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Brominated flame retardants; Toxicity and ecotoxicity

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Contents

Foreword

The Danish EPA has prepared a list of substances that are undesirable in products due to their effects on man and/or the environment, in production, use and/or final disposal. Brominated flame retardants (BFR) are on this list of undesired substances. Increasing amounts of some of these substances have been detected in the marine environment (Norén, K. and Meironyté, D., 1998), and within the last few years they have been found in human breast milk and fat tissue in Sweden (Darnerud, P. O., Atuma, S., Aune, M., and Cnattingius, S., 1998, Lindström, G., Hardell, L., van Bavel, B., Wingfors, H., Sundelin, E., Liljegren, G., and Lindholm, P., 1998).

The BFR included in OECD's Risk Reduction Programme are the polybrominated biphenyls (PBB) and the polybrominated diphenyl ethers (PBDE). A voluntary agreement has been made in the OECD between the producers to reduce the risks of the substances PBDE and PBB. Tris(2,3-dibrompropyl)phosphate and PBB are prohibited in the European Union in textiles intended for skin contact ("Miljø- og Energiministeriets bekendtgørelse nr. 1042 af 17. december 1997 om begrænsning af salg og anvendelse af visse farlige stoffer og produkter til specielt angivne formål. §16"). Many of the BFR have not yet been classified or restricted. When this edition was closed for contributions in January 2000, the commercial PBDE products, penta-, octa- and decabromodiphenyl ether, as well as hexabromocyclododecane were still undergoing risk assessment in the EU. Later results from these assesments are therefore not included in this report.

In Denmark, a project was started for substance flow analysis of the most frequently used BFR, including those imported in manufactured goods. Consumption, use and possibilities of substitution have been investigated.

The objective of this project is to outline the existing knowledge about the environmental and health hazards of the BFR that are relevant for Denmark, based on the preliminary result of the substance flow analysis project. The method is a data screening, which naturally does not allow full identification and thorough evaluation of all existing relevant data.

2 English Summary

A toxicological and ecotoxicological data screening was made on BFR used in Denmark. The data screening in relevant sources was performed in ultimo 1998. Although a thorough data search was made this is not a garantie that all relevant information was identified and retrieved, e.g. relevant unpublished data may exist, and information may have been published since 1998.

Data on 12 out of 19 initially selected BFR were retrieved from generally well recognised handbooks and reviews as well as from documents/publications and data found via well known on-line and off-line databases. The amount and quality of retrieved data was variable.

With the exception of vinyl bromide and 2,2-Bis(bromomethyl)propan-1,3-diol (DBNPG), most of the BFR have a high n-octanol-water partition coefficient, which indicates potential accumulation in living organisms. The high molecular weight of some of these BFR may preclude their bioaccumulation in living organisms as indicated by the low bioconcentration factors (BCF) determined for decabromobiphenyl (DeBB) and octabromodiphenyl ether (OBDE). However, a very high BCF of 18,100 was measured for hexabromocyclododecane, which has a molecular weight of 642. This indicates that the bioconcentration of high-molecular-weight substances is not fully understood and, hence, the data on these chemicals should be carefully evaluated.

Both vinyl bromide and DBNPG are suspected to be carcinogenic. Other data indicate that commercial products of decabromobiphenyl (DeBB) and brominated styrene homopolymer may also have a carcinogenic potential. Two of the compounds, 2,4,6-tribromophenol and octabromodiphenylether (OBDE), represent a possible risk of harm to the human foetus. OBDE has an effect on the liver, which is considered the primary target organ. Hexabromocyclododecane (HBCD) and pentabromodiphenylether (PeBDE) have an effect on the liver and thyroid gland. It is not known if it is a specific endocrine effect on the thyroid gland, and if the effect observed in rodents is relevant for human beings. Future research may come closer to the answer. Of all the BFR screened, only the PBDE has been found in humans. Congeners of the commercial PeBDE product were detected in adipose tissue, blood and breast milk. An OBDE congener has been identified in human adipose tissue and blood serum. DeBDE was detected and quantified in blood serum from 3 categories of workers. The general lack of data of the occurrence of BFR in human tissues and liquids may be because of missing investigations and/or inadequate analyses.

The substances HBCD, 2,4,6-tribromophenol, and tetrabromobisphenol A (TBBPA) are toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment. Pentabromotoluene, OBDE, PeBDE, and DeBDE are considered not

readily biodegradable. Brominated styrene, vinyl bromide, DBNPG and DeBB were not assessed due to scarcity of data.

Some of the frequently used brominated flame retardants, TBBPA, HBCD and PBDEs, are present in sediment, mussels and fish. PBDEs have been found in whales and seals. Some of the PBB and the PBDE are highly hydrophobic and resistant to degradation processes. It is therefore possible that these chemicals may accumulate in aquatic sediments or bioconcentrate in living organisms. Signs of toxicity of individual PBB and PBDE to early life stages in rainbow trout were reported. The presence of some of the PBBs and PBDEs in mussels, fish, seals and dolphins as well as in sperm whales, which normally stay and feed in deep ocean water, combined with the ongoing industrial production of these compounds indicate that an environmental problem is rising.

Because of their environmental properties the continued release of HBCD, TBBPA, 2,4,6-tribromophenol, 5BT, OBDE, PeBDE and DeBDE may represent an increasing risk to aquatic organisms.

3 Danish Summary

En toksikologisk og økotoksikologisk datasøgning blev foretaget på nogle udvalgte bromerede flammehæmmere (BFR), som forekommer i Danmark. Der blev fundet data om miljø-og sundhedsegenskaber for 12 ud af de 19 først udvalgte BFR i anerkendte håndbøger, oversigtsværker samt i en række publikationer fundet via søgning i velkendte on-line og off-line databaser. Mængden og kvaliteten af de fundne data er meget svingende for de udvalgte bromerede flammehæmmere.

Det er svært at konkludere noget generelt om de bromerede flammehæmmeres skadelighed for sundheden. Med undtagelse af vinylbromid og 2,2-Bis(brommethyl)propan-1,3-diol (DBNPG) har de fleste bromerede flammehæmmere en høj n-octanol-vand fordelingskoefficient, som indikerer en potentiel bioakkumulering i vandlevende organismer. Den høje molekylevægt af nogle af disse BFR kan forhindre bioakkumulering i vandlevende organismer, som det antydes af de lave biokoncentreringsfaktorer (BCF), der er blevet bestemt for decabrombiphenyl (DeBB) and octabromdiphenyl ether (OBDE). Der er dog målt en meget høj BCF på 18.100 for hexabromcyclododecan, der har en molekylevægt på 642. Dette indikerer, at biokoncentrering af stoffer med høj molekylevægt ikke er fuldstændigt belyst, og derfor bør data om disse stoffer vurderes omhyggeligt. Både vinylbromid og DBNPG er mistænkt for at være kræftfremkaldende, og der er også data, som tyder på, at handelsprodukter af decabrombiphenyl (DeBB) og bromeret styren homopolymer kan have et kræftfremkaldende potentiale. To af stofferne, 2,4,6-tribromphenol og octabromdiphenylether (OBDE), er mistænkt for at være fosterskadende. OBDE har en effekt på leveren, som anses for at være målorganet. Hexabromcyclododecan (HBCD) og pentabromdiphenylether (PeBDE) har en effekt på lever og skjoldbruskkirtlen. Hvorvidt det drejer sig om en specifik endokrin effekt på skjoldbruskkirtlen, og om effekten, som er set hos gnavere, også har relevans for mennesker, må fremtidige undersøgelser vise. Af de undersøgte stoffer er det kun PBDE, som er fundet i mennesker. PeBDE er fundet i fedtvæv, blod og mælk, OBDE er fundet i fedtvæv og blod og DeBDE er fundet hos arbejdere på tre forskellige arbejdspladser. De sparsomme/manglende humane data kan skyldes manglende undersøgelser og/eller utilstrækkelige analyser.

Stofferne HBCD, 2,4,6-tribromphenol og tetrabrombisphenol A er giftige over for akvatiske organismer og kan forårsage uønskede langtidsvirkninger i vandmiljøet. Pentabromtoluen (5BT), OBDE, PeBDE og DeBDE betragtes som ikke let bionedbrydelige. Bromeret styren, vinylbromid, DBNPG og DeBB kunne ikke vurderes fuldt ud på det foreliggende datamateriale.

De mest udbredte bromerede flammehæmmere (TBBPA, HBCD, PBB og PBDE) forekommer i sediment, muslinger og fisk. PBB og PBDE er desuden genfundet i delfiner, kaskelothvaler og sæler.

Nogle PBB og PBDE er hydrofobe samt svært nedbrydelige. Det er derfor muligt, at disse stoffer kan akkumuleres i akvatiske sedimenter eller biokoncentreres i levende organismer. Tegn på toksisk virkning overfor tidlige livsstadier i regnbueørreder blev observeret fra enkelte PBB og PBDE. Tilstedeværelsen af PBB og PBDE i muslinger, fisk, sæler og delfiner såvel som i kaskelothvaler, der normalt fouragerer og opholder sig i oceanernes dybhav, kombineret med den igangværende industrielle produktion af disse stoffer indikerer et muligt miljøproblem.

HBCD, TBBPA, 2,4,6-tribromophenol, 5BT, OBDE, PeBDE og DeBDE vil på baggrund af deres miljømæssige egenskaber kunne udgøre en risiko for akvatiske organismer.

4 Method

The preliminary result of the substance flow analysis project indicates that the substances in table 1 are used in Denmark, as pure substances or in manufactured goods. A health and environmental assessment was made, if possible, on these substances after the method outlined below.

Table 1. Chemical substances selected

CAS No.	Chemical name	Abbreviation
79-94-7	Tetrabromobisphenol A	TBBPA
87-83-2	Pentabromotoluene	5BT
118-79-6	2,4,6-Tribromophenol	
593-60-2	Vinylbromide	
632-79-1	Tetrabromophtalic acid anhydride	TBPA
1163-19-5	Decabromodiphenylether	DeBDE
3194-55-6	1,2,5,6,9,10-hexabromocyclododecane	1,2,5,6,9,10-HBCD
3234-02-4	2,3-Dibromo-2-butene-1,4-diol	
3296-90-0	2,2-Bis(bromomethyl)propane-1,3-diol	DBNPG
13654-09-6	Decabromobiphenyl	DeBB
25637-99-4	Hexabromocyclododecane	HBCD
32534-81-9	Pentabromodiphenylether	PeBDE
32536-52-0	Octabromodiphenylether	OBDE
32588-76-4	Ethylene bis(tetrabromophtalimide)	EBTBP
32844-27-2	TBBPA carbonate oligomer	
37853-59-1	1,2-bis(2,4,6-tribromophenoxy)ethane	
58965-66-5	1,2,4,5-tetrabromo-3,6-bis(pentabromophenoxy)-benzene	
68441-62-3	Brominated polyetherpolyol	
88497-56-7	Brominated styrene homopolymer	

Data were retrieved primarily from well recognised handbooks and reviews of toxicological and ecotoxicological relevance. Furthermore, a data search was made in the draft EU risk assessments and in relevant bibliographic databases. In appendix 3 of this report is a list of used standard sources. This list is part of CETOX's standard operating procedure for data screening of chemical substances and is a further development of the strategy described by the Danish EPA in 1993 "Retningslinier for datasøgning og udarbejdelse af klassifikationsskemaer undtagen miljøfarlige egenskaber" (Miljøstyrelsen 1993).

Based on the data screening the substances were divided into three groups:

1. Substances with some data
2. Substances with few data
3. Substances with (nearly) no data

It is known from experience that it is often difficult to find relevant data on chemical substances, when there is almost no information in the standard sources. Therefore and because of limited resources, it was decided not go further with those substances in this project.

A more thorough data search was made on each of the substances in groups 1 and 2 in the following databases: Toxline, HSDB, RTECS, IRIS and CCRIS. A more focused data search was performed in the databases Medline (from 1990), Embase (from 1990), Biosis (from 1993) and Toxline with respect to endocrinological and immunotoxic effects, effects on human beings and contents of the substances in body fluids. Further a focused data search was performed in the database Current Contents (from 1994-1998) for data with ecotoxicological relevance.

On few occasions, and when no data were available, structure activity relation analyses was used in the environmental assessment. In these cases, the similar chlorinated compound was used on a "worst case" basis. Especially the potential bioaccumulation of BFR is difficult to assess as the broadly accepted use of the otanol-water partition coefficient may lead to an overestimation of the bioaccumulation because the potential of a substance to bioconcentrate decreases above certain molecular dimensions. It has been proposed that chemicals with a molecular weight above 700 should not be considered potentially bioaccumulative (European Commission, 1996). However, this cut-off value has been subject to criticism and an alternative cut off value of 1000 has been proposed (SCTEE, 1999).

Based on the data retrieved, a short toxicological and ecotoxicological profile was made on each substance. Each profile was closed by a conclusion on the amount and quality of data retrieved and on the possible hazards of the substance.

5 Results

Twelve substances (two were isomers) were selected for further evaluation (table 2). The health and environmental assessment is presented in appendix 2. The substances not assessed in this project because of missing data in the preliminary data screening are listed in table 3. The main conclusions on all evaluated compounds are presented in table 4.

Many of the data and conclusions of some of the BFR were found in well recognised international evaluations/reviews, e.g. WHO's International Programme on Chemical Safety and International Agency for Research on Cancer. It was not possible to locate good national or international assessments on all selected BFR, and many data were found in old and not easily accessible documents. The validity of these tests varies and is often not possible to evaluate. A thorough evaluation of each study was not possible within the limits of this project.

The chemical composition of commercial PBDE products varies with respect to purity and composition of isomers and impurities (see Appendix 2 and Table 5). The documentation of the selected PBDE (PeBDE, OBDE and DeBDE) is seldom based on "pure" substances, and the purity of the individual PBDE is often lower in old products compared to new commercial products. Based on the typical composition of commercial PeBDE, OBDE and DeBDE products, it appears difficult to extrapolate toxic effects from one PBDE to another.

Table 2. Chemical substances subjected to health and environmental assessment

CAS No.	Chemical name
79-94-7	Tetrabromobisphenol A
87-83-2	Pentabromotoluene
118-79-6	2,4,6-Tribromophenol
593-60-2	Vinyl bromide
1163-19-5	Decabromodiphenylether
3194-55-6	1,2,5,6,9,10-hexabromocyclododecane
3296-90-0	2,2-Bis(bromomethyl)propane-1,3-diol
13654-09-6	Decabromobiphenyl
25637-99-4	Hexabromocyclododecane
32534-81-9	Pentabromodiphenylether
32536-52-0	Octabromodiphenylether
88497-56-7	Brominated styrene homopolymer

Table 3. Chemical substances with no or only very few data in the preliminary data screening.

CAS No.	Chemical name
632-79-1	Tetrabromophtalic acid anhydride
3234-02-4	2,3-Dibromo-2-butene-1,4-diol
32588-76-4	Ethylene bis(tetrabromophtalimide)
32844-27-2	TBBPA carbonate oligomer
37853-59-1	1,2-bis(2,4,6-tribromophenoxy)ethane
58965-66-5	1,2,4,5-tetrabromo-3,6-bis(pentabromophenoxy)benzene
68441-62-3	Brominated polyetherpolyol

Table 4. The main conclusions from the health and environmental assessment

CAS No.	Chemicals and conclusions
79-94-7	Tetrabromobisphenol A (TBBPA) The data available do not indicate that TBBPA represent a special health hazard to man. Based on the available information, TBBPA is considered not readily biodegradable. TBBPA is considered to be very toxic to aquatic organisms, and it may cause long-term adverse effects in the aquatic environment
87-83-2	Pentabromotoluene (5BT) The very few data available do not indicate that 5BT represent a special health hazard to man. Based on the available information, 5BT is considered not readily biodegradable.
118-79-6	2,4,6-Tribromophenol Based on the available data it may be concluded that 2,4,6-tribromophenol indicate a possible risk of harm to the human foetus. The available data indicate that 2,4,6-tribromophenol is toxic to aquatic organisms, and that it may cause long-term adverse effects in the aquatic environment.
593-60-2	Vinyl bromide Vinyl bromide is considered to be potential carcinogenic and is classified Carc 2;R45 Fx;R12 (Index No. 602-024-00-2 in Annex 1, Council Directive 67/548/EEC) No ecotoxicity and environmental fate data were available for environmental assessment.
1163-19-5	Decabromodiphenylether (DeBDE) The data available do not indicate that DeBDE represent a special health hazard to man. Based the few data available, DeBDE is considered not readily biodegradable.

CAS No.	Chemicals and conclusions
3194-55-6 25637-99-4	1,2,5,6,9,10-hexabromocyclododecane Hexabromocyclododecane (HBCD) There are some indications of a skin sensitising potential of HBCD, and there may be risk of accumulation in adipose tissue and effects on the liver and thyroid gland in case of repeated exposure. Further research is needed for an adequate evaluation of these effects. Based on available data HBCD is considered to be very toxic for aquatic organisms, and it may cause long-term adverse effects in the aquatic environment.
3296-90-0	2,2-Bis(bromomethyl)propane-1,3-diol (DBNPG) Based on available data DBNPG may be considered harmful if swallowed and potential carcinogenic. No ecotoxicity or environmental fate data were available for environmental assessment.
13654-09-6	Decabromobiphenyl (DeBB) There is some evidence for carcinogenicity of commercial mixtures of PBB to experimental animals. Polybrominated biphenyls (PBB) are in general considered to be potentially bioaccumulative. Too few ecotoxicity and environmental fate data for DeBB were available for environmental assessment.

CAS No.	Chemicals and conclusions
32534-81-9	Pentabromodiphenylether (PeBDE) Studies in rodents with commercial preparations containing PeBDE indicated that the liver is the key target organ affected. The effects observed included macroscopic and histologic changes in liver as well as induction of a range of liver enzymes, and disturbances in cholesterol and porphyrin synthesis. Probably as a consequence of the induction of liver enzymes, the thyroid gland was also affected. Toxicokinetic studies in rats and mice indicate a moderate retention in the organism, and traces have recently been detected in human plasma, milk and fat tissue. Further research is needed for an adequate evaluation of the observed effects. Based on the few available data, PeBDE is considered not readily biodegradable.
32536-52-0	Octabromodiphenylether (OBDE) Exposure of pregnant rats and rabbits to commercial OBDE products of low OBDE purity and high HpBDE content indicated that the foetuses were more sensitive than the dams. Evidence of teratogenicity was found in one rat study, and OBDE may represent a possible risk of harm to the human foetus. Based on the few available data, OBDE is considered not readily biodegradable.
88497-56-7	Brominated styrene homopolymer Brominated polystyrene is not a chemically well defined substance and the molecular formula, $(C_8H_xBr_y)_z$ (x = 5-6, y = 2-3, z = 4-100), indicates the existence of a range of different molecules. The high molecular weight of the material indicates a low potential for transport to the systemic circulation, and the associated toxicity is considered very low. Monomers, solvents and other impurities may account for the mutagenic potential found in some gene mutation assays. The only impurity listed, ethylene dichloride (CAS No. 107-06-2), occurred at very low concentrations, but it is a well known potential carcinogen. No ecotoxicity or environmental fate data were available for environmental assessment.

Table 5. Typical chemical composition of selected PBDE (%)

PBDE	**PeBDE**	**OBDE**	**DBDE**
TrBDE	0-1		
TeBDE	24-38		
PeBDE	50-60	10.5-12.0	
HxBDE	4-8		
HpBDE		43.7-44.5	
OBDE		31.3-35.3	
NBDE		9.5-11.3	Some
DeBDE		0-0.7	97-98

Abbreviations see Appendix 1.

6 Conclusion

The amount and quality of data on the selected BFR varied considerably.

It is difficult to make a general conclusion on the health effects of BFR. With the exception of vinyl bromide and 2,2-Bis(bromomethyl)propane-1,3-diol (DBNPG), most of the BFR have a high n-octanol-water partition coefficient, which indicates potential accumulation in living organisms.

Both vinyl bromide and DBNPG are suspected to be carcinogenic and other data indicate that commercial products of decabromobiphenyl (DeBB) and brominated styrene homopolymer may also have a carcinogenic potential.

Two of the compounds, 2,4,6-tribromophenol and octabromodiphenylether (OBDE), represent a possible risk of harm to the human foetus. Hexabromocyclododecane (HBCD) and pentabromodiphenylether (PeBDE) have an effect on the liver and thyroid gland. It is not known if it is a specific endocrine effect on the thyroid gland, and if the effect observed in rodents is relevant for human beings. Future research may come closer to the answer.

Of all the BFR screened, only the PBDE has been found in humans. PeBDE was detected in adipose tissue, blood and breast milk of human beings. OBDE has been identified in human adipose tissue (up to 8 µg/kg fat) and blood serum (not quantified). DeBDE was detected and quantified in blood serum from all of 3 categories of workers: Hospital cleaners, clerks working full-time at computer screens and personnel at an electronics dismantling plant. The highest blood serum concentrations were in workers at the electronics dismantling plant (median 4.8 µg/kg fat). The serum conc. decreased during summer vacation in the electronics dismantling workers, and results indicated a shorter half-life with increasing degree of bromination. The exposure to PBDE may occur via contaminated food as well as via inhalation of airborne particulate matter.

The substances 2,4,6-tribromophenol, HBCD and tetrabromobisphenol A (TBBPA) were considered to be toxic to aquatic organisms and they may cause long-term adverse effects in the aquatic environment. The substances pentabromotoluene (5BT), OBDE, PeBDE and DeBDE are not readily biodegradable in screening tests. Brominated styrene, vinyl bromide, DBNPG and DeBB were not assessed due to scarcity of data.

Some of the brominated flame retardants included in this investigation are potentially toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment. The brominated flame retardants, most frequently used (TBBPA, HBCD, PBB and PBDE) are present in sediment, mussels and fish. PBB and PBDE

are further present in dolphins, sperm whales and seals. Similar to the polychlorinated biphenyls (PCB) and polychlorinated diphenyl ethers (PCDE) some of the PBB and the PBDE are highly hydrophobic and resistant to degradation processes (de Boer, J., Wester, P. G., Klamer, H. J., Lewis, W. E., and Boon, J. P., 1998). It is therefore possible that these chemicals may accumulate in aquatic sediments or bioconcentrate in living organisms. Signs of toxicity of individual PBB and PBDE to early life stages in rainbow trout were reported (Hornung, M. W., Zabel, E. W., and Peterson, R. E., 1996). Both PBB and PBDEs are slowly degraded in the environment (Pijnenburg, A. M., Everts, J. W., de Boer, J., and Boon, J. P., 1995). The presence of PBBs and PBDEs in mussels, fish, seals and dolphins as well as in sperm whales, which normally stay and feed in deep ocean water, combined with the ongoing industrial production of these compounds indicate that an environmental problem is rising (de Boer, J., Wester, P. G., Klamer, H. J., Lewis, W. E., and Boon, J. P., 1998).

The scientific basis for a risk evaluation of the BFR, included in this investigation, in the aquatic environment is very small and more knowledge is required to improve this. Because of their environmental properties the continued release of HBCD, TBBPA, 2,4,6-tribromophenol, 5BT, OBDE, PeBDE and DeBDE may represent an increasing risk to aquatic organisms.

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8 Appendix 1 – Abbreviations

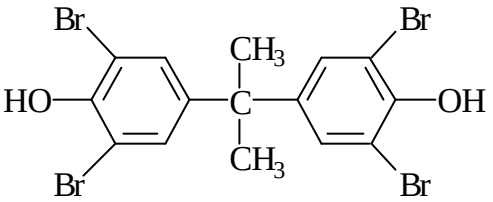
DeBB	Decabromobiphenyl
DeBDE	Decabromodiphenyl ether
DiBB	Dibromobiphenyls
DiBDE	Dibromodiphenyl ethers
HpBDE	Heptabromodiphenyl ethers
HxBB	Hexabromobiphenyls
HxBDE	Hexabromodiphenyl ethers
MBDE	Monobromodiphenyl ethers
MoBB	Monobromobiphenyls
NBDE	Nonabromodiphenyl ethers
NoBB	Nonabromobiphenyls
OBDE	Octabromodiphenyl ethers
OcBB	Octabromobiphenyls
PBB	Polybrominated biphenyls
PBDE	Polybrominated diphenyl ethers
PCB	Polychlorinated biphenyls
PCDE	Polychlorinated diphenyl ethers
PeBB	Pentabromobiphenyls
PeBDE	Pentabromodiphenyl ethers
TeBB	Tetrabromobiphenyls
TeBDE	Tetrabromodiphenylethers
TrBB	Tribromobiphenyls
TrBDE	Tribromodiphenyl ethers

Other abbreviations

approx.	Approximately
b.w.	Body weight
BFR	Brominated flame retardants
ca.	Circa
CAS No.	Chemical Abstract Service registration number
EC 50	Effect concentration
LC50	Lethal concentration
LD50	Lethal dose, median
No.	Number
NOAEL	No observed adverse effect level
LOAEL	Lowest observed adverse effect level

9 Appendix 2 - Data sheets

	Name	CAS No.
1	Tetrabromobisphenol A	79-94-7
2	Pentabromotoluene	87-83-2
3	Tribromophenol	118-79-6
4	Vinyl bromide	593-60-2
5	Decabromodiphenyl ether	1163-19-5
6	Hexabromocyclododecane, isomers (1,2,5,6,9,10-HBCD)	3194-55-6 (25637-99-4)
7	2,2-Bis(bromomethyl)propane-1,3-diol	3296-90-0
8	Decabromobiphenyl	13654-09-6
9	Pentabromodiphenyl ether	32534-81-9
10	Octabromodiphenyl ether	32536-52-0
11	Benzene, ethenyl-, homopolymer, brominated	88497-56-7

1.	**Tetrabromobisphenol A**	
1.1	**Identification of the substance**	
1.1.1	CAS No.	79-94-7
1.1.2	EINECS No.	201-236-9
1.1.3	EINECS Name	Phenol, 4,4' (1-metholethylidene)bis[2,6-dibromo-]
1.1.4	Synonyms	Tetrabromobisphenol A TBBPA 2,2-bis(3,5-bromo-4-hydroxyphenyl)propane 4,4'-isopropylidenebis(2,6-dibromophenol) 4,4'-(1-methylethylidene)bis(2,6-dibromophenol) Tetrabromodihydroxydiphenyl propane
1.1.5	Molecular Formula	$C_{15}H_{12}Br_4O_2$
1.1.6	Structural Formula	
1.1.7	Known uses	Used as flame retardant for plastics, paper, textiles and used as a plasticiser (1)
1.1.8	EU Classification	Not included in Annex I to Directive 67/548/EEC
1.2	**Physico-chemical Characteristics**	
1.2.1	Physical Form	Off-white powder (1)
1.2.2	Molecular Weight	543.92
1.2.3	Melting Point/range (°C)	180-184 (1), 181-182 (2)
1.2.4	Boiling Point/range (°C)	Approx. 316°C
1.2.5	Decomposition Temperature (°C)	No data were found
1.2.6	Vapour Pressure (Pa (°C))	< 1 mmHg at 20 °C (2)
1.2.7	Relative Density (D_4^{20})	2.1 g/ml (3)
1.2.8	Vapour Density (air=1)	No data were found

1.2.9	Conversion Factor (1011 hPa at 25^{o} C)	1 ppm=mg/l (No data available) 1 mg/l=ppm
1.2.10	Solubility	Water: 0.72 mg/l at 15 °C (2) Water: 4.16 mg/l at 25 °C (2) Water: 1.77 mg/l at 35 °C (2) Methanol: 920 mg/l at 25 °C (2) Acetone: 2400 mg/l at 25 °C (2)
1.2.11	Partition Coefficient (log P_{ow})	4.5-5.3 (2)
1.2.12	Flammability	No data were found
1.2.13	Explosivity	No data were found
1.2.14	Oxidising properties	No data were found
1.3	**Toxicological Data**	
1.3.1	Observations in humans	No signs of sensitisation were observed in tests with human volunteers (3, 4) Forty plasma samples from a "random" population in Sweden were examined. Preliminary results from analyses indicated the presence of TBBPA at low ppb level in all samples (5)
1.3.2	Acute Toxicity	
1.3.2.1	Oral	Oral LD50, rats: > 5 g/kg body weight (b.w.) (2) Oral LD50, mice: 3.2 g/kg b.w. (2)
1.3.2.2	Dermal	Dermal LD50, rabbits: > 2 g/kg b.w. (2)
1.3.2.3	Inhalation	Inhalation LC50, rats: > 0.5 mg aerosols/kg b.w./8 hours (2)
1.3.2.4	Other Routes	
1.3.2.5	Skin Irritation	TBBPA was tested in several skin irritation assays in rats and rabbits and did not reveal skin irritation (2)
1.3.2.6	Eye Irritation	TBBPA is not considered to be eye irritating Eye irritation assays in rabbits occasionally showed mild irritation of the conjunctiva, and TBBPA (2).
1.3.2 7	Irritation of Respiratory Tract	Groups of rats were exposed to an atmosphere containing 2, 6 or 18 mg micronised TBBPA/litre air, 4 hours/day, 5 days/week for 2 weeks. Some or all animals in the two highest dose groups had excessive salivation, lacrimation and nasal discharge, which indicated some irritation of conjunctiva and the mucous membranes of the upper res-

		piratory tract (2).
1.3.2.8	Skin Sensitisation	TBBPA was not a skin sensitiser in two guinea pig sensitisation tests (2).
1.3.2.9	Sensitisation by Inhalation	No data were available
1.3.3	Subchronic Toxicity	
1.3.3.1	Oral	1) Charles River CD rats (25 rats/sex/dose level) were exposed to TBBPA in the diet (0, 1, 10, 100, or 1,000 mg/kg diet (ppm ≈ 0, 0.05, 0.5, 5 or 50 mg/kg b.w./day)) for 28 days. Bromine contents of the liver and in fat were higher in the 1,000 ppm group as compared with the controls, but not statistically significant. The no observed adverse effect level (NOAEL) was 50 mg/kg b.w./day (2). 2) Sprague-Dawley rats were exposed to TBBPA for 90 days in the diet corresponding to the following doses: 0 (21 males + 21 females), 0.3 (7 males + 7 females), 3 (21 males + 21 females), 30 (7 males + 7 females) and 100 (7 males + 7 females) mg/kg b.w./day. The NOAEL was 100 mg/kg b.w./day. (2, 6). 3) In a Japanese study B6C3F1 mice (10 mice/sex/group) were fed TBBPA in the diet at 0, 500, 4,900, 15,600 or 50,000 mg/kg diet (ppm, ≈ 0, 71, 700, 2,200, or 7,100 mg/kg b.w.). All mice died at the highest dose level, probably because of malnutrition and anaemia. No deaths were observed at lower doses. At 15,600 mg/kg the following signs were noted: decreased weight gain (food intake was not affected), decreased number of red blood cells, decreased haemoglobin, haematocrit, serum triglycerides, and total serum proteins. The NOAEL was 700 mg/kg b.w./day (2)
1.3.3.2	Inhalation	Groups of rats were exposed to an atmosphere containing 2, 6 or 18 mg micronised TBBPA/litre air, 4 hours/day, 5 days/week for 2 weeks. As mentioned before, some or all animals in the two highest dose groups had excessive salivation, lacrimation and nasal discharge. A decrease in the relative liver weight of the female rats from the three dose levels might have been compound related; but otherwise, no changes in weight gain, food consumption, haematological, biochemical, or urine analytical parameters, gross or microscopic observations were noted. The no observed adverse effect concentration (NOAEC) was 2mg/l (2).

1.3.3.3	Dermal	Groups of 4 rabbits/sex/dose level were exposed to 0, 100, 500, or 2,500 mg TBBPA/kg b.w. for 6 hours/day, 5 days/week, and for 3 weeks. The exposed skin area of one-half of the rabbits in a group was abraded twice each week. No animals died, and no overt toxicity or unusual behaviour was observed. No changes in haematology, biochemistry, urinalysis or in body weight gain were noted. Very light erythema was occasionally seen in the 100 mg/kg dose group and in every animal in the 500 and 2,500 mg/kg dose groups (2).
1.3.4	Chronic Toxicity and Carcinogenicity	No data were available
1.3.5	Mutagenicity	
1.3.5.1	Gene Mutation	TBBPA was tested in several *in vitro* gene mutation assays using *Salmonella typhimurium* or *Saccharomyces cerevisiae*, with or without metabolic activation. All tests were negative (2).
1.3.5.2	Chromosome Abnormalities	No data were available
1.3.5.3	Other Genotoxic Effects	TBBPA was tested in two recently developed *in vitro* assays for intragenic recombination in mammalian cells, the Sp5/V79 recombination assay and the SPD8 recombination assay. TBBPA did not induce statistically significant increases in recombination frequencies in the Sp5 or SPD8 assay system (7)
1.3.6	Reproductive Toxicity, Embryotoxicity, and Teratogenicity	
1.3.6.1	Reproductive Toxicity	No data were available
1.3.6.2	Teratogenicity	TBBPA was administrated, by gavage, at dose levels of 0, 30, 100, 300, 1000, 3000, or 10,000 mg/kg b.w., on gestation days 6-15, to groups of 5 Charles River CD female rats. They were sacrificed on day 20. Three out of 5 dams given 10,000 mg/kg b.w. died, and the two other rats of the group showed slightly reduced weight gain, green, soft faeces, and an increase in matted hair in the anogenital area. There were no embryotoxic or teratogenic effects. The maternal NOAEL was 3,000 mg/kg b.w., and the foetal NOAEL was 10,000 mg/kg b.w. (2).
1.3.7	Other Toxicity Studies	No data were available

1.3.8	Toxicokinetics	TBBPA is very soluble in fat and was previously thought to be poorly absorbed by the gastro-intestinal tract (see below). The uptake by skin and lungs is not known. The following tissue half-lives have been reported after a single oral dose of radioactive labelled TBBPA to rats: 19.9 hours (h) in blood, 70.8 h in fat, 17.1 h in kidneys, 10.8 h in liver, 48.0 in muscle and 60.5 h in gonads (2)
1.4	**Ecotoxicity**	TBBPA is very toxic to aquatic organisms. EC/LC50 is below 1 mg/l: Fish (96h) LC50=0.4 mg/l; Daphnia (48h) LC50=0.96 mg/l; Algae (72h) EC50= 0.09 mg/l (10). NOEC (96h) to fish was 0.1 mg/l for *Lepomis macrochirus*, 0.18 mg/l for *Salmo gairdneri* and 0.26 mg/l for *Pimephales promelas* (10). Bioaccumulation studies with aquatic invertebrates and vertebrates indicate bioconcentration factors ranging from 20 to 3200 (2). The bioconcentration in fish given as BCF was 1200 for *Pimephales promelas* (10).
1.5	**Environmental Fate**	Biodegradation was 0% after 14 days (BOD) activated sludge. The biodegradation in soil (time not indicated) was 36-82% and 44-91% in anaerobic soil (highest in clay loam and lowest in sandy loam soil) (2,10).
1.6	**Environmental Concentrations**	TBBPA was detected in sediments in Japan and Sweden (µg/kg levels) (2). TBBPA residue level in a sediment from Japan was about 20 µg/kg (ppb) on dry weight basis by GC determination (9). The TBBPA dimethyl ether could be identified in mussels and sediment. (2). The residue level of the TBBPA dimethyl ether was 5 µg/kg (w.w) in mussels, Japan (9).
1.7	**Conclusion**	
1.7.1	Health Assessment	Sufficient toxicological data were identified for a health assessment of TBBPA. Most of the data are found in reviews, and many tests have probably not been performed according to internationally accepted guidelines. No data on chronic toxicity, carcinogenicity or reproductive toxicity in multi-generation studies were identified. No chromosome aberration tests or any other mutagenicity

tests except the gene mutation tests were found.

The available data lead to the conclusion that TBBPA seems to be only slightly acute toxic after oral, dermal or inhalation exposure. TBBPA has slightly irritating effects to eyes, skin and respiratory tract, and was not sensitising when tested on guinea pigs and human volunteers. TBBPA was not mutagenic when tested in *in vitro* gene mutation tests. The tests for subchronic toxicity and teratogenicity did not show any indications of possible danger or risks of irreversible health effects by prolonged exposure. There may be a risk of cumulative effects, because of the long half-life of TBBPA in some body tissues.

1.7.2 Environmental Assessment

Based on the available information about TBBPA (it is considered not readily biodegradable, log Pow is 4.5-5.3 and BCF is in the range 20-3200 and L(E)C_{50} for aquatic organisms < 1 mg/l) the substance is considered to be toxic to aquatic organisms, and it may cause long-term adverse effects in the aquatic environment.

1.8 References

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Brominated flame retardants induce intragenic recombination in mammalian cells. Mutation Research - Genetic Toxicology and Environmental Mutagenesis 1999; 439(2):137-47.

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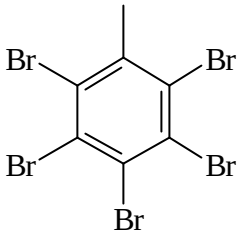
2. Pentabromotoluene

2.1 Identification of the substance

2.1.1	CAS No.	87-83-2
2.1.2	EINECS No.	201-774-4
2.1.3	EINECS Name	2,3,4,5,6-Pentabromotoluene
2.1.4	Synonyms	Pentabromomethylbenzene
		Pentabromotoluene
2.1.5	Molecular Formula	$C_7H_3Br_5$
2.1.6	Structural Formula	
2.1.7	Known Uses	Used in the formulation of glass reinforced unsaturated polyester compounds used in electrical applications as flame retardant bulk moulding compounds (6)
2.1.8	EU Classification	Not included in Annex I to Directive 67/548/EEC

2.2 Physico-chemical Characteristics

2.2.1	Physical Form	Colourless powder
2.2.2	Molecular Weight	486.62
2.2.3	Melting Point/range (°C)	299 (6)
		288 (5)
2.2.4	Boiling Point/range (°C)	No data were available
2.2.5	Decomposition Temperature (°C)	No data were available
2.2.6	Vapour Pressure (Pa (°C))	No data were available
2.2.7	Relative Density (D_4^{20})	3.15 at 20 °C (6)
2.2.8	Vapour Density (air=1)	No data were available
2.2.9	Conversion Factor (1011 hPa at 25^o)	No data were available
2.2.10	Solubility	Water: Insoluble (6)
		Ethanol: Slightly soluble (5)

		Benzene: Soluble (5)
2.2.11	Partition Coefficient (log P_{ow})	5.43 (3)
2.2.12	Flammability	Flash point: 280-282 °F (6)
2.2.13	Explosivity	No data were available
2.2.14	Oxidising properties	No data were available
2.3	**Toxicological Data**	
2.3.1	Observations in humans	No data were available
2.3.2	Acute Toxicity	
2.3.2.1	Oral	No data were available
2.3.2.2	Dermal	No data were available
2.3.2.3	Inhalation	No data were available
2.3.2.4	Other Routes	No data were available
2.3.2.5	Skin Irritation	No data were available
2.3.2.6	Eye Irritation	No data were available
2.3.2 7	Irritation of Respiratory Tract	No data were available
2.3.2.8	Skin Sensitisation	No data were available
2.3.2.9	Sensitisation by Inhalation	No data were available
2.3.3	Subchronic Toxicity	
2.3.3.1	Oral	Sprague-Dawley rats (15 rats/sex/dose level) were exposed to 5BT in the diet (0, 0.05, 0.5, 5.0, 50.0 or 500.0 mg/kg diet (≈ 0, 0.003-0.004, 0.03-0.04, 0.35-0.4, 3.5-4.0 or 34-40 mg/kg b.w./day)) for 91 days. No clinical signs of toxicity was observed, and growth rate and food consumption was not affected. 5BT caused no dramatic changes in biochemistry, haematology and gross pathology. Mild dose-dependent histological changes were observed in the thyroid, liver, and kidney of rats fed 5BT diets. The no observed adverse effect level (NOAEL) was 5.0 mg/kg diet (≈ 0.35 mg/kg b.w./day) (4).
2.3.3.2	Inhalation	No data were available
2.3.3.3	Dermal	No data were available
2.3.4	Chronic Toxicity and Carcinogenicity	No data were available
2.3.5	Mutagenicity	

2.3.5.1	Gene Mutation	5BT was tested for mutagenicity in the Salmonella/microsome preincubation assay using a protocol approved by the National Toxicology Program. A wide range of doses (0, 100, 333, 1000, 3333, and 10,000 µg/plate) was tested in four *Salmonella typhimurium* strains (TA98, TA100, TA1535, and TA1537) in the presence and absence of Aroclor-induced rat or hamster liver S9. These tests were negative and the highest ineffective dose level tested (not causing the formation of a precipitate) in any Salmonella tester strain was 100 µg/plate (1, 2).
2.3.5.2	Chromosome Abnormalities	No data were available
2.3.5.3	Other Genotoxic Effects	No data were available
2.3.6	Reproductive Toxicity, Embryotoxi-city, and Teratogenicity	
2.3.6.1	Reproductive Toxicity	No data were available
2.3.6.2	Teratogenicity	According to an abstract by Ruddick et al. published in Teratology in 1984, no adverse foetal effects were observed when doses up to 600 mg/kg b.w. were given orally to rats during organogenesis (7)
2.3.7	Other Toxicity Studies	No data were available
2.3.8	Toxicokinetics	No data were available
2.4	**Ecotoxicity**	The LC_{50} for fish was > 5 mg/l (48h). The bioconcentration factor was 4.5-39. Log Pow=5.43 (3)
2.5	**Environmental Fate**	5BT is not readily biodegradable (7% of BOD, 4w, 100mg/l substance, 30 mg/l sludge) (3)
2.6	**Environmental Concentrations**	No data were available.
2.7	**Conclusion**	
2.7.1	Health Assessment	Only few toxicological data were identified making an adequate health assessment of 5BT impossible. 5BT was not mutagenic when tested in *in vitro* gene mutation tests. The tests for subchronic toxicity and teratogenicity did not show any indications of possible danger or risks of irreversible health effects by prolonged exposure.

2.7.2 Environmental Assessment

The features log Pow>3, LC_{50} >5 mg/l and not readily biodegradable indicate that 5BT may be able to cause long-term adverse effects in the aquatic environment.

2.8 References

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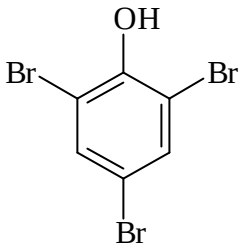
3.	**2,4,6-Tribromophenol**	
3.1	**Identification of the substance**	
3.1.1	CAS No.	118-79-6
3.1.2	EINECS No.	204-278-6
3.1.3	EINECS Name	2,4,6-Tribromophenol
3.1.4	Synonyms	Bromol
3.1.5	Molecular Formula	$C_6H_3Br_3O$
3.1.6	Structural Formula	
3.1.7	Known Uses	Antiseptic & germicide (e.g., in pharmaceutical prepns). Flame retardant in thermoplastic polyester & epoxy resins, in acrylonitrile-butadiene-styrene resins, in phenolic resins & polystyrene. Chemical intermediate for its bismuth salt (antiseptic), for pentachlorophenol and for 2,4,6-tribromophenoxy compounds (19).
3.1.8	EU Classification	Not included in Annex I to Directive 67/548/EEC
3.2	**Physico-chemical Characteristics**	
3.2.1	Physical Form	Long crystals (20). Long crystals or needles from ethanol, and prisms from benzene (22). The odour is penetrating bromine, and the taste is sweet (19).
3.2.2	Molecular Weight	330.80
3.2.3	Melting Point/range (°C)	87-89 (22) 94-96 (20) 95.5 (23) Sublimes at 95°C (22)

3.2.4	Boiling Point/range (°C)	244 (20)
		282-290 (26)
		286 (23)
		Sublimes at 282-290°C, 764 mmHg (19)
3.2.5	Decomposition Temperature (°C)	When heated to decomposition it emits toxic fumes of Br^- (22).
3.2.6	Vapour Pressure (Pa (°C))	No data were available
3.2.7	Relative Density (D_4^{20})	No data were available
3.2.8	Vapour Density (air=1)	11.4 (26)
3.2.9	Conversion Factor (1011 hPa at 25^o)	No data were available
3.2.10	Solubility	Water: Slightly soluble (23)
		Water: 71 mg/l at 15°C (26)
		Water: 996 ppm (15°C), 969 ppm (25°C), and 884 (35°C) (18)
		Ethanol: Very soluble (23)
		Ether: Soluble (23)
		Benzene: Soluble (23)
3.2.11	Partition Coefficient (log P_{ow})	4.020 (26)
		3.3 (18)
3.2.12	Flammability	No data were available
3.2.13	Explosivity	No data were available
3.2.14	Oxidising properties	No data were available
3.3	**Toxicological Data**	
3.3.1	Observations in humans	No data were available
3.3.2	Acute Toxicity	
3.3.2.1	Oral (LD50 values with 95% confidence limits)	Oral LD50, male rats: 1,995 (1,728-2,304) mg/kg body weight (b.w.)
		Oral LD50, female rats: 1,819 (1,513-2,187) mg/kg b.w. (3, 7)
		Oral LD50, male rats: 500 - 5,000 mg/kg b.w. None of the rats (5) died after the administration of 500

		mg/kg b.w., and all five rats died at the 5,000 mg/kg dosage level (8). Oral LD50, male rats: 5,012 (4,034-6,227) mg/kg b.w. Oral LD50, female rats: 5,012 (3,863-6,503) mg/kg b.w. Signs of toxicity included decreased motor activity, nasal discharge, lacrimation, decreased motor activity, tremors, prostration, clonic convulsions and death (6).
3.3.2.2	Dermal	Dermal LD50, rabbits: >2,000 mg/kg b.w. (8) Dermal LD50, rabbits: >8,000 mg/kg b.w. All four rabbits appeared normal during the 24 hours exposure to 8 g/kg b.w. (occluded) and the 14 days observation period (4).
3.3.2.3	Inhalation	Dust inhalation LC50, rats: >1.63 mg/l/4 hours. 65% of the particles were less than 6 microns (16) (IBT). Dust inhalation LC50, rats: >200 mg/l/1 hour; 10 rats were exposed in a whole-body-exposure chamber to atmospheric dust concentrations of 2 or 200 mg/l. Signs at both concentrations included nasal discharge, eye squint, increased followed by decreased respiratory rates, prostration, salivation, lacrimation, erythema, increased followed by decreased motor activity, and ocular and nasal porphyrin discharge. No details were available about f.ex. particle size distribution. All rats appeared normal from day 7 post exposure, except on day 10 of the 14 day observation period when one rat at low exposure level exhibited nasal porphyrin discharge (8). Dust inhalation LC50, rats: >50 mg/l/4 hours; 10 rats were exposed in a whole-body-exposure chamber to atmospheric dust concentrations of 50 mg/l for 4 hours. Signs included eye squint, slight dyspnoea, erythema, decreased motor activity, ocular porphyrin discharge, nasal discharge and diarrhoea. From 5 days to 14 days post exposure

		several rats continued to show diarrhoea and nasal discharge. Particle size distribution was not measured (5).
3.3.2.4	Other Routes	No data were available
3.3.2.5	Skin Irritation	Grading of dermal reactions (mean of the 24 and 72 hours examinations/max. score): Erythema and eschar: 0.17/4 Oedema: 0.00/4 (8, 15)
3.3.2.6	Eye Irritation	Grading of ocular lesions (mean of the 24, 48 and 72 hours examinations/max. score): Cornea opacity: 0.06/4 Iris: 0.28/2 Conjunctivae, erythema: 1.78/3 Conjunctivae, oedema: 1.00/4 The effects appeared reversible, but at the end of the observation period of 7 days, 3 out of 6 rabbits had slight or very slight conjunctival redness. The 4/6 worst affected rabbits had a conjunctival redness score of 2.08/3. (8, 11)
3.3.2 7	Irritation of Respiratory Tract	Irritating to mucous membranes (26)
3.3.2.8	Skin Sensitisation	Eight guinea pigs were induced by 10 intradermal injections with 0.05-0.10 ml 0.1% 2,4,6-tribromophenol in salt water. A group of 4 guinea pigs received 2,4-dinitro-1-chlorobenzene as a positive control. Two weeks after the 10^{th} sensitising dose a challenge dose of 0.05 ml 0.1% 2,4,6-tribromophenol in salt water was given to all animals. The reactions were read 24 and 48 hours after the challenge. Four of the eight guinea pigs responded to the challenge dose, exhibiting a flare response slightly greater than that obtained in the sensitising doses. Two of the four animals in the control group exhibited a flare response slightly greater than that obtained in the sensitising doses. The vehicle was negative. The test compound was considered positive under the conditions of this preliminary test (10)

3.3.2.9	Sensitisation by Inhalation	No data were available
3.3.3	Subchronic Toxicity	
3.3.3.1	Oral	No data were available
3.3.3.2	Inhalation	Three groups of rats each consisting of 5 males and 5 females were exposed (whole-body) to atmospheric dust concentrations (analytical) of 0, 0.10 and 0.92 mg/l, respectively, for 6 hours/day, 5 days/week, for 3 weeks. The particle size distribution was not measured. Two high-dose animals died after 10-11 exposures. The clinical signs in both treatment groups included hypoactivity, salivation, lacrimation and red nasal discharge. Reduced weight gain was observed in low and high dose females and in high dose males. No test material related changes in haematology, clinical chemistry or urinalysis were observed. Gross and histopathological changes were observed in liver and kidneys of high dose rats. The NOAEL in this study appears to be <0.10 mg/l for females and 0.10 mg/l for males. (16) (IBT)
3.3.3.3	Dermal	A 28-day subacute dermal toxicity study was conducted with 2,4,6-tribromophenol in albino rabbits. The test material was applied to the clipped, unoccluded skin as a 50% suspension in aqueous methyl cellulose. This test suspension was applied 5 days/week for a period of 4 weeks at dose levels of 0, 100, 300 and 1,000 mg/kg/day to 4 rabbits/sex/dose level. The test skin sites of 2 rabbits/sex/dose level were abraded. The only treatment related effects observed were local skin reactions of all animals. One high dose animal died of unknown reasons. (1, 2) and (9, 17) (IBT)
3.3.4	Chronic Toxicity and Carcinogenicity	No data were available
3.3.5	Mutagenicity	
3.3.5.1	Gene Mutation	2,4,6-Tribromophenol was tested for mutagenicity in the Salmonella/microsome preincubation assay using a protocol approved by the National Toxicology Program. A wide range of doses (0, 3, 10, 33, 100, and 333 µg/plate) was tested in four *Salmonella typhimurium* strains (TA98, TA100, TA1535, and TA1537) in the presence and absence of Aro-

		clor-induced rat or hamster liver S9. These tests were negative and the highest ineffective dose level tested (not causing a slight clearing of the background lawn) in any Salmonella tester strain was 100 µg/plate (19). 2,4,6-Tribromophenol was tested for mutagenicity in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, and in *Saccharomyces cerevisiae* strain D4 in the presence and absence a metabolic activation system. 2,4,6-Tribromophenol was negative in all test assays. (12)
3.3.5.2	Chromosome Abnormalities	No data were available
3.3.5.3	Other Genotoxic Effects	No data were available
3.3.6	Reproductive Toxicity, Embryotoxi-city, and Teratogenicity	
3.3.6.1	Reproductive Toxicity	No data were available
3.3.6.2	Teratogenicity	In a pilot study, mated Charles River CD female rats were dosed with 2,4,6-tribromophenol by gavage at 0, 10, 30, 100, 300, 1,000 and 3,000 mg/kg/day from gestation day 6 through day 15. The study was performed to determine dosage levels for a teratology study. All animals died at the highest dose group after one day of treatment. There were slight decreases in body weight gains between days 6 and 12, an increase in post implantation losses, and a slight decrease in the number of viable foetuses at the 1,000 mg/kg/day dose group. The NOAEL appears to have been 300 mg/kg/day for both dams and foetuses (embryotoxicity). (14) In order to investigate the developmental neurotoxicity and immunotoxicity, pregnant Wistar rats were exposed to 2,4,6-tribromophenol by inhalation in a whole body exposure chamber (0, 0.03, 0.1, 0.3 and 1.0 mg/m^3, 24 hours/day, and 7 days/week, from day 1 to 21 of gestation. The results suggested that 2,4,6-tribromophenol during this exposure regime may be a developmental neurotoxicant, embryotoxicant and foetotoxicant but not immunotoxicant.

		The NOAEL for developmental neurotoxicity could not be established (<0.03 mg/m^3), and the NOAEL for maternal neurotoxicity was 0.3 mg/m^3 (24).
3.3.7	Other Toxicity Studies	No data were available
3.3.8	Toxicokinetics	A single oral dose of ^{14}C-labeled 2,4,6-tribromophenol (4.0-5.3 mg/kg b.w.) was rapidly absorbed in rats. 48 hours after the administration, 77% of the radioactivity was excreted via the urine and 2-14% via faeces, and detectable radioactivity was measured in kidneys, lungs and liver. Blood concentrations peaked 1 hour after dosing at 4.57 ppm and then plunged to 0.002 ppm by 24 hours (half-life in blood: 2.03 hours). The pharmacokinetics appeared to follow a one-compartment open model. 2,4,6-tribromophenol was rapidly distributed in the body, and the elimination in the urine was proportional to the concentration in the blood (13). May be absorbed dermally (22).
3.4	**Ecotoxicity**	For tribromophenol the LC_{50} (fish) was 6.5-6.8 mg/l (96h, *Pimephales promelas*) (25). LC_{50} 1.1 mg/l (96h, fathead minnow, flow through bioassay) (26)
3.5	**Environmental Fate**	Tribromophenol is not readily biodegradable (49% of BOD, 4w, 100 mg/l substance, 30 mg/l sludge) (21)
3.6	**Environmental Concentrations**	2,4,6-tribromophenol was measured in wild-harvested prawns, and ocean fish, Eastern Australia. The levels ranged from 0.1 to 230 ng/g in fish (gut, flesh) and 0.12-460 ng/g in prawns (head, tail) (27, 28).
3.7	**Conclusion**	
3.7.1	Health Assessment	Sufficient toxicological data were identified for a health assessment of 2,4,6-tribromophenol. Most of the data were found in documents submitted to the U.S. EPA. These documents contain study reports of tests performed in the late nineteen seventies, not according presently accepted international guidelines and Good Laboratory Practice. A few of the tests were conducted by Industrial Bio-Test Laboratories, a concern later found to have submitted many flawed or fraudulent reports on its procedures and results. No data on chronic toxicity,

carcinogenicity or reproductive toxicity in multi-generation studies were identified. No chromosome aberration tests or any other mutagenicity tests except the gene mutation tests were found. No data on humans were identified.

Although the results may sometimes be conflicting, the available data lead to the conclusion that 2,4,6-tribromophenol seems to be only slightly acute toxic after oral, dermal or inhalation exposure. 2,4,6-tribromophenol is slightly skin irritating and moderately eye irritating. Based on a preliminary test, it may have a skin sensitising potential. 2,4,6-Tribromophenol was not mutagenic when tested in *in vitro* gene mutation tests. The tests for sub-chronic inhalation and dermal toxicity did not reveal any indications of possible danger or risks of irreversible health effects by prolonged exposure. A preliminary study indicated that 2,4,6-tribromophenol might be embryotoxic at oral dosage levels causing only a slight decrease in maternal weight gain during the gestational exposure period. A study published in 1998 suggested that inhalation of 2,4,6-tribromophenol may cause specific developmental neurotoxicity, embryotoxicity and foetotoxicity. Despite a high n-octanol-water partition coefficient (3.3-4.0), toxicokinetic studies did not indicate a cumulative or persistent effect of 2,4,6-tribromophenol in mammalian systems.

3.7.2 Environmental Assessment

The features 1 mg/l < LC_{50}< 10 mg/l, Log Pow>3 and not readily biodegradable indicate that tribromophenol may be considered to be toxic to aquatic organisms and may also be able to cause long-term adverse effects in the aquatic environment.

3.8 References

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2. 28-Day subacute dermal toxicity study with 2,4,6-tribromophenol in albino rabbits with attachments and cover letter dated 011978. EPA/OTS; Doc #88-7800069 1978. NTIS/OTS0200055.

3. Acute oral toxicity (ld50) study in rats with cover letter and attachment. EPA/OTS; Doc #88-

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4. Acute dermal toxicity in male and female albino rabbits with test data and cover letter dated 03-08-90. EPA/OTS; Doc #86-900000306 1990. NTIS/OTS0523298.

5. Acute inhalation toxicity in the albino rat with test data and cover letter. EPA/OTS; Doc #86-900000305 1990. NTIS/OTS0523297.

6. Acute oral toxicity ld50 study in albino rats with test data and cover letter dated 03-08-90. EPA/OTS; Doc #86-900000307 1990. NTIS/OTS0523299.

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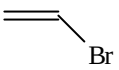
4.	**Vinyl bromide**	
4.1	**Identification of the substance**	
4.1.1	CAS No.	593-60-2
4.1.2	EINECS No.	209-800-6
4.1.3	EINECS Name	Bromoethylene
4.1.4	Synonyms	Bromoethene
4.1.5	Molecular Formula	C_2H_3Br
4.1.6	Structural Formula	
4.1.7	Known Uses	Intermediate in organic synthesis and in the manufacture of polymers, copolymers, flame retardant, pharmaceuticals and fumigants (9). Purity: 99.8% min (9) Impurities: Water, 100 mg/kg; non-volatile matter (including inhibitor), 500 mg/kg max. inhibitor (hydroquinone methyl ether), 175-225 mg/kg (9)
4.1.8	EU Classification	Carc 2;R45 Fx;R12 (Index No. 602-024-00-2 in Annex 1, Council Directive 67/548/EEC)
4.2	**Physico-chemical Characteristics**	
4.2.1	Physical Form	Gas, colourless liquid under pressure, characteristic pungent odour (9)
4.2.2	Molecular Weight	106.96
4.2.3	Melting Point/range (°C)	-139.5 (9)
4.2.4	Boiling Point/range (°C)	15.8 (9)
4.2.5	Decomposition Temperature (°C)	When heated to decomposition it emits toxic fumes of Br^- (11)
4.2.6	Vapour Pressure (Pa (°C))	119.32×10^3 at 20°C (9)
4.2.7	Relative Density (D_4^{20})	1.4933 (9)
4.2.8	Vapour Density (air=1)	3.7 (9)
4.2.9	Conversion Factor (1011 hPa at 25^o)	1 ppm = 0.00437 mg/l 1 mg/l = 228.833 ppm (9)

4.2.10	Solubility	Water: Insoluble Ethanol: soluble Ether: soluble Acetone: soluble (12)
4.2.11	Partition Coefficient (log P_{ow})	1.38 (1)
4.2.12	Flammability	Vinyl bromide has no flash point by standard tests in air (15). It is a very dangerous fire hazard when exposed to heat of flame, and it can reacts with violently with oxidizing materials (11)
4.2.13	Explosivity	With a high-energy ignition source the explosive limits are 9 to 15% by volume in air (15)
4.2.14	Oxidising properties	No data available
4.3	**Toxicological Data**	
4.3.1	Observations in humans	There have been no reported cases of cancer in humans associated with exposure to vinyl bromide. However, vinyl bromide has only been in commercial production since 1971. Due to the long latency period of cancer, no cases would have been expected (3).
4.3.2	Acute Toxicity	
4.3.2.1	Oral	Oral LD50, rats: approx. 500 mg/kg, when chilled 50% solution in corn oil was fed to male rats (15)
4.3.2.2	Dermal	No data available
4.3.2.3	Inhalation	7 mmol/l (1,700 ppm) was the highest tolerable concentration for mice exposed for 10 minutes. Half that concentration produced pronounced anaesthesia (15).

		Exposure of rats to a nominal concentration of 100,000 ppm (438 mg/l) resulted in deep anaesthesia and death within 15 min. Exposure of rats to a nominal concentration of 50,000 ppm (219 mg/l) resulted in unconsciousness within 25 min. All animals survived 1½-hour exposure, but not a 7-hour exposure. Exposure of rats to a nominal concentration of 25,000 ppm (109 mg/l) resulted in unconsciousness but no death within 7 hours of exposure. Necropsy of survivors of the 50,000 ppm group 2 weeks after the exposure revealed macroscopic liver and kidney damage. These effects were not seen in the 25,000 ppm group (15).
4.3.2.4	Other Routes	No data available
4.3.2.5	Skin Irritation	Nonirritating to the intact skin of rabbits, and produce no frostbite from evaporation of the liquid (15)
4.3.2.6	Eye Irritation	Slightly to moderately irritating to the eyes (15)
4.3.2 7	Irritation of Respiratory Tract	No data available
4.3.2.8	Skin Sensitisation	No data available
4.3.2.9	Sensitisation by Inhalation	No data available
4.3.3	Subchronic Toxicity	
4.3.3.1	Oral	No data available
4.3.3.2	Inhalation	Male and female rats, rabbits, and monkeys were exposed to 250 ppm or 500 ppm, 6 hours/day, for 6 months. Except for an increase in blood bromine ion concentration no apparent effect was observed (15)
4.3.3.3	Dermal	30 mice received topical applications of vinyl bromide (15 mg/animal in 0.1 ml acetone, three times/week). No skin tumours were observed after 60 weeks. When testing for initiating action of vinyl bromide, applying phorbol myristate acetate (PMA) as a promoter, 1 mouse of 30 developed skin papilloma at day 412, whereas no skin tumours occurred in the 160 control animals (16) and (9).

4.3.4 Chronic Toxicity and Carcinogenicity

In this study, 120 Sprague-Dawley rats/sex/group (144 in the control) were in whole-body exposure chambers exposed to target concentrations of 0, 10, 50, 250, and 1250 ppm [actual concentrations were 0, 9.7, 52, 247, or 1235 ppm (0, 0.043, 0.230, 1.095, or 5.474 mg/l), respectively] vinyl bromide vapour for 6 hours/day, 5 days/week for 6, 12, 18, or 24 months. Purity: 99.9%. Impurities: 197 ppm (0.02%) hydroquinone methyl ether (CAS No. 150-76-5) as stabiliser, 282 ppm (0.03%) ethylene oxide (CAS No. 75-21-8), 7 ppm (0.0007%) acetylene (CAS No. 74-86-2), and 80 ppm (0.008%) aldehydes and ketones.

Dose-related decrease in body weight and an increase in mortality. The 5.4625 mg/l group was terminated at 18 month due to excessive mortality. Some blood parameters were changed. Angiosarcoma, primarily of the liver, was induced in both male and female in all four exposure groups. Also a significant increase in the number of Zymbal's gland neoplasms was seen as well as increased incidence of hepatocellular neoplasms (4, 9, and 2)

Newborn Wistar rats were exposed from their first day of life to an atmospheric concentration of 8.74 mg/l 8 hours/day, 5 days/week, for up to 15 weeks. Two weeks after cessation of exposure, the animals were sacrificed and the liver taken for histochemical evaluation of ATPase deficient foci as a measure of pre-neoplastic foci. An obvious oncogenic potential approx. 0.1 of that of vinyl chloride was seen (6).

4.3.5 Mutagenicity

4.3.5.1 Gene Mutation

Salmonella typhimurium strains TA-1530 and TA-100 were exposed to vinyl bromide in air for various time periods. Vinyl bromide was mutagenic both in the absence and presence of a metabolic system from the liver of Aroclor-induced rats or phenobarbital-induced mice or humans (9).

Vinyl bromide was strongly positive in three test strains of *Drosophila* and weakly positive in three test strains (w/w^+ eye mosaic assay) (13)

		The *in vivo* genotoxicity of vinyl bromide was tested in the alkaline single cell gel electrophoresis (comet) assay in mouse organs (stomach, liver, kidney, bladder, lung, brain, and bone marrow). Vinyl bromide resulted in DNA damage in all organs investigated except for the bone marrow. The DNA damage was apparently not attributed to cytotoxicity (14).
4.3.5.2	Chromosome Abnormalities	No data available
4.3.5.3	Other Genotoxic Effects	No data available
4.3.6	Reproductive Toxicity, Embryo-toxicity, and Teratogenicity	
4.3.6.1	Reproductive Toxicity	No data available
4.3.6.2	Teratogenicity	No data available
4.3.7	Other Toxicity Studies	Vinyl bromide can act as a direct alkylating agent. Following exposure of rats to vinyl bromide by inhalation, protein and nucleic acid adducts were found in various tissues (5).
4.3.8	Toxicokinetics	Vinyl bromide is readily absorbed by the lungs in rats and is rapidly metabolised. Metabolism was saturable at exposure concentration > 55 ppm and was associated with release of bromine in to the plasma. *In vitro* experiments indicate that the primary metabolite of vinyl bromide is the epoxide, 2-bromoethylene oxide (CAS No. unknown), which rearranges to 2-bromoacetaldehyde (CAS No. 17157-48-1). Both metabolites are alkylating agents (5) and (7).
4.4	**Ecotoxicity**	As no ecotoxicity data were available, the data for the analogous substance vinyl chloride (CAS: 75-01-4) were used. For vinyl chloride the LC_{50} (fish) was 356-406 mg/l (*Leuciscus idus melanotus*). The bioconcentration factor in fish was 7, LogPow 1.38 (1)
4.5	**Environmental Fate**	As no environmental fate data were available, the data for the analogous substance vinyl chloride (CAS: 75-01-4) were used. Vinyl chloride (75-01-4) is not readily biodegradable (1)
4.6	**Environmental Concentrations**	No data were available.

4.7 Conclusion

4.7.1 Health Assessment

Sufficient toxicological data were identified for a health assessment of Vinyl bromide. Most of the data were cited from recognized scientific toxicological reviews. No data on sensitisation or reproductive toxicity were identified. No chromosome aberration tests or any other mutagenicity tests except the gene mutation tests were found. No relevant data on humans were identified.

Vinyl bromide is a very dangerous fire hazard when exposed to heat of flame, and it can react violently with oxidizing materials. The Commission of the European Communities has classified it: "Extremely flammable" (Fx; R12) (Annex 1, Council Directive 67/548/EEC).

Vinyl bromide possesses a moderate acute toxicity. Because of the high vapour pressure inhalation is the most relevant route of exposure. Direct contact of undiluted vinyl bromide to the eye may result in a slightly to moderately irritation, whereas it is apparently not skin irritating.

Some evidence mutagenic activities *in vitro* and *in vivo* have been found. The carcinogenicity of vinyl bromide was considered by IARC last time in 1987. They concluded that there is sufficient evidence for the carcinogenicity of vinyl bromide in experimental animals, and that vinyl bromide is probably carcinogenic to humans (Group 2A) (8, 9, 10). The Commission of the European Communities with has recently adjusted the classification of vinyl bromide: "May cause cancer" (Carc2; R45) (Annex 1, Council Directive 67/548/EEC).

4.7.2 Environmental Assessment

No ecotoxicity or environmental fate data for vinyl bromide were available for environmental assessment.

Vinyl chloride is officially classified with Carc1; R45 F_x;R12 (1). The available data indicate no environmental classification of the substance.

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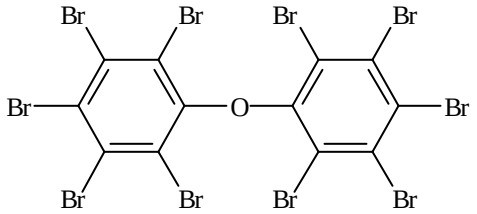
5. Decabromodiphenyl ether

5.1 Identification of the substance

5.1.1	CAS No.	1163-19-5
5.1.2	EINECS No.	214-604-9
5.1.3	EINECS Name	Benzene, 1,1'-oxybis[2,3,4,5,6-pentabromo-
5.1.4	Synonyms	Bis(pentabromophenyl) ether Decabromobiphenyl oxide Decabromobiphenyl ether Decabromodiphenyl oxide Ether, bis(pentabromophenyl) DeBDE
		Typical composition for commercial DeBDE products would be 97-98% DeBDE with 0.3-3.0% of other brominated diphenyl ethers, mainly nonabromodiphenyl ether (NBDE, CAS No. 63936-56-1). Older products may contain less DeBDE. For instance a composition of 77.4% DeBDE, 21.8% NBDE and 0.85% octabromodiphenyl ether (OBDE, CAS No. 32536-52-0) has been reported for an older product ((Dow) FR-300-BA) (7).
5.1.5	Molecular Formula	$C_{12}Br_{10}O$
5.1.6	Structural Formula	Based on the chemical structure, DeBDE is fully brominated and there is only one congener.



5.1.7	Known Uses	Organic synthesis and flame retardant
5.1.8	EU Classification	Not included in Annex I to Directive 67/548/EEC

5.2	**Physico-chemical Characteristics**	
5.2.1	Physical Form	Off white powder, depending on the manufacturer (7)
5.2.2	Molecular Weight	959.22
5.2.3	Melting Point/range (°C)	290-306
5.2.4	Boiling Point/range (°C)	Boiling point is not applicable to this substance
5.2.5	Decomposition Temperature (°C)	> 320 - 425 (different products) (7)
5.2.6	Vapour Pressure (Pa (°C))	$< 1.3x10^{-4}$ (20)
		< 133 (250)
		271 (278)
		661 (306)
		(1, 7)
5.2.7	Relative Density (D_4^{20})	3.0 or 3.25 (7)
5.2.8	Vapour Density (air=1)	No data
5.2.9	Conversion Factor (1011 hPa at 25^o)	No data
5.2.10	Solubility	Water: ca. 0.002 - 0.003 mg/l
		(Dow FR-300-BA: 77.4% DeBDE, 21.8% NBDE, and 0.8% OBDE) (1)
		Acetone: 0.5 or 1.0 g/l
		Benzene: 1.0 or 4.8 g/l
		(7)
5.2.11	Partition Coefficient (log P_{ow})	5.24* or 9.97** (7)
		* (Dow FR-300-BA: 77.4% DeBDE, 21.8% NBDE, and 0.8% OBDE) (1)
		** (Unknown composition)
5.2.12	Flammability	Non-flammable (7)
5.2.13	Explosivity	Not applicable on the basis of its structure and physical properties nor is it known to contribute explosive properties with other materials
5.2.14	Oxidising properties	Not considered to be an oxidiser

5.3 Toxicological Data

5.3.1	Observations in humans	In a human patch test, 5% DeBDE (FR-300-BA) in petrolatum was repeatedly applied, 3 times a week for 3 weeks, to skin of 50 human subjects. This treatment did not result in skin sensitisation reactions during the sensitising period or on challenge two weeks subsequent to the last induction application. In 9 out of 50 subjects a slight to moderate skin irritation was observed (7) and (1). In a recent Swedish study, DeBDE was detected and quantified in blood serum from 3 categories of workers (median (range) in pmol/g lipid weight): Hospital cleaners (control group): <0.7 (<0.3-3.9), Clerks working full-time at computer screens: <0.7 (<0.3-8.0) and Personnel at an electronics dismantling plant: 5.0 [≈ 4.8 µg/kg fat] (<0.3-9.9). The serum conc. decreased during summer vacation in the electronics dismantling workers, and results indicated a shorter half-life with increasing degree of brominating. The exposure to DeBDE may occur via contaminated food and inhalation of airborne particulate matter (8).
5.3.2	Acute Toxicity	
5.3.2.1	Oral	Oral LD50, female Sprague-Dawley rats: > 2,000 mg/kg b.w. No clinical signs of toxicity were observed during the 14 day observation period. No gross lesions were detected at necropsy. The test material was FR-300-BA (7) and (1). Oral LD50, male Sprague-Dawley rats: > 5,000 mg/kg b.w. No clinical signs of toxicity were observed during the 14 day observation period (7).
5.3.2.2	Dermal	Dermal LD50, rabbits: > 2,000 mg/kg b.w.

		Commercial DeBDE was applied and occluded on the clipped intact skin of 2 male and 2 female New Zealand white rabbits each at a dosage of 200 or 2000 mg/kg body weight for 24 hours. Animals were observed for 14 days. No mortality occurred. (7) and (1).
5.3.2.3	Inhalation	Inhalation LC50, Sprague-Dawley rats: > 48.2 mg/l/1 hour. Groups of 10 rats/sex were exposed for 1 hour to concentrations of DeBDE of 2 or 48.2 mg/l in air and subsequently observed for 14 days. There was no information on particle size distribution. All rats survived. At 2 mg/l salivation was noted in 2 rats on the first day, but thereafter all the rats of this group appeared normal, except one with respiratory difficulties and another with ocular discharge during the observation period. At 48.1 mg/l eye squint and increased motor activity was noted in the animals through day four. Respiratory difficulties were noted in 2 rats at days 3 to 6 and in one rat on day 8 and one on day 7. A few rats showed eye squint and ocular discharge on days 7 to 12. All rats were normal on day 14 (7) and (1).
5.3.2.4	Other Routes	No data were available
5.3.2.5	Skin Irritation	Two commercial DeBDE products were tested in rabbits, and no evidence of skin irritation was observed (7) and (1). The potential for DeBDE to produce chloracne was studied in rabbits. A commercial product (Saytex 102 as a 10% chloroform solution) caused a slight irritation but no chloracnegenic activity (7) and (1).
5.3.2.6	Eye Irritation	Two commercial DeBDE products were tested in rabbit eyes, and only a transient mild irritation of the conjunctival membranes was observed (7) and (1).
5.3.2 7	Irritation of Respiratory Tract	No data were available
5.3.2.8	Skin Sensitisation	No data were available
5.3.2.9	Sensitisation by Inhalation	No data were available
5.3.3	Subchronic Toxicity	
5.3.3.1	Oral	Groups of 10 male and 10 female F344/N rats and B6C3F1 mice were fed diets containing 0, 3.1, 6.2,

		12.5, 25.0 or 50.0 g DeBDE/kg diet for 13 weeks. The purity of DeBDE was 94-99%. All rats and mice lived to the end of the study. DeBDE did not adversely affect food consumption or final mean body weights. No compound related clinical signs or gross or microscopic pathologic effects were observed. NOAEL was 50.0 mg/kg diet. Liver weights were not recorded in these studies, but, in subsequent studies, liver weights were significantly increased in F344/N rats at dose levels of 25 and 50 g DeBDE (92%)/kg diet, for 14 days (7) and (1).
5.3.3.2	Inhalation	Fifty rats were observed up to 556 days after a single intratracheal installation of 20 mg DeBDE (77.4%) dust (length mean diameter 2.65 µm, surface mean diameter 2.91 µm, and volume mean diameter 3.17 µm) suspended in 1 ml of rat serum. The half-life of DeBDE particles in the lung was ca. 150 days. No evidence of proliferative response was detected in the lungs or regional lymph nodes (7).
5.3.3.3	Dermal	No data available
5.3.4	Chronic Toxicity and Carcinogenicity	A 2 year study of DeBDE (FR-300-BA) for chronic toxicity and carcinogenicity to male and female Sprague-Dawley rats (25 male and 25 females/dose group) maintained on diets providing 0, 0.01, 0.1 or 1.0 mg/kg body weight/day indicated no discernable alteration in appearance, behaviour, body weight, feed consumption, haematological analysis, urinalysis, clinical chemistry, organ weights, survival, or tumour incidence. The dose levels selected were too low (6) and (1). In the U.S. National Toxicology Program (NTP), groups of 50 male and 50 female F344/N rats were exposed to DeBDE (purity 94-99%, no brominated dioxins or furans) in the diet at levels of 0, 25 or 50 g/kg for 103 weeks. The average DeBDE consumption was: 25 g/kg, male rats: 1,120 mg/kg/day 25 g/kg, female rats: 1,200 mg/kg/day 50 g/kg, male rats: 2,240 mg/kg/day 50 g/kg, female rats: 2,550 mg/kg/day Body weights of dosed male and female rats in the 2

year study were comparable to those of the control animals. No treatment related effect on survival was noted. Minimal chronic toxicity was exhibited.

The incidence of neoplastic nodules in the liver of low and high dose male rats (1/50; 7/50; 15/49) and high dose female rats (1/50; 3/49; 9/50) were statistically greater than those in the controls.

Under the conditions of this 2 year feed study of DeBDE, there was some evidence of carcinogenicity for male and female F344/N rats as shown by increased incidence of neoplastic nodules of the liver in low dose (25 g/kg diet) males and high dose (50 g/kg diet) groups of each sex.

The incidence of acinar-cell adenomas of the pancreas in males was significantly increased (1/49; 0/50; 4/49), but not significantly different from the controls. The incidence of mononuclear-cell leukaemia was also increased in males. Several non-neoplastic lesions were observed at increased incidence (1, 6 and 7).

In the U.S. National Toxicology Program (NTP), groups of 50 male and 50 female B6C3F1 mice were exposed to DeBDE (purity 94-99%, no brominated dioxins or furans) in the diet at levels of 0, 25 or 50 g/kg for 103 weeks.

The average DeBDE consumption was:

25 g/kg, male mice: 3,200 mg/kg/day

25 g/kg, female mice: 3,760 mg/kg/day

50 g/kg, male mice: 6,650 mg/kg/day

50 g/kg, male mice: 7,780 mg/kg/day

Body weights of dosed male and female mice in the 2 year study were comparable to those of the control animals. No treatment related effect on survival was noted. Minimal chronic toxicity was exhibited.

Hepatocellular adenomas or carcinomas occurred at marginally increased incidence in dosed male mice only (8/50; 22/50; 18/50), but not increased in comparison with historical control groups. The incidences of thyroid gland follicular cell adenomas or carcinomas (combined) were increased, but not significantly, in dosed

		male mice (0/50; 4/50; 3/50) and females (1/50; 3/50; 3/50). Under the conditions of this 2 year feed study of DeBDE, there was equivocal evidence of carcinogenicity for male B6C3F1 mice as shown by increased incidence of hepatocellular adenomas or carcinomas (combined) in the low dose group and of thyroid gland follicular cell adenomas or carcinomas (combined) in both dosed groups. There was no evidence of carcinogenicity for female B6C3F1 mice receiving 25 or 50 g/kg diet. Thyroid gland follicular cell hyperplasia was in creased in both groups of treated male and female mice (7) and (1).
5.3.5	Mutagenicity	
5.3.5.1	Gene Mutation	DeBDE (in various purities) was tested in two Ames tests with *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100, or *Saccharomyces cerevisiae*, with and without metabolic activation. No evidence of mutagenic activity was found (1, 2, 7).
5.3.5.2	Chromosome Abnormalities	Commercial grade DeBDE was not mutagenic in a Mouse lymphoma L5178Y/TK+/- assay or in Chinese Hamster Ovary Cells for Sister Chromatid Exchange or Chromosome Aberrations, all with and without metabolic activation (7) and (1).
5.3.5.3	Other Genotoxic Effects	No data available
5.3.6	Reproductive Toxicity, Embryotoxicity, and Teratogenicity	
5.3.6.1	Reproductive Toxicity	A one-generation reproduction study was performed with 10 male and 20 female Sprague-Dawley rats at the two lower dose levels (3 and 30 mg/kg b.w./day) and 15 male and 30 female rats at the higher dose level (100 mg/kg b.w./day).Twenty males and 40 females served as controls. The reproductive capacity of rats was not affected by diets providing those dose levels of DeBDE (FR-300-BA) given for 60 days prior to mating, 15 days during mating, and throughout gestation and lactation. NOAEL was 100 mg/kg/day. This is the highest dose tested. No adverse effect on fertility was observed (7).
5.3.6.2	Teratogenicity	Pregnant female rats (number unknown) were given 0, 10, 100, or 1,000 mg DeBDE (FR-300-BA)/kg bw

suspended in corn oil by intragastric gavage on days 6-15 of gestation. There was no evidence of toxicity or teratogenicity at any dose level. Maternal food consumption and body weight did not differ from controls. Body weights, food consumption, and liver weights of the treated animals were comparable with those of the controls. The position and number of foetuses *in utero*, the number of *corpora lutea*, individual pup weight, crown-rump length and sex ratio comparable with those of the controls. A significant increase in resorptions was found at the low dose levels but not at the high dose levels. No gross external abnormalities were seen in the foetuses of dams treated at any dose level. Soft tissue and skeletal examinations revealed an increased number of litters with subcutaneous oedema and delayed ossification of bones of the skull of foetuses of dams treated with 1,000 mg/kg, but not at 100 mg/kg bw. Analysis of maternal and foetal livers for total bromine revealed a significantly increased concentration in maternal livers of rats treated with 1,000 mg/kg. With 100 mg/kg and lower no increase in total bromine content was found. In livers of foetuses from dams receiving any dose level of DeBDE, no increase in total bromine content was observed. Maternal NOEAL: 1,000 mg/kg/day

Foetal LOAEL: 10 mg/kg/day, since it can not be shown that the observed foetal effects are without toxicological significance (7)

5.3.7 Other Toxicity Studies

DeBDE seems to have low enzyme-inducing potency (5)

5.3.8 Toxicokinetics

Based on results from several studies it may be concluded that (7):

- The DeBDE absorption is low from the gastrointestinal tract.
- The principal route of elimination is via the bile and faeces.
- After oral administration, only traces of bromine compounds were found in tissues.
- A slight but significant accumulation was noted in rat liver and adipose tissue after long term feeding

with very high doses of DeBDE.

5.4 Ecotoxicity

No toxicity data for daphnia were available. EC_{50} for algae >1 mg/l (72h, *Skeletonema costatum*; 96h *Chlorella sp*.) (1). LC_{50} for fish was >500 mg/l (Killi-fish, 48h,) in a part of a six week bioconcentration study (4). Little or no DeBDE bioconcentrate in carp (4). BCF<5 (60 µg/l test conc.) and BCF<50 (6 µg/l test conc.) (3). Log Pow=5.24 was reported (7).

5.5 Environmental Fate

Only one test result available. No biodegradation of DeBDE was found (2 Week), measured by BOD in a test equivalent to MITI I (3). DeBDE was found not readily biodegradable (4).

5.7 Conclusion

5.7.1 Health Assessment

Sufficient toxicological data were identified for a health assessment of DeBDE. Most of the data were taken from reviews performed by WHO and IARC. Many of the toxicological studies were performed on old commercial DeBDE products of low purity and are not performed according to the new standards. No data on sensitisation were identified. Few relevant data on humans were identified.

DeBDE has a low acute and subacute toxicity. Evidence of carcinogenicity was found in rats and mice. The International Agency for Research on Cancer (IARC) concluded DeBDE was not classifiable as to its carcinogenicity to humans, because there was only limited evidence for the carcinogenicity of DeBDE in experimental animals. IARC assigned DeBDE to Group 3.

A rat teratogenicity study indicated some developmental effects of an old commercial DeBDE product at a high dose level not affecting the dams. The purity of DeBDE was low (presumably 77.4%), and the data available are, however, too sparse to permit an adequate evaluation. No treatment related effects were observed in a one-generation reproduction study. The dose levels were however too low.

The potential for bioaccumulation of DeBDE is considered low because of low gastrointestinal absorption, but the retention of absorbed DeBDE in adipose tissue may be pronounced.

5.7.2 Environmental Assessment

Few data were available for environmental assessment. Based on the features log Pow=5.24 and not readily biodegradable, DeBDE may be considered to cause long-term adverse effects in the aquatic environment.

5.8 References

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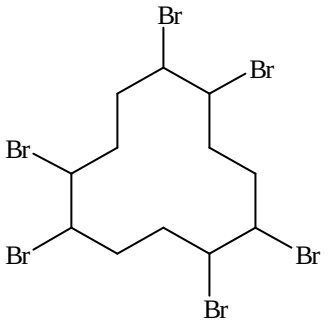
8. Sjödin A, Hagmar L, Klasson-Wehler E, Kronholm-Diab K, Jakobsson E, Bergman Å. Flame Retardant

Exposure: Polybrominated Diphenyl Ethers in Blood from Swedish Workers. Environ Health Perspect. 1999 Aug;107(8):643-648.

6. Hexabromocyclododecane, isomers

6.1 Identification of the substance

6.1.1	CAS No.	3194-55-6 (1,2,5,6,9,10-HBCD) 25637-99-4 (HBCD)
6.1.2	EINECS No.	221-695-9 (1,2,5,6,9,10-HBCD) 247-148-4 (HBCD)
6.1.3	EINECS Name	1,2,5,6,9,10-Hexabromocyclodecane (1,2,5,6,9,10-HBCD) Hexabromocyclododecane (HBCD)
6.1.4	Synonyms	None were available
6.1.5	Molecular Formula	$C_{12}H_{18}Br_6$
6.1.6	Structural Formula	 (1,2,5,6,9,10-HBCD)
		[Purity: min. 96 % w/w. Impurities: Tetrabromocyclododecane and other brominated cyclododecanes. Technical HBCD is manufactured in two forms, high-melting (HM) and low-melting (LM). It consists of three isomers (α, β and γ-isomers) each. The low-melting HBCD consists of 70-80 % γ-isomer and 20-30 % of α- and β-isomers. The high-melting HBCD consists of 90 % or more of the γ-isomer (13)]
6.1.7	Known Uses	Flame retardant in polystyrene (15, 20)
6.1.8	EU Classification	Not included in Annex I

6.2	**Physico-chemical Characteristics**	
6.2.1	Physical Form	White to off-white odourless solid or crystalline powder
6.2.2	Molecular Weight	641.7
6.2.3	Melting Point/range (°C)	175 - 195 (14)
		178-183 (15)
6.2.4	Boiling Point/range (°C)	Decomposition occurs at 230 ^{o}C (15)
6.2.5	Decomposition Temperature (°C)	230 ^{o}C (15)
6.2.6	Vapour Pressure (Pa (°C))	1.6 x 10^{-9} (20) (calculated)
		1.7 x 10^{-8} (50)
		1.3 x 10^{-7} (80)
		3.8 x 10^{-7} (100)
		(15)
6.2.7	Relative Density (D_4^{20})	2.38 (14)
6.2.8	Vapour Density (air=1)	
6.2.9	Conversion Factor (1011 hPa at 25^{o})	1 ppm = 0.026 mg/l
		1 mg/l = 38.1 ppm
6.2.10	Solubility	Water: 0.008 mg/l (temperature not stated) (14)
		Water: 0.12 mg/l (23°C) (15)
6.2.11	Partition Coefficient (log P_{ow})	5.81 (calculated) (14)
		7.59 (calculated) (15)
6.2.12	Flammability	No data available
6.2.13	Explosivity	No data available
6.2.14	Oxidising properties	No data available

6.3	**Toxicological Data**	
6.3.1	Observations in humans	In a human patch test fibres (Tyvek T-12 with 10% 1,2,5,6,9,10-HBCD) were tested. One square inch of the test sample was applied to the arms of ten men and arms and legs of ten women and held in place for 6 days. After a two-week rest period new patches were applied for 48 hours. No skin reactions were observed on any subject (9).

		No other data were available.
6.3.2	Acute Toxicity	
6.3.2.1	Oral	Oral LD50, rats: >10,000 mg/kg None of the CD rats died in this limit test. At 2,5-4 hours, 3/5 males and 1/5 females were hypoactive, and the female had diarrhoea. Thereafter, the females showed signs of toxicity. From day 6, 3/5 males had corneal opacity, which persisted through the 14 days observation period, and ptosis that persisted in 1 male at the end of the observation period (1). Results from several other studies were available (15)
6.3.2.2	Dermal	Dermal LD50, rabbits: > 20,000 mg/kg (1)
6.3.2.3	Inhalation	Inhalation LC50, rats: > 202 mg/l/4 hours Limit test study. Ten animals (5 males & 5 females) were exposed to HBCD as dust (202 mg/l, calculated). No information on particle size distribution was available. The animals responded by preening the first 10 minutes, then settled down. From 1.5 hours to the end of the exposure, the animals showed slight dyspnoea. The animals were observed for 14 days. No animals died. (1) Results from other studies are available (15)
6.3.2.4	Other Routes	No data was available
6.3.2.5	Skin Irritation	In a study performed in accordance with standard EU-guideline, slight erythema was seen in 1 out of 3 females 30-60 minutes after the treatment. No visible signs at 24, 48 or 72 hours (11). Similar results from several other studies were available (15)
6.3.2.6	Eye Irritation	Grading of ocular lesions (mean of the 24, 48 and 72 hours examinations/max. score): Cornea opacity: 0.00/4 Iris: 0.00/2 Conjunctivae, erythema: 0.17/3 Conjunctivae, oedema: 0.06/4 All signs had disappeared after 7 days (1). Another study showed similar results (12)
6.3.2 7	Irritation of Respiratory Tract	No data were available.
6.3.2.8	Skin Sensitisation	The induction concentrations in a Guinea Pig

		Maximization Test were 0.05, 0.5 or 5% HBCD in olive oil. Challenge concentrations were 0.005, 0.05, 0.5 or 5% HBCD in acetone. Induction concentrations higher than 0.5% and challenge concentrations higher than 0.05% gave positive responses. Increase in the induction or challenge concentrations did not further increase the percentage of positive responders or the intensity of the responses (17) (based on an abstract in English) For the induction in another guinea pig maximisation test 5,000 or 50,000 ppm HBCD in olive oil was used for the intra-dermal injection and 250,000 ppm HBCD in petrolatum for the topical application on shaved skin. For the challenge, 21 days after the intra-dermal injection, 500, 5000 or 50 000 ppm HBCD in acetone was used in an open patch test on shaved skin. At the highest concentration of induction and challenge 9/10 animals were sensitised and there was a clear dose-effect relationship (18)
6.3.2.9	Sensitisation by Inhalation	No data were available
6.3.3	Subchronic Toxicity	
6.3.3.1	Oral	Sprague-Dawley rats were fed a diet containing 0, 1.0, 2.5, or 5.0% 1,2,5,6,9,10-HBCD for 28 days (≈ ca. 833, 2083, and 4167 mg/kg/day). Twenty animals (10/sex) at each dose level. At the two highest dose levels, reduced body weight gain and reduced food intake were seen after 14 days. At all 3 dose levels, absolute and relative liver weights were increased; but no histological changes were seen. In the thyroid gland, dose dependent micro-follicular hyperplasia proliferating into adenomatous hyperplasia and epithelial hyperactivity was seen. At the highest dose level, oogenesis was reduced. No changes in blood biochemistry were seen. A NOAEL could not be established. (6). Rats were fed a diet containing 0, 0.16, 0.32, 0.64 or 1.28% 1,2,5,6,9,10-HBCD for 13 weeks (≈ ca. 133 - 1067 mg/kg/day). Forty Sprague-Dawley rats (20/sex) at each dose level, and further twenty animals (10/sex) at the zero and the highest dose level for a 42-days reconstitution period. One male at the highest dose level died on the 43rd study day. At the 0.32%-level and higher dose levels, the absolute liver weight was in-

		creased; a dose dependent focal lipid phanerosis was the only histological change. At the 1.28%-level, diminished body weight increase and reduced food intake were seen in the males. The increased liver weight and the lipid phanerosis diminished during the reconstitution period, but were not fully normalized. A NOAEL could not be established (6, 7).
6.3.3.2	Inhalation	No data were available
6.3.3.3	Dermal	No data were available
6.3.4	Chronic Toxicity and Carcinogenicity	In a Japanese test on carcinogenicity on carcinogenicity B6C3F1 mice were exposed orally to HBCD for 18 months. There were four exposure levels, 100, 1000 and 10 000 ppm and a control group (this is equivalent to about: 13, 130, 1300, and 0 mg/kg b.w., respectively), with 50 males and 50 females at each level. The study was not performed according to current guidelines, it has not been published in an international journal and it is poorly documented and poorly reported. It is impossible to assess the carcinogenic potential of HBCD based on the available study, a long-term study in mice (13).
6.3.5	Mutagenicity	
6.3.5.1	Gene Mutation	HBCD was tested in several in vitro gene mutation assays with *Salmonella typhimurium* strains, both in the absence and presence of a metabolic activating system (S-9 mix). The results were generally negative but on one occasion HBCD induced frame shift mutations (TA100 and TA1535) with and without S9-mix (3, 2, 5, 8, 10, 22)
6.3.5.2	Chromosome Abnormalities	No data were available
6.3.5.3	Other Genotoxic Effects	HBCD was tested in primary rat hepatocyte culture for unscheduled DNA synthesis (UDS). Highest dose (500 mg/l) was cytotoxic. UDS was counted by autoradiography. A dose-dependent increase in silver grains was seen from 2.5 mg/l. HBCD induced more cells with UDS and higher UDS activity (more than 5 silver grain per cell) than vehicle controls. HBCD was positive in this UDS test (4). 1,2,5,6,9,10-HBCD was tested in two recently developed *in vitro* assays for intragenic recombination in mammalian cells, the Sp5/V79 recombination assay and the SPD8 recombination assay. HBCD induced statisti-

		cally significant increases in recombination frequencies in both the Sp5 and SPD8 assay system (16)
6.3.6	Reproductive Toxicity, Embryotoxicity, and Teratogenicity	
6.3.6.1	Reproductive Toxicity	No data were available
6.3.6.2	Teratogenicity	Wistar rats were fed a diet containing 0.01, 0.1 or 1% HBCD (≈ ca. 6.7, 69, and 658 mg/kg/day) from day 0 through day 20 of pregnancy. No embryo- or foetotoxicity nor teratogenicity observed. At the highest dose, reduced food intake and increased liver weight of the dams were found. NOAEL for maternal toxicity was 69 mg/kg/day, and NOAEL for teratogenicity was 658 mg/kg/day (15)
6.3.7	Other Toxicity Studies	No data were available
6.3.8	Toxicokinetics	Radiolabelled material was rapidly absorbed from the gastrointestinal tract after a single oral dosage of ^{14}C-HBCD to rats. HBCD was rapidly metabolised, and 70% of the radioactive dose was eliminated via the faeces and 16% via the urine within 72 hours of dosing. The elimination from fat tissue was slower than from other body compartments (15).
6.4	**Ecotoxicity**	The toxicity data for algae were EC_{50}: >500 mg/l (96h, *Scenedesmus subspicatus*); >2.5 µg/l (4d, *Selenastrum capricornutum*); 9.3-12.0 µg/l (72h, *Skeletonema costatum*); 50-370 µg/l (72h, *Thalassiosira pseudonana*) and >1500 µg/l (96h, *Chlorella* sp.). For daphnia the EC_{50} were: >3.2 µg/l (48h, *Daphnia magna*) and 146.34 mg/l (48h, *Daphnia magna*). The LC_{50} for fish were: > 100 mg/l (96h, *Lepomis macrochirus*) and >10000 mg/l (96h, *Leuciscus idus*) (15).

		Bioconcentration factors in fish (*Pimephales promelas*) have been reported as: 18100 (Fathead minnow; CAS No. 3194-55-6) (21). LogPow=5.81 were reported (14)
6.5	**Environmental Fate**	No test results available.
6.6	**Environmental Concentrations**	HBCD in fish samples, river, Sweden, showed levels ranging from <50 to 8000 ng/g (lipid weight in muscle) and <1-7600 ng/g in sediments (ignition loss). HBCD was not further specified with CAS-number (19)
6.7	**Conclusion**	
6.7.1	Health Assessment	Sufficient toxicological data were identified for a health assessment of HBCD. No adequate data on chronic toxicity, carcinogenicity, or reproductive toxicity over several generations were identified. No chromosome aberration tests were found, and none *in vivo* mutagenicity tests were identified. Few relevant data on humans were identified. The available data lead to the conclusion that HBCD is not an acute toxicant after oral, dermal or inhalation exposure. HBCD is slightly irritating to the eyes and the skin. Animal testing showed indications of a skin sensitising potential; but this was not confirmed in a preliminary human patch test. In subacute and subchronic studies with exposures to fairly high doses, HBCD caused reversible lipid phanerosis in the liver and increase in liver weight. In one of the studies, pathological changes were observed in the thyroidea. HBCD did not induce embryo toxicity (teratogenicity). It was generally not mutagenic in *Salmonella typhimurium*, but induced unscheduled DNA synthesis in rat hepatocytes and intragenic recombination in mammalian cells. Toxicokinetic data and the high n-octanol-water-partition coefficient indicate a risk of accumulation in adipose tissue in case of repeated exposure.
6.7.2	Environmental Assessment	The EC_{50} for HBCD was below 1 mg/l for some algae species; log Pow>3; BCF>100 and the substance was found not readily biodegradable under aerobic condi-

tions. Based on this hexabromocyclododecane is considered to be toxic for aquatic organisms and may also cause long-term adverse effects in the aquatic environment.

6.8 References

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6. Hexabromocyclododecane 28-day feeding trials with rats with test data and cover letter. EPA/OTS; Doc #86-900000274 1990. NTIS/OTS0523266.

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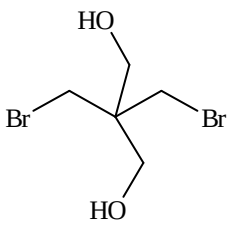
7. 2,2-Bis(bromomethyl)propane-1,3-diol

7.1 Identification of the substance

7.1.1	CAS No.	3296-90-0
7.1.2	EINECS No.	221-967-7
7.1.3	EINECS Name	2,2-Bis(bromomethyl)propane-1,3-diol
7.1.4	Synonyms	2,2-Bis(bromomethyl)-1,3-propanediol 1,3-Dibromo-2,2-dimethylolpropane 2,2-Dibromomethyl-1,3-propanediol Dibromoneopentyl glycol Dibromopentaerythritol FR-1138 FR-522 Pentaerythritol dibromide Pentaerythritol dibromohydrin DBNPG Some of the studies are performed on a flame retardant, FR-1138, composed of 79-88% DBNPG, 3-8% monobromoneopentyl triol (CAS No. 19184-65-7), 8-15% tribromoneopentyl alcohol (CAS No. 36483-57-5 or 1522-92-5) and traces of various esters, ethers and other derivatives (5). Other studies were performed on another flame retardant, FR-522, with an approx. purity of 100% (7).
7.1.5	Molecular Formula	$C_5H_{10}Br_2O_2$
7.1.6	Structural Formula	
7.1.7	Known Uses	Fire retardant in unsaturated polyester resins, in molded products, and in rigid polyurethane foam (13)

7.1.8	EU Classification	Not included in Annex I

7.2 Physico-chemical Characteristics

7.2.1	Physical Form	Off-white powder (FR-1138) (9) White solid or free flowing powder (FR-522) Brown crystalline material ("Dynol" ≈ FR-522) (7)
7.2.2	Molecular Weight	261.94
7.2.3	Melting Point/range (°C)	75-95 (FR-1138) (5) 109-111 (FR-522) (7)
7.2.4	Boiling Point/range (°C)	134 (at 133.322 Pa) (FR-522) (7)
7.2.5	Decomposition Temperature (°C)	Decomposes at 235°C, with the release of toxic, irritant HBr and bromine fumes (7)
7.2.6	Vapour Pressure (Pa (°C))	133.322 (129.7) (FR-1138) 5332.88 (213.6) (FR-1138) (5) 1,333.22 (178) (FR-522) 3,333.05 (200) (FR-522) (7)
7.2.7	Relative Density (D_4^{20})	No data were available
7.2.8	Vapour Density (air=1)	No data were available
7.2.9	Conversion Factor (1011 hPa at 25^o)	No data were available
7.2.10	Solubility	Water: 21 g/l at 25°C (FR-1138) Water: 1000 g/l at 100°C (FR-1138) Acetone: 825 g/l at 25°C (FR-1138) Benzene: 70 g/l at 25°C (FR-1138) (5) Water: 20 g/l at 25°C (FR-522) (7)
7.2.11	Partition Coefficient (log P_{ow})	1.1 (5) 1.06 (14)

7.2.12	Flammability	Not flammable (7)
7.2.13	Explosivity	Will not support combustion (7)
7.2.14	Oxidising properties	No data were available
7.3	**Toxicological Data**	
7.3.1	Observations in humans	No data were available
7.3.2	Acute Toxicity	
7.3.2.1	Oral (95% confidence limits)	Purity: 81.1% (FR-1138) Impurities: 7.6% monobromoneopentyl glycol and 11.3% tribromoneopentyl alcohol. LD50, male rats: 3458 (2810-4257) mg/kg b.w. No significant untoward effects were observed at dose levels as high as 3160 mg/kg b.w. (4, 6) Purity: approx. 100% ("Dynol" ≈ FR-522) LD50, rats: 1,880 (1,691-2,120) mg/kg b.w. Treatment related signs included reduced motor activity, ataxia, and prostration preceding unconsciousness within 30 min of dosing and death. All animals that survived appeared normal within 3 days. Fluid dissention and irritation of the gastro-intestinal tract was observed at macroscopic examination of decedents (7). Purity: approx. 100% (FR-522) LD50, mice: 1,200 mg/kg b.w.
7.3.2.2	Dermal	No data were available
7.3.2.3	Inhalation	Purity: 81.1% (FR-1138) Impurities: 7.6% monobromoneopentyl glycol and 11.3% tribromoneopentyl alcohol. Exposure of rats to vapours of DBNPG maintained at 100°C, at a nominal concentration of 2.49 mg/l for a period of 7 hours resulted in slightly laboured breathing and slight nasal irritation but no mortality (6, 4).
7.3.2.4	Other Routes	No data were available
7.3.2.5	Skin Irritation	Grading of dermal reactions (mean of the 24 and 72 hours examinations/max. score) of "Dynol" ≈ FR-522

		on intact skin of 6 rabbits: Erythema and eschar: 0.00/4 Oedema: 0.00/4 (7)
7.3.2.6	Eye Irritation	Grading of ocular lesions (mean of the 24, 48 and 72 hours examinations/max. score) after installation of 100 mg test material ("Dynol" ≈ FR-522) into the conjunctival sac: Cornea opacity: 0.39/4 Iris: 0.00/2 Conjunctivae, erythema: 0.78/3 Conjunctivae, oedema: 0.11/4 The effects appeared reversible, but at the end of the observation period of 8 days, 2 out of 6 rabbits still had slight conjuntival redness. The 4/6 worst affected rabbits had a conjunctival redness score of 0.92/3 (7) Installation of DBNPG (FR-1138) into the conjunctival sac of rabbits resulted in slight pain, slight conjunctival inflammation, inflammation of iris, and corneal injury. The effects had disappeared at one week after exposure (1).
7.3.2 7	Irritation of Respiratory Tract	No data were available
7.3.2.8	Skin Sensitisation	The skin sensitising potential of DBNPG (FR-1138) was evaluated in male guinea pigs by two methods very sparsely reported. No evidence of FR-1138 related skin sensitisation was observed (1).
7.3.2.9	Sensitisation by Inhalation	No data were available
7.3.3	Subchronic Toxicity	
7.3.3.1	Oral	1) DBNPG was administered to F344/N rats (10/sex/dose level) by oral gavage in corn oil 5 days/week for 13 weeks at doses of 0, 50, 100, 200, 400, and 800 mg/kg b.w. NOAEL was 200 mg/kg/day for males and 400 mg/kg/day for females 2) DBNPG was administered in the feed to F344/N rats (10/sex/dose level) for 13 weeks at concentrations of 0, 1,250, 2,500, 5,000, 10,000, and 20,000 ppm. NOAEL was approx. 135 mg/kg/day for males and 148

		mg/kg/day for females 3) DBNPG was administered orally to B6C3F1 mice (10/sex/dose level) by gavage in corn oil 5 days/week for 13 weeks at doses of 0, 25, 50, 100, 200, and 400 mg/kg b.w. NOAEL was 100 mg/kg/day for both males and females 4) DBNPG was administered in the feed to B6C3F1 mice (10/sex/dose level) for 13 weeks at concentrations of 0, 625, 1,250, 2,500, 5,000, and 10,000 ppm. NOAEL was approx. 113 mg/kg/day for males and could not be established for females (< approx. 174 mg/kg/day). 1-4) The kidney and urinary bladder were target organs when DBNPG was administered by gavage or the dosed-feed route; mice were more sensitive than rats for the development of kidney and bladder lesions. Male rats and mice were more sensitive than females for the development of renal papillary degeneration or necrosis (10)
7.3.3.2	Inhalation	No data were available
7.3.3.3	Dermal	No data were available
7.3.4	Chronic Toxicity and Carcinogenicity	Groups of Sprague-Dawley rats were maintained on diets supplying nominal doses of 0, 5 or 100 mg DBNPG (FR-1138)/kg b.w./day for up to two years. Toxic effects were observed at the high dose level in liver, lenses of the eyes, and thyroids. The NOAEL was 5 mg/kg b.w./day, and no evidence of FR-1138 related carcinogenicity was observed (8). 1) DBNPG was administered in the feed to F344/N rats (60/sex/dose level) for 2 years at concentrations of 0, 2,500, 5,000, and 10,000 ppm. Up to 10 in each group were used for interim evaluation at 15 months. An additional high dose, 20,000 ppm, was selected for a recovery group consisting of 60 males treated for 3 months and subsequently not exposed for the remainder of the 2 year study period. Ten additional control and 20,000 ppm males were used for interim evaluation at 3 months. A NOAEL could not be established because of treat-

ment related neoplastic and hyperplastic effects observed from the lowest dosage level in subcutaneous tissue, mammary gland, oral cavity, pancreas and kidneys.

2) DBNPG was administered in the feed to B6C3F1 mice (60/sex/dose level) for 2 years at concentrations of 0, 312, 625, and 1,250 ppm.

NOAEL was 312 ppm for males and could not be established for females because of treatment related neoplastic effects observed from the lowest dosage level in the Harderian gland.

1-2) The batch of DBNPG used in these studies was also used in some of the 13-week studies. The purity of DBNPG was analysed to 78.6%, and the impurities identified were 6.6% 2,2-bis(hydroxymethyl)-1-bromo-3-hydroxypropane (CAS No. 19184-65-7), 6.9% 2,2-bis(bromomethyl)-1-bromo-3-hydroxypropane (CAS No.1522-92-5), 0.2% pentaerythritol (CAS No. 115-77-5), and 7.7% dimers and structural isomers.

Chemical exposure caused neoplasms of the skin, subcutaneous tissue, mammary gland, Zymbal's gland, oral cavity, oesophagus, forestomach, small intestine, large intestine, mesothelium, kidney, urinary bladder, lung, thyroid gland, seminal vesicle, haematopoietic system, and pancreas in the male rat; mammary gland, oral cavity, oesophagus, and thyroid gland in the female rat; lung, kidney, and Harderian gland in male mice; and subcutaneous tissue, lung, and Harderian gland in the female mouse. The recovery group of male rats presented with the same spectrum of treatment-related neoplasms as in the core study. In this recovery group, DBNPG (at 20,000 ppm) caused irreversible effects at numerous sites after 13 weeks of exposure that was not detectable by histological examination, but without further exposure eventually resulted in the development of neoplasms at multiple sites (9, 13)

7.3.5 Mutagenicity

7.3.5.1 Gene Mutation

In vitro assay with *Salmonella typhimurium* strains TA-1535, TA-1537 and TA-1538 and *Saccharomyces cerevisiae* strain D4, +/- S-9 mix. DBNPG ("pure" and "plant") was considered negative in this test (2, 3).

		In vitro assay with *Salmonella typhimurium* strains TA-98, TA-100, TA-1535, and TA-1537, +/- S-9 mix. DBNPG (purity unknown) was considered negative in this preliminary test (7). In vitro gene mutation Salmonella: Negative (12)
		Purity of DBNPG: approx. 84%. In vitro gene mutation assay with *Salmonella typhimurium* strains TA-98 and TA-100, +/- S-9 mix derived from Aroclor-induced hamster or rat liver. Negative in both strains without S-9 mix. Negative in both strains with rat S-9 mix. In the presence of hamster S-9 mix, positive in TA-100 but negative in TA-98. (16)
7.3.5.2	Chromosome Abnormalities	*In vitro* cytogenetics Positive (chromosome aberrations in Chinese Hamster Ovary cells +/- S-9 mix) (11) *In vivo*, DBNPG induced significant increases in the frequencies of micronucleated erythrocytes in male and female mice. Significant increases in micronuclei were observed in peripheral blood samples from male and female mice exposed to DBNPG for 13 weeks via dosed feed. Results of a bone marrow micronucleus test in male mice, where DBNPG was administered by gavage, were considered to be equivocal due to inconsistent results obtained in two trials. An additional bone marrow micronucleus test was performed with male and female mice and DBNPG was administered as a single intraperitoneal injection; results of this test were positive in females and negative in males (13).
7.3.5.3	Other Genotoxic Effects	*In vitro* cytogenetics Inconclusive (sister chromatid exchanges in Chinese Hamster Ovary cells +/- S-9 mix) (11)
7.3.6	Reproductive Toxicity, Embryotoxicity, and Teratogenicity	
7.3.6.1	Reproductive Toxicity	DBNPG was tested for its effects on reproduction and fertility in CD-1 mice using the reproductive assess-

ment by continuous breeding (RACB) protocol. The mice were fed diet containing 0, 0.1, 0.2, and 0.4% DBNPG. Based on body weights and food consumption, the estimated doses were approx. 141, 274, and 589 mg/kg/day.

Body weight gain for all treated groups was less than in controls. Both male and female F_0 mice (20/sex/dose level, 40/sex in control group) were dosed 7 days prior to and during a 98-day cohabitation period. Although the fertility index was unchanged in the high-dose group, DBNPG exposure significantly decreased the numbers of litters per pair, pups born alive per litter, and pup weight when adjusted for litter size. Crossover mating between treated and control F_0 animals indicated a specific effect only on female reproductive capacity. At the highest dose, DBNPG caused a body weight decrease in the F_0 animals of both sexes with no effect on relative organ weights. Sperm concentration, motility, morphology, and oestrous cyclicity were unaffected by DBNPG exposure. Histopathology in the F_0 animals revealed specific kidney lesions in both sexes; males were more sensitive than females. The last litter born in the 98-day breeding phase was reared to age 74 days and then mated to non-siblings of the same treatment group. The effect of high-dose DBNPG exposure on F_1 fertility, body and organ weights, sperm parameters, and oestrous cyclicity was the same as that for the F_0 animals, with the exception of the lack of renal lesions seen in the F_1 females. The study showed that DBNPG impaired fertility in female mice in both generations in the absence of an effect on reproductive organ weights and oestrous cyclicity. DBNPG is not a selective reproductive toxicant, as these effects were seen concomitant with the general toxicity (15).

7.3.6.2	Teratogenicity	No data were available
7.3.7	Other Toxicity Studies	No data were available
7.3.8	Toxicokinetics	No data were available
7.4	**Ecotoxicity**	The octanol/water partition coefficient reported was 1.1 (5)
7.5	**Environmental Fate**	No data were available
7.6	**Environmental Concentrations**	No data were available

7.7 Conclusion

7.7.1 Health Assessment

Sufficient toxicological data were identified for a health assessment of DBNPG. Most of the data were found in documents submitted to the U.S. EPA. These documents contain results from tests not performed according to presently accepted international guidelines and Good Laboratory Practice. Some of the studies are performed on a flame retardant called, FR-1138, which was composed of 79-88% DBNPG and the structurally related impurities monobromoneopentyl triol (3-8%), tribromoneopentyl alcohol (8-15%) and traces of various esters, ethers and other derivatives. Other studies were performed on another flame retardant, FR-522, with an approx. purity of 100%. No data on humans were identified.

The available data indicate that DBNPG is acute toxic after oral exposure and should be classified as harmful. DBNPG is very slightly skin irritating and slightly eye irritating. Based on a preliminary test, it does not seem to be a skin sensitiser. The results from the *in vitro* gene mutation tests varied, but in most cases DBNPG was not mutagenic. An *in vitro* test for chromosome aberrations was positive, and *in vivo* tests also showed some evidence of clastogenicity. The tests for subchronic oral toxicity did not reveal any clear indications of possible danger or risks of irreversible health effects by prolonged exposure. Under the conditions of these 2-year feed studies with mice and rats, there was clear evidence of multi-site carcinogenic activity of DBNPG (FR-1138).

Based on available data DBNPG should be considered potential carcinogenic.

7.7.2 Environmental Assessment

No ecotoxicity or environmental fate data were available for environmental assessment.

7.8 References

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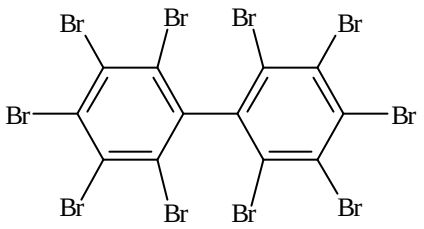
8.	**Decabromobiphenyl**	
8.1	**Identification of the substance**	
8.1.1	CAS No.	13654-09-6
8.1.2	EINECS No.	237-137-2
8.1.3	EINECS Name	1,1'-Biphenyl, 2,2',3,3',4,4',5,5',6,6'-decabromo-
8.1.4	Synonyms	2,2',3,3',4,4',5,5',6,6'-Decabromo-1,1'-biphenyl DeBB
		Commercial DeBB (ex. Adine 0102) contains about 96-98% DeBB, 2-4% nonabromodiphenyl (NoBB, CAS No. 27753-52-2) and 0-0.3% octabromodiphenyl (OcBB, CAS No. 61288-13-9) (2)
8.1.5	Molecular Formula	$C_{12}Br_{10}$
8.1.6	Structural Formula	
8.1.7	Known Uses	DeBB (Adine 0102®) is used as a flame retardant for thermoplastics thermosets, for elastomers, and for cellulosics. It is sometimes applied with antimony trioxide (5)
8.1.8	EU Classification	Not included in Annex I to Directive 67/548/EEC
8.2	**Physico-chemical Characteristics**	
8.2.1	Physical Form	Solid
8.2.2	Molecular Weight	943
8.2.3	Melting Point/range (°C)	380-386 (5)
8.2.4	Boiling Point/range (°C)	No data were available
8.2.5	Decomposition Temperature (°C)	395 or > 400 (5)
8.2.6	Vapour Pressure (Pa (°C))	$< 6 \times 10^{-6}$ (temperature unknown) (5) Volatility: <5% weight loss at 341°C (5)

8.2.7	Relative Density (D_4^{20})	3.2 (5)
8.2.8	Vapour Density (air=1)	No data were available
8.2.9	Conversion Factor (1011 hPa at 25^o)	No data were available
8.2.10	Solubility	Water: < 30 µg/l (25°C) Carbon tetrachloride: 10 g/kg (28°C) (5)
8.2.11	Partition Coefficient (log P_{ow})	8.6 (calculated) (5)
8.2.12	Flammability	Not applicable
8.2.13	Explosivity	No data were available
8.2.14	Oxidising properties	No data were available
8.3	**Toxicological Data**	
8.3.1	Observations in humans	Human exposure to polybrominated biphenyls (PBB) has occurred through occupational contact and as a result of the accidental contamination of livestock feed in Michigan, U.S.A., in 1973. The unintentional addition of FireMaster FF-1 (mainly hexabromobiphenyl, but also some pentabromobiphenyl and heptabromobiphenyl), instead of magnesium oxide, to farm feed, resulted in exposure of large numbers of rural population Michigan (2). The general PBB half-life in humans has been estimated to approx. 11 years (4).
8.3.2	Acute Toxicity	
8.3.2.1	Oral	Oral LD50, rats: > 5 g/kg b.w. No mortality was observed after oral administration of 5 g/kg b.w. DeBB (96.8% pure) to rats during an observation period of 14 days (2) Oral LD50, rats: > 20 g/kg b.w. (5)
8.3.2.2	Dermal	Dermal LD50, rats: > 5 g/kg b.w. No mortality was observed after cutaneous administration of 5 g/kg b.w. DeBB (96.8% pure) to rats during an observation period of 14 days (2)
8.3.2.3	Inhalation	No data were available
8.3.2.4	Other Routes	No data were available
8.3.2.5	Skin Irritation	50% DeBB in olive oil was mild skin irritating (5)

8.3.2.6	Eye Irritation	50% DeBB in olive oil was not eye irritating. DeBB powder caused mild irritation (5)
8.3.2 7	Irritation of Respiratory Tract	No data were available
8.3.2.8	Skin Sensitisation	No data were available
8.3.2.9	Sensitisation by Inhalation	No data were available
8.3.3	Subchronic Toxicity	
8.3.3.1	Oral	No data were available
8.3.3.2	Inhalation	No mortality was observed after exposure to 5 mg DeBB dust/l for 6 hours/day, 5 days/week, for 4 weeks. An increase in liver weights was observed. No details were available. (2, 5)
8.3.3.3	Dermal	No data were available
8.3.4	Chronic Toxicity and Carcinogenicity	No data were available
8.3.5	Mutagenicity	
8.3.5.1	Gene Mutation	A commercial DeBB was not mutagenic to Salmonella typhimurium strains TA-1535, TA-1537 and TA-1538, in the presence or absence of metabolic activation. The product was also negative in a host-mediated assay with strain TA-1538, in mice receiving oral doses of 5, 10 and 20 g/kg b.w. (3)
8.3.5.2	Chromosome Abnormalities	A micronucleus test was performed on male and female mice administered a total dose of 5, 10 or 20 g/kg b.w. at 2 doses. DeBB was negative in this test (5).
8.3.5.3	Other Genotoxic Effects	No data were available
8.3.6	Reproductive Toxicity, Embryotoxi-city, and Teratogenicity	
8.3.6.1	Reproductive Toxicity	No data were available
8.3.6.2	Teratogenicity	Groups of Sprague-Dawley rats were administered doses of 0, 10 or 1,000 mg/kg/day gestation day 6 through 15. No maternal effects were noted. No teratogenicity or embryotoxicity was observed (5)
8.3.7	Other Toxicity Studies	No data were available
8.3.8	Toxicokinetics	No data were available
8.4	**Ecotoxicity**	The LC_{50} for fish was 250 mg/l (48h). The bioconcen-

		tration factor was 0.6-5.4 (6w, 0.15 mg/l) (1)
8.5	**Environmental Fate**	DeBB is not readily biodegradable (0.8% of BOD, 2w, 100 mg/l substance, 30 mg/l sludge) (1)
8.6	**Environmental Concentrations**	No data were available
8.7	**Conclusion**	
8.7.1	Health Assessment	Only few data on mainly acute toxicity and genotoxicity were available. DeBB apparently has a low toxicity by the oral, dermal and pulmonal route of exposure. It was not mutagenic in *Salmonella typhimurium* assays or in a micronucleus test. Based on carcinogenicity studies with Firemaster FF-1, composed mainly on hexabromobiphenyl with smaller amounts of penta- and heptabrominated isomers, IARC found sufficient evidence for the carcinogenicity of commercial mixtures of PBB to experimental animals. There was inadequate evidence for the carcinogenicity of PBB to humans. PBB is in general considered to be bioaccumulative.
8.7.2	Environmental Assessment	As very few ecotoxicity and environmental fate data were available for DeBB, data for the analogous substance decachlorobiphenyl (CAS No. 2051-24-3) were searched, but no data were available on that substance. Too few ecotoxicity and environmental fate data for DeBB were available for environmental assessment.
8.8	**References**	1. Chemical Inspection and Testing Institute. Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan, compiled under the supervision of chemical products safety Division Basic industries. Japan: Japanese Chemical Industry Ecology-Toxicology & Information Center, 1992. 2. IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some Halogenated Hydrocarbons and Pesticide Exposures. Switzer-land: International Agency for Research on Cancer, World Health Organisation, 1986: 261-92. (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans; 41). 3. IARC Working Group on the Evaluation of the Car-

cinogenic Risk of Chemicals to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Switzerland: International Agency for Research on Cancer, World Health Organisation, 1987: 73. (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans; Supplement 7).

4. Rosen DH, Flanders WD, Friede A, Humphrey HE, Sinks TH. Half-life of polybrominated biphenyl in human sera. Environmental Health Perspectives 1995; 103(3):272-4.

5. WHO working group. Polybrominated Biphenyls. Environmental Health Criteria 1994; 152.

9.	**Pentabromodiphenyl ether**	
9.1	**Identification of the substance**	
9.1.1	CAS No.	32534-81-9 60348-60-9 (2,2’,4,4’,5-PeBDE) 182346-21-0 (2,2’,3,4,4’-PeBDE) 189084-64-8 (2,2’,4,4’,6-PeBDE)
9.1.2	EINECS No.	251-084-2
9.1.3	EINECS Name	Benzene, 1,1'-oxybis-, pentabromo derivative
9.1.4	Synonyms	Pentabromodiphenyl oxide Diphenyl ether, pentabromo derivative Pentabromophenoxybenzene PeBDE Saytex 125 2,2’,4,4’,5-PeBDE Benzene, 1,2,4-tribromo-5-(2,4-dibromophenoxy)- 2,2',4,4',5-Pentabromodiphenyl ether 2,2',4,4',5-Pentabromodiphenyl oxide BDE 99 PBDE 99 Tardex 50 Tardex 50L 2,2’,3,4,4’-PeBDE Benzene, 1,2,3-tribromo-4-(2,4-dibromophenoxy)- BDE 85 2,2’,4,4’,6-PeBDE Benzene, 1,3,5-tribromo-2-(2,4-dibromophenoxy)-

2,2',4,4',6-Pentabromodiphenyl ether

BDE 100

PBDE 100

Commercial PeBDE is a mixture of approx. 0-1% TrBDE (tribromodiphenyl ether, CAS No. 49690-94-0), 24-38% TeBDE (tetrabromodiphenyl ether, CAS No. 40088-47-9), 50-60% PeBDE and 4-8% HxBDE (hexabromodiphenyl ether, CAS No. 36483-60-0) (8).

There are 46 possible isomers of PeBDE and 42 possible isomers of TeBDE. The commercial products seem to contain 3 main components, i.e., 2,2',4,4',5-PeBDE, 2,2',4,4'-TeBDE (CAS No. 5436-43-1) and an unidentified congener containing 5 bromines (23).

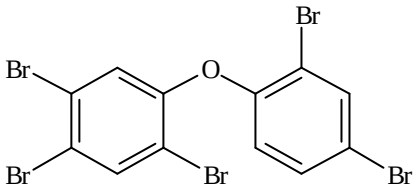
A commercial PeBDE product (Tardex 50) was reported to consist of 25-35% TeBDE, 55-70% PeBDE, 0-5% HxBDE and 0-1% HpBDE (heptabromodiphenyl ethers, CAS No. 68928-80-3) (20)

DE-71 is primary a mixture of TeBDE, PeBDE and HxBDE containing low levels of TrBDE (< 1%) and HpBDE (< 2%) (23)

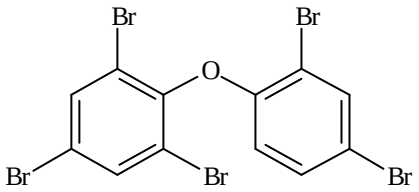
9.1.5 Molecular Formula

$C_{12}H_5Br_5O$

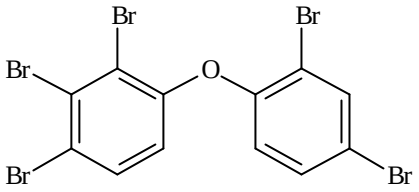
9.1.6 Structural Formula



2,2',4,4',5-PeBDE



2,2',4,4',6-PeBDE



2,2',3,4,4'-PeBDE

9.1.7	Known Uses	PeBDE is used as an additive in epoxy resins, phenol resins, polyesters and polyurethane, and textiles (23)
9.1.8	EU Classification	Not included in Annex I to Directive 67/548/EEC
9.2	**Physico-chemical Characteristics**	
9.2.1	Physical Form	Amber solid
9.2.2	Molecular Weight	564.8
9.2.3	Melting Point/range (°C)	202 °C (estimated) (19)
9.2.4	Boiling Point/range (°C)	> 300 °C (decomposition starts above 200 °C) (19)
9.2.5	Decomposition Temperature (°C)	Pyrolysis studies with commercial PeBDE showed that polybrominated dibenzofurans and polybrominated dibenzodioxins was formed (700-800°C). When PeBDE was pyrolysed in the absence of oxygen, polybromobenzenes, polybromophenols, and polybrominated dibenzofurans were formed (23).
9.2.6	Vapour Pressure (Pa (°C))	1240 (22) (19) 835-888 (25) (19)
9.2.7	Relative Density (D_4^{20})	2.28 at 25 °C; 1.78 at 40 °C (19)
9.2.8	Vapour Density (air=1)	No data available
9.2.9	Conversion Factor (1011 hPa at 25^o)	No data available
9.2.10	Solubility	Water: 9×10^{-7} mg/l at 20 °C (19)
9.2.11	Partition Coefficient (log P_{ow})	6.5 - 7.0 (8) Log Pow>6, measured (23) 7.66 (QSAR estimation)
9.2.12	Flammability	No data available
9.2.13	Explosivity	No data available
9.2.14	Oxidising properties	No data available
9.3	**Toxicological Data**	
9.3.1	Observations in humans	Forty plasma samples from a "random" population in

Sweden were examined. The mean concentration of polybrominated diphenyl ethers was 2.1 ± 1.4 ng/g lipid weight, which was at least two orders of magnitude lower than polychlorinated diphenyls. 2,2',4,4'-TeBDE and 2,2',4,4',5-PeBDE were the most abundant and constituted approximately 70% of the total mean polybrominated diphenyl ethers in each sample (14)

Milk samples from 39 primiparous mothers (22 to 36 years old) from the Uppsala county in Sweden were analysed for the content of the five most frequently found polybrominated diphenyl ethers. The mean of total polybrominated diphenyl ethers was 4.5 ng/g lipid weight. 2,2',4,4'-TeBDE was the major congener in breast milk, comprising approx. 57%, while 2,2',4,4',5-PeBDE and 2,2',4,4',6-PeBDE represented approx. 16% and 11%, respectively (7)

Samples of milk from mothers living in the Stockholm region have been analysed for the presence of polybrominated diphenyl ethers. The samples analysed covered the years 1972-1997. The main congener found in the samples was 2,2',4,4'-TeBDE (60-70% of total), but other congeners found were 2,4,4'-TrBDE, 2,3',4,4'-TeBDE, 2,2',4,4',5-PeBDE, 2,2',4,4',6-PeBDE, 2,2',3,4,4'-PeBDE, 2,2',4,4',5,5'-HxBDE and 2,2',4,4',5,6'-HxBDE. The levels of polybrominated diphenyl ether were shown to increase exponentially over the time period, with a doubling time of around 5 years. The total levels found in the 1997 samples were 4 µg/kg lipid compared with 0.072 µg/kg in 1972, (17, 18)

Levels of polybrominated diphenyl ethers (probably TeBDE and PeBDE congeners) of 0.6-11 µg/kg lipid have been found in human breast milk from Germany (9).

The levels of the components of commercial PeBDE have been measured in adipose tissue and blood a 21 year old Israeli man, and also in cows milk and poultry fat from Israel. The levels found in adipose tissue were: 2 µg 2,2',4,4'-TeBDE/kg wet wt, 4 µg 2,2',4,4'5-PeBDE/kg wet wt and 1 µg/kg wet wt of an unknown PeBDE. The substances were not detected in blood, cows milk or poultry fat (9).

9.3.2 Acute Toxicity

9.3.2.1 Oral

Oral LD50, rats: 5 g/kg b.w. (4)

Oral LD50, Wistar rats: 6,200 (5,391 - 7,130) mg/kg b.w.

Oral LD50, male rats: 7,400 mg/kg b.w.

Oral LD50, female rats: 5,800 mg/kg b.w.

Groups of male and female rats were administered single doses of up to 9,600 mg/kg of PBDPE (commercial grade) in corn oil by gavage.

Signs of toxicity observed included diarrhoea, piloerection, reduced weight gain, reduced activity, tremors and red staining around the nose and eyes. Animals which died showed pale, enlarged, necrotic livers and multiple small ulcerations of the gastric mucosa (3, 23)

In a study designed to assess the immunological and endocrine effects of DE-71 (a commercial PeBDE mixture), groups of 6 female C57BL/6J mice were dosed once by gavage with 0, 0.8, 4, 20, 100 or 500 mg/kg DE-71 in peanut oil. Two days post-dosing all animals were given an intraperitoneal injection of sheep erythrocytes (SRBC). The potential immunotoxicity of DE-71 was assessed by measuring the plaque-forming cell (PFC) response to SRBC and also natural killer cell (NKC) activity in vitro. All animals were sacrificed 8 days post-treatment. No clinical signs of toxicity were reported. Relative liver weight and hepatic cytochrome P450 activity were increased at 500 mg/kg, compared with controls, with no effects being observed at any other doses. The serum concentrations of total thyroxin (T4) were decreased at all dose-levels, but no dose-response relationship was apparent. No conclusions regarding the immunotoxicant potential of PBDPE could be drawn from this study (12)

In a behavioural study, groups of neonatal male NMRI-mice were given a single oral dose of 0.8 or 12 mg 2,2',4,4',5-PeBDE/kg on postnatal day 10. Spontaneous motor behaviour was assessed at 2 and 4 months and a swim maze study performed at 5 months post-exposure. Minor behavioural changes were noted in this sparsely reported study. No conclusions as to the significance to human health of these minor changes

		can be drawn (10).
9.3.2.2	Dermal	Dermal LDLo, rats: 5,500 mg/kg (4)
		Dermal LD50, rabbits: > 2,000 mg/kg b.w.(3, 23)
9.3.2.3	Inhalation	Inhalation LC50, CD rats: > 200 mg/l/1 hour
		Groups of 5 rats/sex were exposed to an aerosol mist of 2 or 200 mg/l PBDPE in corn oil for 1 hour in a whole body exposures chamber. Aerosol droplet size was not given. No treatment-related mortalities occurred at either concentration. Animals in the high concentration group showed general signs of toxicity such as lacrimation, salivation and tachypnoea. Animals in both groups displayed increased, followed by decreased motor activity, eye squint and erythema (site not stated) during exposure. Nasal and respiratory "congestion" were noted in 3 rats at 200 mg/l up to day 3. Animals appeared normal by 24 hours after the lower dose and by day 4 after the higher dose (3)
9.3.2.4	Other Routes	No data were available
9.3.2.5	Skin Irritation	Application of PeBDE to rabbit skin caused mild to moderate irritative effects (3, 4, 23)
9.3.2.6	Eye Irritation	The application of PeBDE to the conjunctival sac in rabbits caused only mild, transient effects (3, 23)
9.3.2 7	Irritation of Respiratory Tract	Evidence of tachypnoea and nasal and respiratory congestion are reported in rats following single inhalation exposures to very high concentrations 200 mg/l (8333 ppm) PBDPE aerosol mist for 1 hour (3)
9.3.2.8	Skin Sensitisation	No data were available
9.3.2.9	Sensitisation by Inhalation	No data were available
9.3.3	Subchronic Toxicity	
9.3.3.1	Oral	Groups of 20 male and 20 female Charles River COBS CD rats were administered 0, 0.01, 0.05, 0.1, 0.5 or 1.0 mg/kg/day of a commercial PeBDE mixture of unknown composition, in the diet daily for 30 days. Groups of 5 rats per sex at each dose level were sacrificed at 30 days, and after recovery periods of 6, 12 and 24 weeks. No treatment-related changes in survival, body weight, food consumption, behavioural or clinical signs, haematology, clinical chemistry, macroscopic or histopathological changes were observed.

There were no treatment-related changes in liver and urinary porphyrins. No test material-related effects were noted in this study, except for the elevated bromine levels in the thyroid gland and liver after 4 weeks of treatment. The NOAEL was 1 mg/kg/day (1)

Groups of six male Sprague-Dawley rats were administered PeBDE (commercial grade) in corn oil by gavage for 90 days. Two dosing regimens were used: a high-dose series of 0, 6.25, 12.5, or 25 µmol/kg/day (equivalent to 0, 3.53, 7.06, or 14.12 mg/kg/day, respectively) and a low-dose series of 0, 0.78, 1.56, or 3.13 µmol/kg/day (equivalent to 0, 0.44, 0.88, or 1.77 mg/kg/day, respectively).

Liver enzyme induction occurred at all dose levels, and some of these changes were persistent, lasting for 30-60 days after the cessation of treatment. No histologic liver abnormalities were observed in rats administered the low-dose series. Histologic evaluation was not performed on the high-dose rats. The NOAEL for PeBDE is considered to be 1.77 mg/kg/day, the highest dose for which liver enzyme induction occurred, but no histologic liver abnormalities were found (5)

Groups of 30 Sprague-Dawley rats/sex were administered 0, 2, 10 or 100 mg/kg/day DE-71 (a commercial PeBDE mixture) in corn oil, in the diet for up to 90 days. Ten animals per sex from each group were sacrificed on day 28 of dosing and a further 10 per sex at the end of the 90-day dosing period. Of the remaining animals, 5 per sex per group were sacrificed after recovery periods of 6 and 24 weeks.

The results indicated that the liver is the target organ. The effects included increased liver weight associated with microscopic cytoplasmic changes, together with disturbances in porphyrin and cholesterol synthesis. Porphyrin levels in urine and liver were increased in both sexes at 100 mg/kg/day at week 4 and 13. By week 13, urinary porphyrins were increased by 2-fold and 13-fold in males and females respectively, and liver porphyrins were correspondingly increased by 8- and 400-fold. Slight thyroid hyperplasia and reductions in plasma T4 levels were also observed, but these effects are considered to be indirect consequences of the in-

		duction of liver enzymes, and due to species differences in thyroid metabolism are not likely to be of relevance to human health. In view of the effects on the liver, a clear NOAEL cannot be identified from this study (< 2 mg DE-71/kg/day) (3, 23) In a study designed to assess the immunological and endocrine effects of DE-71 (a commercial PeBDE mixture), groups of 6-8 female C57BL/6J mice were dosed by gavage with 0, 18, 36, or 72 mg/kg DE-71 in peanut oil for 14 days. The potential immunotoxicity of DE-71 was assessed by measuring the plaque-forming cell (PFC) response to an intraperitoneal injection of sheep erythrocytes (SRBC), natural killer cell (NKC) activity in vitro and cytochrome P450 IA1 and IIB1 activity. All animals were sacrificed on day 15 of the study and spleen, thymus, liver and body weights were measured. There was evidence of dose-related increase in relative liver weight, reduced relative thymus weight at the top dose, increased cytochrome P450 activity and reduced serum T4 levels (as seen in studies in rats). No conclusions regarding the immunotoxic potential of PeBDE could be drawn from this study (12)
9.3.3.2	Inhalation	No data are available
9.3.3.3	Dermal	No data are available
9.3.4	Chronic Toxicity and Carcinogenicity	No data are available
9.3.5	Mutagenicity	
9.3.5.1	Gene Mutation	PeBDE (purity unknown) was not mutagenic in a *Salmonella typhimurium* assay, in which four strains (TA-98, TA-100, TA-1535, and TA-1537) were utilized both with and without metabolic activation (24) PeBDE was evaluated for mutagenicity by plate assay in two microorganisms, *Saccharomyces cerevisiae*, strain D4, and *Salmonella typhimurium*, strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100, both in the presence and absence of metabolic activation. No evidence of mutagenic activity from PeBDE was seen in any of the assays conducted in this evaluation (2)
9.3.5.2	Chromosome Abnormalities	No data are available

9.3.5.3	Other Genotoxic Effects	No data are available
9.3.6	Reproductive Toxicity, Embryotox-c-ity, and Teratogenicity	
9.3.6.1	Reproductive Toxicity	No data were available
9.3.6.2	Teratogenicity	Groups of 25 pregnant Sprague-Dawley rats were administered doses of 0, 10, 100 or 200 mg/kg/day of Saytex 115 (commercial preparation of PeBDE, CAS No. 117148-85-3, unknown composition) in corn oil, on days 6 to 15 of gestation. Caesarean sections were conducted on day 20 of gestation and the foetuses examined for external, visceral and skeletal alterations. The only test material related sign of maternal toxicity observed was a reduced body weight gain of 20 and 30% compared to controls, and the test material was not teratogenic. The maternal NOAEL was 10 mg/kg/day and the foetal NOAEL was 100 mg/kg/day (13, 23)
9.3.7	Other Toxicity Studies	Mitogen-induced DNA synthesis and immunoglobulin synthesis by lymphocytes from blood donors were examined following 2,2',3,4,4'-PeBDE (purity ≥ 98%) exposure *in vitro* in order to determine the immunotoxic potential. Despite rather high concentrations, 2,2',3,4,4'-PeBDE did not affect human peripheral lymphocyte proliferation or immunoglobulin synthesis *in vitro*. The negative findings in this study indicate that certain functions of human peripheral lymphocytes, i.e. proliferation and immunoglobulin synthesis, are insensitive to the direct action of polybrominated diphenyl ethers and polychlorinated biphenyls (11) The potency of some pure polybrominated diphenyl ethers as Ah-receptor (ant)agonists was investigated. 2,2',3,4,4'-PeBDE, 2,2',4,4',5-PeBDE, and 2,3',4,4',6-PeBDE (not 2,2',4,4',6-PeBDE) were reported to exhibit varying degrees of partial Ah-receptor agonist and antagonist activities in an *in vitro* study in H4IIE rat hepatoma cells (CALUX assay). No signs of cytotoxicity were reported to be observed. No conclusions with regard to the significance of these findings can be drawn from the limited information reported (16).
9.3.8	Toxicokinetics	The half-life of PeBDE has been investigated in the perirenal fat in rats after a single oral dose of 300 mg

Bromkal 70 (mainly PeBDE)/kg b.w. The average half-life of two different PeBDE congeners were between 25 and 47 days, depending on the sex of the animal and the type of isomer determined (23).

Preliminary results from a distribution study with 14C-labelled 2,2',4,4',5-PeBDE and 2,2',3,3',4-PeBDE (No CAS No. available) in mice indicated that relatively high concentrations of radioactivity was accumulated in fat depots, liver, adrenal, ovary, lung and initially the brain. Absorption from the gastrointestinal tract appeared to be effective. The radioactivity was slowly eliminated from adipose tissue and milk from lactating mice. Studies on pregnant animals indicated low foetal uptake (8)

PeBDE behave as mixed-type inducers of cytochrome P-450 types (8, 23)

9.4 Ecotoxicity

No toxicity data for fish, daphnia or algae were available.

Different bioconcentration factors in fish have been reported: 10,200-11,700 (10 µg/l test conc, 8w); <3.4 (10 µg/l test conc., 8w) and 20 (3.5 mg/kg food/day, 3.5 month) (6).

The following Log Pow>6, measured (23) and 7.66 (QSAR estimation) were reported.

9.5 Environmental Fate

Only one test result available. No biodegradation of pentabromobiphenyl ether was found in an OECD 301B ready biodegradation test (29d, CO_2, GLP) (21). Pentabromodiphenyl ether was found not readily biodegradable (2.4% CO_2 evolved after 93 days) (21).

9.6 Environmental Concentrations

Pentabromobiphenyl ether in sediment samples from rivers and estuaries in Japan showed levels ranging from <2 µg/kg (detection limit) up to 28 µg/kg dry weight. In Sweden, the concentrations in sediment samples from rivers were up to 1200 µg 2,2',4,4','5-PeBDE/kg (23). Highest concentration near a producer of pentabromobiphenyl ether was 560.7 µg/kg d.w (15). In Japan, (1981-85), concentrations of 0.4 and 2.8 µg/kg ww were found in mussel. But no pentabromobi-

phenyl ether was detected in fish (< 0.2 µg/kg). In cod (liver) from the North Sea concentrations of 1.9-22 µg/kg, fresh weight, were reported. Concentrations in freshwater whitefish and herring (Sweden, different places) were 7.2 and 64 µg 2,2',4,4',5-PeBDE/kg fat (23). Highest conc., in fish, UK was 108 µg/kg ww (15) and 9400 µg/kg lipid weight, Sweden (22).

Pooled blubber of ringed seal and grey seal, Sweden (1979-85) contained average concentrations of 1.7 and 40 µg 2,2',4,4',5-PeBDE/kg fat respectively (23).

9.7 Conclusion

9.7.1 Health Assessment

Sufficient toxicological data were identified for a health assessment of PeBDE. Most of the data are found in reviews, and many tests have probably not been performed according to internationally accepted guidelines. No data on allergenicity, chronic toxicity, carcinogenicity or reproductive toxicity in multi-generation studies were identified. No chromosome aberration tests or any other mutagenicity tests except the gene mutation tests were found. There are 46 possible isomers of PeBDE, and most of the studies found in literature were made on various commercial formulations of PeBDE, which contain one or a few of these isomers plus some other polybrominated diphenyl ethers. This makes it difficult to make generalised safety evaluation of PeBDE.

Studies in rats with commercial preparations containing PeBDE indicate that these preparations are of low acute toxicity via inhalation or via the oral and dermal routes of exposure. The available data indicate that PeBDE produces only minimal to mild signs of dermal and eye irritation in animals following single exposure. PeBDE did not cause any substantial skin or eye irritancy, and respiratory tract irritation was seen in animals only following exposure to very high concentrations of PeBDE (>8000 ppm).

Repeated oral exposure of rats and mice to PeBDE indicated that the liver is the key target organ affected. The effects observed included increases in liver weight and hepatocytomegaly, cellular microscopic changes, induction of a range of liver enzymes, and disturbances in cholesterol and porphyrin synthesis. Probably as a

consequence of the induction of liver enzymes, T4 levels were reduced in rats and mice leading to increases in thyroid gland weight. However, due to species differences in thyroid metabolism the effects on thyroid status are of unclear relevance to human health. The liver and thyroid changes produced by PeBDE are apparent within 4 weeks of repeated oral dosing, with effects on the liver at 2 mg/kg/day and above, and changes in thyroid status at 10 mg/kg/day and above. A NOAEL of 1.77 mg/kg/day was identified.

PeBDE was not a bacterial cell mutagen. From the limited data available there is no evidence for developmental toxicity with PeBDE. Toxicokinetic studies in rats and mice indicate a moderate retention in the organism, and traces have recently been detected in human plasma, milk and fat tissue.

9.7.2 Environmental Assessment

Only few data were available for environmental classification. Based on the features log P_{ow}>6 and not readily biodegradable, PeBDE may cause long-term adverse effects in the aquatic environment.

9.8 References

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3. Initial submission: Letter from great lakes chem corp to USEPA regarding ITC request for information on brominated flame retardants (53 FR 5466) with attachments, dated 05/17/88. EPA/OTS; Doc #FYI-OTS-0794-1106 1994. NTIS/OTS0001106.

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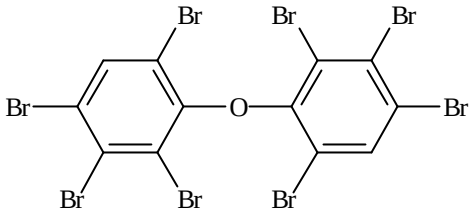
10. Octabromodiphenyl ether

10.1 Identification of the substance

10.1.1	CAS No.	32536-52-0
10.1.2	EINECS No.	251-087-9
10.1.3	EINECS Name	Diphenyl ether, octabromo derivative
10.1.4	Synonyms	Benzene, 1,1'-oxybis-, octabromo deriv. Phenyl ether, octabromo deriv. Octabromobiphenyl ether Octabromodiphenyl oxide OBDE
		The commercial product is a mixture of polybrominated diphenyl ethers (10): OBDE: 31.3-35.3% PeBDE and HxBDE: 10.5-12.0% HpBDE: 43.7-44.5% NBDE: 9.5-11.3% DeBDE: 0-0.7%
		Saytex 111 (a commercial product) (10): OBDE: 33.5% PeBDE: 0.2% HxBDE: 8.6% HpBDE: 45.0% NBDE: 11.2% DeBDE: 1.4%
		DE-79 (another commercial product of unknown composition)
10.1.5	Molecular Formula	$C_{12}H_2Br_8O$

10.1.6	Structural Formula	 1,1'-oxybis[2,3,4,6-tetrabromobenzene] CAS No. 117964-21-3 Based on the chemical structure, there are 12 possible isomers of OBDE.
10.1.7	Known Uses	Used as a flame retardant in nylon, high impact polystyrene, low density polyethylene, polypropylene copolymer, adhesives and coatings (10)
10.1.8	EU Classification	Not included in Annex I to Directive 67/548/EEC
10.2	**Physico-chemical Characteristics**	
10.2.1	Physical Form	Off-white powders with faint odour (10)
10.2.2	Molecular Weight	801.38
10.2.3	Melting Point/range (°C)	75 - 257 depending on the product (10)
10.2.4	Boiling Point/range (°C)	
10.2.5	Decomposition Temperature (°C)	
10.2.6	Vapour Pressure (Pa (°C))	$< 1.33 \times 10^{-5}$ (10, 25)
10.2.7	Relative Density (D_4^{20})	2.76 (10)
10.2.8	Vapour Density (air=1)	
10.2.9	Conversion Factor (1011 hPa at 25^o)	
10.2.10	Solubility	Water: < 1 g/l (25°C) Benzene: 200 g/l (25°C) (10)
10.2.11	Partition Coefficient (log P_{ow})	5.5 or 8.35-8.90 (10)
10.2.12	Flammability	Not applicable
10.2.13	Explosivity	None
10.2.14	Oxidising properties	None

10.3	**Toxicological Data**	
10.3.1	Observations in humans	OBDE has been found in human adipose tissue. The levels were from "not detected" to 8 μg/kg fat (8)
10.3.2	Acute Toxicity	
10.3.2.1	Oral	Oral LD50, rats: > 5,000 mg/kg (DE-79). No rats died during the 14-day observation period (1) Oral LD50, rats: > 10,000 mg/kg (Saytex 111) Twenty rats (2/sex) were orally administered OBDE at 500, 2,500, 5,000, 7,500, and 10,000 mg/kg. None of the animals died during the study (72 hr) (3)
10.3.2.2	Dermal	Dermal LD50, rabbits: > 2,000 mg/kg (DE-79). No rabbits died during the 14-day observation period (1, 3)
10.3.2.3	Inhalation	Inhalation LC50, CD rats: > 60 mg/l/1 hour (DE-79). Groups of male and female rats were exposed to 2 or 60 mg OBDE/l air for 1 hour in a whole body exposure chamber. Particle size distribution was not characterised. No treatment-related mortalities occurred at either concentration. Animals in the high concentration group showed tachypnoea, and animals in both groups displayed decreased motor activity, eye squint, and erythema (site not stated) during exposure(1). Inhalation LC50, rats: >52.8 mg/l/1 hour (Saytex 111). One group of 5 male and 5 female rats was exposed to a dust atmosphere of milled OBDE for 1 hour followed by a 14 day observation period. None of the rats died on the study. No gross lesions related to test article were found at gross necropsy (3)
10.3.2.4	Other Routes	No data were available
10.3.2.5	Skin Irritation	OBDE (Saytex 111) was not skin irritating (3, 10)
10.3.2.6	Eye Irritation	OBDE (Saytex 111) was not eye irritating (3, 10)
10.3.2 7	Irritation of Respiratory Tract	No data were available
10.3.2.8	Skin Sensitisation	No data were available
10.3.2.9	Sensitisation by Inhalation	No data were available
10.3.3	Subchronic Toxicity	

10.3.3.1 Oral

Groups of 35 Charles River CD rats/sex were fed a diet containing 0, 100, 1,000 or 10,000 ppm commercial OBDE for 90 days.

Clinical signs, body weight, food consumption, haematology, biochemical and urinalysis were studied after 1 and 2 months and at the end of the study in groups of 5 rats/sex per group. The remaining 20 rats per group were used to study the recovery and 5 rats/sex/group were sacrificed after 13 and 21 weeks and 6 months of withdrawal. A few rats died on test; mainly as a result of blood collection.

In the 100 ppm group, absolute and relative liver weight was increased. Hepatic changes in 4 of 10 rats were characterized by granular cytoplasmic changes. Liver total bromine was increased at 13 weeks, but declined during the recovery period.

In the 1,000 ppm group a decrease in body weight gain was found, but haematology, blood chemistry and urinalysis were comparable to control. Absolute and relative liver and thyroid weights were increased at 13 weeks, but not at recovery. Hepatic changes included centrolobular and midzonal vacuolisation and hyaline intracytoplasmic inclusions.

In the 10,000 ppm group, a decrease in body weight gain was found during treatment and recovery. Changes in some haematology and serum chemistry values were detected. Absolute and relative liver, kidney, thyroid weights were observed. Hepatic changes included granular cytoplasmic changes, cytoplasmic vacuolisation, scattered necrosis, centrilobular fibrosis and pigmented Kupfer cells. Renal changes included the occurrence of small to moderate numbers of cortical regenerative tubules. Lesions in the thyroid were also found. During recovery, the histologic changes decreased in severity and frequency. The total bromine content in the liver increased during the 13 week treatment period and decreased during the recovery period. At the end of the recovery period, bromine levels remained higher than the control values for the liver.

A NOAEL could not be established (< 100 ppm ≈ approx. 5 mg/kg/day) (3, 10)

10.3.3.2	Inhalation	Groups of 5 rats/sex were exposed to dust of commercial OBDE introduced into a inhalation chamber at nominal concentrations of 0, 0.0012, 0.012, 0.12, and 1.2 mg/l air for 8 hours/day for 14 days. The actual concentrations were about 15-45% of the nominal concentrations. Particle size distribution was not characterised. No animals died on test. Food consumption, body weight gain, haematology, blood chemistry and urinalysis in all dose groups were normal. The total bromine concentrations in lung, liver and fat were statistically significantly higher than in the controls. The average total bromine in lung and fat ranged from about 1.5 to 12.5 times higher than in the liver. The relative liver weights in the 0.012, 0.12, and 1.2 mg/l dose groups were statistically significantly increased in a dose-related manner. These changes were accompanied by histologic lesions consisting of focal to multifocal cytoplasmic enlargement of the hepatocytes, and focal acidophilic degeneration of individual and small groups of liver cells. At the two highest dose levels, the enlargement of the hepatocytes was multifocal to diffuse in distribution and small to large areas had necrosis in the centrolobular regions of the affected liver lobules, especially in the 1.2 mg/l group. The NOAEL was 0.0012 mg/l (nominal concentration) (3, 10)
10.3.3.3	Dermal	No data were available
10.3.4	Chronic Toxicity and Carcinogenicity	No data were available
10.3.5	Mutagenicity	
10.3.5.1	Gene Mutation	Commercial OBDE was examined *in vitro* for mutagenic activity at a number of concentrations in the Ames assay using *Salmonella typhimurium* and *Saccharomyces cerevisiae* with and without metabolic activation. The results of these tests were all negative. (2, 3, 10)
10.3.5.2	Chromosome Abnormalities	In an *in vitro* assay for sister chromatid exchange, Chinese hamster ovary cells were exposed to several concentrations of commercial OBDE for 2 hr in the presence or absence of a metabolic activation system.

		The exposure period was followed by a 24 hr expression period. No statistically significant increase in the number of exchanges per chromosome or the number of exchanges per cell was seen at any dose level tested (3, 10).
10.3.5.3	Other Genotoxic Effects	An unscheduled DNA synthesis (UDS) assay (*in vitro*), a test to induce DNA damage followed by repair in mammalian cells, was carried out with WI-38 human fibroblast cells which were exposed to commercial OBDE in the presence of radiolabelled thymidine. OBDE was tested in 5 concentrations with and without metabolic activation. OBDE was negative in this test (3, 10).
10.3.6	Reproductive Toxicity, Embryo-toxicity, and Teratogenicity	
10.3.6.1	Reproductive Toxicity	No data were available
10.3.6.2	Teratogenicity	Female rats (number not specified) were dosed daily by gavage from days 6 through 15 of gestation with 0 (vehicle), 2.5, 10, 15, 25 and 50 mg commercial OBDE (DE-79)/kg b.w. in a range-finding study. All animals survived to gestation day 20, when sacrificed. Mean maternal body weight gain was reduced at 50 mg/kg. Increased number of late resorptions and statistically significantly reduced mean foetal weight were observed at the highest dose level. No compound-related microscopic findings were observed in the liver and kidneys of the dams. No compound related effects were observed at 15 mg/kg or lower. Malformations and developmental variations observed in the 50 mg/kg groups were associated with maternal toxicity. These included foetal anasarca, bent limb bones, reduced ossification of the skull, various unossified bones, and two instances of bent ribs (3, 10). NOAEL Maternal: 25 mg/kg b.w. NOAEL Teratogenicity: 15 mg/kg b.w.
		Four groups of 25 pregnant Charles River Crb:COBS CD (SD) BR rats were administered by gavage corn oil suspensions of commercial OBDE (Saytex 111) at doses of 0, 2.5, 10, or 25 mg/kg bw/day on gestation days 6-15. The dams were sacrificed at day 20 of

gestation and the foetuses were examined for gross visceral and skeletal abnormalities.

The substance was more toxic to the conceptus than to the dam. At the 25 mg/kg dose level, effects on the conceptus included reduce average foetal b.w., increased embryo/foetal deaths (resorptions), foetal malformations such as enlarged heart, rear limb malformation, and delayed skeletal ossification. At 10 mg/kg, the only observed effect was a statistically reduction in average foetal body weight (3, 10).

The maternal NOAEL was 25 mg/kg.

The embryo/foetal NOAEL was 2.5 mg/kg.

The NOAEL for teratogenicity was 10 mg/kg.

Groups of 26 inseminated adult New Zealand white rabbits (weight 3.5-4.5 kg) were treated with 0 (corn oil), 2, 5 or 15 mg commercial OBDPO (Saytex 111)/kg bw/day by gavage on days 7-19 of gestation. Body weight gain was recorded on gestation day 0, 7, 10, 13, 16, 20 and 28. Maternal liver, kidneys and gravid uterine weights were measured at sacrifice. The offspring were examined on day 28 of gestation.

A statistically significant increase in liver weight and a decrease in body weight gain was observed in the 15 mg/kg group. There was no statistically significant deviation in maternal mortality, number of pregnancies, number of litters with viable pups, corpora lutea/dam, implantations/dam, liver foetuses/litter, percentage of resorptions and foetal body weight. Slight foetal toxicity was observed in the 15 mg/kg group as evidenced by a significant increase in delayed ossification of the sternebrae. 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 group. These increases were not dose related. It was concluded by the authors that there was no evidence for teratogenic activity but slight foetotoxicity at the maternally toxic dose level, (e.g., 15 mg/kg bw), was seen (3, 10).

The maternal NOAEL was 5 mg/kg.

The embryo/foetal NOAEL was 2 mg/kg.

The NOAEL for teratogenicity was 15 mg/kg.

10.3.7	Other Toxicity Studies	Liver enzymes was induced by OBDE (commercial products) in a dose and time dependent manner (10) When investigated in cultured chick embryo liver cells, OBDE was strongly pophyrinogenic (10)
10.3.8	Toxicokinetics	Measurement of total bromine content in various tissues after repeated oral or inhalation exposure to OBDE (commercial products) indicate some absorption by these routes (10)
10.4	**Ecotoxicity**	Only few data were available. LC_{50} in fish was > 0.5 mg/l (*Oryzias latipes*, 48h) in 20 g/l dispersing agent (4). NOEC daphnia was >0.002 mg/l (*Daphnia magna*, 21d) in a OECD 202, GLP, flow through test (5). The bioconcentration Factor (BCF) in fish was <4 (carp, 8 week exposure) at 10 µg/l and 100 µg/l exposure concentration (9). Different Log Pow 8.35-8.9 (9) and 10.33 (QSAR estimation) have been reported.
10.5	**Environmental Fate**	No biodegradation of octabromobiphenyl ether was found in a closed bottle test (OECD 301D; 28d) (7).
10.6	**Environmental Concentrations**	Octabromobiphenyl ether was found in sediments in concentrations of 0.008 to 0.53 mg/kg ww highest close to manufacturer site. In fish the highest concentration of 0.325 mg/kg was measured in dab (liver), UK. <0.001 - 0.179 mg/kg were reported in fish liver and muscle, UK (6).
10.7	**Conclusion**	
10.7.1	Health Assessment	Sufficient toxicological data were identified for a health assessment of OBDE. Most of the data were taken from a review performed by WHO. Many of the toxicological studies were performed on old commercial OBDE products of low OBDE purity and high HpBDE content, and they were not performed according to today's standards. No data on sensitisation and long term toxicity and carcinogenicity were identified. Few relevant data on humans were identified. OBDE has a low acute toxicity and low irritative potential. Repeated doses of OBDE induced liver changes, indicative of an inducer effect. OBDE is not considered mutagenic. Exposure of pregnant rats and rabbits indicated that the foetuses were more sensitive than the dams. Evidence of teratogenicity was found in

one rat study.

10.7.2 Environmental Assessment

Only few data were available for environmental classification. OBDE is suspected to cause long-term adverse effects in the aquatic environment.

10.8 References

1. Initial submission: Letter from great lakes chem corp to USEPA regarding ITC request for information on brominated flame retardants (53 FR 5466) with attachments, dated 05/17/88. EPA/OTS; Doc #FYI-OTS-0794-1106 1994. NTIS/OTS0001106.

2. Final report, bacterial reverse mutation assay with octabromodiphenyl oxide, with cover letter dated 9/25/96. EPA/OTS; Doc #86960000603 1996. NTIS/OTS0558804.

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6. Law RJ, Allchin CR, Morris S, Reed J. Analysis of brominated Flame Retardants in Environmental Samples. Ministry of Agriculture, Fisheries and Food, Directorate of Fisheries Research, Burnham-on Crouch, 1996.

7. Schaefer EC, Harberlien D. Octabromodiphenyl oxide (OBDPO): Closed Bottle Test. Wildlife International Ltd, Maryland, United States, 1996.

8. Stanley JS, Cramer PH, Thornburg KR, Remmers JC, Breen JJ, Schwemberger J. Mass spectral confirmation of chlorinated and brominated diphenylethers in human adipose tissues. Chemosphere 1991; 23(8-10):1185-95.

9. Watanabe I, Tatsukawa R. Anthropogenic brominated aromatics in the Japanese environment. Workshop on Brominated Aromatic Flame Retardants. Swedish National Chemicals Inspectorate (KemI), Solna Sweden, 1990.

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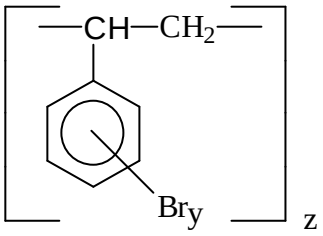
11.	**Benzene, ethenyl-, homopolymer, brominated**	
11.1	**Identification of the substance**	
11.1.1	CAS No.	88497-56-7
11.1.2	EINECS No.	Not listed
11.1.3	EINECS Name	Not listed
11.1.4	Synonyms	Ethenylbenzene homopolymer, brominated Brominated polystyrene JM-631, K0768A and S-346 are sample designations for Pyro-Chek 68PB type materials from Ferro Corporation. K0768A is characterised by a molecular weight of 200,000 and a melting point of approx. 190°C (3) KH97, KN707 and LD-544 are sample designations for Pyro-Chek LM type materials from Ferro Corporation. KH97 and LD-544 are identical. In Pyro-Chek LM. Lot no. OV-779W the following impurities were identified: ethylene dichloride (0.047%, CAS No. 107-06-2) and water (0.020%) (6)
11.1.5	Molecular Formula	$(C_8H_xBr_y)_z$ (x = 5-6, y = 2-3, z = 4-100)
11.1.6	Structural Formula	
11.1.7	Known Uses	Used as a flame retardant, melt-blendable (at approx. 180°C) additive to polymeric products including acrylonitrile-butadiene-styrene products, polyethylene (high density), polyamide, polybutylene terephthalate, and others, and typically in conjunction with antimony oxide (16)
11.1.8	EU Classification	Not included in Annex I
11.2	**Physico-chemical Characteristics**	
11.2.1	Physical Form	Typically fine white to slight off-white powder with odourless or slight aromatic odour. Particles may in-

		clude portion below 10 μm diameter (16)
		JM-631: Fine, beige powder (8) (IBT)
		KH97: Grey amorphous powder(2)
		LD-544: Tan powder (11)
		Pyro-Chek LM: Light orange powder (10)
		Pyro-Chek LM (sample OV-779W): Beige powder (9)
11.2.2	Molecular Weight	1,000 - 200,000; typically 750-1,500 (16)
11.2.3	Melting Point/range (°C)	No data were available
11.2.4	Boiling Point/range (°C)	No data were available
11.2.5	Decomposition Temperature (°C)	No data were available
11.2.6	Vapour Pressure (Pa (°C))	2.0×10^{-5} (20, 16)
11.2.7	Relative Density (D_4^{20})	2.1 (16)
11.2.8	Vapour Density (air=1)	No data were available
11.2.9	Conversion Factor (1011 hPa at 25^o)	No data were available
11.2.10	Solubility	Water: insoluble
		Benzene: 780 g/l
		Acetone: 580 g/l
		(16)
11.2.11	Partition Coefficient (log P_{ow})	No data were available
11.2.12	Flammability	No data were available
11.2.13	Explosivity	No data were available
11.2.14	Oxidising properties	No data were available
11.3	**Toxicological Data**	
11.3.1	Observations in humans	No data were available
11.3.2	Acute Toxicity	
11.3.2.1	Oral	JM-631. Oral LD50, rats: > 15,380 mg/kg (8) (IBT)
		Pyro-Chek LM. Oral LD50, rats: > 5,000 mg/kg (7)
11.3.2.2	Dermal	Oral LD50, rabbits: > 3,038 mg (JM-631)/kg. No systemic toxicity was noted; but the test material was moderately irritating to the skin (4) (IBT)
11.3.2.3	Inhalation	JM-631. Dust inhalation LC50, rats: >1.92 mg/l/4 hours. Ten Charles River rats were exposed in a whole-body-

exposure chamber to atmospheric dust concentration 1.92 mg/l (max attainable). 39.7% of the particles were less than 6 microns, and another 39.7% were within the range 6-10 microns. The only exposure related sign was red nasal discharge in 4 rats on day 1 of the 14 day observation period (5) (IBT).

Pyro-Chek LM. Dust inhalation LC50, rats: >5.25 mg/l/4 hours. Ten Charles River rats were exposed in a whole-body-exposure chamber to atmospheric dust concentration 5.25 mg/l (mean gravimetric concentration). 96.5% of the particles were less than 1.01 microns, and the mass median aerodynamic diameter was determined to be 3.8 microns. The only exposure related sign was body weight loss in 4 animals within the 14 day observation period (6, 15)

11.3.2.4 Other Routes

No data were available

11.3.2.5 Skin Irritation

Pyro-Chek LM. Grading of dermal reactions (mean of the 24 and 72 hours examinations/max. score) (14):

Erythema and eschar:	0.17/4
Oedema:	0.00/4

11.3.2.6 Eye Irritation

JM-631. Grading of ocular lesions (mean of the 24, 48 and 72 hours examinations/max. score) (8) (IBT):

Cornea opacity:	0.00/4
Iris:	0.00/2
Conjunctivae, erythema:	0.61/3
Conjunctivae, oedema:	0.00/4

Pyro-Chek LM. Grading of ocular lesions (mean of the 24, 48 and 72 hours examinations/max. score) (13):

Cornea opacity:	0.22/4
Iris:	0.00/2
Conjunctivae, erythema:	0.61/3
Conjunctivae, oedema:	0.17/4

11.3.2 7	Irritation of Respiratory Tract	No data were available
11.3.2.8	Skin Sensitisation	Pyro-Chek LM was tested in a guinea pig maximisation test. After the challenge (and re-challenge) with Pyro-Chek LM notably greater dermal reactions (grade 2 erythema with oedema) were observed in 2/10 test animals at the 24 and 48 hour scoring interval. The result indicated a weak dermal sensitisation (6)
11.3.2.9	Sensitisation by Inhalation	No data were available
11.3.3	Subchronic Toxicity	
11.3.3.1	Oral	No data were available
11.3.3.2	Inhalation	No data were available
11.3.3.3	Dermal	No data were available
11.3.4	Chronic Toxicity and Carcinogenicity	No data were available
11.3.5	Mutagenicity	
11.3.5.1	Gene Mutation	JM-631 was tested for mutagenicity in five *Salmonella typhimurium* strains (TA-98, TA-100, TA-1535, TA-1537, and TA-1538) in the presence and absence of Aroclor-induced rat liver S9. These tests were all negative (1). K0768A was tested negative for mutagenicity in five *Salmonella typhimurium* strains (TA-98, TA-100, TA-1535, TA-1537, and TA-1538) in the presence and absence of Aroclor-induced rat liver S9. (3) KH97 was generally negative in a test for mutagenicity in five *Salmonella typhimurium* strains (TA-98, TA-100, TA-1535, TA-1537, and TA-1538) in the presence and absence of Aroclor-induced rat liver S9; but a significant increase in the number of point mutations was noted in strain TA-1537 without S-9 mix.(2) LD-544 was tested negative for mutagenicity in five *Salmonella typhimurium* strains (TA-98, TA-100, TA-1535, TA-1537, and TA-1538) in the presence and absence of Aroclor-induced rat liver S-9 mix.(11) Pyro-Chek LM sample #NF556W was tested for mutagenicity in five *Salmonella typhimurium* strains (TA-98, TA-100, TA-1535, TA-1537, and TA-1538) in the presence and absence of Aroclor-induced rat liver S-9

		mix. The test material was positive in strains TA-98 and TA-100, only in the absence of S-9 mix(10) Pyro-Chek LM sample #NF 556 WRD was tested for mutagenicity in five *Salmonella typhimurium* strains (TA-98, TA-100, TA-1535, TA-1537, and TA-1538) in the presence and absence of Aroclor-induced rat liver S-9 mix. The test material was positive in strain TA-100, only in the absence of S-9 mix (12). Different samples were tested in *Salmonella typhimurium* strain TA-100 in the absence of S-9 mix. Some were positive. The identification of the mutagenic species was not possible although it appeared to be an artefact of the fractional precipitation procedures (9). Pyro-Chek LM (sample OV-779W) was tested for mutagenicity in five *Salmonella typhimurium* strains (TA-98, TA-100, TA-1535, TA-1537, and TA-1538) in the presence and absence of Aroclor-induced rat liver S-9 mix. The test material was negative in all strains tested (9).
11.3.5.2	Chromosome Abnormalities	No data were available
11.3.5.3	Other Genotoxic Effects	No data were available
11.3.6	Reproductive Toxicity, Embryotoxicity, and Teratogenicity	
11.3.6.1	Reproductive Toxicity	No data were available
11.3.6.2	Teratogenicity	No data were available
11.3.7	Other Toxicity Studies	No data were available
11.3.8	Toxicokinetics	No data were available
11.4	**Ecotoxicity**	No data were available.
11.5	**Environmental Fate**	No data were available.
11.6	**Environmental Concentrations**	No data were available.
11.7	**Conclusion**	
11.7.1	Health Assessment	Sufficient toxicological data were identified for a health assessment of brominated polystyrene. Most of the data were found in documents submitted to the U.S. EPA. These documents contain study reports of tests performed in the late nineteen seventies, and only a few is performed according presently, generally accepted international guidelines and Good Laboratory

Practice. A couple of the tests were conducted by Industrial Bio-Test Laboratories, a concern later found to have submitted many flawed or fraudulent reports on its procedures and results. No data on subchronic toxicity, chronic toxicity, carcinogenicity or reproductive toxicity were identified. No chromosome aberration tests or any other mutagenicity tests except the gene mutation tests were found. No data on humans were identified.

Brominated polystyrene is not a chemically well defined substance and the molecular formula, $(C_8H_xBr_y)_z$ (x = 5-6, y = 2-3, z = 4-100), indicate the existence of a range of different molecules. The high molecular weight of the molecular material of the molecular material indicate a low potential for transport to the systemic circulation, and the associated toxicity is considered very low.

Monomers, solvents and other impurities may account for the mutagenic potential found in some gene mutation assays. The only impurity listed, ethylene dichloride (CAS No. 107-06-2), occurred at very low concentrations, but it is a well known potential carcinogen (Carc2; R45).

11.7.2 Environmental Assessment

No ecotoxicity or environmental fate data were available for environmental assessment.

11.8 References

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