, the relative liver weights were significantly increased in a dose-related manner. Histopathological lesions consisted of focal to multifocal cytoplasmic enlargement of the hepatocytes and focal acidophilic degeneration of cells.

Oral exposure to OBDE (100, 1000, or 10,000 mg/kg diet for up to one month) produced an increase in liver weights (Great Lakes Chem. Corp., 1987; cited by IPCS, 1994). Histopathological liver lesions consisted of enlarged centrolobular and midzonal hepatocytes in which cytoplasm had large areas of finely granular appearance and contained eosinophilic "round bodies". Dose-related increases in liver total bromine content was also seen in all rats. In a separate study, findings included increased kidney and splenic weights and the occurrence of kidney lesions in the animals, and at the highest dose, a significant decrease in packed cell volume and total erythrocyte count (Dow Chem. Co., 1971 [authors: Sparschu et al.]). At a longer exposure period of 13 weeks, oral administration of technical OBDE included decreases in hemoglobin, hematocrit, and blood glucose levels (Great Lakes Chem. Corp., 1987; cited by IPCS, 1994).

Diets formulated with mixed lower brominated diphenyl oxides (MBDO) containing 37.4% OBDE (8, 80, or 800 mg/kg bw/day for four weeks) caused a significant reduction in body weight and a dose-related increase in liver size in all rats (Dow Chem. Corp., 1982 [authors: Gorzinki et al.]; Ethyl Corp., 1982). In addition, all or most rats had a diffuse darkening of the kidney at the highest dose. In males only, food consumption was markedly decreased at the highest dose, while SGPT and SGOT were significantly increased along with relative kidney and testicular weights and total bromine concentration in adipose tissue. In females, only blood urea nitrogen was significantly increased.

9.1.5 Chronic Exposure

No studies were identified.

9.1.6 Synergistic and Antagonistic Activity

No studies were identified.

9.2 Reproductive, Developmental, and Teratological Effects

No studies are available for TeBDE or HxBDE as a single test substance (IPCS, 1994).

The details of the following studies are presented in **Table 17**.

Technical Pentabromodiphenyl Ether

Adult mice receiving PeBDE 99 (8.0 mg/kg; 14 mol/kg) exhibited behavioral aberration (Eriksson et al., 1999). Those exposed at postnatal day 10 displayed a non-habituating behavioral profile (hypoactive condition during the first part of the one-hour test period and a hyperactive condition toward the end). Mice exposed at postnatal day 3 showed the same behavior but to a lesser extent. Neonatal treatment of the PeBDE 99-exposed animals on postnatal day 10 with the cholinergic substance nicotine caused the same non-habituating behavior seen in adult mice.

In rats orally exposed to technical PeBDE (10-5000 mg/kg) on gestation days 6 through 15, levels of ≥100 mg/kg produced reduced weight gain, while doses ≥500 mg/kg were maternally lethal (BFRIP, 1990; cited by IPCS, 1994; Ethyl Corp., 1984). Clinical signs were observed but not gross lesions. Except for a small effect on implantation efficiency with 500 mg/kg, fetuses/conceptuses exhibited no developmental adverse effects.

In three-spined sticklebacks (*Gasterosteus aculeatus*), oral doses of Bromkal 70-5DE (0.45-10.39 mg) caused a reduction in spawning at the high dose compared to control fish (Holm et al., 1993, 1994). Fry had low frequencies of defects, the most common being an accumulation of fluid in the yolk-sac. In the ovaries, a significantly higher 6β-progesterone hydroxylase activity occurred compared with controls, except with a mixture containing Bromkal 70-5DE, Halowax 1014, and Clophen A50.

Table 17. Reproductive and Developmental Toxicity and Teratology of Polybrominated Diphenyl Ethers

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Technical Pentabromodiphenyl Ether (PeBDE)				
Mice, NMRI, 3-, 10-, or 19-days-old, number n.p., M	unlabelled and ^{14}C-labelled PeBDE 99, purity n.p.	oral; single dose of 8 mg PeBDE (14 mol)/kg bw (behavioral study) or 1.5 MBq [^{14}C]PeBDE 99 (uptake and retention study) per kilogram in 20% fat emulsion at age 3, 10, or 19 days Spontaneous behavior test was performed in male mice at 4 mo of age; amounts of radioactivity were found in the brain 24 h and 7 days after administration of dose.	In 3- or 10-day-old mice, a significant behavioral aberration was observed. Adult mice (4 mo of age) exposed on postnatal day 10 showed a nonhabituating behavioral profile namely, a hypoactive condition during the first part of the one-hour test period, but toward the end became demonstrably hyperactive. This was also seen in mice exposed on postnatal day 3 but to a lesser extent. No significant behavioral aberrations were observed in mice treated at age 19 days. In control animals, hyperactivity was seen after treatment with 80 g nicotine base, whereas the PBDE 99-treated mice were obviously hypoactive after low-dose nicotine treatment. The authors concluded that the neurotoxicity induced during the brain growth spurt may involve changes in the cholinergic system. Retention was found to be similar to that observed after neonatal exposure to PCB 52, PCB 153 and DDT.	Eriksson et al. (1999)
Rats, strain and age n.p., number n.p., F	technical PeBDE, purity n.p.	oral (by gavage); 10, 100, or 200 mg/kg bw daily as corn-oil suspensions on days 6-15 of gestation; observation period n.p.	The maternal no-effect level was 10 mg/kg bw, and the embryo/fetal no-effect level was 100 mg/kg bw. At the MD and HD, inhibition of maternal body weight gain was observed. At the HD, a slight reduction in average fetal body weight per litter was seen.	BFRIP (1990; cited by IPCS, 1994)
Rats (presumed pregnant), CRL;COBS CD (SD) BR, age n.p., 40 F (8 rats per dose group)	suspension of Saytex® 115, purity n.p.	oral (by gavage); 100, 500, 2500, or 5000 mg/kg/day on days 6-15 of gestation [All were administered at dosage volume of 5 mL/kg (20, 100, 500, and 1000 mg/mL, respectively), which was adjusted daily according to the observed bw.] The bw of rats were recorded on days 0 and 6 through 20 of presumed gestation. All rats were sacrificed on day 20 of presumed gestation.	At all levels, moderate to severe inhibitory effects on average maternal bw gain were produced. Doses of ≥500 mg/kg/day were maternally lethal and agent-related clinical signs occurred (e.g., lesions of the gastrointestinal tract and liver). Dose-dependent thin appearance, ungroomed coat, ptosis, tremors, ataxia, and labored breathing were among other signs noted. With the exception of a slight effect on implantation efficiency at the 500 mg/kg/day dosage, there were no adverse effects on the development of the conceptuses of dams that survived to day 20. No gross lesions were observed in the surviving dams.	Ethyl Corp. (1984)

Table 17. Reproductive and Developmental Toxicity and Teratology of Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Three-spined sticklebacks, *Gasterosteus aculeatus*, age n.p., 20 F	Bromkal 70-5DE, purity n.p.	oral; 6.29 or 10.39 mg in freeze-dried chironomids supplied 2x/day for 3.5 mo. 8-11 F were then transferred into spawning aquaria with unexposed males.	Eighty percent of controls spawned. Exposure to the low dose of Bromkal 70-5DE resulted in all fish spawning, whereas exposure to the high dose resulted in only a 20% spawning success. The values, however, were not significantly different from those in the control group. The number of eggs laid also did not differ significantly. Fry had low frequencies of defects. Abnormalities included an accumulation of fluid in the yolk-sac (most common finding), occasional spinal cord curvatures, and micro-ophthalmia.	Holm et al. (1993)
Three-spined sticklebacks, *Gasterosteus aculeatus*, age n.p., 9-10 F per dose group	Bromkal 70-5DE, purity n.p.	oral; 0.45 or 4.5 mg in freeze-dried chironomids for 2.5 mo	In the ovaries, there were no significant differences in the gonadosomatic index, the mean proportion of atretic oocytes per total number of oocytes, and 17α-progesterone hydroxylase activity between treated fish and control fish. All exposed groups, however, had significantly higher 6β-progesterone hydroxylase activity compared with the control group, except for groups given the mixture containing high doses of the test compound, Halowax 1014 (a polychlorinated naphthalene), and Clophen A50 (a polychlorinated biphenyl).	Holm et al. (1994)
Technical Octabromodiphenyl Ether (OBDE)				
Rats, strain and age n.p., number n.p., F	DE-79, purity n.p.	oral (by gavage); 2.5, 10.0, 15.0, 25.0, or 50.0 mg/kg bw daily from days 6-15 of gestation; sacrificed on gestation day 20	No compound-related effects were observed at ≤15.0 mg/kg. At 25.0 mg/kg, increased serum bromide levels were found. At the highest dose, mean maternal body weight gain and mean fetal weights were reduced, but the numbers of late resorptions, which lead to increase post implantation loss (which were not statistically significant when compared to controls), were increased. In dams cholesterol level was also slightly increased, but no compound-related microscopic findings were observed in the liver and kidneys. The malformations and developmental variation observed (e.g., fetal anasarca and bent limb bones) at the highest dose were associated with maternal toxicity. Reduced ossification of the skull, various unossified bones, and two instances of bent ribs were also seen at this dose.	Great Lakes Chem. Corp. (1987 abstr.; cited by IPCS, 1994)

Table 17. Reproductive and Developmental Toxicity and Teratology of Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, Charles River CD (of Sprague-Dawley origin), ~66- to 75-days-old, 141 F, producing 3 groups of 22 mated rats	FR-1208, purity n.p.	oral (intragastric gavage); 2.5, 10.0, or 25.0 mg/kg/day on days 6-15 *post coitum*; sacrificed on gestation day 20	Maternal NOEL≥25.0 mg/kg/day; fetal NOEL=2.5 mg/kg/day No adverse maternal effects were observed. No treatment-related fetal visceral or skeletal malformations or variation and delayed or retarded ossification were observed. At 10.0 and 25.0 mg/kg/day, post-implantation loss (covering gestation days 10 to 20) was significantly higher than in the control group (no FR-1208); however, the biological significance of this was unclear, since all values were within the normal range of historical controls.	Life Sci. Res. Israel (1987)
Rats (pregnant), strain and age n.p., number n.p., F	mixture of OBDE and HpBDE [68928-80-3], purity n.p.	oral (by gavage); 2.5, 10, or 25 mg/kg/day on days 5-16 of gestation; observation period n.p.	Maternal toxicity (weight loss) was not observed at any dose level. At 2.5 mg/kg/day, no adverse effects were observed. At 10 mg/kg/day, fetal body weights were reduced compared to controls (no mixture given). At 25 mg/kg/day, embryo/fetal death (resorption), reduced fetal body weights, fetal malformation, and delayed skeletal ossification were observed.	Dow Chem. Co. (1992)
Rats (pregnant), Charles River Crl:COBS¤ CD¤ (SD) BR, 66-days-old, 100 F (25 per dose group)	corn oil suspensions of SAYTEX¤ 111, 100% purity (assumed for the purposes of dosage calculation)	oral (by gavage); 2.5, 10.0, or 25.0 mg/kg/day during days 6-15 of gestation [All dosages were given at a dosage volume of 5 mL/kg/day, using suspension concentrations of 0.5, 2.0, and 5.0 mg/mL in corn oil, respectively; dosages were adjusted daily on the basis of the recorded bw.] Animals were sacrificed on gestation day 20; bw was recorded on day 0 and days 6-20 of gestation.	The embryo/fetal no-effect level was 2.5 mg/kg/day. The maternal no-effect level was >25.0 mg/kg/day. At 10 mg/kg, a statistically insignificant reduction in average fetal body weight was the only observed effect. At 25.0 mg/kg, overall average maternal body weight gain during gestation was significantly decreased compared with those of controls (corn oil only). Additionally, at this level, dose-dependent effects on the conceptus, which included reduced average fetal body weight, increased embryo/fetal deaths (resorptions), and fetal malformations (e.g., enlarged heart, rear limb malformation, and delayed skeletal ossification, delayed brain development [slight dilation of the lateral ventricles]) were seen.	Ethyl Corp. (1985)

Table 17. Reproductive and Developmental Toxicity and Teratology of Polybrominated Diphenyl Ethers (Continued)

Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rabbits, New Zealand white, age n.p., 26 F	Saytex 111, purity n.p.	oral (by gavage); 2.0, 5.0, or 15 mg/kg bw daily on days 7-19 of gestation; observed up to gestation day 28	At the highest dose, a statistically significant increase in liver weight and a decrease in body weight gain were observed. Slight fetal toxicity, as evidenced by a slight increase in delayed ossification of the sternebrae, was also observed in the HD group. There was an increase in the incidence of retrocaval ureter in the 5 and 15 mg/kg group and fused sternebrae in the 5 mg/kg groups. Although there seemed to be no evidence for teratogenic activity, slight fetotoxicity was seen at maternally toxic dose levels (e.g., 15 mg/kg bw).	Breslin et al. (1989; cited by IPCS, 1994)

Abbreviations: bw = body weight; DDT = dichlorodiphenyltrichloroethane; F = female(s); HD = high dose; LD = low dose; M = male(s); MD = mid dose; n.p. = not provided; PCB 52 = 2,2«,5,5«-tetrachlorobiphenyl; PCB 153 = 2,2«,4,4«,5,5«-hexachlorobiphenyl

Technical Octabromodiphenyl Ether

Oral administration of technical OBDE (DE-79, FR-1208, a mixture of OBDE and HpBDE, or Saytex 111) (2.5-50.0 mg/kg bw) on gestation days 6 through 15 (or 5-16 in one experiment) in rats produced no adverse maternal effects (Great Lakes Chem. Corp., 1987 abstr., cited by IPCS, 1994; Life Sci. Res. Israel, 1987; Dow Chem. Co., 1992; Ethyl Corp., 1985). At 25 mg/kg serum bromide levels were increased, while at 50 mg/kg cholesterol levels were slightly increased in dams. Additionally, at the highest dose, mean maternal and fetal body weights were reduced and postimplantation loss was increased. The observed fetal malformation and developmental variation were associated with maternal toxicity.

In rabbits, Saytex 111 (2, 5, or 15 mg/kg bw/day) given on gestation days 7 through 19 significantly increased liver weight and decreased body weight gain at the highest dose (Breslin et al., 1989; cited by IPCS, 1994). Slight fetal toxicity was also observed at the maternally toxic dose.

9.3 Carcinogenicity

No studies were identified.

9.4 Initiation/Promotion Studies

No studies were identified.

9.5 Anticarcinogenicity

No studies were identified.

9.6 Genotoxicity

No studies were identified for PeBDE and HxBDE.

The details of the following studies are presented in **Table 18**.

Table 18. Genotoxicity Studies of Polybrominated Diphenyl Ethers

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form and Purity	Dose	Endpoint Response/ Comments	Reference
Tetrabromodiphenyl Ether (TeBDE)						
SPD8 duplication cell line	Chinese hamster intragenic SPD8 recombination assay (Recombination excises exon duplication and restores function to the *hprt* gene.)	NA	TeBDE (BDE-47 synthesized and purified)	10, 20, 30, and 40 g/mL (21, 41, 62, and 82 M)	Statistically significant increase in recombination frequency at 40 g/mL (1.8-fold increase over control value) was observed. (Reversion to wild type in the SPD8 system is by homologous recombination.) Growth inhibition (IC_{50}-G), measured 48 h after treatment, was 0.07 mM, and reduction in colony formation (IC_{50}-C), determined 9 days after termination of treatment, was 0.09 mM.	Helleday et al. (1999)
Sp5 duplication cell line	Chinese hamster intragenic Sp5/V79 recombination assay (Recombination excises exon duplication and restores function to the *hprt* gene.)	NA	TeBDE (BDE-47 synthesized and purified)	10, 20, and 40 g/mL (21, 41, and 82 M)	No changes in recombination frequency were observed. (Reversion to wild type in the Sp5 system requires nonhomologous recombination.) The IC_{50}-G and IC_{50}-C values were 0.06 and >0.08 mM, respectively.	Helleday et al. (1999)
Technical Pentabromodiphenyl Ether (PeBDE)						
Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 (preincubation assay)	histidine-revertant (his^+) colony formation	+/-	technical PeBDE, purity n.p.	100, 333, 1000, 3333, and 10,000 g/plate	negative	Zeiger et al. (1987)
S. typhimurium strains TA100, TA1535, TA1536, TA1537, and TA1538	histidine-revertant (his^+) colony formation	+/-	Tardex 50, purity n.p.	0.01, 0.1, 1, and 10 mg/plate	-S9: positive for strains TA1535 and TA1536 at the highest dose. +S9: greater number of histidine revertants per plate compared to -S9 at low doses (≤1 mg) in some strains.	Dow Chem. Co. (1977); ISC Chem. Ltd. (1977)

Table 18. Genotoxicity Studies of Polybrominated Diphenyl Ethers (Continued)

Test System or Species, Strain, and Age	Biological Endpoint	S9 Metabolic Activation	Chemical Form and Purity	Dose	Endpoint Response/ Comments	Reference
human peripheral blood lymphocytes (HPBL) from healthy females aged 39 and 40 yr old	chromosome aberration (initial assay)	+/-	technical PeBDE, purity n.p.	0.25, 0.75, 2.5, 7.5, 25, 75, 250, 750, and 2500 g/mL for 20 h (-S9; top dose 250 g/mL) or 4 h (+S9); 20-h harvest	-S9: negative. At the highest dose, mitotic inhibition of 47% was observed. +S9: weakly positive. At the highest dose, a statistically significant increase in chromosome aberrations was observed compared to control group (DMSO only). The Cochran-Armitage test was positive for a dose-responsive trend.	Chem. Manuf. Assoc. (1996b; authors: Gudi and Schadly)
human peripheral blood lymphocytes (HPBL) from healthy females aged 39 and 40 yr old	chromosome aberration (independent repeat assay)	+/-	technical PeBDE, purity n.p.	-S9: 32, 63, 125, 250, and 500 g/mL for 20 or 44 h; 20- and 44-h harvest times +S9: 313, 625, 1250, 2500, and 3750 g/mL for 4 h; 20- and 44-h harvest times	-S9: negative. At the highest dose, mitotic inhibition was 50% and 79% at the 20- and 44-h harvests, respectively. +S9: negative. At the two highest doses, mitotic inhibition was 44% and 85% at the 20- and 44-h harvests, respectively. There were no statistically significant increases in structural or numerical chromosome aberration ins either the non-activated or S9-activated studies, regardless of dose level.	Chem. Manuf. Assoc. (1996b; authors: Gudi and Schadly)
Technical Octabromodiphenyl Ether (OBDE)						
monolayers of WI-38 human fibroblast cells	DNA damage (unscheduled DNA synthesis [UDS])	+/-	technical OBDE, purity n.p.	60-300 g/mL in the presence of radiolabelled thymidine	negative	Great Lakes Chem. Corp. (1987; cited by IPCS, 1994)
Chinese hamster ovary (CHO) cells	sister chromatid exchanges (SCE)	+/-	technical OBDE, purity n.p.	7.5, 25, 75, 250, and 750 g/mL in DMSO for 2 h, followed by a 24-h expression period	negative	Great Lakes Chem. Corp. (1987; cited by IPCS, 1994)

Note: Zeiger et al. (1987) used male Syrian hamster liver S9 fractions as well as Aroclor 1254-induced male Sprague-Dawley rat liver fractions; all other experiments used liver microsomal enzyme preparations from Aroclor-induced rats.
Abbreviations: (+) = presence; (-) = absence; DMSO = dimethyl sulfoxide; h = hour(s); NA = not applicable; n.p. = not provided

Tetrabromodiphenyl Ether

In an *in vitro* assay for intragenic recombination at an endogenous locus in Chinese hamster V79 cells, BDE-47 TeBDE (10-40 g/mL; 21-82 M) was found to be weakly recombinogenic in the Chinese hamster SPD8 cell line, producing a 1.8-fold induction at the highest dose (Helleday et al., 1999). However, in the Sp5 assay system, statistically significant increases in recombination frequency did not occur.

Technical Pentabromodiphenyl Ether

In *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, technical PeBDE (100-10,000 g/plate) was nonmutagenic in the absence and in the presence of metabolic activation (Zeiger et al., 1987). In *in vitro* microbial assays submitted by Great Lakes Chem. Corp. (undated a; cited by IPCS, 1994) using the same *Salmonella* strains and *Saccharomyces cerevisiae*, with and without liver microsomal enzyme preparations from Aroclor-induced rats, technical PeBDE also failed to show any mutagenic activity (study details not provided). However, in the absence of metabolic activation, PeBDE as Tardex 50 (0.01-10 mg/plate) was positive for mutagenicity for *S. typhimurium* strains TA1535 and TA1536 at the highest dose (Dow Chem. Co., 1977; ISC Chem. Ltd., 1977). In human peripheral blood lymphocytes, technical PeBDE (0.25-2500 g/mL) was found to be negative for the induction of structural and numerical chromosome aberrations, in both the presence and absence of metabolic activation (Chem. Manuf. Assoc., 1996b [authors: Gudi and Schadly]).

Technical Octabromodiphenyl Ether

In *in vitro* microbial assays using *S. typhimurium* and *S. cerevisiae*, with and without liver microsomal enzyme preparations from Aroclor-induced rats, technical OBDE failed to show any mutagenic activity (study details not provided) (Great Lakes Chem. Corp., 1987; cited by IPCS, 1994). In the presence or absence of a metabolic activation system, technical OBDE (7.5-750 g/mL) did not induce unscheduled DNA synthesis (UDS) in monolayers of WI-38 human fibroblast cells or sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells.

9.7 Cogenotoxicity

No studies were identified.

9.8 Antigenotoxicity

No studies were identified.

9.9 Immunotoxicity

The details of the following studies are presented in **Table 19**.

In mice, acute oral exposures to DE-71 (a technical PeBDE) (0.8-500 mg/kg bw) were not immunotoxic (Fowles et al., 1994). Subchronic oral exposures to DE-71 (18, 36, or 72 mg/kg/day for 14 days) produced a moderately suppressed plaque-forming cell (PFC) response to sheep erythrocytes only at the highest dose. Furthermore, thymus weight was significantly decreased at the highest dose, while spleen and body weights were unchanged. An elevation of corticosterone (CS) levels was also seen. Resting and polyinosinic:cytidylic acid-induced natural killer cell (NKC) activities were not affected. Excluding the 100 mg/kg acute dose, total serum thyroxine (T4) levels were significantly suppressed following all doses of DE-71 given both acutely and subchronically. [In C57BL/6 mice, an association between the induction of hepatic microsomal ethoxyresorufin-*O*-deethylase (EROD) activity and humoral immunotoxicity to the response to anti-sheep erythrocytes from exposure to halogenated aromatic hydrocarbons has been reported. However, in some studies, including those above, congeners of chlorinated diphenyl ethers did not follow the correlation. (See Section 9.10, *Effects on Liver Enzymes*.)]

When administered to guinea pigs via intradermal injections and topical applications (maximization test), Tardex 50L (a technical PeBDE) at 1.25% w/v in Liquid Paraffin B.P. and 12.5% w/w in petrolatum, respectively, was classified as a mild contact allergen; at higher concentrations, 60% of animals died during the induction phase (Dow Chem. Co., 1977; ISC Chem. Ltd., 1977). In a separate study, technical PeBDE (5% in corn oil or 50:50 corn oil/Freund's adjuvant solution) and technical OBDE (2.5% in corn oil or 50:50 corn oil/Freund's adjuvant solution) both failed to produce any erythema or edema in the animals (Chem. Manuf. Assoc., 1996 a,c [author: Wenk]).

In human peripheral lymphocytes, mitogen-induced proliferation and immunoglobulin synthesis *in vitro* were not affected by BDE-47 (TeBDE) or BDE-85 (2,2«,3,4,4«-PeBDE) (up to concentrations of 0.01 mM) (Fernl f et al., 1997).

9.10 Other Data

Effects on Liver Enzymes

Tetrabromodiphenyl Ether: In male rat liver microsomes, TeBDE increased 2- and 4-hydroxylation activity of estradiol (2.5- and 1.6-fold, respectively, above that of controls) (Segura-Aguilar et al., 1997). In female rat microsomes, the activities were decreased and unchanged, respectively.

In rainbow trout (*Oncorhynchus mykiss*) fed TeBDE (total dose of 21 mg/kg) ethoxyresorufin-*O*-deethylase (EROD) activity decreased to a value 25% of the control value on days 6 (5.13 vs. 20.6 pmol/min mg/protein, respectively) and to a value 19% of the control value on day 22 (7.81 vs. 40.4 pmol/min mg/protein, respectively) (Tj rnlund et al., 1998).

Technical Pentabromodiphenyl Ether: In mice, acute exposures to technical PeBDE (as DE-71) (500 mg/kg bw) produced a modest induction of pentoxyresorufin-*O*-deethylase (PROD) liver enzyme activity (2-fold) (Fowles et al., 1994). Subchronic exposures to DE-71 (18, 36, or 72 mg/kg/day for 14 days) produced an overall weak induction of both liver PROD (maximal with 250 mg/kg [4.7-fold]) and EROD (maximal at 500 mg/kg [3.3-fold]) activities as well as a dose-dependent induction of total microsomal P450 content (up to 40% above controls).

When administered by gavage to male Sprague-Dawley rats for 90 days, technical PeBDE (0.78, 1.56, 3.13, 6.25, 12.5, and 25 mol/kg/day) in corn oil resulted in extensive

Table 19. Immunotoxicity Studies of Polybrominated Diphenyl Ethers

Test System or Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
***In Vivo* Assays**				
Mice, C57BL/6J, 8-wk-old, 6 F per dose group	DE-71 (technical PeBDE mixture), purity n.p.	oral; single doses of 0.8, 4.0, 20, 100, or 500 mg/kg bw in peanut oil [injected with sheep erythrocytes (SRBC)] Mice were sensitized by i.p. injection with SRBC 2 days after a single DE-71 exposure, or after 9 days of the 14-day exposure regimen. Mice were killed 5 days after immunization in each study. Effector:target (YAC-1 cells) ratios of 100:1, 500:1, 25:1, and 12.5:1 were tested.	The plaque-forming cell (PFC) response in spleen cells to SRBC was not significantly altered. Serum thyroxine (T4) concentrations were decreased at all doses except the 100 mg/kg dose; this effect was apparent at the lowest dose.	Fowles et al. (1994)
Mice, C57BL/6J, 8-wk-old, 6-8 F per dose group	DE-71 (technical PeBDE mixture), purity n.p.	oral; 18, 36, or 72 mg/kg/day in peanut oil for 14 days for total doses of 250, 500, or 1000 mg/kg, respectively [not injected with SRBC when measurements of NKC activity or other endocrine or P450 endpoints were made] Mice were sensitized by i.p. injection with SRBC 2 days after a single DE-71 exposure, or after 9 days of the 14-day exposure regimen. Mice were killed 5 days after immunization in each study. Effector:target (YAC-1 cells) ratios of 100:1, 500:1, 25:1, and 12.5:1 were tested.	Only in mice that received a total dose of 1000 mg/kg, the PFC response was modestly suppressed (63% of controls). In all mice, total serum T4 levels were suppressed in a dose-dependent manner, with maximum suppression to 60% of control. Free serum T4 was also suppressed and paralleled the response seen for total T4. Serum corticosterone (CS) levels increased with increasing dosage and with order of kill. In addition, a highly significant statistical interaction of dose and order of kill occurred for CS elevation. Resting (basal) and polyinosinic:cytidylic acid-induced natural killer cell (NKC) activities were not affected. Thymus weight was significantly decreased at the highest dose, while spleen (as well as body) weight was unchanged.	Fowles et al. (1994)

Table 19. Immunotoxicity Studies of Polybrominated Diphenyl Ethers (Continued)

Test System or Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Guinea pigs, Hartley albino, age n.p., 15 M	Tardex 50L, purity n.p.	induction phase: 3 pairs of intradermal injections of test substance (suspended at a concentration of 1.25% w/v) in Liquid Paraffin B.P., the test substance in Freund's adjuvant, or Freund's adjuvant alone into the shoulder, followed 7 days later with occluded topical application of test substance dispersed at a concentration of 12.5% w/w in petrolatum for 48 h challenge dose (2 wk after final induction phase): occluded topical application of test substance in undiluted form for 24 h Lesions were evaluated 24 and 48 h after challenge application.	At 48 h, 3 animals showed a very slight erythema, which disappeared at 72 h in 2 animals. A further challenge dose after 5 days gave the same responses. This was calculated as a 20% rate of sensitization in the test population.	Dow Chem. Co. (1977); ISC Chem. Ltd. (1977)
Guinea pigs, Hartley albino, age n.p., 10 M	Tardex 50L, purity n.p.	induction phase: 3 pairs of intradermal injections of 0.1 mL of test substance (suspended at a concentration of 5% w/w) in Liquid Paraffin B.P., the test substance in Freund's adjuvant, or Freund's adjuvant alone into the shoulder, followed 7 days later with occluded topical application of test substance dispersed at 25% w/w in petrolatum for 48 h challenge phase (2 wk after final induction phase in 4M): occluded topical application of the undiluted form for 24 h Lesions were evaluated 24 and 48 h after challenge application.	After the topical induction phase, weight loss, poor condition, diarrhea, and excess salivation were observed in 6 animals between days 9 and 12. All died by day 13. After the challenge phase (remaining 4 animals), slight erythema occurred in 2 animals; this, however, may have been the result of contact with the plastic tape.	Dow Chem. Co. (1977); ISC Chem. Ltd. (1977)

Table 19. Immunotoxicity Studies of Polybrominated Diphenyl Ethers (Continued)

Test System or Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Guinea pigs, Dunkin Hartley albino, ~5-wk-old, 30 M (10 controls, 20 treated)	technical PeBDE, purity n.p.	induction dose: 3 pairs of intradermal injections; 0.1 mL of 50:50 corn oil/Freund's adjuvant mixture, 5.0% test substance in corn oil, or 5.0% test substance in 50:50 corn oil/Freund's adjuvant solution to the shaved interscapular area, followed 7 days later with topical application of 0.5 g of undiluted or "neat" test substance via a chamber for 48 h challenge dose (following a 2-wk rest period): topical application; 0.5 g neat test substance to the left flank via a chamber for 24 h. (Experimental design followed OECD Guideline 406, 1992.) Lesions were scored 24, 48, 72, 96, and 120 h after the challenge dose.	Negative for delayed contact hypersensitivity in the guinea pig maximization test. No erythema or edema was observed in any animals.	Chem. Manuf. Assoc. (1996c; author: Wenk)
Guinea pigs, Dunkin Hartley albino, ~5-wk-old, 30 M (10 controls, 20 treated)	technical OBDE, purity n.p.	induction dose: 3 pairs of intradermal injection; 0.1 mL of 50:50 corn oil/Freund's adjuvant mixture, 2.5% test substance in corn oil, or 5.0% test substance in 50:50 corn oil/Freund's adjuvant solution to the shaved interscapular area, followed 7 days later with topical application of 0.5 g of neat test substance via a chamber for 48 h challenge dose (following a 2-wk rest period): topical application; 0.5 g neat test substance to the left flank via a chamber for 24 h. (Experimental design followed OECD Guideline 406, 1992.) Lesions were scored 24, 48, 72, 96, and 120 h after challenge dose.	No erythema or edema was observed in any animals.	Chem. Manuf. Assoc. (1996a; author: Wenk)

Table 19. Immunotoxicity Studies of Polybrominated Diphenyl Ethers (Continued)

Test System or Species, Strain, Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
***In Vitro* Assays**				
human peripheral mononuclear lymphocytes from buffy coats from 15 female blood donors younger than 40 years of age	BDE-47 (TeBDE) and BDE-85 (2,2«,3,4,4«-PeBDE), purities ≥98%	proliferation experiments: cells were cultured with 0.001 M-0.01 mM PBDEs for 68 h before addition of [^{3}H]thymidine and cultured for another 4 h before harvest. immunoglobulin synthesis: lymphocytes were exposed to PWM and 0.001 M-0.01 mM test substances and cultured for 7 days. Immunoglobulin G was detected by a standard indirect ELISA.	Overall, mitogen-induced proliferation was not affected. There was a tendency towards increased proliferative responses in PHA-stimulated cells exposed to the lowest concentrations of BDE-85. Immunoglobulin synthesis: There were no consistent differences between controls and exposed cells. Note: Bromkal 70-5DE consisted of 42% BDE-47 and 7% (questionable) BDE-85.	Fernl f et al. (1997)

Abbreviations: CS = corticosterone; F = female(s); h = hour(s); NA = not applicable; NKC = natural killer cell; n.p. = not provided; OECD = Organization for Economic Cooperation and Development; PFC = plaque-forming cell; PHA = phytohemagglutinin; PWM = pokeweed mitogen; SRBC = sheep erythrocytes; T4 = thyroxine; wk = week(s)

increases in NADPH cytochrome c reductase, cytochrome P450 activity, *O*-ethyl-*O*-*p*-nitrophenyl phenylphosphonothioate (EPN) detoxification, and *p*-nitroanisole demethylation (Carlson, 1980b; cited by IPCS, 1994). A clear dose-response relationship was found for the latter two, and after a 30-day recovery period following the 90th dose, elevations in these two measurements were still observable at all doses. Additionally, increased NADPH cytochrome c reductase activity was found only at the highest dose, and the cytochrome P450 content had returned to normal. After 60 days of recovery, elevations were still seen in EPN detoxification and *p*-nitroanisole demethylation at the 1.56 and 3.13 mol/kg levels. Histological liver abnormalities were not observed in rats treated with doses of ≤3.13 mol/kg.

In a separate rat study, an increase in the activity of UDP-glucuronyl transferase and benzo[*a*]pyrene hydroxylase was observed 24 hours after the seventh dose (0.1 mmol/kg/day for 14 days) of technical PeBDE (Carlson, 1980a; cited by IPCS, 1994).

In a study of the hepatic microsomal enzyme-inducing potential of technical PeBDE (as Bromkal 70) in Wistar rats, single (up to 300 mg/kg bw) and repeated (50 mg/kg bw/day for 28 days) oral doses caused increases in liver weight (31-53%), cytochrome P450 c levels (2.3- to 3.9-fold), benzo[*a*]pyrene oxidation (2.2- to 5.3-fold), benzphetamine *N*-demethylation activity (≤2-fold), and EROD (not detectable to 0.35 nmol/min mg in control groups and 4.1 and 16.6 nmol/min mg in treatment groups) (von Meyerinck et al., 1990; cited by IPCS, 1994). In addition, EROD activity was induced in H-4-II E cells by technical PeBDE (Bromkal 70-5DE) (Hanberg et al., 1991; cited by IPCS, 1994).

In two fish experiments, Bromkal 70-5DE was a weak inducer of the cytochrome P450 system. In three-spined sticklebacks (*Gasterosteus aculeatus*) fed Bromkal 70-5DE (6.29 or 10.39 mg in freeze-dried chironomids supplied twice a day for 3.5 months), EROD activity was slightly increased; the compound did not significantly induce the enzyme system (Holm et al., 1993). [Additionally, morphological examination of the liver showed intracellular lipid accumulation; the frequency of lipid globuli was greater than in controls, where liver fat globuli were sporadic.] When Bromkal 70-5DE (0.45 or 4.5 mg) was fed as a mixture containing Halowax 1014 (a polychlorinated naphthalene) and/or Clophen A50 (a polychlorinated biphenyl), the low dose produced no significant difference in EROD activity versus control fish (Holm et al., 1994). All groups fed the high dose, however, had significantly higher EROD activities compared to those of the controls. In rainbow trout yolk-sac fry, injection of a mixture of Bromkal 70-5DE (0.04 g/ L) and Halowax 1014 significantly induced EROD activity.

<u>Technical Octabromodiphenyl Ether</u>: Technical OBDE (6.25, 12.5, and 25 mol/kg/day) given to male Sprague-Dawley rats by gavage in corn oil for 90 days also caused induction of NADPH cytochrome c reductase and cytochrome P450 (Carlson, 1980b; cited by IPCS, 1994). At lower doses (0.78-3.13 mol/kg/day), EPN detoxification and *p*-nitroanisole demethylation were increased in a dose-dependent manner while no liver histopathology was evident. After a 30-day recovery period, an induced state was seen only in animals receiving 3.13 mol/kg/day and was still observable 60 days after the last dose.

As with technical PeBDE, technical OBDE caused an increase in the activity of UDP-glucuronyl transferase and benzo[*a*]pyrene hydroxylase 24 hours after the seventh dose (0.1 mmol/kg/day for 14 days) (Carlson, 1980a; cited by IPCS, 1994).

In cultures of chick embryo liver cells, technical OBDE (10 g/mL medium), with and without pretreatment with β-naphthoflavone (NF), an inducer of P450, P448, and δ-aminolevulinic acid synthetase, induced a strong porphyrinogenic effect (Koster et al., 1980; cited by IPCS, 1994).

Ah Receptor-Mediated Effects

Although no tests on the ability of polybrominated diphenyl ethers to bind to the Ah receptor were located, results such as the induction of EROD activity and mechanistic studies show that some congeners have significant Ah receptor-mediated (e.g., dioxin-like) effects, with the activity of PeBDE being greater than that of TeBDE (Hooper and McDonald, 2000). Some congeners have been found to act as Ah-receptor agonists, while others were antagonists when co-treated with TCDD (Meerts et al., 1998b; cited by Hooper and McDonald, 2000).

Effects on Other Enzymes

Polybrominated phenols and diphenyl ethers and their metabolites (BDE-47, 66, 68, 85, 108, 120, 123, and 159) from *Dysidea* sponges inhibited 15-lipoxygenase (15-LO), inosine monophosphate dehydrogenase (IMPDH), and guanosine monophosphate synthetase (GMPS) (Fu et al., 1995). No activities occurred with protein tyrosine kinase (PTK) or matrix metalloprotease (MMP).

Endocrine Modulation

In subchronic studies (see **Section 9.1.4** and **Table 4**), rats orally exposed to technical PeBDE or technical OBDE had a slight to moderate hyperplasia of the thyroid; however, it was unclear if this was compound-related (Great Lakes Chem. Corp., 1987, undated a; cited by IPCS, 1994). Additionally, TeBDE (BDE-47) reduced thyroid hormone levels in female rats, which was an additive effect when coadministered with PCBs or chlorinated paraffins (Hallgren and Darnerud, 1998; cited by Hooper and McDonald, 2000). In mice, PeBDE significantly suppressed total serum T4 levels (Fowles et al., 1994).

In an *in vitro* assay, incubation of NF-induced microsomes enriched with CYP1A or with phenobarbital (PB)-induced microsomes enriched with CYP2B with pure PeBDE (BDE-99) in the presence of NADPH resulted in the formation of hydroxylated metabolites that inhibited 3,3«-diiodothyronine (T2) sulfotransferase (Schuur et al., 1998). With BDE-47, only the CYP2B-enriched microsomes catalyzed the formation of the metabolites, whereas incubation with the technical brominated diphenyl ether mixture Bromkal 70-5DE or with HxBDE (BDE-153) with either NF- or PB-induced microsomes did not produce any such metabolites. Percent inhibition was given as between 20 and 60% compared to controls. The results from testing BDE-99 were comparable to those using Aroclor 1254.

In a more recent study, incubation of BDE-47 and BDE-99 with PB-induced microsomes in the presence of NADPH was found to yield metabolites capable of competing with T4 binding to transthyretin (TTR) (Meerts et al., 2000). BDE-47 showed a greater than 60% competition compared to controls. Both compounds and BDE-153, however, failed to compete with T4-

binding in NF- and clofibrate (CYP4A3-enriched)-induced microsomes. (Tables 2-4 of the cited paper reports the T4-TTR competition binding of other polybrominated diphenyl ethers and related compounds [hydroxylated forms and brominated bisphenols]. Almost none of the higher brominated diphenyl ethers showed any competitive activity.) Binding potency was found to depend on the degree of bromine substitution (lesser degree showed lower or no competitive binding to TTR) and the nature of the halogen substitution (chlorinated analogues had lower potency versus brominated analogues). In the binding of the brominated bisphenols to TTR, potency was observed to also depend on hydroxylation at the para position with one, but preferably two, adjacent halogen substitutions. These requirements were similar to those observed for chlorinated compounds.

Effects on Blood

In rainbow trout fed PeBDE (total dose of 19.5 mg/kg at day 22), a very small but significant impairment of hematocrit and blood glucose was seen after only six days of exposure (total dose of 4.9 mg/kg) (Tj rnlund et al., 1998). [Noted: Additionally, a significant decrease of glutathione reductase activity in the liver was seen after the 22-day exposure period.]

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

TeBDE, PeBDE, HxBDE, and OBDE are structurally related to decabromodiphenyl ether (BDE-209). The polybrominated diphenyl ethers are also structurally similar to PCBs, PBBs, DDTs, PBDDs/PBDFs, PCDDs/PCDFs, the herbicide nitrofen, and T4, as well as share some of the same biological effects (e.g. enzyme induction, liver and thyroid effects)

10.1 Decabromodiphenyl Ether (DeBDE)

DeBDE is not acutely toxic to mammalian and aquatic species, nor is it irritating to the eyes and skin (Hardy, 1999a,b). It is not a sensitizer, a reproductive toxicant, teratogenic, nor an inducer of chloracne or liver enzymes. In chronic studies, it produced toxic effects, which were quite mild due to its poor absorption, rapid elimination, and fast metabolization. A toxicological summary is presented in the cited papers.

Carcinogenesis studies of DeBDE have also been conducted (NTP, 1986). Administered at 25,000 and 50,000 ppm in the diet (concentrations at which no toxicity was observed in a two-week or 13-week study) for 103 weeks to male and female F344/N rats and $B6C3F_1$ mice, increased incidences of nonneoplastic lesions were observed. In high-dose male rats, thrombosis and degeneration of the liver, fibrosis of the spleen, and lymphoid hyperplasia were produced, while in low-dose female rats, degeneration of the eye was seen. In male mice, granulomas and/or hypertrophy in the liver and follicular cell hyperplasia in thyroid glands were observed. Increased incidences of neoplastic nodules in the livers of low- and high-dose male rats and high-dose female rats were also seen. Additionally, in male rats, mononuclear cell leukemia, acinar cell adenomas in the pancreas, and a sarcoma in the spleen occurred. In male mice, increased incidences of hepatocellular adenomas or carcinomas (combined) and thyroid gland follicular cell adenomas or carcinomas (combined) were observed. Female mice showed no

carcinogenic effects. Therefore, the conclusions were that there was *some evidence of carcinogenicity* for male and female F344/N rats, an *equivocal evidence of carcinogenicity* for male $B6C3F_1$ mice, and *no evidence of carcinogenicity* for female $B6C3F_1$ mice.

In the presence or absence of metabolic activation, DeBDE was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 nor in the mouse lymphoma $5178Y/TK^{+/-}$ assay (NTP, 1986). Furthermore, it was negative for induction of SCEs and chromosomal aberrations in CHO cells *in vitro*. However, a positive result was obtained in the micronucleus test (NTP, 2000).

In rainbow trout, DeBDE (7.5-10 mg/kg bw/day for up to 71 days of depuration) was not acutely toxic but did cause an increased liver weight after 120 days compared to controls (Kierkegaard et al., 1999b). Furthermore, significant increases occurred in blood lactate concentrations after 120 days of exposure and after depuration and in the number of leucocytes in the depuration group compared to those in controls. There were significant decreases in the number of lymphocytes after 120 days of exposure and in hemoglobin at 16 days of exposure, which disappeared at 120 days. DeBDE had no significant effects on EROD (unlike BDE-47 or BDE-99), ethoxycoumarin-*O*-deethylase (ECOD), or transketolase activities.

10.2 Other Structurally Related Compounds (Selected Data)

Effects on Liver Enzymes

In male rat liver microsomes, 4-hydroxylation activity was significantly increased by Tris(*p*-chlorophenyl)methanol, 3,4,5-trichloroguaiacol, and 3,3«,4,4«,5-pentachlorobiphenyl (Segura-Aguilar et al., 1997). 3,3«,4,4«,5-Pentachlorobiphenyl was the only compound found to also induce a significant increase in the activity in female rat microsomes.

Endocrine Modulation

In rats, three congeners of PCDEs 2«,3,4,6«-tetraCDE, 2,2«,4,5,6«-pentaCDE, and 2,2«,4,4«,5,5«-hexaCDE reduced T4 levels in dams and in offspring exposed *in utero* (Rosiak et al., 1997; cited by Hooper and McDonald, 2000).

Hydroxylated metabolites of PCBs, PCDDs, and PCDFs were potent inhibitors of T2 sulfotransferase activity *in vitro* (Schuur et al., 1998). For the PCB metabolites, when the hydroxyl group was in the para or meta position, the greatest inhibition occurred; the most potent inhibitor was 3-hydroxy-2,3«,4,4«,5-pentachlorobiphenyl. The ortho hydroxy-substituted PCBs were much less effective, while none of the parent polyhalogenated aromatic hydrocarbons was found to inhibit T2 sulfotransferase activity. Other related hydroxylated halogenated compounds pentachlorophenol, 3,3«,5,5«-tetrachlorobisphenol A, 3,3«,5,5«-tetrabromobisphenol A, and 2«-OH-2,4,4«-trichlorodiphenyl ether were found to be potent inhibitors of the activity.

Incubation of NF-induced microsomes enriched with CYP1A or with PB-induced microsomes enriched with CYP2B with 2,2«,4,4«-TCDE in the presence of NADPH resulted in the formation of hydroxylated metabolites that inhibited T2 sulfotransferase more than 60% compared to controls (Schuur et al., 1998). Incubation of Aroclor 1254 or Clophen A50 with

NF- or PB-induced microsomes also resulted in the production of metabolites inhibiting activity from 20 to >60% of controls. With nitrofen and 3,3«,4,4«-TCDE, only the latter microsomes caused the formation of the metabolites.

Other Activity

Polybrominated diphenyl ether derivatives and congeners of the sponge *Dysidea herbacea* (BDE-41, 43, 48, 68, 86, and 137) were active against the Gram-positive bacteria *Bacillus subtilis*, the phytopathogenic fungus *Cladosporium cucumerinum* (except for the methyl derivative of BDE-43), and in the brine shrimp lethality test (eggs of *Artemia salina*), in which BDE-86 and BDE-137 were the most active (Handayani et al., 1997). Testing for antibacterial and fungicidal activities and the response in the brine shrimp lethality test, derivatives of the 2«-bromophenoxy ether ring system were found to be more active than their 2«,4«-dibromophenoxy ether congeners. The absence of a bromine substituent at C-6, which is ortho to the hydroxyl group of the phenolic ring system (e.g., 3,4,5«-tribromo-2-[2«-bromophenoxy]phenol), decreased the compound's bioactivity. Biological activity, however, was directly proportional to the number of bromine substituents in the brine shrimp lethality test. Methylation of the hydroxyl group resulted in a weakening or in the loss of activity in the bioassays performed.

11.0 ONLINE DATABASES AND SECONDARY REFERENCES

11.1 Online Databases

Chemical Information System Files

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

DIALOG Files

CEH (Chemical Economics Handbook)

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

AGRICOLA	EMBASE	NTIS
BIOSIS	HSDB	PROMT
CA	LIFESCI	Registry
CABA	MEDLINE	RTECS
CANCERLIT	NIOSHTIC	TOXLINE

TOXLINE includes the following subfiles (which do not always have all the records in the standalone versions):

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

In-House Databases

CPI Electronic Publishing Federal Databases on CD
Current Contents on Diskette¤

11.2 Secondary References

No secondary references were used.

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APPENDIX A: UNITS AND ABBREVIATIONS

°C = degrees Celsius

µg/L = microgram(s) per liter

µg/m^3 = microgram(s) per cubic meter

µg/mL = microgram(s) per milliliter

µM = micromolar

ABS = acrylonitrile-butadiene-styrene

ACGIH = American Conference of Governmental Industrial Hygienists

AP = alkaline phosphatase activity

BDE-28 = 2,4,4«-tribromodiphenyl ether

BDE-35 = 3,3«,4-tribromodiphenyl ether

BDE-41 = 2,2«,3,4-tetrabromodiphenyl ether

BDE-43 = 2,2«,3,5-tetrabromodiphenyl ether

BDE-47 = 2,2«,4,4«-tetrabromodiphenyl ether

BDE-48 = 2,2«,4,5-tetrabromodiphenyl ether

BDE-49 = 2,2«,4,5«-tetrabromodiphenyl ether

BDE-51 = 2,2«,4,6«-tetrabromodiphenyl ether

BDE-66 = 2,3«,4,4«-tetrabromodiphenyl ether

BDE-68 = 2,3«,4,5«-tetrabromodiphenyl ether

BDE-85 = 2,2«,3,4,4«-pentabromodiphenyl ether

BDE-86 = 2,2«,3,4,5-pentabromodiphenyl ether

BDE-99 = 2,2«,4,4«,5-pentabromodiphenyl ether

BDE-100 = 2,2«,4,4«,6-pentabromodiphenyl ether

BDE-108 = 2,3,3«,4,5«-pentabromodiphenyl ether

BDE-120 = 2,3«,4,5,5«-pentabromodiphenyl ether

BDE-123 = 2«,3,4,4«,5-pentabromodiphenyl ether

BDE-137 = 2,2«,3,4,4«,5-hexabromodiphenyl ether

BDE-138 = 2,2«,3,4,4«,5«-hexabromodiphenyl ether

BDE-153 = 2,2«,4,4«,5,5«-hexabromodiphenyl ether

BDE-154 = 2,2«,4,4«,5,6«-hexabromodiphenyl ether

BDE-155 = 2,2«,4,4«,6,6«-hexabromodiphenyl ether

BDE-159 = 2,3,3«,4,5,5«-hexabromodiphenyl ether

BDE-185 = 2,2«,3,4,5,5«,6-heptabromodiphenyl ether

BDE-209 = decabromodiphenyl ether

BDF = brominated dibenzo-*p*-furan(s)

bw = body weight

CHO = Chinese hamster ovary

CS = corticosterone

DeBDE = decabromodiphenyl ether

DMSO = dimethyl sulfoxide

DOT = U.S. Department of Transportation

ECNI = electron capture negative ionization

EI = electron impact

ELCD = electrolytic conductivity detector

EPA = U.S. Environmental Protection Agency

EROD = ethoxyresorufin-*O*-deethylase

F = female(s)

g = gram(s)

g/mL = gram(s) per milliliter

GC = gas chromatography

GPC = gel permeation chromatography

h = hour(s)

HD = high dose

HIPS = high-impact polystyrene

HpBDE = heptabromodiphenyl ether(s)

HxBDE = hexabromodiphenyl ether(s)

i.p. = intraperitoneal(ly)

i.v. = intravenous(ly)

K_{ow} = octanol-water partition co-efficient

kg = kilogram(s)

L = liter(s)

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

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

lb = pound(s)

LD = low dose

M = male(s)

MD = mid dose

MeO-PBDE = methoxylated polybrominated diphenyl ether(s)

MeO-PeBDE = methoxylated pentabromodiphenyl ether(s)

MeO-TeBDE = methoxylated tetrabromodiphenyl ether(s)

mg/kg = milligram(s) per kilogram

mg/m^3 = milligram(s) per cubic meter

mg/mL = milligram(s) per milliliter

mL/kg = milliliter(s) per kilogram

mm = millimeter(s)

mM = millimolar

mmol = millimole(s)

mmol/kg = millimoles per kilogram

mo = month(s)

mol = mole(s)

mol. wt. = molecular weight

NA = not applicable

NBDE = nonabromodiphenyl ether(s)

NF = β-naphthoflavone

NHATS = National Human Adipose Tissue Survey

NIEHS = National Institute of Environmental Health Sciences

nm = nanometer(s)

n.p. = not provided

OBDE = octabromodiphenyl ether(s)

OECD = Organization for Economic Cooperation and Development

PB = phenobarbital

PBB = polybrominated biphenyl

PBDD = polybrominated dibenzo-*p*-dioxins

PBDE = polybrominated diphenyl ether

PBDF = polybrominated dibenzo-*p*-furans

PBT = polybutylene terephthalate

PCB = polychlorinated biphenyl

PCDD = polychlorinated dibenzo-*p*-dioxins

PCDF = polychlorinated dibenzo-*p*-furans

PeBDE = pentabromodiphenyl ether(s)

PFC = plaque-forming cell

POTW = publicly owned treatment works

ppb = parts per billion

ppm = parts per million

ppt = parts per trillion

PROD = pentoxyresorufin-*O*-deethylase

RfD = oral reference dose

s = second(s)

s.c. = subcutaneous(ly)

SGC = silica gel chromatography

SGOT = glutamic oxaloacetic transaminase

SGPT = glutamic pyruvic transaminase activity

SRBC = sheep erythrocytes

T2 = 3,3«-diiodothyronine

T4 = 3,3«,5,5«-tetraiodothyronine; thyroxine

TeBDE = tetrabromodiphenyl ether(s)

TBBP-A = tetrabromobisphenol A

TSH = thyroid stimulating hormone

TTR = transthyretin

wk = week(s)

yr = year(s)