European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

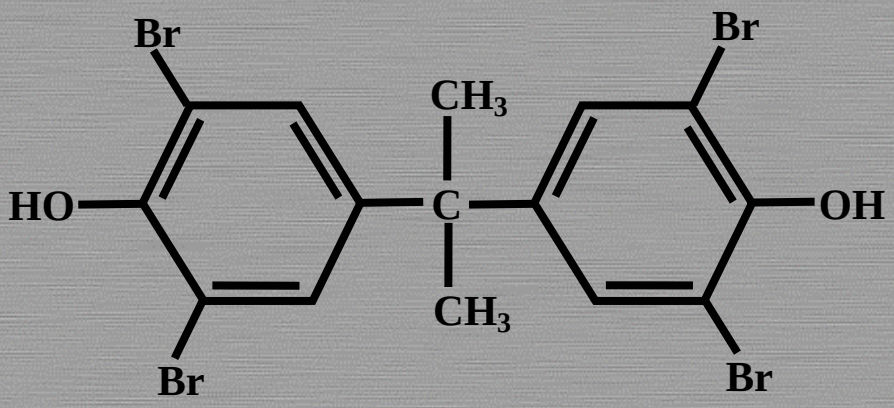
Existing Substances

European Union Risk Assessment Report

CAS: 79-94-7

EINECS: 201-236-9

2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol (tetrabromobisphenol-A or TBBP-A) Part II – human health



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European Union Risk Assessment Report
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European Union Risk Assessment Report

2,2',6,6'-TETRABROMO-4,4'-ISOPROPYLIDENEDIPHENOL (TETRABROMOBISPHENOL-A or TBBP-A)

Part II – Human Health

CAS No: 79-94-7

EINECS No: 201-236-9

RISK ASSESSMENT

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Part II – Human Health

CAS No: 79-94-7

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RISK ASSESSMENT

Final Report, 2006

United Kingdom

The rapporteur for the risk assessment of 2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol (tetrabromobisphenol-A or TBBP-A) is the United Kingdom.

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Review of report by MS Technical Experts finalised:	**2005**
Final report:	**2006**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.
The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.
The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.
The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992 and confirmed in the Johannesburg Declaration on Sustainable Development at the World Summit on Sustainable Development, held in Johannesburg, South Africa in 2002.
This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.

Roland Schenkel
Director General
DG Joint Research Centre

Mogens Peter Carl
Director General
DG Environment

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[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS Number: 79-94-7
EINECS Number: 201-236-9
IUPAC Name: 2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol (tetrabromobisphenol-A or TBBP-A)

Environment

(to be added later).

Human health

No health effects of concern have been identified for TBBP-A.

Workers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

No health effects of concern to adults have been identified. Therefore **conclusion (ii)** is reached in relation to all endpoints and for all exposure scenarios.

Consumer

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Given that consumer exposure is negligible **conclusion (ii)** is reached in relation to all endpoints.

Humans exposed via the environment

Regional exposures

No health effects of concern to adults have been identified. Therefore, **conclusion (ii)** is reached for regional exposures.

Local exposures

No health effects of concern to adults have been identified. Therefore **conclusion (ii)** is reached for all local exposure scenarios.

Infants

MOS values of 210 and 10^6 have been obtained by comparing the NOAEL for nephrotoxicity in newborn rats with the highest environmental exposure estimate of an adult and the highest concentration of TBBP-A found in breast milk, respectively. These MOS values are considered to be sufficient to allow for interspecies and intraspecies differences, and therefore **conclusion (ii)** is reached.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Combined exposure

Given that consumer exposures are negligible calculation of combined exposure is not necessary. Therefore **conclusion (ii)** is reached.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human health (risks from physico-chemical properties)

There are no significant risks from physico-chemical properties.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

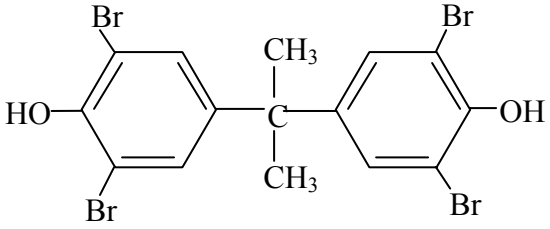
CONTENTS

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No: 79-94-7
EINECS No: 201-236-9
IUPAC-Name: 2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol (tetrabromobisphenol-A or TBBP-A)
Molecular formula: $C_{15}H_{12}Br_4O_2$
Molecular weight: 543.9 g/mole
Structural formula:



Other names, abbreviations, trade names and registered trademarks for the substance include the following.

2,2-bis(3,5-dibromo-4-hydroxyphenyl) propane	F-2016
3,3',5,5'-tetrabromobisphenol-A	F-2400
4,4'-isopropylidene-bis(2,6-dibromophenol)	F-2400E
phenol, 4,4'-isopropylidinebis, (dibromo-)	FR-1524
phenol, 4,4'-(1-methylethylidene)bis(2,6-dibromo-)	Fire Guard FG2000
tetrabromodihydroxy diphenylpropane	Firemaster BP 4A
TBBA	Saytex RB-100
TBBP-A	Tetrabrom
BA-59P	Tetrabromodian

The common name tetrabromobisphenol-A or the abbreviation TBBP-A will be used in this assessment.

1.2 PURITY/IMPURITIES, ADDITIVES

1.2.1 Purities/impurities

The purity of commercial tetrabromobisphenol-A has been reported as 98.5% (WHO, 1995). The main impurities are 0.1% water, a maximum of 60 mg hydrolysable bromine/kg and a maximum of 100 mg ionic bromide/kg (WHO, 1995). Recent tests carried out using composite samples from the main current suppliers of the substance report that the current purity of the substance is around 98.9% (Wildlife International, 2001a and 2001b) to 99.17% (Wildlife International 2002e), which is slightly higher than the value given in WHO (1995). Trace analysis of the current products indicates that the impurities include o,p'-tetrabromobisphenol-A (~0.05%) and tribromobisphenol-A (~0.79% to ~1.0%) (Wildlife International, 2001b and 2002a).

Brominated dibenzo-*p*-dioxins and furans may also be present at trace levels. The available data are discussed in Appendix A. In all cases the amounts found are below the levels specified in the German Dioxin Ordinance and the USEPA Dioxin Test Rule.

1.2.2 Additives

The commercially available form of tetrabromobisphenol-A has no stated additives.

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties of commercial tetrabromobisphenol-A

Property	Value	Validity[a]
Chemical formula	$C_{15}H_{12}Br_4O_2$	1
Molecular weight	543.9 g/mole	1
Bromine content	58.8% by weight	1
Melting point	178°C; 181-182°C	2
Boiling point	~316°C (decomposes at 200-300°C)	2
Relative density	2.12; 2.18	2
Vapour pressure	<1.19 · 10^{-5} Pa at 20°C 6.24 · 10^{-6} Pa at 25°C	1 2
Water solubility	pH 5 - 0.148 mg/l at 25°C pH 7 - 1.26 mg/l at 25°C pH 9 - 2.34 mg/l at 25°C pure water - 0.063 mg/l at 21°C and 0.24 mg/l at 25°C	1
Log octanol-water partition coefficient (log Kow)	5.90	1
Flammability	Not applicable - flame retardant	1
Autoflammability	Decomposes at 200-300°C	1
Explosive properties	None	1
Oxidising properties	None	1
Acid dissociation constants (pKa)	pKa_1= 7.5 pKa_2 = 8.5	4 4
Henry's Law constant	<0.1 Pa m^3/mole at 20-25°C	2
Conversion factor[4]	1 ppm = 22.6 mg/m^3 at 20°C	1

a) Validity markings
1 Valid without restriction
2 Use with care
3 Not valid
4 Not assignable

[4] We acknowledge that while these figures are technically correct, they are of limited relevance as the substance is unlikely to be present as a vapour in view of its low vapour pressure.

1.3.1 Physical state (at n.t.p)

Tetrabromobisphenol-A is a white crystalline powder at 20^{o}C and 101,325 Pa (WHO, 1995).

1.3.2 Melting point

The melting point of tetrabromobisphenol-A has been reported to be 181-182^{o}C. A similar melting point of 178^{o}C is reported in IUCLID (2000).

1.3.3 Boiling point

The boiling point of tetrabromobisphenol-A is reported to be approximately 316^{o}C (WHO, 1995). However, the substance is likely to decompose over the temperature range 200-300^{o}C liberating Br_2/HBr gas as this reaction accounts for its flame-retarding properties, and so this boiling point could represent the decomposition temperature rather than the true boiling point of the substance. Further details of the method used to measure the boiling point of 316^{o}C are not available and so this hypothesis cannot be verified.

Using the Syracuse Research Corporation MPBPWIN program (Version1.28) a boiling point of 486^{o}C can be estimated for tetrabromobisphenol-A from its chemical structure.

1.3.4 Density

The relative density of tetrabromobisphenol-A has been quoted as 2.18 (WHO, 1995). A similar value of 2.12 at 20^{o}C has been quoted in IUCLID (2000).

1.3.5 Vapour pressure

The vapour pressure of tetrabromobisphenol-A at 20^{o}C has been investigated using the spinning rotor gauge method (Wildlife International, 2001a). The method used was based on the OECD 104 Vapour Pressure Curve method and the USEPA Product Properties Test Guideline OPPTS 830.7950. The substance used in the test was a composite sample from three current manufacturers of tetrabromobisphenol-A and the substance had a purity of 98.91%. Hexachlorobenzene (purity 99%) was used as a reference material in the study.

The limit of detection of the method for tetrabromobisphenol-A (defined as three times the standard deviation of the blank measurements) was determined as $3.57 \cdot 10^{-6}$ Pa and the limit of quantification (defined as ten times the standard deviation of the blank measurements) was determined to be $1.19 \cdot 10^{-5}$ Pa for tetrabromobisphenol-A. The vapour pressure for tetrabromobisphenol-A was below the limit of quantification of the method used i.e. $<1.19 \cdot 10^{-5}$ Pa at 20^{o}C.

The mean measured vapour pressure for the hexachlorobenzene reference material was $5.12 \cdot 10^{-4}$ Pa, which is reasonably consistent with the published values for the vapour pressure of hexachlorobenzene of $2.6 \cdot 10^{-3}$ Pa at 20^{o}C by the gas saturation method and $1.1 \cdot 10^{-3}$ Pa at 20^{o}C by the vapour pressure balance method.

The vapour pressure of tetrabromobisphenol-A has been reported to be <1 mmHg at 20°C (WHO, 1995). No further details of this study were reported. This value is equivalent to <133 Pa at 20°C.

Watanabe and Tatsukawa (1989) reported a vapour pressure for tetrabromobisphenol-A at 25°C of $4.68 \cdot 10^{-8}$ Torr, which is equivalent to $6.24 \cdot 10^{-6}$ Pa. This was determined by a gas chromatography (GC) method, but few other details are available. The value is not inconsistent with the more recent determination using the spinning rotor method, but it is not possible to determine the reliability of this value. In particular, the nature of the substances used as references in the method is not given and so it is not clear if the method used was appropriate for a polar substance such as tetrabromobisphenol-A.

The vapour pressure is an important physico-chemical property for modelling the possible emissions of tetrabromobisphenol-A to the environment and also the subsequent distribution of the substance in the environment (see Section 3, which will be added later). For this reason, a reliable indication of the actual vapour pressure of the substance is desirable. One approach to this is to use quantitative structure-activity relationships (QSAR) to estimate the vapour pressure to support the available measured data. The Syracuse Research Corporation MPBPWIN (Version 1.28) computer program has been used to estimate the vapour pressure of tetrabromobisphenol-A from its structure by the Modified Grain Method. The estimate was carried out three times, firstly allowing the program to estimate the melting point and boiling point, then using the measured melting point (see Section 1.3.2) and finally using the reported boiling point (see Section 1.3.3). The results are shown in **Table 1.2**.

Table 1.2 Estimated vapour pressure of tetrabromobisphenol-A

Input data		Calculated vapour pressure at 25°C
Melting point	Boiling point	
Estimated (206°C)	Estimated (486°C)	$2.35 \cdot 10^{-9}$ Pa ($1.76 \cdot 10^{-11}$ mmHg)
Measured (180°C)	Estimated (486°C)	$4.73 \cdot 10^{-9}$ Pa ($3.55 \cdot 10^{-11}$ mmHg)
Measured (180°C)	Measured (316°C)[a)]	$3.13 \cdot 10^{-4}$ Pa ($2.24 \cdot 10^{-6}$ mmHg)

a) The measured boiling point may represent the decomposition temperature rather than the true boiling point.

The predicted values using a boiling point of 486°C are consistent with the upper limit for the vapour pressure for tetrabromobisphenol-A as measured by the spinning rotor method but are well below that reported using a GC method. The value estimated using a boiling point of 316°C is higher than the upper limit for the measured vapour pressure, reflecting the fact that this may not be a true boiling point but a decomposition temperature.

For comparison, the vapour pressure of bisphenol-A is $5.3 \cdot 10^{-6}$ Pa at 25°C (European Commission, 2002b).

Based on the available data, the vapour pressure of tetrabromobisphenol-A at ambient temperature will be assumed to be $<1.19 \cdot 10^{-5}$ Pa, and is probably considerably lower than this value. Where an actual value for the vapour pressure is needed the value of $6.24 \cdot 10^{-6}$ Pa determined by Watanabe and Tatsukawa (1989) will be used in the environmental risk

assessment, but it should be recognised that the reliability of this value is uncertain. The implications of this value for the Henry's law constant, and hence subsequent environmental distribution, are considered in Section 1.3.14.1.

1.3.6 Solubility

The water solubility of tetrabromobisphenol-A has recently been determined using the OECD 105 method. The substance used was a composite sample from three manufacturers of the substance. A preliminary test was carried out by stirring an excess of the substance (nominal concentration 29 mg/l) in double distilled water for 2 days at 21°C. After this time the solution was centrifuged several times and the supernatants were analysed for tetrabromobisphenol-A. The concentration of tetrabromobisphenol-A in the dissolved phase was determined to be 0.077-0.081 mg/l. The pH of the solution was 6.6 (NOTOX, 2000).

The definitive test was carried out using the column elution technique (NOTOX, 2000). In this test, two columns were filled with inert carrier material onto which the test substance had been coated. The columns were then eluted with double distilled water at various flow rates at 21°C and the concentration of tetrabromobisphenol-A in the column effluent was determined by a high performance liquid chromatography (HPLC) method. The results of the experiment are shown in **Table 1.3**. The solubilities determined at the various flow rates were broadly similar, although there was a trend to lower values at lower flow rates. This trend could not be explained, and is the opposite of what would be expected if equilibrium was not reached. The overall mean value from the study is 0.063 mg/l, which agrees reasonably well with the value from the preliminary test.

Table 1.3 Measured water solubility from column elution experiments (NOTOX, 2000)

Flow rate (ml/hour)	Column	Effluent pH	Mean measured solubility
23	I	7.9	0.082 mg/l
24	I	7.9	0.066 mg/l
22	II	7.6	0.081 mg/l
23	II	7.9	0.070 mg/l
12	I	7.8	0.058 mg/l
12	I	7.9	0.053 mg/l
10	II	7.9	0.069 mg/l
10	II	7.9	0.056 mg/l
6	I	7.9	0.046 mg/l
5	II	8.1	0.048 mg/l
			Average value = 0.063 mg/l

A second similar generator column solubility study has recently been completed (Wildlife International, 2002b). This study differs slightly from the above study in that the solubility was determined in a series of buffered solutions (pH 5 (0.05 mole/l potassium hydrogen phthalate and 0.023 mole/l sodium hydroxide), pH 7 (0.05 mole/l potassium dihydrogen phosphate and 0.029 mole/l sodium hydroxide) and pH 9 (0.05 mole/l sodium borax and 0.014 mole/l hydrochloric acid), as well as pure water, and the study was carried out at 25°C.

The method used was based on OECD Test Guideline 105. The substance used in the test was again a composite sample from three manufacturers of the substance and had a purity of 99.17%. The results of this experiment are shown in **Table 1.4**. There was good agreement between the solubilities obtained at the two different flow rates and the mean solubility was 0.148 mg/l at pH 5, 1.26 mg/l at pH 7, 2.34 mg/l at pH 9 and 0.240 mg/l in the non-buffered water.

Table 1.4 Measured water solubility at various pH's using the column elution method (Wildlife International, 2002b)

pH	Flow rate (ml/minute)	Measure solubility		
		Range	Mean value	Overall mean for both flow rates
5	1	0.145 - 0.156	0.149 ± 0.004	0.148 ± 0.005
	0.5	0.139 - 0.154	0.146 ± 0.006	
7	1	1.25 - 1.28	1.27 ± 0.006	1.26 ± 0.012
	0.5	1.25 - 1.26	1.26 ± 0.006	
9	1	2.33 - 2.49	2.41 ± 0.070	2.34 ± 0.156
	0.5	2.03 - 2.51	2.27 ± 0.20	
Pure (non-buffered) water (pH of water was 6.71; the pH of column effluent was 6.83-7.23 at a flow rate of 1 ml/minute and 6.79-7.12 at a flow rate of 0.5 ml/minute)	1	0.236 - 0.243	0.239 ± 0.0024	0.240 ± 0.0019
	0.5	0.240 - 0.242	0.241 ± 0.0008	

As can be seen from the results of this study, the solubility of tetrabromobisphenol-A increases with increasing pH. The values obtained in this study using pure water (solubility 0.240 mg/l) are slightly higher than found in the NOTOX (2000) study (solubility around 0.063 mg/l) but these differences could, in part, be due to differences in the temperatures used in the two studies (the NOTOX (2000) study was carried out at 21°C whereas the later study was carried out at 25°C). Taken overall, both the NOTOX (2000) and Wildlife International (2002b) studies can be considered as valid studies that reflect the fact that the solubility of tetrabromobisphenol-A is dependent on, amongst other things, the pH of the water.

A further water solubility determination has been carried out using ^{14}C-labelled tetrabromobisphenol-A (Yu and Atallah, 1978). The radiochemical purity of the substance used was >98% and the substance was mixed with unlabelled tetrabromobisphenol-A to give the required specific activity. An excess of the test substance was shaken overnight with distilled water at 35°C. The solution was then centrifuged for 1 hour at either 15°C, 25°C or 35°C and the supernatant was analysed for tetrabromobisphenol-A by a radiochemical method. The average solubility determined for tetrabromobisphenol-A was 0.72 mg/l at 15°C, 4.16 mg/l at 25°C and 1.77 mg/l at 35°C. This method is dependent on the centrifuging step being effective at removing all undissolved test material from the overlying water. Further, the experiment only appears to have allowed 1 hour for equilibrium to occur at the lower two temperatures. This may explain why variable results appear to have been obtained at the various temperatures (normally the water solubility would be expected to increase with increasing temperature). Therefore, the values obtained from this test should be considered as less reliable than the values obtained from the column elution method above. The pH of the water used in this study was not reported.

An apparent water solubility of 917 mg/l has been reported for tetrabromobisphenol-A (Ogino et al., 1987). However the paper is in Japanese and so it has not been possible to check the details of this test. This value appears to be out of line with the other water solubility data available and so is not considered further in the assessment.

Using a log Kow value of 5.90 (see Section 1.3.7) a water solubility of 0.039 mg/l can be estimated for tetrabromobisphenol-A using the Syracuse Research Corporation WSKOW (version 1.30) estimation software. This is lower than, but of a similar order to, the value obtained in the column elution method for pure water (0.063 mg/l and 0.24 mg/l in the two determinations available).

Since tetrabromobisphenol-A can exist in an ionised form at pHs around 7 and above (see Section 1.3.14.2), the water solubility of tetrabromobisphenol-A would be expected to be dependent on the pH of the water. This is clearly confirmed in the Wildlife International (2002b) study reported above. The pH of the water used in the Yu and Atallah (1978) study was not reported but the values obtained in this study are consistent with those obtained in the Wildlife International (2002b) and NOTOX (2000) studies.

Based on the available data, the most reliable value for the experimentally determined water solubility of tetrabromobisphenol-A is 0.148 mg/l at pH 5, 1.26 mg/l at pH 7, 2.34 mg/l at pH 9 and 0.063-0.240 mg/l in pure water.

In the environment, the natural buffering capacity of natural waters means that the results obtained in buffered solution have some relevance to the solubility of the substance in the environment and also the solubility of the substance in aquatic toxicity tests. Indeed, there is some evidence that the solubility of tetrabromobisphenol-A in some of the test media used for aquatic toxicity testing is around 0.5-1 mg/l (see Section 3, which will be added later), which is consistent with the recent solubility data obtained by the column elution method.

In terms of the environmental risk assessment, the water solubility is important for determining the distribution behaviour of the substance as it is used to define the Henry's law constant. This is discussed further in Section 1.3.14.1.

1.3.7 Octanol-water partition coefficient (log Kow)

The octanol-water partition coefficient has been determined using ^{14}C-labelled tetrabromobisphenol-A (Yu, 1978). The radiochemical purity of the substance used was >98%. The experiment was carried out using two concentrations, with each concentration being determined in duplicate. The experiment was carried out by adding the required amount of test substance in a solvent to a centrifuge tube, evaporating the solvent and then adding 2 ml of n-octanol to dissolve the test substance. Distilled water (5 ml) was then added to the tube and each tube was shaken for 5 minutes and then centrifuged for 15 minutes. The organic and water phases were then analysed for tetrabromobisphenol-A by a radiochemical method. The mean Kow value determined was 34,644 (log Kow = 4.54).

The octanol-water partition coefficient for tetrabromobisphenol-A has recently been determined by a generator column method (Wildlife International, 2001b). The method used was based on the USEPA Product Properties Test Guideline OPPTS 830.7560. The substance used in the test was a composite sample from three manufacturers of tetrabromobisphenol-A, and had a purity of 98.91%. The main impurities present were 0.05% o,p'-tetrabromobisphenol-A, <0.01% 2,4,6-tribromophenol and 1.04% tribromobisphenol-A.

The glass column used in the test was around 20 cm long with an outside diameter of around 6 mm. The column was maintained at 25°C throughout the experiment using a water jacket. The column was filled with an inert support material and a solution of the test substance in octanol (around 15 ml of an 8.295 g/l solution of the test substance) was used to charge the column. The column was then back-flushed with octanol-saturated water to remove any entrapped air. Octanol-saturated water was then allowed to flow through the column at a rate of 0.5 ml/minute overnight to equilibrate the system. Following the overnight equilibration period, the flow-rate of the octanol-saturated water was increased to 1 ml/minute and a further 1 hour was allowed for equilibration before the effluent from the column was collected in three consecutive 5 ml samples and analysed for the concentration of tetrabromobisphenol-A by a direct injection high performance liquid chromatography-mass spectrometry (HPLC-MS) technique. The mean measured concentration found in the column effluent was 0.0104 ± 0.0008 mg/l. The measured concentration in the octanol phase was 8.295 ± 0.140 g/l at the start of the experiment, the mean log Kow value determined was 5.90 ± 0.034.

A log Kow of 3.25 has been reported for tetrabromobisphenol-A (Ogino et al., 1987). However the paper is in Japanese and so it has not been possible to check the details of this test.

Watanabe and Tatsukawa (1989) reported a log Kow of 6.4 for tetrabromobisphenol-A determined by a HPLC method. No other experimental details of this study are available.

Other values for the octanol-water partition coefficient of <4 (Lee et al., 1993 and Steinberg et al., 1992) and 5.3 (WHO, 1995) have been reported for tetrabromobisphenol-A. No further details of how the values were determined are available.

A log Kow value of 5.9 will be used for tetrabromobisphenol-A in the risk assessment as it is from a well reported study and the generator column method used is an appropriate method to use for substances with high log Kow values (the OECD 307 shake flask method, which is similar to the method used in the Yu (1978) study, is recommended for log Kow values in the range -2 to 4, whereas the generator column method can be used for substances with log Kow values in the range 1 to >6). Similar to the case with water solubility, the log Kow value might be expected to depend on the pH as increasing pH leads to ionisation of the tetrabromobisphenol-A which may increase its solubility in the aqueous phase and decrease its solubility in the octanol phase (strictly the coefficient in this case is a distribution coefficient). Thus the log Kow value would be expected to decrease with increasing pH. The actual pH of the aqueous phase in the log Kow determinations reported is not given.

1.3.8 Flash point

The substance is used as a flame retardant and so this parameter is not relevant. The substance does not have a flash point.

1.3.9 Autoignition

The material does not undergo autoignition but decomposes at elevated temperatures. The decomposition properties are consistent with the use of this material as a flame retardant.

1.3.10 Explosivity

Explosive properties are not expected on the basis of chemical structure and physical properties. Tetrabromobisphenol-A is not known to exhibit explosive properties with other materials.

1.3.11 Oxidising properties

Tetrabromobisphenol-A does not contain any structural alerts for oxidising effects and so is not considered to be an oxidiser.

1.3.12 Granulometry

The overall mass median diameter for two samples of tetrabromobisphenol-A has been determined as 31.81 μm (Inveresk, 2001) and 52.20 μm (Inveresk, 2002). The more recent study also reported that only approximately 4% of the particles had an aerodynamic diameter of < 15 μm, i.e. towards the respirable range.

1.3.13 Surface tension

No value could be found for the surface tension of an aqueous solution.

1.3.14 Other physico-chemical properties

1.3.14.1 Henry's law constant

The Henry's law constant can be estimated from the vapour pressure and water solubility. For tetrabromobisphenol-A, there is no precise measured value available for the vapour pressure, and so a measure limit value of $<1.19 \cdot 10^{-5}$ Pa and a measured value of $6.24 \cdot 10^{-6}$ Pa (see Section 1.3.5) will be considered here.

Based on these values and a water solubility of 0.063-0.240 mg/l for pure water (see Section 1.3.6), a Henry's law constant of <0.10 Pa m^3/mole or 0.014-0.054 Pa m^3/mole can be estimated for tetrabromobisphenol-A. However, as indicated in Section 1.3.6, the water solubility of tetrabromobisphenol-A is dependent on the pH, with the solubility increasing with increasing pH, and so the Henry's law constant for natural waters, particularly those with pHs of 7 or above, may be lower than estimated using the solubility in pure water.

Another estimate for the Henry's law constant has been obtained from the Syracuse Research Corporation HENRY (version 3.00) computer software. This estimates the Henry's law constant from chemical structure using a bond contribution method and a group contribution method. For tetrabromobisphenol-A only the bond contribution method could be used (values were missing for some groups present in tetrabromobisphenol-A) and the Henry's law constant was estimated as $2.2 \cdot 10^{-8}$ Pa m^3/mole.

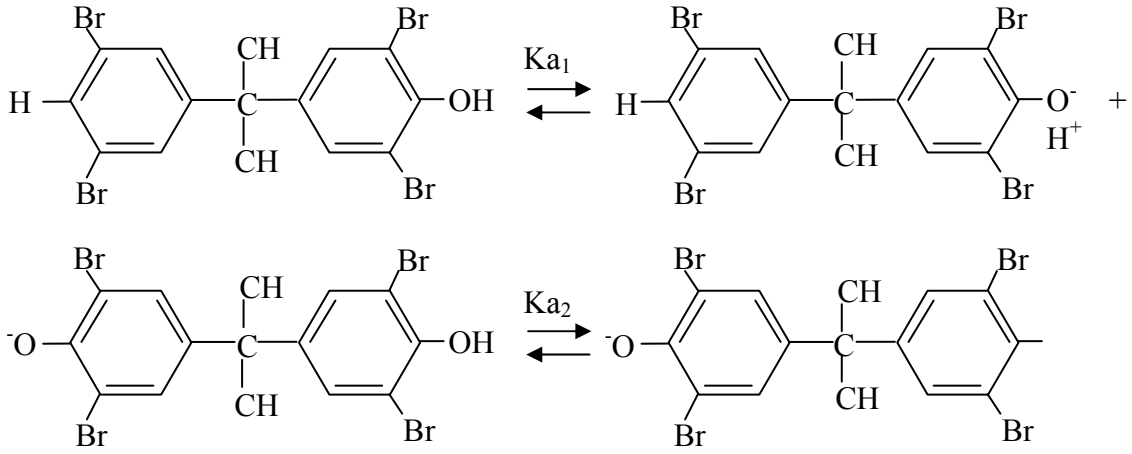
Clearly there is a large discrepancy between the values estimated from vapour pressure and water solubility and the value estimated from structure, however, all methods indicate that the

actual Henry's law constant is <0.1 Pa m^3/mole, probably at most around 0.014-0.054 Pa m^3/mole and so this value will be used in the risk assessment.

1.3.14.2 Acid dissociation constant

Tetrabromobisphenol-A has two acidic hydrogen atoms as shown in **Figure 1.1**. The pKa values are reported to be pKa_1 = 7.5 and pKa_2 = 8.5 (WHO, 1995). No further details of this study are available.

Figure 1.1 Acid dissociation constants for tetrabromobisphenol-A



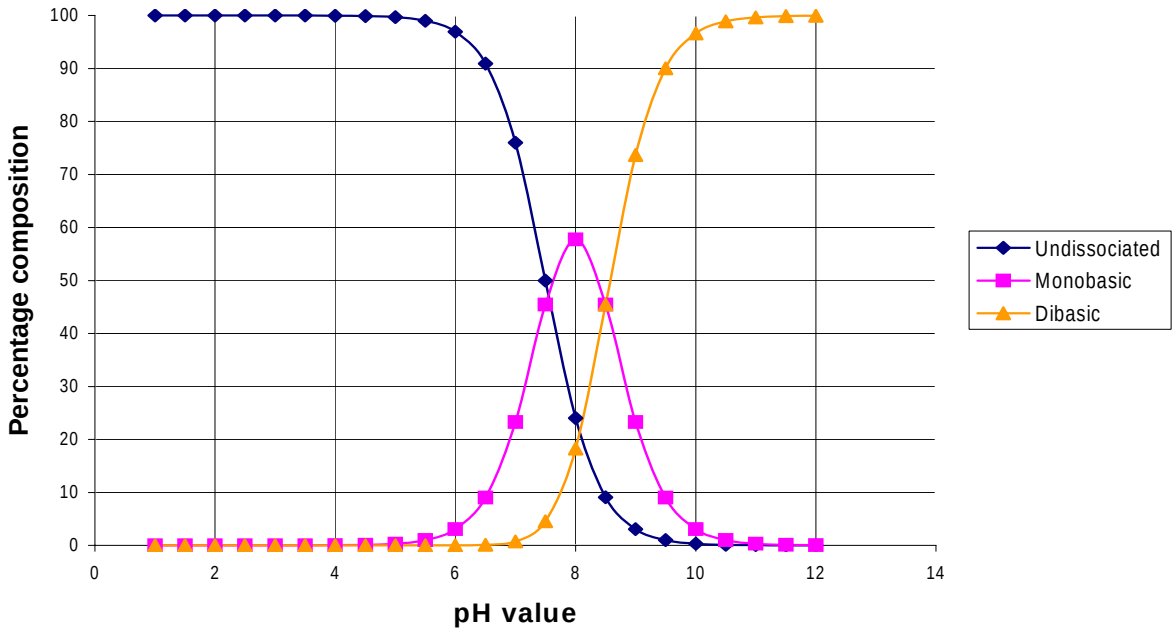
pKa_1 = 7.5

A further determination of the pKa values for tetrabromobisphenol-A has been recently carried out (Wildlife International, 2002c). The method used was based broadly on OECD Guideline 112. In this experiment the relative amounts of the dissociated and undissociated forms present in solution were determined at pHs covering the range 6.0 to 12.0 at 0.5 pH intervals. Only a single pKa value of 9.40 was found using this method. However, the analytical method used to determine the amounts of dissociated and undissociated acid present in solution involved solvent extraction (using hexane) of the undissociated form from the solution prior to analysis by HPLC. As acid-base equilibria are generally very rapidly attained, this method would cause the equilibrium to shift in solution as the undissociated form was removed. In addition, the analytical method would not distinguish between the two dissociated forms of tetrabromobisphenol-A (which would be a pre-requisite for determination of both pKa values). Thus, this study effectively determined the effect of pH on the extraction of tetrabromobisphenol-A by hexane from solution (which is a function of the pKa values) rather than the actual pKa values and so the result is considered unreliable.

In the absence of other reliable data, the values for pKa_1 and pKa_2 will be assumed to be 7.5 and 8.5 respectively. These pKa values mean that the ionised forms of tetrabromobisphenol-A will become prevalent in the environment at pHs >7-8. At lower pHs tetrabromobisphenol-A will be present essentially as the undissociated form. The expected distribution of the various species at various pHs is shown in **Figure 1.2** based on the pKa_1 and pKa_2 being 7.5 and 8.5.

As can be seen from **Figure 1.2**, a significant fraction of the total tetrabromobisphenol-A is predicted to be present in an ionised form at pHs of 7 and above. Below this pH the undissociated form predominates.

Figure 1.2 Dissociation of tetrabromobisphenol-A at various pHs



The pH profile given in Figure 1.2 is consistent with the available data on the variation of solubility with pH as the monobasic and dibasic forms of tetrabromobisphenol-A would be expected to be of a higher solubility than the undissociated form. (see Section 1.3.6).

1.3.15 Hazardous products formed under pyrolysis conditions

Under certain high temperature pyrolysis conditions, tetrabromobisphenol-A can form and release brominated dibenzofurans and dibenzo-*p*-dioxins. These reactions, and their environmental significance, are considered further in Section 2.3 and in detail in Appendix A.

1.4 CLASSIFICATION

1.4.1 Current classification

Tetrabromobisphenol-A is not currently classified for environmental or human health effects.

1.4.2 Proposed classification

The proposed classification for the environment is:

N; R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

This proposal is based on the toxic effects seen in acute toxicity studies with fish and daphnia ($L(EC)_{50}$ <1 mg/l), the lack of biodegradation seen in standard ready biodegradation tests and the high bioconcentration factors (BCF>100) measured in fish.

No classification for human health is proposed.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

Tetrabromobisphenol-A is produced by the bromination of bisphenol-A in the presence of a solvent. The bromination reaction may be conducted in the presence of hydrocarbon solvent only or with water, 50% hydrobromic acid or aqueous alkyl monoethers. When methanol is used as solvent the fumigant methyl bromide is produced as a co-product. The production process is largely conducted in closed systems (WHO, 1995).

Tetrabromobisphenol-A is produced in the USA, Israel and Japan but not in the EU. The current total amount of tetrabromobisphenol-A produced is estimated at >120,000 tonnes/year (Hakk, 2001) and 150,000 tonnes/year (Arias, 2001). BKH (2000) reported that global demand for tetrabromobisphenol-A had increased from 50,000 tonnes/year in 1992 to 145,000 tonnes/year in 1998, with an average growth of 19% per annum. Global demand for tetrabromobisphenol-A was expected to grow by 8-9% per annum between 1998 and 2004.

2.2 CONSUMPTION AND USES

2.2.1 Consumption, Import and Export

Table 2.1 gives details of consumption figures for tetrabromobisphenol-A as a raw chemical. From the table it appears that the consumption in the EU has been around 13,800 tonnes/year over recent years.

Leisewitz et al. (2000), quoting figures supplied by the Bromine Science Environmental Forum (BSEF), reported that the total market demand for tetrabromobisphenol-A in 1999 was 21,600 tonnes/year in the United States, 13,800 tonnes/year in Europe, and 85,900 tonnes/year in Asia, giving a total consumption in these three areas of 121,300 tonnes/year.

As well as the substance itself, tetrabromobisphenol-A can be imported into a country in finished or partially finished products. Examples include plastic compound, printed circuit boards and finished electronic equipment. The tetrabromobisphenol-A in these products may be present as the substance itself or may be reacted into the polymer matrix. These imports may be an important source of tetrabromobisphenol-A in the EU. Some information is available for imports into several EU countries from these types of sources and this is given below. It should be noted that the amounts imported into these countries are not necessarily from sources outside the EU.

Svensson and Hellsten (1989) carried out a survey of brominated flame retardant use in Sweden. They found that brominated flame retardants were not produced in Sweden, but were imported into the country by three main routes:

as pure chemicals for further use in the plastics industry;
as components (either reacted or as an additive) in plastic compounds and other semi-finished products;
as components (either reacted or as an additive) in retail goods like computers, vehicles etc.

Table 2.1 Consumption of tetrabromobisphenol-A (tonnes/year)

Country	Consumption (tonnes/year)	Year	Reference
Australia	32 (including resins)	1998/1999	NICNAS, 2001
	37 (TBBP-A derivatives)	1988/1999	NICNAS, 2001
Asia	85,900	1999	Leisewitz et al., 2000
Japan	15,000		WHO, 1995
	12,000	1986	WHO, 1997
	14,000	1987	Watanabe and Tatsukawa, 1989
	14,400	1987	WHO, 1995
	18,000	1988	WHO, 1995
	23,000	1990	WHO, 1995
	3,000 (TBBP-A epoxy oligomer)	1990	WHO, 1997
	24,500	1991	WHO, 1995
	23,000	1992	WHO, 1995
	22,000	1993	WHO, 1995
	8,500	1997	Japan Chemical Weekly (1998)
	24,000	1994	Danish Environmental protection Agency, 1999; WHO, 1997
	9,500 (TBBP-A derivatives)	1994	Danish Environmental Protection Agency, 1999
	2,500 (TBBP-A polycarbonate oligomer)	1994	WHO, 1997
	7,000 (TBBP-A epoxy oligomer)	1994	WHO, 1997
	~40,000 (including derivatives)	~2000	Nagayama et al., 2000
USA	16,000		WHO, 1995
	16,000	1986	WHO, 1997
	18,000	1991	WHO, 1997
	21,600	1999	Leisewitz et al., 2000

Table 2.1 continued overleaf

Table 2.1 continued Consumption of tetrabromobisphenol-A (tonnes/year)

Country	Consumption (tonnes/year)	Year	Reference
Europe	12,500		OECD, 1994
	10,000		WHO, 1995
	13,150 3,659 (TBBP-A derivatives)	1998	Danish Environmental Protection Agency, 1999
	2,150 (TBBA polycarbonate oligomer)	1998	Danish Environmental Protection Agency, 1999
	1,500 (TBBP-A bis(2,3-dibromopropylether))	1998	Danish Environmental Protection Agency, 1999
	13,800	1999	RPA, 2001; Leisewitz et al., 2000
UK	Up to 620	2001	BPF, 2001
Benelux, France, UK, Germany	9,700	1996	Danish Environmental Protection Agency, 1999
Germany	3,500-4,500	1997	Leisewitz et al., 2000
	2700	1999	Leisewitz et al., 2000
	500-1000 (TBBP-A derivatives)	1999	Leisewitz et al., 2000
The Netherlands	~200		Klingenberg, 1989
Norway	7.9 (9.5 imported and 1.6 exported)	1998	SFT, 1999
Sweden	~300	1988	Svensson and Hellsten, 1989
	~550	1988	Svensson, 1991
	~490 (including derivatives)	1993	KEMI, 1996; de Wit, 2000
	450 (including carbonate oligomer)	1994	de Wit, 2000
	258 (including carbonate oligomer)	1995	de Wit, 2000
	291 (including carbonate oligomer)	1996	de Wit, 2000
	303 (including carbonate oligomer)	1997	de Wit, 2000
	269 (including carbonate oligomer)	1998	de Wit, 2000
	427-439	2000	KEMI, 2002
Global	41,000		WHO, 1995
	121,300	1999	Leisewitz et al., 2000
	150,000 (including derivatives)	2001	Arias, 2001
	>120,000		Hakk, 2001

Svensson and Hellsten (1989) estimated that in 1988, the total amount of brominated flame retardants imported in Sweden by these routes was around 1,400-2,000 tonnes/year. For tetrabromobisphenol-A it was estimated that around 300 tonnes/year were used in the manufacture of printed circuit boards within Sweden, with 150-200 tonnes/year being imported into Sweden in printed circuit boards manufactured elsewhere and a further 150-250 tonnes/year being imported in finished products.

A further estimate of the amounts of tetrabromobisphenol-A imported into Sweden in 1988 is given in Svensson (1991). Here it was estimated that 550 tonnes/year of tetrabromobisphenol-A was imported into Sweden as the pure compound, with around 600 tonnes/year being imported in glass-fibre epoxy laminate printed circuit boards.

De Wit (1999) reported that the amount of tetrabromobisphenol-A supplied to Sweden in products was around 334 tonnes in 1991.

Information from the Swedish Product Register for 2000 (KEMI, 2002 indicates that around 415-424 tonnes of tetrabromobisphenol-A were used as a raw material (flame retardant additive) in three plastic products, 11 tonnes were used in binders/adhesives agents in five products for office machinery and computers, and 1-4 tonnes were used for other uses (e.g. intermediates in plastic manufacture) in three plastic products. None of the products produced were reported to be used directly by consumers.

The amount of total brominated flame retardants imported into Denmark has been estimated to be around 320-660 tonnes in 1997 (Danish Environmental Protection Agency, 2001). Of this tetrabromobisphenol-A (and derivatives) accounted for around 180-360 tonnes. Tetrabromobisphenol-A (and derivatives) was found to be imported as a chemical (up to 2.1 tonnes/year), in plastic compound and master batch (around 34-42 tonnes/year), in semi-manufactured plastic products (around 2-5.2 tonnes/year), in laminates for printed circuit board production (100-180 tonnes/year) and in finished articles (the figure for this was not given in the paper but is presumably around 40-150 tonnes/year by difference). A large proportion of articles containing tetrabromobisphenol-A manufactured in Denmark were also subsequently exported. A detailed breakdown of the applications of imported tetrabromobisphenol-A and derivatives in Denmark is given in **Table 2.2**.

Table 2.2 Breakdown for use of tetrabromobisphenol-A and derivatives in Denmark in 1997 (Danish Environmental Protection Agency, 1999)

Application		Consumption (tonnes/year)
Printed circuit board assemblies	Epoxy laminates	92-150
	Paper/phenolic laminates	2.3-3.8
	Electronic component encapsulates	7.4-22
	Other plastic parts	<2
	Approximate total	100-180
Housings for electrical and electronic equipment	Computer monitors	35-52
	Notebook computers	2-3
	Printers	12-18
	Other office machines	5-7.4
	TV sets	1-2
	Other consumer electronics	0.5-2
	Medical and industrial electronics	1-4
	Small household appliances	0.5-1
	Approximate total	56-89

Table 2.2 continued overleaf

Table 2.2 continued Breakdown for use of tetrabromobisphenol-A and derivatives in Denmark in 1997 (Danish Environmental Protection Agency, 1999)

Application		Consumption (tonnes/year)
Other components of electric and electronic appliances	Switches, relay parts etc.	2-6
	Moulding fillers	-
	Wires	-
	Foam	-
	Other plastic parts	1-2
	Approximate total	3-8
Lighting	Sockets in lamps and fluorescent tubes	4-7
	Compact fluorescent tubes	-
	Plastic cover parts	<2
	Switches, electronic parts etc.	<2
	Approximate total	4-11
Wiring and power distribution	Rubber cables	-
	Other cables	-
	Wiring of houses	2-7
	Contactors, relays, switches etc. for automation and power distribution	2-8
	Approximate total	4-15
Textiles	Protective clothing	-
	Curtains, carpets and tents	-
	Furniture	-
	Foam and stuffing	-
	Approximate total	-
Building materials	Expanded polystyrene	-
	Extruded polystyrene foam	-
	Polyurethane foam	-
	Roofing foil	-
	Other uses	0-2
	Approximate total	0-2
Paints and fillers	Paint	-
	Fire proofing for wood	-
	Joint fillers etc.	-
	Approximate total	-

Table 2.2 continued overleaf

Table 2.2 continued Breakdown for use of tetrabromobisphenol-A and derivatives in Denmark in 1997 (Danish Environmental Protection Agency, 1999)

Application		Consumption (tonnes/year)
Transportation (parts and accessories)	Cars	12-36
	Lorries and buses	0.4-1.2
	Trains	0.3-4
	Other means of transport	1-10.5
	Approximate total	14-52
Overall total		180-360

- No use identified.

A mass balance for the amounts of tetrabromobisphenol-A present in finished products, either produced in or imported into Norway, has been reported by SFT (1999) for the year 1998. The net import of tetrabromobisphenol-A as the compound itself amounted to around 7.9 tonnes/year (9.5 tonnes/year imported and 1.6 tonnes/year exported), however this amount was much smaller than the amount estimated to be imported in finished products such as TVs, computers and other electrical equipment (138-195 tonnes/year), transport applications (5-35 tonnes/year), printed circuit boards (47-59 tonnes/year) and laminated prepods (9-13 tonnes/year). The total net import of tetrabromobisphenol-A was therefore around 207-310 tonnes/year.

Hedelmalm et al. (1995) estimated that the amount of tetrabromobisphenol-A present in products in the Nordic countries was around 4,000 tonnes in 1994.

BKH (2000) estimated that the total demand for tetrabromobisphenol-A in the Netherlands in 2000 would be around 1,700 tonnes/year and the total demand in the EU would be around 40,000 tonnes/year.

A survey of the amount of tetrabromobisphenol-A present in several types of products in Germany has been carried out (Leisewitz et al., 2000). It was estimated that around 3,200 tonnes/year of tetrabromobisphenol-A were used to make base material for printed circuit boards, and the amount of tetrabromobisphenol-A present in printed circuit boards in electronic scrap was around 4,200-5,100 tonnes/year. The difference between these two figures effectively represents the net import of tetrabromobisphenol-A in printed circuit boards in finished articles.

Although the above estimates clearly show that a large amount of tetrabromobisphenol-A is imported into EU countries in finished or partially finished products, it is not possible to estimate the total amount imported into the EU in products from these data as the available figures generally do not distinguish between imports from other countries within the EU and imports from outside the EU.

An estimate of the amount of tetrabromobisphenol-A imported into the EU in finished or partly finished products can be made by comparing the known consumption of tetrabromobisphenol-A in the EU (around 13,800 tonnes/year) with the total amount of tetrabromobisphenol-A supplied world-wide (around 120,000 tonnes/year). Based on these figures the amount of tetrabromobisphenol-A consumed in the EU is only around 11.5% of the amount used worldwide. However, given that tetrabromobisphenol-A is widely used in electrical and electronic equipment, it would be expected that the EU demand for such

products would be higher than implied by the consumption of tetrabromobisphenol-A alone. Thus, if, as a worst case, it is assumed that the EU demand for electrical and electronic products (and hence tetrabromobisphenol-A) is around 1/3 of the world-wide total (there is no information available on the actual demand but a similar assumption was used in the Risk Assessment Report for octabromodiphenyl ether which has some similar uses to tetrabromobisphenol-A (European Commission, 2002a)), then the amount of tetrabromobisphenol-A present in new products in the EU can be estimated at around 40,000 tonnes/year. Thus, the import of tetrabromobisphenol-A into the EU in finished or partly finished products can be estimated to be around 26,200 tonnes/year. Some of this may be imported as partly finished products such as polymer masterbatch and uncured epoxy resins (which need further processing (conversion or curing) in the EU before they are formed into the product), but the majority is likely to be in the form of finished products or components such as printed circuit boards. The actual split between partly finished and finished products is unknown. However, in order to try to take into account the possible releases from the further processing in the EU of partly finished products it will be assumed for the emission estimates that around 6,000 tonnes/year of tetrabromobisphenol-A (which corresponds to around 50% of the amount used directly in the EU) are in the form of partly finished products, with the remainder as finished products and components. Information on the actual amounts imported in partly finished or finished products would be useful to refine these assumptions.

In terms of trying to estimate how much tetrabromobisphenol-A may be imported into the EU in partially-finished or finished articles, it should be born in mind that the majority of tetrabromobisphenol-A is used as a reactive flame retardant and is chemically bound into the polymer structure, and so only trace amounts of free tetrabromobisphenol-A will be present in the imported partially-finished or finished articles.

In summary, the following figures will be used in the risk assessment:

Tetrabromobisphenol-A imported into the EU as the substance	= 13,800 tonnes/year
Tetrabromobisphenol-A imported into EU as partly finished products (e.g. masterbatch, epoxy resins)	= 6,000 tonnes/year
Amount of tetrabromobisphenol-A imported into the EU in finished products and components	= 20,200 tonnes/year
Total	= 40,000 tonnes/year

2.2.2 Uses

The primary use of tetrabromobisphenol-A is as a reactive intermediate in the manufacture of flame-retarded epoxy and polycarbonate resins. It may also be used as an additive flame retardant, for example in the manufacture of acrylonitrile-butadiene-styrene (ABS) resins, high impact polystyrene (HIPS) and phenolic resins. Where tetrabromobisphenol-A is used as an additive flame retardant, it is generally used with antimony oxide for maximum performance (Hakk, 2001). Antimony oxide is generally not used in conjunction with tetrabromobisphenol-A in reactive flame retardant applications (Industry Consortium, 2002).

Tetrabromobisphenol-A is also used in the manufacture of derivatives. The main derivatives produced from tetrabromobisphenol-A are tetrabromobisphenol-A dimethylether, tetrabromobisphenol-A dibromopropylether, tetrabromobisphenol-A bis(allylether), tetrabromobisphenol-A bis(2-hydroxyethyl ether), tetrabromobisphenol-A brominated epoxy oligomer, and tetrabromobisphenol-A carbonate oligomers (WHO, 1995). The main use of these derivatives is as flame retardants, usually in niche applications.

A breakdown of use world-wide was provided by Leisewitz et al. (2000), who indicated that around 70% is used for epoxy resins in printed circuit boards, 15% is used additively in HIPS for casing materials, 10% is used for the production of derivatives and 5% is used as additives for other polymers such as ABS and thermoplastic polyesters.

Industry has questioned the figures given above by Leisewitz et al. (2000) for the use of tetrabromobisphenol-A as an additive flame retardant in HIPS (Industry Consortium, 2002). They indicated that they are unaware that tetrabromobisphenol-A is or has ever been used as an additive in HIPS, and indicated that in their experience; tetrabromobisphenol-A is not an effective flame retardant for HIPS. However, other sources, such as fact sheets on tetrabromobisphenol-A produced by the European Flame Retardants Association (EFRA, 2002) and the Bromine Environmental Science Forum (BSEF, 2002); indicate that one of the possible uses of tetrabromobisphenol-A is in HIPS. Therefore, although it is recognised that there is some uncertainty over whether tetrabromobisphenol-A is used currently in this application in the EU, it is relevant to consider it as a possible use in the risk assessment.

Private information from Industry indicates that the ratio between reactive and additive flame retardant use in the EU is around 9:1, with ABS being the main additive use of tetrabromobisphenol-A. At the moment the situation with regards to production of derivatives of tetrabromobisphenol-A in the EU is unclear, and this use is not considered explicitly in the assessment although default calculations are given for this use.

Tetrabromobisphenol-A is considered as an alternative additive flame retardant to octabromodiphenyl ether in ABS. The use of octabromodiphenyl ether in this application within the EU has fallen in recent years, and if this trend continues it is possible that the amount of tetrabromobisphenol-A used in this application in particular could increase in the future. This possibility is considered further in Appendix E.

The current uses and the potential emissions of tetrabromobisphenol-A are discussed further below.

2.2.2.1 Reactive flame retardants

The primary use of tetrabromobisphenol-A, accounting for approximately 90% of tetrabromobisphenol-A used, is as an intermediate in the manufacture of epoxy and polycarbonate resins. When used as an intermediate it becomes covalently bound in the polymer and is effectively lost. The only potential for exposure is from unreacted tetrabromobisphenol-A, which may exist where excess has been added during the production process.

When used as a flame retardant in the production of epoxy resins, tetrabromobisphenol-A along with bisphenol-A, is reacted with epichlorohydrin. Commercial flame retardant epoxy resins contain up to approximately 20% bromine (the maximum bromine content that can be achieved in epoxy resins is 48% if no bisphenol-A is used in the formulation). The main use

of these resins is in the manufacturing of rigid epoxy laminated printed circuit boards. There are estimated to be at least seven to ten major producers of flame retardant epoxy resins in Europe.

There are two main types of rigid or reinforced laminated printed circuit boards that are commonly used (Danish Environmental Protection Agency, 1999). These are usually either based on glass fibre reinforced epoxy resin (designated FR4) or cellulose paper reinforced phenolic resin (designated FR2), but a range of types are available.

The FR4-type laminate is by far the most commonly used laminate and is typically made by reaction of around 15-17% tetrabromobisphenol-A in the epoxy resin (Danish Environmental Protection Agency, 1999). The bromine content of these circuit boards has been given by Leisewitz et al. (2000) as around 18-20% on a resin weight basis or 9-10% on a laminate weight basis (the resin makes up around 50% of the total weight of the laminate). The most commonly used laminate is approximately 1.6 mm thick and the tetrabromobisphenol-A content has been estimated at around 0.42 kg/m^2 (Danish Environmental Protection Agency, 1999). This type of laminate is typically used in computers and telecommunications equipment.

The FR2-type laminates may also contain tetrabromobisphenol-A (Danish Environmental Protection Agency, 1999), but in this case it acts as an additive flame retardant rather than a reactive flame retardant and so this is considered in the next section.

Glass-fibre reinforced laminates are produced by impregnating the glass-fibre fabric with the epoxy resin. The resin is then dried during which it hardens into an intermediate state (B-state; also known as prepregs). A copper foil is then applied using a hot-press process, during which the resin re-melts and is irreversibly and completely hardened under pressure and temperature.

Epoxy resins are also used as the base material for other types of printed circuit boards such as the composites (CEM1, CEM3) (Leisewitz et al., 2000). These composites consist of either a core of hard paper with epoxy resin (CEM1) or glass-fibre with epoxy resin (CEM3). In both cases the outer layers consist of glass-fibre/epoxy resin laminate. The bromine content of a CEM3-type composite is 4-7% in the resin.

As well as use in the printed circuit board laminate itself, epoxy resins containing tetrabromobisphenol-A are also used to encapsulate certain electronic components (e.g. plastic/paper capacitors, microprocessors, bipolar power transistors, IGBT (Integrated Gate Bipolar Transistor) power modules, ASICs (Application Specific Integrated Circuits) and metal oxide varistors) on the printed circuit board. The concentration of tetrabromobisphenol-A in the production of the resins used for encapsulation is relatively low, for example around 2% or 90 g/m^2.

It is also used as a reactive flame retardant in polycarbonate and unsaturated polyester resins. Polycarbonates are used in communication and electronics equipment, electronic appliances, transportation devices, sports and recreation equipment, lighting fixtures and signs. Unsaturated polyesters are used for making simulated marble floor tiles, bowling balls, glass-reinforced panels, furniture parts, sewer pipes coupling compound, automotive patching compounds, buttons, and for encapsulating electrical devices.

The production of base material for printed circuit boards in Germany in 1999 has been estimated at around 21,000 tonnes of laminate, which is equivalent to >10,000 tonnes of resin

(the resin makes up around 50% of the weight of the laminate) (Leisewitz et al., 2000). The FR4-type printed circuit boards account for >90% of the market in Germany and there are thought to be 4 resin manufacturers in Germany. The resin used in the printed circuit boards cannot be recycled, although the copper content can be recovered in primary copper smelters (recovery in secondary copper smelters is not carried out in Germany as flue gas purification is needed). Particle downcycling is carried out in a limited scale in Germany. This involves grinding waste from laminate and printed circuit board production and separating this into metal and plastic fractions. The plastic fraction can be used as a supplement or filler in other products made from flame-retarded thermosetting resins.

The most important application areas for FR4-type printed circuit boards are in telecommunications, computers, industrial controls and automotive electronics (Leisewitz et al., 2000).

2.2.2.2 Additive flame retardant

As an additive flame retardant tetrabromobisphenol-A, is added to polymers to impart flame retardant properties. It does not react chemically with the other components of the polymer, and, therefore may leach out of the polymer matrix. Additive use accounts for approximately 10% of tetrabromobisphenol-A used. Its main uses as an additive flame retardant are in acrylonitrile-butadiene-styrene (ABS) resins, high impact polystyrene and phenolic resins. Recommended starting levels of tetrabromobisphenol-A in ABS (medium to high impact) are 17.6-22.0% and 14% in high impact polystyrene. ABS resins are used in automotive parts, pipes and fittings, refrigerators, other appliances, business machines, and telephones. Polystyrene is used in packaging, consumer products, disposables, electrical and electronic equipment, furniture and in building and construction materials. (WHO, 1995). The main applications where plastic containing tetrabromobisphenol-A may be used include TV-set back casings and business equipment enclosures (RPA, 2001).

According to OECD (1994) polystyrene containing 15% tetrabromobisphenol-A and 4% antimony trioxide, or ABS containing 20% tetrabromobisphenol-A and 4% antimony trioxide, meets the UL94 V-0 fire classification.

According to the BPF (2001) approximately 620 tonnes tetrabromobisphenol-A is used as an additive flame retardant in electric and electronic applications in the UK, often in conjunction with antimony trioxide as a synergistic system. The largest use is in television casings with approximately 450 tonnes of tetrabromobisphenol-A used per year. Other uses include: PCBs; PC monitoring casings; components in printers; fax machines and photocopiers; vacuum cleaners, coffee machines and plugs/sockets. The total amount of plastics used in electrical/electronic applications is about 220,000 tonnes; of this amount about 20% will have flame retardants added. It is difficult to determine the exact number of sites used in polymer processing because of the changeable nature of the industry with processors sometimes taking on short term contracts. However, there are approximately 2,000 injection moulders in the UK.

As indicated in Section 2.2.2.1, tetrabromobisphenol-A is used as an additive flame retardant in FR2-type laminates for printed circuit boards (Danish Environmental Protection Agency, 1999). The typical usage rate is around 4% of the laminate or around 0.036 kg/m^2. These types of laminates have traditionally been used in printed circuit boards for television sets and home electronic appliances, but there is now a trend towards printed circuit boards based on

the FR4-type laminate (see Section 2.2.2.1), especially in the high-priced market segment. Industry have confirmed this trend and indicate that the FR2-type laminates are now mainly used in low energy applications such as remote controllers for televisions, video recorders etc., with FR4-type laminates being used in the television sets, computer equipment etc. themselves (Industry Consortium, 2002).

Hard paper laminates are produced by impregnation of the paper with the phenolic resin which is then dried (Leisewitz et al., 2000). The impregnated paper is then hot-pressed with a copper foil.

2.2.2.3 Derivatives

The total amount of tetrabromobisphenol-A derivatives used is less than the amount of tetrabromobisphenol-A used (approximately 25% on a weight basis). They are believed to be used in specialised (or niche) applications. (WHO, 1995)

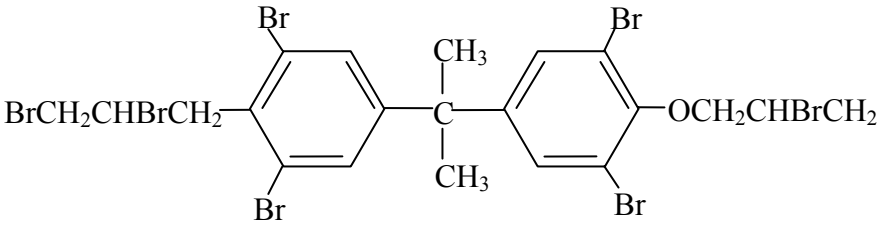
The derivatives may be used as either reactive or additive intermediates in polymer manufacture. In this risk assessment it is important to consider the potential generation of tetrabromobisphenol-A from the derivative.

2.2.2.3.1 Tetrabromobisphenol-A dimethyl ether

The dimethyl ether of tetrabromobisphenol-A (CAS Number 37853-61-5) is not used itself as a flame retardant but has been found in the environment (see Section 3, which will be added later). The occurrence in the environment can be explained by the O-methylation of tetrabromobisphenol-A by certain biological processes (see Section 3, which will be added later).

2.2.2.3.2 Tetrabromobisphenol-A bis(2,3-dibromopropyl ether)

This substance (CAS Number 21850-44-2) is used as an additive flame retardant in polyolefins and copolymers such as high density polyethylene, low density polyethylene, polypropylene and polybutylenes. (OECD, 1994; WHO, 1995; Ash and Ash, 1997). The structure of tetrabromobisphenol-A bis(2,3-dibromopropyl ether) is shown below.



In polypropylene, Prins et al. (2000) indicated that a loading of 8-10% of the flame retardant meets the UL94 V-0 rating and the minimum amount necessary to meet the UL94 V-2 rating and Glow Wire rating is 1.5% of the flame retardant with 0.5% antimony trioxide and 1% of the flame retardant with 0.33% antimony trioxide respectively. Bar Yaakov et al. (2000)

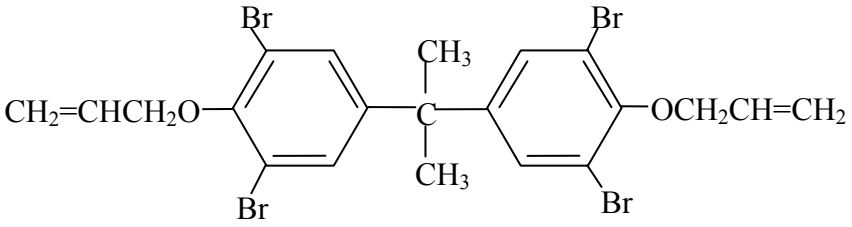
reported that 12% of the flame retardant with 4% antimony trioxide and 14.5% of the flame retardant with 5.2% antimony trioxide are used in formulations to meet the UL94 V-0 rating in polypropylene homopolymers and block copolymers respectively. They also reported that the UL94 V-2 rating is met using formulations containing 3% of the flame retardant with 1% antimony trioxide and 4.5% of the flame retardant with 1.5% antimony trioxide in polypropylene homopolymers and block copolymers respectively.

Flame retarded polypropylene is used in building applications (mainly in pipes for water discharge but also film and sheet for roofing), textiles, and in electrical and electronic applications such as wire nuts, lamp sockets, coil bobbins, connectors, wire and cable, housings of electrical appliances, TV yokes. Tetrabromobisphenol-A bis(2,3-dibromopropyl ether) is the most popular flame retardant for applications such as water discharge pipes passing the B1 class (DIN 4102) and also for lamp sockets meeting the UL94 V-2 or V-0 rating (Bar Yaakov et al., 2000).

DeSchryver et al. (2002) reported that it could also be used in high impact polystyrene at 5% by weight (meets the UL94 V-2 or Glow Wire rating).

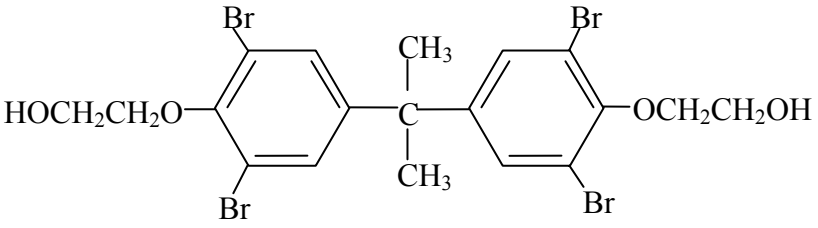
2.2.2.3.3 Tetrabromobisphenol-A bis(allyl ether)

This substance (CAS Number 25327-89-3) is used as a reactive flame retardant in polystyrene foams (expandable polystyrene (EPS)). (OECD, 1994; WHO, 1995; Ash and Ash, 1997). The structure of tetrabromobisphenol-A bis(allyl ether) is shown below.



2.2.2.3.4 Tetrabromobisphenol-A bis(2-hydroxyethyl ether)

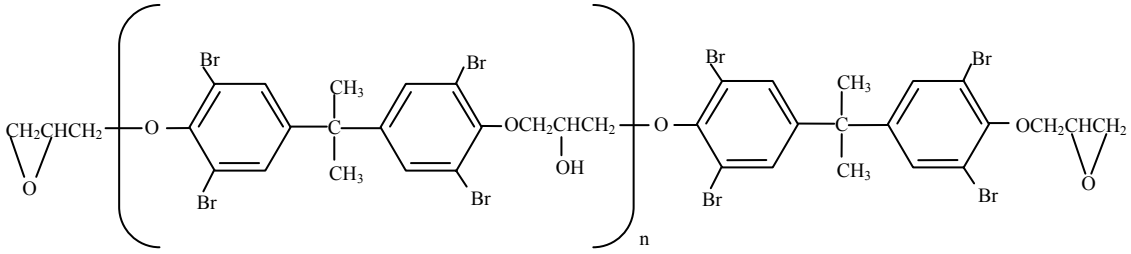
This substance (CAS Number 4162-45-2) is used as an additive flame retardant in engineering polymers (e.g. polybutylene terephthalate and polycarbonate), epoxy resins, thermoset and thermoplastic polyesters, polyurethane, laminates for electronic circuit boards and adhesives and coatings (OECD, 1994; WHO, 1995; Ash and Ash, 1997). The structure of tetrabromobisphenol-A bis(2-hydroxyethyl ether) is shown below.



2.2.2.3.5 Tetrabromobisphenol-A brominated epoxy oligomer

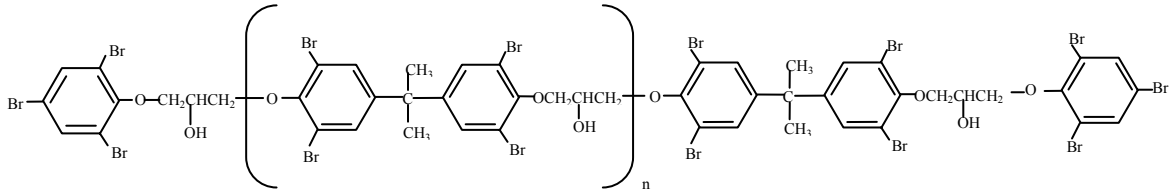
Epoxy oligomers of tetrabromobisphenol-A are also known as tetrabromobisphenol-A diglycidyl ethers (CAS Number 68928-70-1). There are two chemically different types of brominated epoxy oligomers. One has two epoxy groups at the end of the molecule, which is similar to epoxy resins used for printed circuit boards (EP-type). The other has no reactive groups; this is tetrabromobisphenol-A epoxy end-capped with tribromophenol (EC-type). Both types of oligomer are reactive flame retardants. They are used in housings for business machinery and electrical/electronics parts by injection moulding from flame retardant compounds based upon high impact polystyrene (HIPS), ABS, ABS/polycarbonate, polybutylene terephthalate-alloys, polybutylene terephthalate and thermosetting resins. The concentrations of the flame retardant in ABS are 21% of the EP-type and 19% of the EC-type. Brominated epoxy oligomers are used in combination with 5% of antinomy oxide. (WHO, 1995). The structures of the EP-type and EC-type tetrabromobisphenol-A brominated epoxy oligomers are shown below.

Example EP-type (epoxy-terminated) oligomer.



n = 0, 1, 2, 3, etc.

Example EC-type (tribromophenol end-capped)



n = 0, 1, 2, 3, etc.

As well as fully tribromophenol end-capped oligomers, some products are available with around 50% end-capping with tribromophenol (Plaitin et al., 1998).

The molecular weights of the products vary between 700 and 50,000 g/mole, and differ depending on the application.

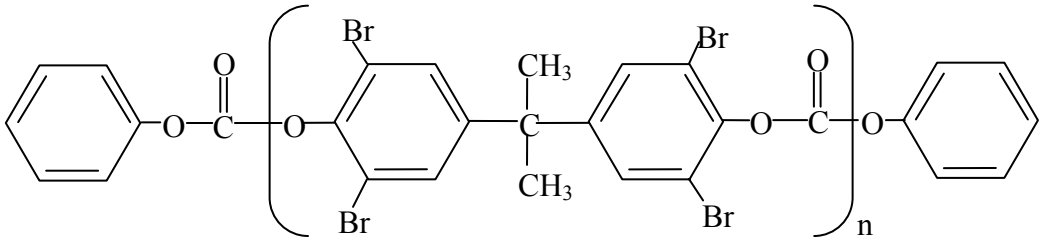
2.2.2.3.6 Tetrabromobisphenol-A carbonate oligomers

Tetrabromobisphenol-A carbonate oligomers are produced by reaction of tetrabromobisphenol-A with phosgene (OECD, 1994). In this respect they can be considered similar to the reactive use of tetrabromobisphenol-A in polycarbonates described above.

These oligomers are used as an additive flame retardant in ABS and engineering thermoplastics such as polybutylene terephthalate, polycarbonate, polyethylene terephthalate

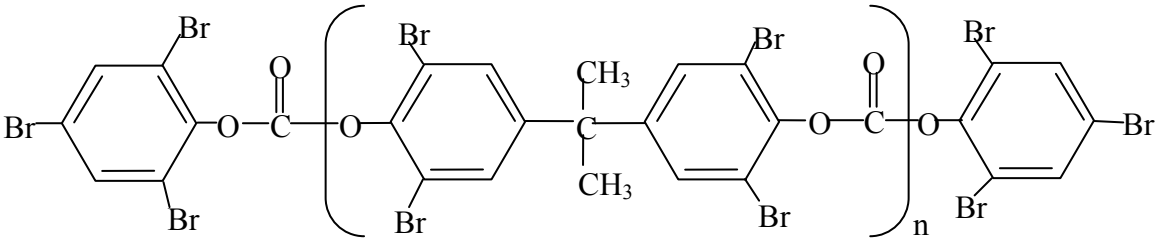
and phenol-formaldehyde resins (OECD, 1994; WHO, 1995). Both phenoxy-terminated tetrabromobisphenol-A carbonate oligomers (CAS Number 94334-64-2) and tribromophenoxy-terminated tetrabromobisphenol-A carbonate oligomers (CAS Number 71342-77-3) are produced (WHO, 1995). The structures of these oligomers are shown below.

Phenoxy-terminated tetrabromobisphenol-A carbonate oligomer.



n = 3-5

Tribromophenoxy-terminated tetrabromobisphenol-A carbonate oligomer.



n = 3-5

Polybutylene terephthalate with 18% tetrabromobisphenol-A oligomer and 4% antimony trioxide is reported to meet the V-0 fire classification (OECD, 1994).

A tetrabromobisphenol-A diglycidyl ether - carbonate oligomer (CAS Number 32844-27-2) has also been reported.

2.2.2.3.7 Others

OECD (1994) reported that a type of polyester fibre can be made from bis(hydroxyethyl) tetrabromobisphenol-A ethylene glycol by reaction with terephthalic acid and that flame retardant polyester-cotton blends containing 30% bromine, 45% polyester fibres and 25% cotton can be made from tetrabromobisphenol-A by reaction with terephthaloyl chloride in methylene chloride.

Ash and Ash (1997) indicated that tetrabromobisphenol-A diacrylate (CAS Number 55205-38-4) can be used in automotive coatings and wire and cable coatings. A tetrabromobisphenol-A bis-(2-ethylether acrylate) derivative (CAS Number 6710-97-2) has also been reported.

The commercial significance of these products is unclear.

2.3 BREAKDOWN/TRANSFORMATION PRODUCTS

There is some evidence that shows that, under certain pyrolysis conditions, the presence of tetrabromobisphenol-A can lead to the formation of small amounts of brominated dibenzo-*p*-dioxins and dibenzofurans. This is discussed in detail in Appendix A. Generally, the amounts of these products formed from tetrabromobisphenol-A appear to be less than from some other brominated flame retardants such as the polybrominated diphenyl ethers (for example see European Commission, 2000a). Factors that appear to affect the formation include the temperature and the residence time at the temperature. At high temperatures (e.g. around 800^{o}C) only trace amounts of mainly mono- and dibrominated dibenzo-*p*-dioxins and dibenzofurans appear to be formed.

Of possible environmental concern is the release of brominated dibenzo-*p*-dioxins and dibenzofurans from incineration of plastics containing tetrabromobisphenol-A and during accidental fires involving articles containing tetrabromobisphenol-A.

In the case of accidental fires, given the large amounts of toxic products known to be formed, notably chlorinated dibenzo-*p*-dioxins and dibenzofurans, but also non-halogenated products such as polycyclic aromatic compounds, the presence of tetrabromobisphenol-A is unlikely to significantly affect the total release of toxic products from fires as, in most cases, tetrabromobisphenol-A will only constitute a small proportion of the total halogenated material present in a fire.

Regulations on the design of municipal incinerators require a minimum incineration temperature of 850^{o}C for 2 seconds (EEC, 1989a and 1989b). A higher incineration temperature of 1,100^{o}C is required for hazardous waste incinerators where waste containing more that 1% halogens is incinerated (EEC, 1994).

In the United Kingdom, incineration processes are covered under the Environmental Protection Act (1990). Under Part 1 of the Act, two separate pollution control regimes were established under which specified industrial processes must apply for authorisation to operate: Integrated Pollution Control (IPC), regulated by the Environment Agency, and Local Authority Air Pollution Control (LAAPC), regulated by the local authorities. Under LAAPC, existing general waste incineration processes under 1 tonne/hour should be subjected to an emission standard for chlorinated dioxins of 1.0 ng TEQ/m^3 by June 2000. New general waste incinerators should meet the 1.0 ng TEQ/m^3 limit from September 1995. Under IPC, municipal solid waste (MSW) incinerators and other specified scheduled processes had to conform to an emission standard for chlorinated dioxins of 1.0 ng TEQ/m^3, with a guide value of 0.1 ng TEQ/m^3 by 2000. All new plants will have to conform to this standard.

Given the similarities between chlorinated and brominated dioxins and the mechanism of their formation, incinerator design and abatement technologies employed for chlorinated dioxins and furans should also be effective in limiting the emissions from the brominated analogues.

Other disposal/recycling practices for articles containing tetrabromobisphenol-A may have the potential to release polybrominated dibenzofurans and dibenzo-*p*-dioxins to the environment, and these are considered further in Appendix A.

2.4 LEGISLATIVE CONTROLS

In 1995 a Voluntary Industry Commitment for risk reduction of brominated flame retardants, including tetrabromobisphenol-A, was agreed within the OECD. This required regular reporting of the risk reduction activities carried out by the global producers of tetrabromobisphenol-A. This initiative has now ended.

A Proposal for a draft Directive on Waste Electrical and Electronic Equipment (WEEE Directive) was adopted on 13th June 2000 by the European Commission. The Proposal contains the following elements:

- Member States shall set up separate collection schemes and ensure the proper treatment, recovery and disposal of WEEE;
- The treatment, recovery and disposal of WEEE shall be financed by producers to create economic incentives to adapt the design of electrical and electronic equipment to the prerequisites of sound waste management;
- Consumers shall have the possibility to return their equipment free of charge. They need to be informed about the possibilities of return WEEE.

The Commission's Proposal encourages producer responsibility for waste management, separate collection of WEEE, improved treatment and reuse/recycling, and improved dissemination to users. In implementing the proposed Directive, producers would be required to set up systems to treat WEEE which would include, amongst other things, removal of plastic containing brominated flame retardants from separately collected WEEE (RPA, 2001).

In parallel, a separate Directive on the restriction of the use of certain hazardous substances in electrical and electronic equipment (RoHS Directive) has been proposed. According to this directive, manufacturers will be required to substitute certain heavy metals and certain brominated flame retardants in new electrical and electronic equipment in order to prevent problems during the waste management phase. Tetrabromobisphenol-A is not included in the current Proposal.

The WEEE/RoHS Proposals have been transmitted to the European Parliament, Council and other Community institutions and are currently under discussion. The Parliament adopted its first reading on 15 May 2001. A Political Agreement in view of a Common Position was adopted by the Council of 7 June 2001. The second reading was due to start at the European Parliament before the end of 2001. It is currently proposed that the measures will come into effect in January 2007 (RPA, 2001).

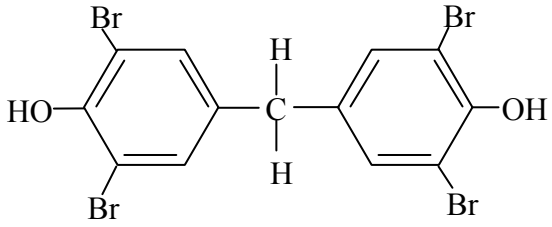
The implications of these Proposals on the future use of tetrabromobisphenol-A in electrical and electronic equipment is unclear.

In Denmark regulations are already in place on the management of waste from electrical and electronic products (Danish Environmental Protection Agency, 2001). According to the Ministry of Environment and Energy's Statutory Order No. 1067 of 22 December 1998, flame-retarded plastic has to be separated out from other waste from electrical and electronic equipment and this plastic has to be recycled, incinerated or deposited at approved facilities. In the case of recycling, the plastic has to be used for products for which special requirements apply for fire safety reasons. There are around 25 companies that separate electronic waste in Denmark.

At present no occupational exposure limits are established in Europe.

2.5 NATURAL SOURCES

A large number of organobromine compounds are known to be produced naturally in the environment, many by marine organisms. Indeed at least 50 simple bromophenols are known to occur naturally, and several natural diphenyl methanes have also been discovered (Gribble et al., 2000). In particular, the following substance (bis(3,5-dibromo-4-hydroxyphenyl)methane) that is structurally similar to tetrabromobisphenol-A has been found to be produced by the segmented marine worm *Thelepus setosus.*



Tetrabromobisphenol-A itself has not yet been identified as being produced by natural sources and so this will be considered to be an insignificant process for tetrabromobisphenol-A in this assessment.

3 ENVIRONMENT

(to be added later)

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 Occupational exposure

4.1.1.1.1 General introduction

Definitions and sources

In this document, unless otherwise stated, the term exposure is used to denote personal exposure as measured or otherwise assessed without taking into account the effect of any personal protective equipment (PPE) which might be used. This definition permits the effects of controls other than PPE to be assessed.

The general discussion sections summarise the important issues arising from the exposure assessments and brings together measured exposure data and predictions from the EASE (Estimation and Assessment of Substance Exposure) model. EASE is a general-purpose predictive model for workplace exposure assessments. It is an electronic, knowledge-based, expert system that is used where measured exposure data are limited or not available. The model is in widespread use across the European Union for the occupational exposure assessment of new and existing substances.

All models are based upon assumptions. Their outputs are at best approximate and may be wrong. EASE is only intended to give generalised exposure data and works best in an exposure assessment when the relevance of the modelled data can be compared with and evaluated against measured data.

EASE is essentially a series of decision trees. For any substance, the model asks a number of questions about the physical properties of the substance and the circumstances of its use. For most questions, the EASE user is given a multiple-choice list from which to select the most appropriate response. Once all the questions have been answered, the exposure prediction is determined absolutely by the choices made. EASE can be used to estimate inhalation and dermal exposure - dermal exposure is assessed as the potential exposure rate to the hands and forearms (a total skin area of approximately 2,000 cm^2). The dermal model is less developed than the inhalation model, and its outputs should be regarded with extreme caution.

The output ranges generated by EASE for inhalation exposure relate to steady-state conditions and estimate the average concentration of the substance in the atmosphere over the period of exposure. The model will not directly predict short-term exposures, but predictions of values for these circumstances are possible by interpreting and modifying the output data using professional judgement. Although short-term exposures may be predicted by EASE in this way, such modifications to the model should be regarded with caution.

Where real data are not available or scant, EASE has been used to predict exposures. Details of the reasoning behind any assumptions made during the course of EASE predictions are made clear in the relevant sections.

In Section 4.1.2.1 findings of TBBP-A in human blood-samples and samples of human breast milk are described. These data show that population exposure to TBBP-A can be reflected in increased internal levels of the substance. However, it is not possible based on the data to point out specific sources to the TBBP-A exposure and to extrapolate the actual exposure levels of the individuals or to evaluate the degree of bioavailability from the exposure.

Overview of exposure

The total number of persons occupationally exposed to TBBP-A in the EU is not known. The chemical is not manufactured in the EC, but its use is becoming more widespread as a flame retardant in plastics.

HSE has no TBBP-A exposure data on its NEDB (National Exposure Database). No data were available from any other competent authorities and little information was found in published papers – only brief reports of low air concentrations of TBBP-A in computer and other electronic equipment shredding. However, there are more "upstream" uses of TBBP-A that showed potential for higher exposures. In consequence, HSE commissioned a small sampling exercise within the UK to inhalable TBBP-A to cover the main uses of TBBP-A. Two sites were chosen that were involved in the production of polymer products where TBBP-A was incorporated into the finished article, and two sites chosen were involved in the recycling of polymer products.

One of the selected sites added TBBP-A to ABS in an additive manner to represent the mixing of TBBP-A powder and polymers. Another selected site manufactured resin laminates and this represented the reactive inclusion of TBBP-A into a product. The two recycling sites shredded computer parts and this is the major recycling area in which there is potential for TBBP-A exposure.

The majority of the data in this Risk Assessment Report is from this sampling exercise. A small quantity of new inhalation exposure data from industry have been added to the RAR in March 2005

Occupational exposure to TBBP-A is discussed in six scenarios.

1. during the addition of TBBP-A powder to mixes of polymer compounds. Data were available from the HSE sampling exercise.
2. during the production of laminates for printed circuit boards. Data were available from the HSE sampling exercise.
3. during recycling of computers and electrical equipment. Data were available from the HSE sampling exercise, and from published literature.
4. during the assembly of printed circuit boards. Data were available from published literature.
5. employees in offices containing electronic equipment. Data were available from published literature.
6. during the recycling of plastic housings. Only modelled data were available.

TBBP-A inhalation exposures varied by several orders of magnitude across the industry sectors. The highest inhalation exposures to TBBP-A were found in the production (loading and mixing) of plastics, with 8-hour time-weighted-averages (TWAs) up to 12,216 $\mu g/m^3$.

At the other end of the range, offices containing computers showed TBBP-A air concentrations of less than 0.001 $\mu g/m^3$. TBBP-A exposures at sites where computers were shredded, or where laminates were manufactured ranged from 0.1 to 75 $\mu g/m^3$.

Yet overall, the data are sparse, even with the added results from the HSE sampling exercise. Reasonable-worst-case scenarios would have been estimated using the 90th percentile if there had been sufficient data. As data were lacking, analogous data and/or professional judgement were used. Even with the addition of the new industry data there was still insufficient data points to estimate 90th percentiles.

Dermal exposures were estimated by using the EASE model and/or analogous data from the Technical Guidance Document (TGD). Loading of TBBP-A powder and associated cleaning gave rise to the highest estimates for dermal exposure.

Occupational exposure limits

There are no occupational exposure limits for TBBP-A.

4.1.1.1.2 Occupational exposure during the addition of TBBP-A powder to mixes of plastic compounds.

The addition of TBBP-A to polymer batches can occur either in the production of pellets or during the processing of these pellets into shaped articles. The process of producing pellets and the processes involved in the production of shaped articles share many similarities and will be considered together in one section.

Measured occupational exposure data

Industry data

No industry exposure data were available.

HSE survey data

HSE visited one site during 2002 to sample for TBBP-A. The factory make up plastics on-site with TBBP-A added as an additive flame retardant. The material is fed through the machine by screws and is heated and mixed in the barrel. Softened plastic is forced out through a shaped die, cooled and cut to length.

The addition of TBBP-A and the mixing of master batches takes place for a full shift but often this is for one day or two only per month.

TBBP-A is supplied as a pure powder in 25 kg paper sacks. Initially, a master batch is prepared, which contains about 30% TBBP-A. Four bags per mix (100 kg) are used and the mixture takes about an hour to prepare.

The master batch mixer, housed in a down-draught booth, has an inlet hatch that requires the operator to stand on a raised platform. Sacks of the raw materials were slit and the contents manually tipped into the open hatch before the lid was closed and locked. Empty sacks were often discarded outside the booth area. After fifteen minutes mixing, the master batch was dispensed into polythene sacks by gravity feed through a tap in the bottom of the mixer. The booth has a flexible, plastic curtain to reduce the size of the open aperture. However, the booth offers the operator little protection from the airborne dust that is generated. Smoke tests showed significant escape of contaminants from the booth into the general workroom.

Full, unsealed sacks of master batch (25 kg) were loaded onto pallets and taken to a second mixer where they were mixed together with any further additives that are necessary, and more pure TBBP-A powder may be added at this stage. There were three secondary mixers available and the inlets to two of them are on a mezzanine floor about 7 metres above the factory floor. Ingredients for the mixers were poured through a hatch which gravity feeds the materials into the mixers. Although the inlets were fitted with LEV, empty bags tend to be discarded away from the influence of the LEV, and during their disposal, more dust is made airborne. The LEV (local exhaust ventilation) consisted of small booths to enclose the hatches and smoke tests showed good capture but operating practices negated some of this control.

A screw extruded the material through a die (at a maximum temperature of 240^{o}C) to form continuous strands of plastic that run through a cooling bath and emerge to a chopper that cuts the plastic into small pellets (typically 5 mm diameter, 5 to 10 mm long). LEV was present where the hot plastic exits the extruder, and consisted of a receptor hood positioned above the plastic. Each hood had flexible curtains on all four sides and there was good capture of the fume.

All workers wore disposable overalls and some wore protective gloves when handling chemicals. Disposable FFP2 respirators were available for use. Although vacuum cleaners were available, dry sweeping is still performed on site.

Exposure results are shown in **Table 4.1**. Because of production constraints, the personal and static samples were performed on different days. This means that the static and personal values may not be directly comparable. The process is continuous on any shift where it is in operation and the 8-hour TWAs (time-weighted averages) are adjusted to take into account the varying shift lengths.

Table 4.1 Inhalable TBBP-A exposure to operators during the production of ABS plastic pellets

Task/area	Sample type	TBBP-A Sampled over a 9.5 hour shift μg/m^3	TBBP-A 8-hour TWA μg/m^3
Loading/mixing	Personal	10,000	12,000
Loading/mixing	Personal	4,300	5,000
Supervisor/extruder	Personal	400	380
Supervisor/mixing	Personal	170	200
Extruder	static	18	
Mixer/extruder	static	120	
Storage	static	8	

Personal exposure to TBBP-A was very high at this site owing to several factors; large quantities of pure TBBP-A are added to the plastic batches; at the master batch mixer the booth is poorly designed; at the other addition stages, poor practice significantly increases the TBBP-A exposure.

Industry data

New information was provided by industry in January 2005, including a small number of data points from two plants in Germany. At Plant A, which compounds ABS plastics, two different jobs were sampled; working at the hopper and working at the extruder. At the hopper, samples were taken during emptying of big-bags containing TBBP-A into several hoppers and during cleaning of the work site afterwards. Emptying of big bags lasts only between 30 to 45 minutes per day. No LEV was provided at the filling site but disposable FFP2 respirators were worn. A shift average was not supplied for work at the hopper. At the extruder samples were taken during compounding of the plastics. This includes; turning out a ribbon of plastic from the rolls and feeding into a water bath, cleaning rolls during production, taking out samples for quality control, remedying defects/interruptions and cleaning of the rolls and the whole area on changing batches. LEV was not provided but disposable FFP" respirators were worn during cleaning operations. At Plant B the operators were sampled when they were added big bags of TBBP-A into a hopper and the work includes cleaning of the area of the hopper. The hopper was filled with 15-25 bags per shift. LEV was not provided but disposable FFP2 respirators were worn.

When the time differences are taken into account these results are not dissimilar to the HSE data. Results are given in **Table 4.2**.

Table 4.2 Industry personal sampling results during compounding of plastics

Plant	Operation	Sampling Duration (minutes)	TBBP-A (µg/m3)
A	Compounding at the extruder (line 2)	150	20
A	Compounding at the extruder (line 2)	170	20
A	Compounding at the extruder (line 2)	180	70
A	Compounding at the extruder (line 2) (Cleaning after the batch)	15	9,500
A	Compounding at the extruder (line 2)	average shift value	410
A	Hopper (line 2) – emptying big bags	10	1,520
A	Hopper (line 3) – emptying big bags	23	1,470
A	Hopper (line 2) – emptying big bags	8	350
B	Hopper operator	100	1,600
B	Hopper operator	50	900
B	Hopper operator	average shift value	1,350

Modelled inhalation exposure

Luijk and Govers (1992) investigated the stability of ABS containing TBBP-A over a range of temperatures. Measurable evaporation of TBBP-A occurred only at temperatures above 200^{o}C and was very low. There is no reliable data on the vapour pressure of TBBP-A at elevated

temperatures but it is likely to be very low. As a result, only the pre-extrusion phase of processes involving the mixing of polymer batches were modelled. Neat TBBP-A powder is added to batches of polymers and synergists for processing and TBBP-A exposure after the extrusion is very low.

Using the EASE assumptions of dry manipulation of inhalable dust for the mixing/loading of the master batches produces an exposure range of 2,000 to 5,000 μg/m^3 if LEV is assumed to be present. If LEV is absent, the exposure range estimate increases to between 5,000 to 50,000 μg/m^3. The measured personal data from the HSE survey (5,137 and 12,216 μg/m^3) are in agreement with the lower end of the latter estimate confirming the lack of efficiency of the LEV.

Dermal exposure

Using EASE for dermal exposure, it is assumed that the TBBP-A is a "dusty" solid, and the pattern of use is "non-dispersive". The pattern of control is "direct handling" because LEV is assumed to be non-operational, and the contact level is "extensive". This predicts a dermal exposure of 1,000 – 5,000 μg/cm^2/day. However, with functioning LEV, the EASE prediction for dermal exposure is "very low".

However, if the data from Table 2 in Appendix 1E of the TGD are used for the dumping of powder in a formulation facility, this gives dermal exposure estimates of 1,900 μg/cm^2 as a RWC and 600 μg/cm^2 as a typical value.

Operators should wear gloves and other protective equipment, and PPE, properly selected and worn, may significantly reduce this exposure.

Values for risk characterisation purposes

The data from the company visited by HSE were symptomatic of poor control that required immediate advice and guidance. Although LEV was present, it functioned poorly and was badly used. It is uncertain how typical this company are of the sector as a whole, both within the UK and within the EU. There were no data from any other member state, and with only two personal samples from only one site, any conclusions must be drawn with caution. The small quantity of additional data provided by industry did not substantially alter this position. Therefore, for risk characterisation purposes, 10,000 μg/m^3 inhalable TBBP-A (8-hour TWA) will be used as a "reasonable-worst-case" inhalation exposure. This value is in the lower range of EASE predictions for powder handling without LEV and is also the RWC exposure from the analogous data given in the TNO report V99.267 "Effectiveness of LEV during dumping of powders from bags". 5,000 μg/m^3 will be used as a "typical" inhalation exposure. This is the second and lower value found at the site visited, and it is believed that this represents a site with poor control despite the presence of LEV.

The effects of respiratory protective equipment (RPE) on personal exposure to TBBP-A have not been considered. Although RPE was available at this site, the general suitability and regular use patterns in the industry are uncertain and therefore assumptions cannot be made about the protection factors that could be afforded.

For dermal exposure the values from Table 2 of Appendix 1E of the TGD for dumping of powders in a formulation facility of 1,900 μg/cm^2 RWC and a "typical" value of 600 μg/cm^2 will be taken forward for risk characterisation.

No amendment has been made to these exposure values to allow for PPE usage generally because there is evidence from only one site.

4.1.1.1.3 Occupational exposure during the production of laminates for printed circuit boards.

TBBP-A is used in the production of epoxy resins and the main use of these flame-retarded resins is in the manufacture of rigid epoxy laminated printed circuit boards, reinforced with glass fibre (FR4 circuit boards). Cellulose paper-reinforced phenolic resin is used to make FR2 circuit boards, which are paper laminates and used predominantly in consumer electronics such as televisions. This manufacture is similar to that of FR4 laminates but a lower proportion of TBBP-A is used in an additive rather than reactive manner. The production of FR4 laminates will be used to represent the worst-case exposure for laminate production in general, because the major source of exposure to TBBP-A is during the addition of TBBP-A to the resin mix.

For FR4 circuit boards, the glass fibre is impregnated with epoxy resin and allowed to dry and harden to an intermediate state. Copper foil is applied by hot pressing and the resin re-melts and hardens under pressure and temperature. The laminates are used as base material for printed circuit boards, where surplus copper is etched and the remaining copper forms the circuits.

Measured occupational exposure data

Industry data

No industry data were available.

HSE survey data

HSE visited one site during 2002 and sampled for TBBP-A. The company manufacture copper/resin laminates that are sold on for production of printed circuit boards. At the resin mixing plant, TBBP-A is added to the resin at a concentration of 25% by weight (two tonnes of TBBP-A is added once every eight hour shift to make a total of eight tonnes of treated resin). Two one-tonne bags are manoeuvred above the hatch of the reaction vessel by a mechanical hoist. When the hatch is opened, the drawstring bottom of the bag is manually opened and the TBBP-A released into the vessel. During this addition, which lasts about fifteen minutes, the vessel remains under negative pressure due to a computer controlled extraction system. Empty bags are rolled up for disposal in an uncontrolled manner and there were powder deposits on the floor nearby.

The operator stayed in the control room for the majority of the shift to monitor the reaction vessel although they are also responsible for housekeeping duties, predominantly bag handling/disposal with occasional short periods (1-2 minutes) of cleaning around the reaction vessel with a hand brush. The operator wore protective glasses, boots, cotton gloves and an FFP3 disposable respirator during TBBP-A addition.

The flame-retarded resin is transferred via pipework to the treater plant where it is spread onto sheets of glass matting and cooled. At this stage, the TBBP-A has been reactively

incorporated into the resin and very little should be available for either dermal or inhalation exposure.

The sheets are cut by guillotines, many of which are automated. However, during manual guillotining some particulate matter is generated, but this material should contain very little available TBBP-A. The guillotine area is continually swept clean by dry-brushing. On the treatment lines, operators routinely sample for Quality Control purposes by grinding up small portions of the composite material, a particularly dusty task. This is undertaken on a small bench fitted with a flexible trunk-type extractor, but its efficiency was doubtful owing to poor positioning.

The composites pass on to be bound to copper foil in heated presses and the final laminate may consist of alternate layers of metal and composite, the raw material for printed circuit boards.

Exposure results are shown in **Table 4.3**.

Table 4.3 Inhalable TBBP-A exposure to operators during laminate production

Area/task	Sample type	TBBP-A μg/m3 8-hour TWA
Resin-mixing plant	personal	75
Treater line plus QC sampling	personal	4.6
Treater line plus QC sampling	personal	0.2
Treater line	static	0.01
Treater line	static	0.003
Guillotine (cleaner)	personal	0.9 μg/m^3 over 5.5 hours which converts to 0.6 μg/m^3 (8-hour TWA)
Guillotine	static	< Limit of Detection
Lamination	static	0.7

The highest TBBP-A exposure was in the plant, where TBBP-A is used in making resins. Much of this exposure could be prevented by controlling the bag disposal and by reducing dry sweeping.

High volume static samplers were employed in areas where the resin had been completely cured and the results (all below 1 μg/m^3) confirmed the assessment that personal exposures to TBBP-A would be very low.

Modelled inhalation exposure

At the resin-mixing plant, the job entails a combination of tasks for varying times. One sequence would be loading up a reaction vessel followed by a variable time in bag disposal/cleaning and the majority of the time in the control room. Using the EASE parameters of dry manipulation of an inhalable dust with LEV produces an estimated exposure of 2,000 – 5,000 μg/m^3, representing only the addition of TBBP-A to the reactor. However this task only takes place for 15 minutes per shift and the EASE estimate then converts to a range of 60 – 150 μg/m^3 as an 8-hour TWA for this task alone. For bag disposal/cleaning tasks at this plant, we can also model using EASE. For "dry manipulation"

as the process without LEV produces an estimated exposure of 5,000 – 50,000 μg/m^3. For the purposes of this assessment the duration of this task has been assumed to be fifteen minutes a day. This is a conservative estimate as it is more usually that this task will last only a few minutes per day. Therefore, the EASE estimate converts to 156.25 – 1562.5 μg/m^3 as an 8-hour TWA. Putting these estimates together produces an overall 8-hour TWA of between 200 and 1,700 μg/m^3. However, this makes large assumptions about the work activities.

For the treater plant, using the EASE model, dry manipulation of an inhalable dust is assumed. With functioning LEV, EASE estimates an inhalation exposure of between 2,000 and 5,000 μg/m^3. Without LEV, this range increases to between 5,000 and 50,000 μg/m^3. However, the TBBP-A is reacted into a laminate during these processes and free TBBP-A is less than 1,000 ppm or 0.1% (see Section 3, which will be added later). Allowing for a free TBBP-A concentration of 0.1% reduces the EASE estimate to between 2 and 5 μg/m^3 (with LEV) and 5 and 50 μg/m^3 (without LEV). The highest measured personal sample was less than 5 μg/m^3 but LEV was present in most areas.

Modelled dermal exposure

The job in the resin mixing area is a combination of tasks; loading the reaction vessel and bag disposal/cleaning. Using the data from Table 2 in Appendix 1E of the TGD gives estimates of 1,900 μg/cm^2 as a RWC and 600 μg/cm^2 as a typical value for loading the reaction vessel. For handling bags in a formulation facility the RWC estimate is 700 μg/cm^2 and the typical estimate is 300 μg/cm^2. Combining the two, mutually exclusive tasks produces and overall RWC value of 2,600 μg/cm^2 and an overall typical value of 900 μg/cm^2.

For the treater plant tasks, the EASE parameters of "wide dispersive use", "direct handling" and "intermittent contact", are used which predicts dermal exposure of between 1,000 and 5,000 μg/cm^2 /day. However, allowance must be made for the low free TBBP-A left in the laminates (less than 1,000 ppm - Section 3, which will be added later). This reduces the dermal exposure to a maximum of between 1 and 5 μg/cm^2 /day. If functioning LEV is present however, EASE predicts that dermal exposure will be very low.

Operators who wear gloves and other protective equipment, and PPE, properly selected and worn, may significantly reduce their exposure. However, no amendment for PPE use has been made because we have only evidence from one site. With no other information, it cannot be assumed that PPE is used generally.

Values for risk characterisation purposes

There is only one personal inhalation result for the resin-mixing plant - 75 μg/m^3 – as there was only one operator, and there are no data from industry or from other Member States. There is no indication of how typical this result is for the industry sector in the UK or in the EU, so any conclusions drawn are very uncertain. The EASE range for the addition of the TBBP-A to the reactor (as a fifteen minute task) straddles this value, but we have assumed that there is added exposure from the house-keeping duties. Fifteen minutes a shift has been allowed for this, but it is a highly variable task. On the day of sampling, the cleaning tasks were not performed and this may explain the relatively good correlation with the modelled data for the addition of TBBP-A alone.

As a "typical" inhalation value, the middle of the EASE range (950 μg/m^3) inhalable TBBP-A, 8-hour TWA, will be taken forward, and for a "reasonable worst case" inhalation

value, the upper limit of the EASE range (1,700 μg/m^3) inhalable TBBP-A, 8-hour TWA, will be taken forward.

For dermal exposure at the resin-mixing stage the values of 2,600 μg/cm^2 RWC and 900 μg/cm^2, typical will be taken forward to risk characterisation.

For work activities in the treater area, the survey shows personal inhalation exposures between 0.2 and 5 μg/m^3 but this site had functioning LEV over most of this area. For a "typical" inhalation exposure, a value of 5 μg/m^3 (the upper limit of the EASE estimate with LEV) will be taken forward. For a "reasonable worst case" inhalation exposure, a value of 30 μg/m^3 (the middle of the EASE range without LEV) will be taken forward. A "typical" dermal exposure is assumed to be the middle of the EASE range (1.3 μg/cm^2/day) and the "reasonable worst case" dermal exposure is assumed to be the upper limit of the EASE range (2.1 μg/cm^2/day).

4.1.1.1.4 Occupational exposure during recycling of computers and electrical equipment

Most specialist recyclers for computers and electronic equipment handle a wide range of equipment. While some only dismantle equipment, other operators use granulators designed specifically for electric and electronic equipment. Companies handling IT equipment usually dismantle it manually and the plastic housings are land filled or incinerated. Potential theoretical exposures to TBBP-A from recycling plastic housings alone are considered in Section 4.1.1.1.7. This section is restricted to the current situation in the EU where only the internal parts of the electrical and electronic equipment are recycled.

Measured occupational exposure data

Industry data

In a Swedish study (Sjodin et al., 2001) air concentrations of a range of brominated flame-retardants at a factory that recycled electronic equipment such as computers, printers and TV sets were investigated. In the dismantling hall, where the outer casings were removed, static samples for TBBP-A ranged from 0.007 to 0.061 μg/m^3 (30 samples). In the shredding hall, where the internal parts of the equipment were ground up, the samplers were placed on a clean shelf 1.8 metres above the floor and about 2 metres from the conveyor belt taking the plastics to the shredder. This was meant to approximate to the operator's breathing zone. Sampling was divided into a day when no brominated flame retardant (bfr) material was shredded and a day when only bfr material was used. When bfr material was absent, TBBP-A air concentrations were measured at 0.034 and 0.041μg/m^3 (duplicate samples). On the day that brominated flame retardant material was used, TBBP-A air concentrations were found to be 0.13 and 0.15 μg/m^3.

HSE survey data

HSE visited two sites that carry out computer recycling during 2002 and sampled for TBBP-A. Most sites in the UK (around thirty) only dismantle electronic equipment and the circuit board shredding is restricted to about five UK sites. Virtually all the shredded circuit boards are the FR4 type – where the TBBP-A has been reacted into the polymer.

At the first company, the main activity was precious metal refining. As part of this process, old printed circuit boards were shredded prior to burning, and this represents the highest potential for TBBP-A exposure.

Old boards were transported in large fabric bags. The bags were slit at the bottom and the boards were manually fed onto an inclined conveyor that carried them to the shredder. The boards fell into the shredder and passed through to another conveyor, which fed them to a receiving bag. The receiving bag was fitted with LEV. When full (450 kg), the bag is removed and replaced. Periodically, the conveyor belt reversed to feed samples of the shredded material into a sample bin that provided material for analysis of the precious metal content. A single operator worked the shredder but the task was rotated and the shredder only operated periodically. The operator wore safety boots, gloves, helmet, safety glasses, and for dusty tasks, such as tying up the top of the full receiving bag and emptying the sampling bin, an FFP2 respirator was provided.

Exposure results are shown in **Table 4.4** and the task-based values over varying time periods have been amended where the shift length is more than eight hours.

Table 4.4 Inhalable TBBP-A exposure to operators during pcb shredding at site 1

Area/task	Sample type	TBBP-A (μg/m³) Over 9 hour shift	Value converted to 8-hour TWA (μg/m³)
Shredding	Personal (lapel 1)	1.0	1.1
Shredding	Personal (lapel 2)	0.12	0.13
Shredder	Static	0.019	
Background of shredder	Static	0.013	

There was a wide variation between the parallel lapel badges on the single shredder operator who worked a nine-hour shift, but both measured levels were below 1 $\mu g/m^3$. The static values were lower because during much of their 24-hour running period, there was no shredder activity.

At the second company, waste computers, printers and monitors were dismantled. Printed circuit boards were shredded and exported for the recovery of precious metals.

Dismantling and shredding were performed in the same building. Dismantling is a manual operation using hammers and screwdrivers providing little potential for TBBP-A exposure. Circuit boards were manually loaded from a hopper onto a conveyor belt that led to a shredder. Boards fell into a shredder and the shredded material emerged onto a vibration plate that directed it into a collection container. A portion of this material was periodically separated into a sampling bin. Samples of this bin were weighed into crucibles and burnt in small furnaces preparatory to precious metal analysis.

The collection container was a large cardboard box, and the shredded material was manually raked to pack it down. A receptor hood for LEV was positioned directly above the container but the design and positioning was poor. Dust also escaped above the shredder and dust was visible on the floor round the shredder. Cleaning is by dry brushing – allowing resuspension of this dust. The shredder operator worked a full eight-hour shift when necessary.

Exposure results are shown in **Table 4.5**. The personal sampling period extended for more than four hours and was representative of the shift (nine hours) as a whole.

Table 4.5 Inhalable TBBP-A exposure to operators during printed circuit board shredding at site 2

Area/task	Sample type	TBBP-A μg/m³	8-hour TWA μg/m³
Shredding	personal	20.8	20.8
Shredding	static	0.095	
Dismantling	personal	0.97	0.97
Dismantling	static	0.022	
Small furnace (sampling)	personal	13.45	13.45
Peripatetic	personal	0.16	0.16

The relatively high personal samples from the shredder operator and furnace operator at this second site represented dustier processes and a dirtier floor than was the case at the first site.

Modelled inhalation exposure

Using the EASE parameters of "dry crushing/grinding" and "LEV present" to assess an inhalable dust produces a prediction of 2,000 – 10,000 μg/m^3. Without LEV, the EASE prediction increases to 50,000 – 200,000 μg/m^3. However, these results do not allow for the fact that TBBP-A is reacted into the matrix material and the free TBBP-A is present at less than 1,000 ppm (see Section 3, which will be added later). Allowing for this reduces the estimate to between 2 and 10 μg/m^3 (with LEV), and to between 50 and 200 μg/m^3 (without LEV).

Modelled dermal exposure

Using the EASE parameters of "wide dispersive use", "non-direct handling", the prediction is for dermal exposure to be very low. However, given the measurable dust levels, dermal exposure is possible.

Values for risk characterisation purposes

For inhalation exposure, the HSE sampling exercises (with LEV) showed values between less than 0.1 and 20 μg/m^3. EASE, with the matrix effect taken into account, estimates a range between 2 and 10 μg/m^3 (with LEV) and between 50 and 200 μg/m^3 (without LEV). Data are sparse and many assumptions have been made but as EASE is based on measurements such as these so it is no surprise that the values agree. A "typical" 8-hour TWA inhalation exposure of 20 μg/m^3 inhalable TBBP-A (the highest measured personal sample) will be taken forward because it is possible some sites will have poor LEV. A "reasonable worst case" 8-hour TWA inhalation of 50 μg/m^3 inhalable TBBP-A (higher than our measured values and at the lower limit of the EASE prediction without LEV) will also be taken forward to the risk characterisation section.

For dermal exposure, EASE predicts very low exposure and thus no values can be taken forward.

4.1.1.1.5 Occupational exposure during the assembly of printed circuit boards

There is no direct information about this activity.

Measured occupational exposure data

Industry data

Sjodin et al. (2001) reported low levels of TBBP-A in air from a factory that assembled printed circuit boards. Static samples were taken in areas where components were soldered onto the circuit boards. No details are given but it is assumed that the process consists of soldering and baking. "Spot ventilation" was reported to be present on site. The six static samples ranged from 0.00011 to 0.00037 μg/m^3 (mean 0.00020 μg/m^3).

It is not possible to model these processes but it is anticipated that exposures will be negligible.

Values for risk characterisation purposes

Based on the only published data available, the mean value of 0.0002 μg/m^3 inhalable TBBP-A (8-hour TWA) for inhalation exposure will be carried forward to the risk characterisation section as representing a "typical" value, and the highest value of 0.00037 μg/m^3 inhalable TBBP-A (8-hour TWA) for inhalation exposure will be carried forward as representing a "reasonable worst case" scenario. However, the scarcity of relevant data should be taken into account.

Printed circuit boards contain TBBP-A reacted into the laminate and free levels are low. For this reason, dermal exposure is assumed to be negligible.

Information about the processes is extremely sparse and we have made assumptions about the nature and extent of any TBBP-A exposure. This uncertainty needs to be taken into account in the risk characterisation process.

4.1.1.1.6 Occupational exposure to employees in offices containing electronic equipment.

Many offices contain computers, printers and other electronic equipment that contains plastics flame-retarded with TBBP-A. Because there is a theoretical risk that dust from these plastics may become airborne or that TBBP-A may leach out or vaporise from plastics where TBBP-A is incorporated in an additive manner, the above scenario has been included in this risk assessment.

Measured occupational exposure data

Industry data

Sjodin et al. (2001) measured TBBP-A air levels in offices containing large numbers of computers. Four static samples showed TBBP-A levels between 0.00001 and 0.00007 μg/m^3 (mean value 0.000036 μg/m^3).

Wolf et al. (2000) showed, using a short term but aggressive purge and trap screening method, that no brominated substances were released from an epoxy resin printed circuit board containing TBBP-A. De Boer et al. (1998) detected no TBBP-A in the air inside or surrounding a TV set even when the flame retardant was present in the printed circuit boards.

Recent research (Ball and Herrmann, 2002) has extended these observations to cases where TBBP-A is incorporated in an additive form. Emissions of TBBP-A from computer monitor housings, where the flame retardant was present in an additive form, were negligible. The test chambers that housed the computers were cleaned before each experiment and the air sampled and the surfaces wipe-sampled. The monitors contained 12% TBBP-A and the circuit boards between 4% and 8% TBBP-A. Static air levels of TBBP-A, measured in an enclosed chamber, varied between 0.0001 and 0.0023 $\mu g/m^3$; wipe samples showed a maximum TBBP-A value of 569 $\mu g/m^2$ at the bottom of the sampling area but particles were seen beforehand and may represent contamination from the housing.

It has not been possible to model these processes because the values calculated will be critically dependent on unverifiable assumptions.

Values for risk characterisation purposes

As there is no personal exposure data, these published static values will be carried forward to the risk characterisation section. A value of 0.00004 $\mu g/m^3$ inhalable TBBP-A (8-hour TWA) for inhalation will be used as being "typical", and a value of 0.00007 $\mu g/m^3$ inhalable TBBP-A (8-hour TWA) for inhalation will be used as a "reasonable worst case" scenario. These values represent the mean value from the published background data and the highest value from the published background data respectively.

It was not possible to model dermal exposure but it is assumed to be negligible. However, these uncertainties need to be taken into account in the risk characterisation process.

4.1.1.1.7 Occupational exposure during recycling of plastics

Thermoset plastics such as epoxy resins are rigid and non-flexible even at high temperatures and cannot be recycled by remelting. Thermoplastics (polycarbonates, HIPS and ABS) can theoretically be remelted and reformed. However, recycling of thermoplastics is still relatively unusual. Four main sorts of plastics are currently recycled – polyethylene, polypropylene, polystyrene and PVC.

Polycarbonates and ABS (the plastics most likely to be flame-retarded) do not have US recycling code numbers and are generally not recycled. There is no evidence yet that plastics flame-retarded with TBBP-A are recycled in any quantities but this may change soon with the introduction of the WEEE Directive. On October 10th 2002, the European Parliament and the European Council agreed with the Commission proposal to introduce mandatory collection, re-use and recycling of waste electrical and electronic equipment throughout the European Union. Parliament and Council also agreed on a ban on some brominated flame-retardants from July 2006, and these decisions may lead to increased use of TBBP-A-containing plastics being recycled.

When plastics are recycled, granulators, crumbers, shredders and extruders are used to convert the native plastic into a form that is amenable for further processing. Shredders and granulators cut up the plastic into small chips that can be reheated. Extruders melt the plastic on site. It is assumed that potential exposure during these processes will occur throughout the shift.

Modelled inhalation exposure

Only the cutting of plastics into a pellet/crumb form that can be bagged for further use has been modelled.

Using the EASE parameters of "dry crushing and grinding" and assuming that that LEV is present, EASE predicts an inhalation exposure range between 2,000 and 10,000 μg/m^3. Without LEV, the estimate increases to between 50,000 and 200,000 μg/m^3. However, both predictions will be massive overestimates for several reasons. With an additive use of TBBP-A as a flame retardant (thermosets will not be recycled), the TBBP-A concentration in the plastic will be less than 20%. This is based on data indicating that for this use, the proportion of TBBP-A in ABS resins, HIPS and phenolic resins ranges from 14% to 22%. However, the industry doubts that HIPS contains any additive TBBP-A at all. Also, it is unlikely that more than a small proportion of the plastic will contain flame-retardants; currently, virtually no TBBP-A-containing, flame-retarded plastics are recycled. Because of these factors, the inhalation will be reduced to 10% (the proportion of plastic containing TBBP-A), of 20% (maximum TBBP-A content) or 40 – 200 μg/m^3 (with LEV) and 1,000 – 4,000 μg/m^3 (without LEV)

The effects of RPE on the exposure to TBBP-A have not been considered as there is no information about RPE practice in this industry.

Modelled dermal exposure

Using the EASE parameters of "wide dispersive use", "non-direct handling", and "extensive contact", the prediction for dermal exposure is very low. However, given the measurable dust levels, dermal exposure is possible.

Surrogate inhalation exposure data

The shredding of printed circuit boards is a similar process to the shredding of flame-retarded plastics, and for that reason, data from the former process is relevant. Personal inhalation samples (with LEV) from the sites shredding circuit boards ranged from 0.1 to 21 μg/m^3 compared to the modelled range (with LEV) for plastic shredding of 40 to 200 μg/m^3. Although the model assumes that only 10% of the plastic contains TBBP-A whereas in the case of printed circuit boards a much larger percentage of the shredded material contains TBBP-A, the latter is in a reacted form and far less is available for inhalation exposure.

Values for risk characterisation purposes

In the near future, it is possible that the recycling of flame-retarded plastics will become significant. Many assumptions about the pattern this recycling will take have been made. An estimate of the proportion of plastics containing TBBP-A has been made and it is assumed that the process will be similar to that of computer shredding. These assumptions must be treated with caution and considered when the risk characterisation takes place. With these provisos, a "typical" 8-hour TWA inhalation exposure of 200 μg/m^3 inhalable TBBP-A (the upper limit of the EASE prediction with LEV), and a "reasonable worst case" 8-hour TWA inhalation exposure of 4,000 μg/m^3 inhalable TBBP-A (the upper limit of the EASE prediction without LEV) will be assumed. The effects of RPE on the exposure to TBBP-A have not been considered as there is no information about RPE practice in this industry.

For dermal exposure, EASE predicts very low exposure and thus no values can be taken forward.

These assumptions are crucially dependent on factors that are predominantly based on judgement because there are no measured data or indeed any modelled data based on knowledge of the processes and feedstock.

4.1.1.1.8 Inhalation exposure (general discussion)

The highest TBBP-A exposure was found during the addition of TBBP-A powder to batches of plastics to produce a masterbatch. The highest personal exposure was just over 12,000 μg/m^3, and EASE predicts a range of 2,000 to 5,000 μg/m^3 for this sort of process with functioning LEV. The data from this company were symptomatic of poor control that required immediate advice and guidance and were intermediate between the EASE predictions with and without LEV. There is no information whether or not this company is typical or extreme for this industry sector, but it has provided the only available personal samples. The figures for "typical" and "reasonable worst case" exposures to be carried forward into the risk characterisation section are based on the judgement that the site surveyed was typical of sites with poor control despite the presence of LEV, as well as, the analogous data given in the TNO report V99.267 "Effectiveness of LEV during dumping of powders from bags". Even though some sites may operate without LEV, there is unlikely to be much difference in levels.

Addition of TBBP-A to a mixture is one of many processes under the heading of "powder handling". It should be possible to reduce occupational exposures to below 5,000 μg/m^3 by making simple changes. Maintenance of down-flow booths and LEV should be stressed. Training and supervision of operators is necessary to gain the benefits of any controls (including RPE and PPE).

Occupational exposures to TBBP-A in other industry sectors were much lower, in some cases many orders of magnitude lower. This is not surprising because the material is used in a different manner. During the manufacture of laminates as a template for FR4 printed circuit boards, the highest TBBP-A inhalation exposure occurs only during the brief (fifteen minute) addition of the powder to the resin and the consequent removal of bags and the clear up. Thereafter, the flame retardant is bound within a matrix and is unavailable for exposure.

This is the case also with recycling of the printed circuit boards, where only small quantities of TBBP-A are available from the dust created. Other potential inhalation exposures to TBBP-A are small and in the case of office workers, very low.

The potential exposure to TBBP-A was modelled during the recycling of flame-retarded plastics, even though there is no clear evidence that this yet occurs. It is likely that in the future, with the encouragement of European legislation, this could be a potential source of occupational TBBP-A inhalation exposure. The EASE prediction is based on TBBP-A being the only flame retardant used, that all plastics are flame retarded, and that all the TBBP-A is available for inhalation. As none of these scenarios are likely, the modelled output has been adapted accordingly.

The possible effects of RPE on the exposure to TBBP-A have not been considered. Although RPE was available at many sites, there is uncertainty over the suitability and regular use patterns in the industry. It is not possible to infer the protection factors that could be afforded.

Table 4.6 summarises the range of inhalation exposures available during the occupational use of TBBP-A and the values to be carried forward into the risk characterisation section.

Table 4.6 Summary of data on inhalation exposure to TBBP-A

	HSE survey - Personal samples 8-hr TWA (μg/m3)	HSE survey - Static samples (μg/m³)	Industry data (μg/m³)	EASE prediction (μg/m³)	Typical exposure (μg/m³)	Reasonable worst case exposure (μg/m³)
Addition of TBBP-A to polymer batches	169; 407; 5137; 12,216	8, 18, 117	410 (shift average) 1,520 (10 mins) 1,470 (23 mins) 350 (8 mins) 1,350 (shift average)	2,000-5,000 (with LEV) 5,000 – 50,000 (without LEV)	5,000	10,000
Production of laminates (bromination)	75	-	-	200 – 1700	950	1,700
Production of laminates (other tasks)	0.2; 0.9; 5	< LOD, 0.003; 0.01; 0.66	-	2 – 5 (with LEV) 5 – 50 (Without LEV)	5	30
Computer recycling	0.12; 0.96: 0.2; 1; 13; 21	0.013; 0.019: 0.022; 0.095	0.007 – 0.06: 0.13 – 0.15 (Sjodin et al., 2001)	2 –10 (with LEV) 50 –200 (without LEV)	20	50
Printed Circuit Board assembly	-	-	0.00011 – 0.00037 (Sjodin et al., 2001)	-	0.0002	0.00037
Office environment	-		0.00001 – 0.00007 (Sjodin et al., 2001)	-	0.00004	0.00007
Plastic recycling	-	-	-	40 - 200 (with LEV) 1,000 – 4,000 (without LEV)	200	4,000

4.1.1.1.9 Dermal exposure (general discussion)

Many of the potential dermal exposures to TBBP-A have been modelled using EASE, and as is explained in the "definitions and sources" section, this is dependent on many variables. These values should be regarded with caution. Analogous data have also been used from the TGD.

The highest dermal exposures occur during the loading and mixing of TBBP-A powder into batches of polymers or for the additon to resins for the production of laminates. The use of pure TBBP-A powder is restricted to these tasks and these are the tasks that are likely to produce the highest dermal exposures. Many of the other industry sectors gave similar and lower EASE exposure estimates.

We have not considered the effects of PPE on the exposure to TBBP-A. Although PPE was available at many sites, there is uncertainty over suitability and regular use patterns in the industry and assumptions cannot be made about the protection factors afforded.

Table 4.7 summarises the modelled data and the dermal exposure ranges to be carried forward into the risk characterisation section.

Table 4.7 Summary of data on dermal exposure to TBBP-A and TBBP-A dermal exposures to be carried forward into risk characterisation

Task	EASE estimates μg/cm²/day	Typical exposure μg/cm²/day	Reasonable worst case exposure μg/cm²/day
Loading/mixing during TBBP-A addition to plastic batches	1,000 – 5,000	600	1,900
Production of laminates (bromination)	300 - 5000	900	2,600
Production of laminates (other tasks)	0.42 – 2.1	1.3	2.1
Computer recycling	-	-	-
PCB assembly	-	-	-
Office environment	-	-	-
Plastic recycling	-	-	-

4.1.1.2 Consumer exposure

TBBP-A is used in a range of consumer goods as a flame retardant. When added to polymers, it enhances the flame-retardancy properties by chemically interfering with the radical chain mechanism in the gas phase during combustion.

As indicated in Section 2.2, the EU usage of TBBP-A is estimated to be approximately 13,800 tonnes annually, and much of this is used for consumer goods. A description of the major uses of TBBP-A is given in Section 2.2.1.

It is possible to differentiate between reactive uses of TBBP-A and additive uses of TBBP-A. Reactive flame-retardants are built chemically into the polymer molecule together with other starting components. This may prevent them from bleeding out of the molecule or vaporising,

thus their flame retardancy is retained. Free residual monomer is likely to be less than 1,000 ppm (see Section 3, which will be added later). Reactive uses of TBBP-A constitute about 90% of the total.

The major reactive use of TBBP-A is in epoxy laminates for printed circuit boards. These epoxy resins are also used in much smaller quantities to encapsulate electronic components on the boards. Minor reactive uses are in polycarbonate and unsaturated polyester resins. Polycarbonates are used for electronic equipment, sports and recreation equipment and lighting fixtures. Unsaturated polyesters are used for bowling balls, furniture parts, buttons and patching compounds.

For additive flame retardant use, where TBBP-A may constitute up to 22% of the article, TBBP-A is usually incorporated into the plastic following polymerisation. It has the theoretical potential to leach from the polymer. Consumer exposure is theoretically possible if leaching occurs, or if vaporisation occurs when consumer products are heated.

The main use of TBBP-A as an additive flame retardant is in acrylonitrile-butadiene-styrene (ABS) resins where it can constitute up to 22% of the material. ABS resins are used in pipes and fittings, refrigerators, telephones and some automotive parts. Other minor additive uses include phenolic resins.

4.1.1.2.1 Screening procedure for consumer exposure to TBBP-A

Consumer exposure can only occur under conditions where dust from the polymer matrix becomes available for inhalation or ingestion or where free, unreacted TBBP-A can leach from the polymer.

There is no evidence that TBBP-A is used in textiles worn by consumers. A recent survey of OECD countries (Sigman, 2002) showed TBBP-A was used predominantly in electronic data processing equipment, and there was no textile use. The only potential exposure occurs where consumers inhale/ingest/contact dust containing TBBP-A or inhale TBBP-A vapour or dust from hot consumer equipment like TVs or computers.

However, the potential for volatilisation of TBBP-A is small. Luijk and Govers (1992) investigated the stability of ABS containing TBBP-A over a range of temperatures. Measurable evaporation of TBBP-A occurred only at temperatures above 200^{o}C and was very low.

Sjodin et al. (2001) measured TBBP-A air levels in offices containing large numbers of computers. Four static samples showed TBBP-A levels between 0.00001 and 0.00007 μg/m^3 (mean value 0.000036).

Wolf et al. (2000) showed, using a short term but aggressive purge and trap screening method, that no brominated substances were released from an epoxy resin printed circuit board containing TBBP-A.

De Boer et al. (1998) detected no TBBP-A in the air inside or surrounding a TV set even when the flame retardant was present in the printed circuit boards.

Recent research (Ball and Herrmann, 2002) has extended these observations to cases where TBBP-A is incorporated in an additive form. Emissions of TBBP-A from computer monitor housings, where the flame retardant was present in an additive form, were negligible. Test

chambers were designed to house the computer and were cleaned before each experiment. The chambers had an air exchange rate of two changes per hour and the air velocity above the monitor was set to between 0.11 and 0.16 m/second. The chamber air was periodically sampled and the surfaces wipe-sampled. An office experiment was also performed, by running the test computer in a typical office in order to mimic "real life" conditions.

The monitors contained 12% TBBP-A and the circuit boards within them contained between 4% and 8% TBBP-A. Air levels of TBBP-A measured in the enclosed chamber varied between 0.0001 and 0.0020 $\mu g/m^3$; air levels of TBBP-A measured in the office investigation peaked at 0.0023 $\mu g/m^3$ (during the first day) before falling slowly to between 0.0001 and 0.0002 $\mu g/m^3$. Wipe samples from the test chambers showed a maximum TBBP-A value of 569 $\mu g/m^2$ at the bottom of the sampling area but particles were seen beforehand and may have represented contamination from the housing.

In Section 4.1.2.1 findings of TBBP-A in human blood-samples and samples of human breast milk are described. These data show that population exposure to TBBP-A can be reflected in increased internal levels of the substance. However, it is not possible based on the data to point out specific sources to the TBBP-A exposure and to extrapolate the actual exposure levels of the individuals or to evaluate the degree of bioavailability from the exposure.

Conclusion

Consumer exposure to TBBP-A is likely to be insignificant. Any attempt at quantitative assessments will result in disproportionately high errors because of the small exposures anticipated.

4.1.1.3 Indirect exposure via the environment

The EUSES 2.0 model has been used to estimate the concentrations of tetrabromobisphenol-A in food, air and drinking water. In the EUSES model, a log Kow value of 5.9 has been used. For fish, a measured BCF value of 1,234 l/kg (representing accumulation of bisphenol-A plus metabolites) has been used in the calculations but for other parts of the food chain, particularly root crops, leaf crops, meat and milk, EUSES estimates the concentrations using methods that rely on the log Kow as no equivalent measured accumulation factors exist for tetrabromobisphenol-A. It is not known if these methods would be applicable to tetrabromobisphenol-A.

As discussed in Section 3, which will be added later, there is some uncertainty and natural variability in the adsorptive behaviour of the substance in the environment. In order to take this into account the calculations have been carried out twice, using different values for the organic carbon-water partition coefficient. The results of the calculations are shown in **Table 4.8** (for Koc = 49,726 l/kg) and **Table 4.9** (for Koc = 1,000,000 l/kg). As can be seen from the tables, the calculations using a Koc of 49,726 l/kg generally lead to the higher estimates of the total human daily intake, and these values will be considered in the risk characterisation.

Of the scenarios relevant to the current situation in the EU (production of tetrabromobisphenol–A does not occur in the EU and the situation over the production of flame retardant derivatives of tetrabromobisphenol A in the EU is unclear at present; these two scenarios are therefore given for information only and are not consider further), the

highest predicted local human intake is for additive flame retardant use in ABS (total human daily intake = 0.19 mg/kg bw/day). The predicted regional human intake is 7.8 · 10-5 mg/kg bw/day. These values will be considered in the risk characterisation.

The total predicted daily human intake figures, particularly the higher figures estimated, are dominated by the predicted contribution from root crops, which accounts for around 17-99% of the total dose. It should be recognised that the calculation methods used are uncertain and their general applicability for a substance such as tetrabromobisphenol–A, where the adsorptive and accumulative behaviour in the environment may be pH-dependent is unknown. Therefore the estimates should be treated as representing a worst case and uncertain estimate of the total human intake.

A total diet survey has been carried out for tetrabromobisphenol-A (Food Standards Agency, 2004). The study was intended to model the average domestic diet in the United Kingdom and included a total of 121 categories of food and drink (these were assigned to one of twenty broad food groups). The food samples were purchased fortnightly from 24 randomly selected locations representative of the UK as a whole, and the food samples were prepared and cooked prior to analysis. The survey for tetrabromobisphenol-A was carried out in 2001 and the concentration of tetrabromobisphenol-A was below the detection limit in all of the main food groups (the detection limit was 2 µg/kg fat in carcase meat, 4.4 µg/kg fat in offals, 1.5 µg/kg fat in meat products, 3/5 µg/kg fat in poultry, 3.6 µg/kg fat in fish, 0.78 µg/kg fat in fats and oils, 9.4 µg/kg fat in potatoes, 15 µg/kg fat in milk, 1.4 µg/kg fat in milk products, 3.2 µg/kg fat in eggs, 5.7 µg/kg fat in miscellaneous cereals, 13.7 µg/kg fat in bread, 1.4 µg/kg fat in nuts, 2.5 µg/kg fat in sugar and preserves, 30 µg/kg fat in fruit products, 30 µg/kg fat in green vegetables, 15 µg/kg fat in other vegetables, 30 µg/kg fat in canned vegetables and 30 µg/kg fat in fresh fruit).

In Section 4.1.2.1 findings of TBBP-A in human blood-samples and samples of human breast milk are described. These data show that population exposure to TBBP-A can be reflected in increased internal levels of the substance. These data also show there is potential for exposure of neonates via mother's milk. However, it is not possible based on the data to point out specific sources to the TBBP-A exposure and to extrapolate the actual exposure levels of the individuals or to evaluate the degree of bioavailability from the exposure.

Table 4.8 Estimated concentrations of tetrabromobisphenol-A in human intake media using a Koc of 49,726 l/kg

Scenario			Predicted concentration in human intake media							Total human daily intake (mg/kg bw/day)
			Wet fish (mg/kg)	Root crops (mg/kg)	Leaf crops (mg/kg)	Drinking water (mg/l)	Meat (mg/kg)	Milk (mg/kg)	Air (mg/m^3)	
Production of tetrabromobisphenol-A	Example calculation		115	389	0.052	0.068	0.837	0.265	$1.0 \cdot 10^{-7}$	2.33
Use as an intermediate in the production of derivatives	Example calculation		98.6	501	0.092	0.087	1.11	0.351	$3.8 \cdot 10^{-6}$	2.92
Reactive flame retardant use	Manufacture of epoxy and/or polycarbonate resins		0.35	1.18	0.064	$2.0 \cdot 10^{-4}$	0.088	0.028	$9.4 \cdot 10^{-6}$	$8.7 \cdot 10^{-3}$
	Processing of epoxy resins		$3.2 \cdot 10^{-3}$	$2.2 \cdot 10^{-3}$	$1.9 \cdot 10^{-5}$	$6.6 \cdot 10^{-7}$	$3.3 \cdot 10^{-5}$	$1.0 \cdot 10^{-5}$	$3.2 \cdot 10^{-9}$	$1.8 \cdot 10^{-5}$
	Processing of polycarbonate resins		$3.2 \cdot 10^{-3}$	$2.2 \cdot 10^{-3}$	$1.8 \cdot 10^{-5}$	$6.6 \cdot 10^{-7}$	$3.1 \cdot 10^{-5}$	$9.9 \cdot 10^{-6}$	$2.7 \cdot 10^{-9}$	$1.8 \cdot 10^{-5}$
Additive flame retardant use	ABS	Compounding	5.3	31.5	0.013	$5.5 \cdot 10^{-3}$	0.080	0.025	$1.3 \cdot 10^{-6}$	0.18
		Conversion	0.24	1.43	0.044	$2.5 \cdot 10^{-4}$	0.063	0.020	$6.5 \cdot 10^{-6}$	$9.5 \cdot 10^{-3}$
		Combined compounding/ conversion	5.54	32.9	0.057	$5.7 \cdot 10^{-3}$	0.14	0.045	$7.8 \cdot 10^{-6}$	0.19
	Phenolic resin	Compounding	0.31	6.38	$1.4 \cdot 10^{-3}$	$1.1 \cdot 10^{-3}$	0.014	$4.6 \cdot 10^{-3}$	$7.5 \cdot 10^{-8}$	0.036
		Conversion	0.017	0.29	$2.5 \cdot 10^{-3}$	$5.0 \cdot 10^{-5}$	$4.0 \cdot 10^{-3}$	$1.3 \cdot 10^{-3}$	$3.7 \cdot 10^{-7}$	$1.7 \cdot 10^{-3}$
		Combined compounding/ conversion	0.32	6.7	$3.9 \cdot 10^{-3}$	$1.2 \cdot 10^{-3}$	0.018	$5.8 \cdot 10^{-3}$	$4.4 \cdot 10^{-7}$	0.037
Electronic equipment collection/recycling site			$3.2 \cdot 10^{-3}$	$7.9 \cdot 10^{-4}$	$2.9 \cdot 10^{-4}$	$6.5 \cdot 10^{-7}$	$4.0 \cdot 10^{-4}$	$1.27 \cdot 10^{-4}$	$4.4 \cdot 10^{-8}$	$1.7 \cdot 10^{-5}$
Regional sources			$3.2 \cdot 10^{-3}$	$6.1 \cdot 10^{-3}$	$1.1 \cdot 10^{-5}$	$1.1 \cdot 10^{-6}$	$4.5 \cdot 10^{-5}$	$1.4 \cdot 10^{-5}$	$1.6 \cdot 10^{-9}$	$3.9 \cdot 10^{-5}$

Table 4.9 Estimated concentrations of tetrabromobisphenol-A in human intake media using a Koc of 1,000,000 l/kg

Scenario			Predicted concentration in human intake media							Total human daily intake (mg/kg bw/day)
			Wet fish (mg/kg)	Root crops (mg/kg)	Leaf crops (mg/kg)	Drinking water (mg/l)	Meat (mg/kg)	Milk (mg/kg)	Air (mg/m^3)	
Production of tetrabromobisphenol-A	Example calculation		23.9	75.1	0.010	0.013	0.87	0.28	$7.9 \cdot 10^{-9}$	0.46
Use as an intermediate in the production of derivatives	Example calculation		20.5	96.6	0.039	0.017	1.16	0.37	$3.8 \cdot 10^{-6}$	0.57
Reactive flame retardant use	Manufacture of epoxy and/or polycarbonate resins		0.073	0.23	0.063	$4.0 \cdot 10^{-5}$	0.088	0.028	$9.4 \cdot 10^{-6}$	$3.1 \cdot 10^{-3}$
	Processing of epoxy resins		$6.9 \cdot 10^{-4}$	$1.1 \cdot 10^{-3}$	$1.9 \cdot 10^{-5}$	$1.9 \cdot 10^{-7}$	$5.3 \cdot 10^{-5}$	$1.7 \cdot 10^{-5}$	$3.2 \cdot 10^{-9}$	$7.8 \cdot 10^{-6}$
	Processing of polycarbonate resins		$6.9 \cdot 10^{-4}$	$1.1 \cdot 10^{-3}$	$1.8 \cdot 10^{-5}$	$1.9 \cdot 10^{-7}$	$5.1 \cdot 10^{-5}$	$1.6 \cdot 10^{-5}$	$2.7 \cdot 10^{-9}$	$7.8 \cdot 10^{-6}$
Additive flame retardant use	ABS	Compounding	1.10	6.07	$9.6 \cdot 10^{-3}$	$1.1 \cdot 10^{-3}$	0.083	0.026	$1.3 \cdot 10^{-6}$	0.036
		Conversion	0.051	0.28	0.044	$4.8 \cdot 10^{-5}$	0.063	0.020	$6.5 \cdot 10^{-6}$	$2.8 \cdot 10^{-3}$
		Combined compounding/ conversion	1.15	6.35	0.054	$1.1 \cdot 10^{-3}$	0.15	0.046	$7.8 \cdot 10^{-6}$	0.039
	Phenolic resin	Compounding	0.063	1.23	$6.7 \cdot 10^{-4}$	$2.1 \cdot 10^{-4}$	0.015	$4.8 \cdot 10^{-3}$	$7.5 \cdot 10^{-8}$	$7.0 \cdot 10^{-3}$
		Conversion	$3.5 \cdot 10^{-3}$	0.056	$2.5 \cdot 10^{-3}$	$9.7 \cdot 10^{-6}$	$4.0 \cdot 10^{-3}$	$1.3 \cdot 10^{-3}$	$3.7 \cdot 10^{-7}$	$3.8 \cdot 10^{-4}$
		Combined compounding/ conversion	0.066	1.29	$3.2 \cdot 10^{-3}$	$2.2 \cdot 10^{-4}$	0.019	$6.0 \cdot 10^{-3}$	$4.4 \cdot 10^{-7}$	$7.4 \cdot 10^{-3}$
Electronic equipment collection/recycling site			$6.8 \cdot 10^{-4}$	$8.2 \cdot 10^{-4}$	$2.9 \cdot 10^{-4}$	$1.4 \cdot 10^{-7}$	$4.2 \cdot 10^{-4}$	$1.3 \cdot 10^{-4}$	$4.4 \cdot 10^{-8}$	$1.4 \cdot 10^{-5}$
Regional sources			$6.8 \cdot 10^{-4}$	$9.5 \cdot 10^{-3}$	$1.2 \cdot 10^{-5}$	$1.7 \cdot 10^{-6}$	$2.9 \cdot 10^{-4}$	$9.1 \cdot 10^{-5}$	$1.6 \cdot 10^{-9}$	$5.6 \cdot 10^{-5}$

4.1.1.4 Combined exposure

The worst case combined exposure would be a consumer who is also exposed indirectly via the environment. Given that consumer exposure to TBBP-A is negligible, calculation of the worst case combined exposure has not been performed.

4.1.2 Hazard identification and Dose (concentration) – response (effect) assessment

Throughout this document where a dose level is defined as mg/kg, this should be taken to read mg/kg bw unless otherwise stated.

4.1.2.1 Toxicokinetics

Studies in animals

Inhalation

No data are available. However, predictions of the fate of TBBP-A following inhalation exposure can be made based on its physico-chemical properties. TBBP-A is a white crystalline powder whose particle size has been measured as 31.8 and 52.3 μm (mass median aerodynamic diameter**,** MMAD) in 2 separate studies (Inveresk 2001 and 2002, respectively). The 2002 study also reports that only 4% of the particles have an aerodynamic diameter of < 15 μm. The respirable range of particles is considered to be < 10 μm (CEN 1993) and the optimum size for particle deposition in the alveolar region of the lungs in the rat is 1-2 μm (Morrow et al., 1964). Thus, only an extremely small percentage of any inhaled TBBP-A particles would be in the size range for optimal deposition in the rat lung. Consequently, a figure of 4% can be considered as very much a worst-case scenario for estimating the fraction of TBBP-A absorbed through the lung in both rats and humans.

Of the particles that will not reach the alveolar region, a certain fraction will be exhaled, while the remainder are likely to deposit in the nasopharyngeal region of the respiratory tract where they will be swallowed and any absorption will occur through the gastrointestinal tract. A realistic estimate for respiratory tract deposition is likely to be around 70%.

Overall, following inhalation of TBBP-A particles, approximately 70% of particles will be available for absorption through the gastrointestinal tract with only a small fraction (< 4%) being absorbed through the lungs.

Oral

In a well-reported and well-conducted study the metabolism, excretion and distribution of tetrabromobisphenol-A (TBBP-A) was assessed in conventional and bile-cannulated rats (Hakk et al., 2000). A single oral dose of ^{14}C-ring labelled TBBP-A (2.0 mg/kg body weight) was administered to 10 male Sprague-Dawley rats (called “conventional rats” below) in 0.5ml peanut oil via gavage. An identical dose was administered to 8 bile duct-cannulated animals.

Urine, bile (from bile-duct cannulated animals only) and faeces were collected between 0-24, 24-48 and 48-72 hours. At 72 hours the animals were sacrificed and selected tissues (epidydimal adipose tissue, blood, intestines, heart, kidney, liver, lung, spleen, testis, thymus) and the carcass were removed for distribution studies. Levels of radioactivity in the various samples were determined by liquid scintillation counting (LSC). The metabolites present in the 0-24 hours biliary sample and 24-48 hours faecal samples of the cannulated rats were also identified using relevant characterization techniques. In addition, pooled 0-48 hours urine samples and 0-24, 24-48 and 48-72 hours bile samples were investigated for binding of radio labelled parent compound/metabolites to carrier proteins.

Over the 72 hour time period the percentage of the administered radioactivity excreted in the faeces and urine of the conventional rats was 91.7% and 0.3% (0.1%, 0.2% and 0.02% between 0-24, 24-48 and 48-72 hours, respectively) respectively. A delay in faecal excretion of the radioactivity was evident in these animals; only 6.6% of the administered radioactivity was excreted between 0-24 as compared to 66% between 24-48 hours and 20% of the administered radioactivity being excreted between 48-72 hours. In the cannulated animals, over the 72-hour time period 26.3% of the administered radioactivity was excreted in the faeces and 0.7% (0.4%, 0.3% and 0.03% between 0-24, 24-48 and 48-72 hours, respectively) in the urine. Total faecal excretion comprised 6% of the administered radioactivity in the 0-24-hour time period (similar to that observed in conventional animals), 15.3% in the 24-48-hourtime period and 5% in the 48-72-hour time period. Biliary excretion in these animals represented 71.3% of the administered radioactivity. This comprised 48.4% of the administered radioactivity in the 0-24-hour time period, 21% in the 24-48-hour time period and 1.9% in the 48-72-hour time period. The total amount of radioactivity which could potentially be excreted in the faeces of the cannulated animals over 72 hours is 97.6% (26.3% + 71.3%) of that administered, which is comparable with that observed in the conventional animals.

The characterisation of the 0-24 hour bile sample, containing approximately 50% of the administered radioactivity, identified three metabolites. These were, a diglucuronide ether conjugate (24% of the 0-24 hour bile radioactivity), a glucuronic acid/sulphate ester diconjugate (14% of the 0-24 hour bile radioactivity) and a monoglucuronic acid conjugate (24% of the 0-24 hour bile radioactivity), equivalent to a total of 62% of the radioactivity excreted in the bile and to approximately 31% of the administered radioactivity. The identity of the remaining radioactivity (approximately 38% of the 0-24 hour bile radioactivity) was not documented.

The 24-48 hour faecal sample contained approximately 15% of the administered radioactivity. The maximum amount of radioactivity obtained after extraction was 8% (of the administered radioactivity) and the majority of this (> 95%) was identified as the parent compound; the remaining radioactivity was not characterised.

Based on the faecal and biliary excretion data obtained from this study, the following conclusions on the toxicokinetics of TBBP-A can be made:

- Approximately 71% of the administered radioactivity is absorbed from the gastrointestinal tract and is excreted via the bile/faeces within 72 hours. Approximately 26% is not excreted via the bile, but appears in the faeces within 72 hours; of this only 6% appears in the faeces within 24 hours post administration. Given that the average transient time through the gastrointestinal tract of the rat is 12 hours, it would be expected that any non-absorbed radioactivity would be excreted in

the faeces within 24 hours post-administration. This suggests that some absorption from the GI tract followed by excretion into the faeces by a non-biliary route is occurring; this could be estimated to be approximately 20% (26.3% minus 6%). Overall, at least 92% (72% found in bile + 20% found in faeces via a non-biliary route + 1% found in urine) of the administered radioactivity is likely to be absorbed from the GI tract. Therefore it can be assumed that following oral administration approximately 100% of TBBP-A is absorbed from the gastrointestinal tract.

- The "faecal lag" that is observed in radiolabel excretion may be suggestive that enterohepatic recirculation of TBBP-A is occurring, however, there is no real evidence to support this hypothesis. This observation could merely be a result of the absorption/excretion process.
- 50% of the administered radiolabel is excreted in the bile after 24 hours. This could be the result of a number of different factors. Some first pass metabolism could be occurring leading to direct excretion of metabolites into the bile/faeces. Equally TBBP-A could be absorbed, pass through the liver unchanged into the systemic circulation and then be eliminated, unchanged or as metabolites, through biliary excretion. Given the log P_{ow} of TBBP-A, it is also possible that TBBP-A could bypass the liver initially by being absorbed from the GI tract into the lymphatic system and then reach the systemic circulation, to be subsequently excreted, unchanged or as metabolites, in the bile/faeces. The fact that only 31% of the administered dose was excreted as metabolites in bile over 24 hours, does not indicate that TBBP-A undergoes extensive first pass metabolism. If that had been the case, a much greater proportion of the administered dose would have been expected to appear as metabolites, but at a much earlier time point than 24 hours (the earliest time point assessed in this study). Twenty-four hours is too broad a period to make any definitive conclusions as to the fate of TBBP-A before it reaches the bile.

Approximately 18% of TBBP-A and/or its metabolites excreted in the urine over 48 hours (0.7% of the administered radioactivity) were associated with carrier proteins (equivalent to 0.12% of the estimated administered radioactivity). However, the amount of protein bound ^{14}C was insufficient for protein characterisation by the methods utilised. In the 0-24 hour bile samples no measurable level of protein binding of TBBP-A and/or its metabolites could be demonstrated. However, in the 24-48 hour bile sample (21% of the administered radioactivity), 2% of the TBBP-A-derived ^{14}C was associated with protein (equivalent to 0.42% of the administered radioactivity); this figure was 6.6% at 48-72 hour (1.3% of the administered dose), equivalent to 0.125% of the administered radioactivity. The protein was characterised as a 79 kDa protein. These data show that binding of TBBP-A and/or its metabolites in excreta was very low.

Given that the majority of radiolabel administered was excreted in the bile/faeces within 72 hours, tissue retention of TBBP-A is predicted to be low. In the conventional rat, approximately 2% of the radioactivity was retained in the tissues, and in the cannulated rat, less than 1% was retained in the tissues. In both groups the highest tissue retention was in the small and large intestine; however, this could be explained by the fact that the intestines were not emptied of their contents prior to analysis. Whether there was distribution to all tissues assayed is not known (a level of "< 0.0005%" was documented for a number of tissues, 0.0005% was the limit of quantification).

Overall, these results demonstrate that in the rat TBBP-A is likely to be fully absorbed from the gut and can undergo metabolism (conjugation) via glucuronidation and/or sulphation.

There is no significant tissue retention 72 hours post-administration with most of the radioactivity being eliminated in the faeces, primarily via the bile, within this time. Urinary excretion is negligible.

The absorption, distribution and excretion of TBBP-A were also assessed in a study conducted in 1978 (Velsicol Chemical Corporation). Ten female Sprague-Dawley rats received a single gavage dose of ^{14}C labelled TBBP-A in corn oil (average dose 7 mg/kg) (the position of the label was not stated).

Urine and faeces were collected separately at 4 and 8 hours in two animals (group I); at 4, 8, 16 and 24 hours in two animals (group II); and at 4, 8, 16, 24, 48 and 72 hours in two animals (group III). Blood samples were collected from a further four animals (group IV): from two animals at 4, 8, 24, 48 and 72 hours after dosing and two animals at 16 hours after dosing. Animals in groups I, II, III were sacrificed at 8, 24 and 72 hours post dosing, respectively. The liver, kidney, brain, muscle, fat, spleen, skin and gonads were excised for assessment of radioactivity. Liquid scintillation counting was used for all quantitative measurements of radioactivity.

In group I animals very little radioactivity was excreted in the urine or faeces in the time periods 0-4 hours (0.03 and 0.0015% of the administered radioactivity, respectively) and 4-8 hours(0.02 and 0.0015% of administered radioactivity, respectively). Analysis of the tissues following sacrifice at 8 hours post-dosing revealed only a further 0.725% of the administered radioactivity, the highest levels being found in the liver (0.4%), muscle (0.12%), skin (0.12%) and fat (0.7%). Thus, analysis of the selected tissues and excreta accounted for less than 1% of the administered radioactivity after 8 hours.

In group II animals, similar excretion of radioactivity in urine and faeces to that reported in group I was observed for the time periods 0-4 hours (0.04 and 0.002% of administered radioactivity, respectively) and 4-8 hours (0.04 and 0.003% of administered radioactivity, respectively). Between 8-16 hours post-dosing, 0.12 and 26% of administered radioactivity was excreted in urine and faeces, respectively, while in the time period 16-24 hours, 0.15 and 7.4% of administered radioactivity was excreted in urine and faeces, respectively. Analysis of the tissues following sacrifice at 24 hours post-dosing revealed only a further 0.85% of the administered radioactivity, the highest levels being found in the liver (0.33), skin (0.18%), muscle (0.16%) and fat (0.16%). Thus, analysis of the selected tissues and excreta accounted for approximately 35% of the administered radioactivity after 24 hours.

In group III animals a similar urinary excretion profile to that reported in groups I and II was observed, with levels gradually increasing over time (0.05, 0.09, 0.12, 0.15, 0.3 and 0.32% of administered radioactivity in time periods 0-4, 4-8, 8-16, 16-24, 24-48 and 48-72 hours, respectively). A slightly different faecal excretion profile was reported in these animals with the majority of the administered radioactivity being excreted between 16-48 hours (0.0015, 0.15, 7.5, 49.6, 36.3 and 1.5% of administered radioactivity in time periods 0-4, 4-8, 8-16, 16-24, 24-48 and 48-72 hours, respectively). Analysis of the tissues following sacrifice at 72 hours post-dosing revealed a further 0.2% of administered radioactivity (this excludes values for skin, as the skin of one animal was contaminated, the individual values reported were 4.7 and 0.13% of administered radioactivity). Thus, analysis of the selected tissues (excluding skin) and excreta accounted for approximately 96% of the administered radioactivity after 72 hours.

Only relatively small amounts of radioactivity, of a similar magnitude, were measured in the blood of a separate group of animals at various time points (0.03, 0.03, 0.02, 0.01 and 0.01% of the administered radioactivity, at 4, 8, 16, 24 and 48 hours, respectively). The half-life in the blood was calculated by the study authors to be approximately 20 hours. The maximum half-life of radioactivity in any tissue was estimated to be 71 hours (for fat).

The findings of this study show that following oral administration, the majority of radio labelled TBBP-A and/or its metabolites were excreted in the faeces within 72 hours. There was limited systemic distribution to the blood (from 4h onwards) and to those tissues that were analysed (from 8 hours onwards). Given the faecal excretion profile observed, the fact that the transit time in the gastrointestinal tract of a rat is 12 hours and the biliary excretion data from the previous study (Hakk et al., 2000), it would be expected that the TBBP-A administered in this study would have been absorbed before being excreted via the bile and/or faeces.

There is no information regarding the "missing" radioactivity in animals sacrificed at 8 hours (> 99% of the administered dose) and 24 hours (approximately 65% of the administered dose). A possible explanation is that it is in the gastrointestinal tract. Another possibility is that it is undergoing enterohepatic circulation; however, if this were the case it may be expected that a larger level of radioactivity would be found in the liver. It is also possible that TBBP-A is present in other tissues not analysed in this study.

The earliest time point for which distribution data is available is 4 hours in blood; prior to this there is no information on the whereabouts of TBBP-A, and no significant radioactivity is detected until the 8-16-hour time period in the faeces. Thus, there is uncertainty concerning the fate of TBBP-A prior to its appearance in faeces.

The distribution and excretion of TBBP-A in the pregnant rat has been investigated in a study, which also investigated the effect of TBBP-A on thyroid homeostasis (see Section 4.1.2.10 for details of the thyroid investigations) (Meerts et al., 1999). Pregnant Wistar rats were orally dosed with 0 or 5 mg/kg ^{14}C-ring labelled TBBP-A in corn oil daily on days 10-16 of gestation (the number of animals/group was not documented). Faeces and urine were collected daily from day 10 of gestation. On gestational day 20, rats were sacrificed via ether anaesthesia, and a number of tissues from the dams and the foetuses (liver, skeletal muscle, abdominal fat, placenta, total plasma, forebrain, kidney, lungs, spleen, heart, cerebellum, pancreas and thymus) and the carcasses were collected for radioactivity measurements, assessed by liquid scintillation counting.

The majority of the radioactivity (79.8%) was excreted in the faeces by 48 hours after the final dose, with limited amounts reported to be excreted in the urine (<0.2% of the administered radioactivity). The tissues of the dams and foetuses between them contained 1.2% of the dosed radioactivity; of this, the highest levels in maternal tissues were detected in the carcass (0.37% of the dose) and the liver (0.26% of the dose). The total amount of radioactivity in the foetus was approximately 0.34% of the administered dose); the highest levels in the foetal tissues were detected in the carcass (0.07% of the dose) and liver (0.06% of the dose). The nature of the labelled substance detected in the tissue was not verified in this study; it may have been a metabolite of TBBP-A rather than TBBP-A itself.

The time course of appearance and elimination of TBBP-A in the blood was determined in a briefly reported study in which six male Sprague Dawley rats were orally administered a single dose (presumably gavage) of 500 mg/kg TBBP-A (the vehicle used was not

documented) (Sato et al., 1996. After 1, 2, 4, 6, 12 and 24 hours, blood samples were taken from the animals, and TBBP-A levels were determined by gas chromatography with an electron capture detector. From an analysis of the graphical data it would appear that the TBBP-A concentration increased to a maximum level during the first hour post dosing (approximately 2,750 pg/ml or 0.18 mg/kg), declined rapidly between 1 and 4 hours (to around 400 pg/ml; 2-hour sampling concentration is not shown) and then declined more gradually, approaching zero by 24 hours.

As part of a limited 28-day study, Charles River rats were administered daily dietary doses of TBBP-A (International Research and Development Corporation, 1972). Bromine analysis was performed at 28 days on liver and fat specimens obtained from 5 animals/sex from a control group, and from a 1,000 ppm (60 mg/kg) group. The bromine content in the fat specimens was similar for both groups of animals, indicating no bioaccumulation in fat. The bromine content in the liver specimens was slightly higher in the treatment group compared with the control group.

In a well-conducted 90-day study Sprague Dawley rats received daily dietary doses of 0, 0.3, 3, 30 or 100 mg/kg TBBP-A (The Dow Chemical Company, 1975). As part of this study, on day 90 liver, kidney, skeletal muscle, fat and serum specimens were collected from 2 rats/sex/group for bromine analysis. Specimens were also collected from the same tissues from 2 rats/sex from the 0 and 3 mg/kg groups for bromine analysis on days 10, 20, 30 and 60. On day 90, 12 rats in the 0 and 3 mg/kg group were placed on a recovery diet of control feed; of these animals, 2 rats/sex/group were killed on days 100, 111 and 132. Evaluation of the tissues for bromine did not reveal any difference in bromine concentration between the control and the treatment groups, again indicating no bioaccumulation.

Dermal

No data are available.

Intraperitoneal

TBBP-A [^{14}C] was administered intraperitoneally to 60 female Wistar rats in a single dose of 250 or 1,000 mg/kg in an olive oil vehicle; the site of the ^{14}C label was not stipulated (Szymanska et al., 2001). The animals were housed in metabolism cages. Urine and faecal samples were collected throughout the 72-hour study. Sixteen blood samples per animal were collected from the tail vein; sampling time was not reported. At 1, 4, 12, 24, 48 and 72 hours after exposure 4 animals from each dose group were decapitated and tissues (liver, kidneys, spleen, brain, fat, muscles, adrenals and sciatic nerve) were extracted. The amount of ^{14}C in the red blood cells, plasma, faeces, tissue extracts and urine was determined. Samples of faeces collected over the first 48 hours were analysed and metabolites were identified via gas chromatography/mass spectrometry.

At 24, 48 and 72 hours, the authors report the fate of the radioactivity in urine, faeces and various tissues at both dose levels (results from 4 rats/timepoint). Irrespective of dose, the majority of the radioactivity detected was found in the faeces. At 24 hours, 37 ± 34% and 25 ± 24% of administered radioactivity was eliminated in faeces in the 250 and 1,000 mg/kg groups, respectively; at 48 hours, 61 ± 25% and 43 ± 19% of the administered radioactivity was eliminated, respectively; and at 72 hours, 65 ± 24% and 51 ± 17% of the administered radioactivity was eliminated, respectively. The urine represented a minor route of excretion; for both doses approximately 0.3% of the administered radioactivity was eliminated by this

route by 72 hours. Radioactivity in the blood of the 250 mg/kg animals was reported to be 1.8 ± 0.3%, 4 ± 0.4% and 3.8 ± 0.7% at 24, 48 and 72 hours, respectively (it was not determined in the 1,000 mg/kg group). At 72 hours, post-administration there was some retention in fat (approximately 3-6%) and muscle (approximately 11-14%); the deposition of ^{14}C within the tissues did not appear to be dose-dependent. However, it is documented by the authors of the study that possible errors exist in these calculations, the nature of which were not described. Thus, the calculations of the amount of ^{14}C in the tissues may be inaccurate. Furthermore, other studies have demonstrated very little retention of TBBP-A in the fat or other body tissue, therefore, the potential for bioaccumulation is not considered to be significant. It should also be noted that radioactivity levels were not detected in the digestive tract, intestinal contents, skin, bone and ligaments amongst others.

The authors present graphically radioactivity levels in plasma and red blood cells from the 250 mg/kg group only; in neither case are figures presented as a proportion of the administered dose. Qualitatively, the maximum level of radioactivity in plasma was observed within the first hour following administration; the subsequent decline of radioactivity followed a biphasic profile. The authors calculated half-lives of 0.9 and 230 hours for phase I and II, respectively. In red blood cells, the maximum level of radioactivity was observed 48 hours post-administration; it declined with a monophasic profile and a calculated half-life of 142 hours. At 72 hours post-administration, radioactivity levels in red blood cells were reported to be 10 times higher than those in plasma, however, it is unclear what the relative significance of this is without more quantitative information. Elevated levels were still reported at 10, 15 and 21 days post-administration, but again, the quantitative significance of these findings is unclear.

The yield of ^{14}C-TBBP-A and/or metabolites extracted from the faeces of animals dosed with 250 mg/kg was approximately 89% of the radiolabel present in the faeces. Gas chromatography of the extract produced two peaks on the chromatogram, which mass spectral analysis identified as tribromobisphenol-A and unchanged TBBP-A. Quantitatively these two substances were present in the faeces in a ratio of approximately 1:9.

From the results of this study, it is apparent that, irrespective of the dose, following intraperitoneal administration, the majority of TBBP-A is excreted in the faeces, apparently unchanged. The elimination follows a similar time course to that reported following oral administration.

Studies in humans

A number of studies are available in which levels of TBBP-A have been measured in human serum and in breast milk. These are summarised below.

The concentration of TBBP-A in blood serum from computer technicians in Sweden has been determined to be in the range <1-3.4 pmol/g lipid (<0.5-1.8 µg/kg lipid). TBBP-A was detected in four out of the 19 samples analysed (Hagmar et al., 2000a).

Hagmar et al. (2000b) determined the concentration of TBBP-A in blood serum in four workers from an electronics equipment dismantling plant in Sweden. Samples were collected just before the summer vacation and at various times during the summer vacation. The concentration found was 2-7 pmol/g lipid (1.1-3.8 µg/kg lipid) in the samples taken prior to the vacation. The concentration was found to decrease during the vacation period and a half-life of 2.2 days was estimated for TBBP-A in blood serum.

Hagmar and Bergman (2001) reported that TBBP-A was found in the blood plasma in one out of nine samples from smelter workers in Sweden. The concentration found was 0.76 µg/kg lipid.

A further study of the levels of TBBP-A in the plasma of computer technicians from Sweden has been carried out by Jakobsson et al. (2002). In this study, volunteers from an information technology unit of a hospital, who worked full time with computer systems, were studied. The blood sampling was carried out during 1999 and all samples from ten individuals were analysed for TBBP-A. TBBP-A was detected in eight out of the ten samples analysed, but was present above the limit of quantification (1 pmol/g lipid or 0.54 µg/kg lipid) in only four of these. The median level of TBBP-A found was <1 pmol/g lipid (<0.54 µg/kg lipid) and the range was <1-3.4 pmol/g lipid (<0.54-1.8 µg/kg lipid).

Thomsen et al. (2001a and 2001c) determined the concentration of TBBP-A in blood plasma from individuals in three occupational groups in Norway: electronic equipment dismantlers, circuit board producers and laboratory personnel. The levels found in the various populations were 0.64-1.8 µg/kg lipid (mean 1.3 µg/kg lipid) in the electronic equipment dismantlers, not detected-0.80 µg/kg lipid (mean 0.54 µg/kg lipid) in the circuit board producers and not detected-0.52 µg/kg lipid (mean 0.34 µg/kg lipid) in the laboratory personnel. The limit of quantification of the method used was 0.4 ng/kg plasma. In another study, Thomsen et al. (2001b) found that TBBP-A was present at a concentration around 0.4 ng/kg plasma in plasma samples taken from a hospital in Norway.

A further study of blood serum levels of TBBP-A in populations from Norway has been carried out by Thomsen et al. (2002a). The study used archived samples from six time periods between 1977 and 1999. For each time point a pooled sample from five males aged 40-50 years old was analysed for the presence of TBBP-A. The substance was not found to be present in the samples from 1977 and 1981 (limit of quantification of the method used was around 0.4-1.6 ng/kg serum), but showed a slight increase in concentration over the period 1986 to 1999 (the concentration was 0.44 µg/kg lipid in 1986 rising to 0.65 µg/kg lipid in 1999). The study also looked at pooled samples from eight groups of individuals of differing age and gender collected in 1998. Each groups consisted of 10-14 individuals, and the level of TBBP-A found in these samples was in the range 0.34 to 0.71 µg/kg lipid, with the highest levels being found in the 0-4 year old group.

The level of TBBP-A in blood of Japanese people has been determined by Nagayama et al. (2001). The blood samples were from 54 volunteers (27 males and 27 females) in the age range 37 to 49 years old in 1998. The median and maximum levels found were reported as 2.4 µg/kg lipid and 12.0 µg/kg lipid respectively. Earlier results from this study indicate a mean level of 1.35 µg/kg from the 14 samples analysed at that time (Nagayama et al., 2000).

DeCarlo (1979) found that TBBP-A was present in a sample of human hair taken from an individual living near to TBBP-A manufacturing facilities in Arkansas, United States. The concentration present in one composite sample was 2 µg/kg.

Watanabe and Tatsukawa (1989) investigated the levels of dimethylated TBBP-A (a possible metabolite of TBBP-A (see Section 3, which will be added later) in human fat from Japanese individuals. The substance was not found in any of the five samples analysed. The detection limit for the method used was 20 µg/kg fat.

The concentration of TBBP-A in mothers milk has been determined by Kemmlein (2000). In the study, samples of milk from four individuals (age range 25-37 years old) from the west

Berlin area were analysed. The samples were collected in 1998/1999. TBBP-A was not found in two of the samples but was present at 0.29 µg/kg lipid and 0.94 µg/kg lipid in the other two samples. In addition, a sample of mother's milk from the Faroe Islands was also analysed. The concentration found in this sample was 11.0 µg/kg lipid.

Thomsen et al. (2002b) have also indicated that TBBP-A was present in breast milk. The sample analysed appears to have been a pooled sample from Norwegian mothers collected in 2001. The concentration of TBBP-A found was 0.067 µg/kg lipid (67 pg/g lipid). The lipid content of the sample was 2.6% and so this concentration is equivalent to a whole milk concentration of 0.0017 µg/kg. In addition, the level of TBBP-A in cow's milk (collected directly from a milk transport vehicle) was 0.013 µg/kg lipid (13 pg/g lipid). The lipid content of this sample was 3.9% and so this concentration is equivalent to a whole milk concentration of $5.1 \cdot 10^{-4}$ µg/kg.

The levels of dimethyl-TBBP-A in mothers milk from Norway has been reported to be in the range ~0.010-0.10 µg/kg lipid (~10-100 pg/g lipid). The samples were collected in 2001 from a coastal area (Tromsø), a rural inland area (Hamar), and an industrialised area with a known dioxin source (Skien/Porsgrunn). Each sample consisted of a pooled sample of milk from ten to twelve mothers. In addition, individual samples were analysed from mothers from Oslo living near to a municipal waste incinerator (again the samples were collected in 2001). The origin of the substance was unknown although it was thought that it may have originated from biological methylation of TBBP-A or from a minor/infrequent use of the substance itself as a flame retardant (Thomsen et al., 2003).

It is noted that a toxicokinetic study in humans has been undertaken as part of the EU FIRE (Flame retardants Integrated Risk assessment for Endocrine effects) project. However, the study report is currently not available to the rapporteur.

Summary of toxicokinetics

The available data indicate that TBBP-A is absorbed in humans given that it has been detected in serum samples of both occupational and non-occupational groups. There is also evidence that once absorbed, TBBP-A and/or its metabolites can be excreted via breast milk.

In experimental animals, toxicokinetic data are available in the rat only. Following oral exposure, 100% of the administered dose of TBBP-A is absorbed from the gastro-intestinal tract. Toxicokinetic studies following inhalation and dermal exposure have not been conducted. With respect to inhalation, the particle size of TBBP-A indicates that very little will be respirable (only 4% < 15 µm) and thus be available for absorption through the lungs. The majority of the particles will deposit in the nasopharyngeal region of the respiratory tract and then be swallowed (a realistic estimate is approximately 70%), while the remainder are likely to be exhaled. Therefore, it is estimated that approximately 75% of TBBP-A particles will be absorbed following inhalation exposure, the majority (70%) through the gastrointestinal tract. Thus, data from oral exposure studies are important for understanding potential health hazards following inhalation exposure. Regarding dermal exposure, the low water solubility, the high *n*-octanol/water partition coefficient (5.9), and the high molecular weight (>500) of TBBP-A, suggest dermal absorption would be low. In view of this a default value of 10% will be assumed for dermal exposure, as indicated in the Technical guidance Document (TGD).

Similarly, information is available on distribution, metabolism and excretion following exposure via the oral route only. Once absorbed, little data are available on the distribution of TBBP-A prior to 8 hours post-administration. From this time point general systemic distribution of TBBP-A (and/or its metabolite(s)) appears to be low (based on the tissues analysed). Quantitative measurements in blood indicate very little of the administered TBBP-A and/or its metabolites are present from 4 hours onwards. It has been postulated that one possible explanation for the low systemic distribution is extensive first pass metabolism of TBBP-A; however, if this were the case it would be expected that the majority of TBBP-A would be excreted as a metabolite in the bile, certainly within 24 hours post-administration. The data do not support this. A more detailed investigation would be required to confirm this hypothesis. Enterohepatic recirculation may also be occurring. However, no significant levels of TBBP-A have been detected in the liver and the blood kinetics have not shown the secondary peak typical of enterohepatic circulation. Also, no analyses of the gastrointestinal tract have been conducted prior to 72 hours. Thus, there is a significant gap about what is known of the fate of TBBP-A between being absorbed and appearing in the faeces.

Analysis of biliary excreta suggests some (up to 30% of the administered dose) metabolism occurs, largely by glucuronide conjugation, although limited sulphate conjugation also occurs.

Following oral administration, TBBP-A and /or its metabolites are excreted predominantly in the faeces (approximately 95% of the administered dose) within 72 hours post-administration, with only a small amount (< 1%) being eliminated through the urine. Following intraperitoneal administration, a similar faecal excretion profile is reported, though characterisation of the faecal radioactivity revealed that the majority appeared as unchanged parent compound.

As the vast majority of TBBP-A is excreted within 72 hours of administration, there is no evidence to suggest that it has the potential to bioaccumulate.

One toxicokinetic study in pregnant animals is available which indicates no significant transfer of TBBP-A or its metabolites to the foetus.

Views expressed by other Member States

One or two Member States expressed concern over the oral absorption of undissolved TBBP-A particles, particularly when administered as a suspension at high dose levels. In the opinion of these Member States, there was some uncertainty as to whether 100% of the administered dose would be absorbed at these higher dose levels and consequently whether the dosing of particles in suspension will underestimate the toxicity. However, the majority of Member States agreed with the position of the UK rapporteur that, although this concept is important, the data do not allow a quantitative estimate of oral absorption at such high dose levels to be determined. Therefore, it was agreed to assume that 100% of an orally administered dose of TBBP-A is absorbed.

4.1.2.2 Acute toxicity

Inhalation

The acute inhalation toxicity of TBBP-A was investigated in a study in which groups of 10 Wistar rats, NMDI mice and guinea pigs (5 male and 5 female of each species) were

exposed whole body in an inhalation chamber for 8 hours to an aerosol of 0.5 mg/l TBBP-A (International Bio-Research, Inc., 1967b). The aerosol was produced by an aerosol apparatus (Draeger/Lubeck) and a continuous airflow was maintained throughout the 8 hours. The rationale for this exposure concentration was not indicated and the report failed to provide droplet size information. No toxic effects were observed during exposure or during the 48 hour post exposure period, after which time the animals were sacrificed. On gross autopsy no treatment related pathological lesions were observed.

In a second inhalation study, 10 male albino rats (Dublin strain) were whole body exposed in an inhalation chamber to 1.3 mg/l TBBP-A aerosol for one hour (Hill Top Research, Inc., 1966). The TBBP-A aerosol was introduced into the chamber atmosphere by bubbling the intake air through molten TBBP-A. During the 14 day observation period no deaths occurred and no other signs of toxicity were reported. At the end of this period animals were sacrificed, but no other information was documented.

Whole body exposure of rats to aerosol concentrations of 1.3 mg/l for 1 hours or 0.5 mg/l for 8 hours produced no mortality and on necropsy no gross pathological lesions were observed. Thus, overall, the results of these studies indicate that the acute inhalation toxicity of TBBP-A is low.

Oral

Rat

Ten Sprague Dawley rats (5 male and 5 female) received a single gavage dose of 5,000 mg/kg TBBP-A in 0.25% methylcellulose (Pharmakon Laboratories, 1981a). This study was conducted in accordance with GLP and to current regulatory standards. During the 14-day observation period no animal died. Moreover, no animal demonstrated any other signs of toxicity. At necropsy no treatment related gross lesions were observed.

In a very briefly reported study (Leberco Laboratories, 1958a) in which 10 Holtzman rats (sex not stated) received gavage doses of 50 mg/kg TBBP-A, no deaths were observed within the 48-hour observation period. No information was given regarding the presence or absence of other signs of toxicity and/or necropsy findings.

In a poorly reported study the hepatotoxicity of a number of different brominated flame-retardants was evaluated, one of which was TBBP-A (Szymanska, 1995). Groups of 4-6 male Wistar rats were administered a single dose of 500-1,000 mg/kg TBBP-A via the oral and intraperitoneal route (see below). Control animals either received no injection or were injected with sunflower oil. Animals were sacrificed at 2, 4, 12, 24, 48, 72, and 120 hours post dosing and serum glutamate-pyruvate transaminase (GPT) and L-γ-glutamyl-transferase (γ-GT) activity and triglycerides (TG), liver glutathione (GSH) and malondialdehyde (MDA) levels were determined. No adverse findings were reported following exposure to TBBP-A.

Seven groups of 5 male albino rats (Dublin strain) were administered gavage doses of 100, 220, 460, 1,000, 2,150, 4,640 and 10,000 mg/kg TBBP-A as 10 or 50% v/v suspensions in corn oil (Hill Top Research, Inc., 1966). During the 14 day observation period, 2 animals in the 10,000 mg/kg (10 g/kg) group died, the remaining animals were sacrificed on day 14. No other information was reported.

In a later study (International Bio-Research, Inc., 1967a), which was also briefly reported, 10 Wistar rats (5 male and 5 female) were given a single 50,000 mg/kg (50 g/kg) dose of TBBP-A by gavage. All animals became slightly to moderately apathetic, and within 5 hours of dosing, three animals died. However, autopsy of these decedents and the remaining animals at 14 days revealed no significant treatment related lesions.

In a very briefly reported range finding study, female rats (strain not stated, 2 animals per dose level) were administered oral doses of 250, 500, 1,000, 2,000 and 4,000 mg/kg TBBP-A as a 20% solution in corn oil (The Dow Chemical Company, 1958). No deaths occurred. However, at autopsy observations described as "slight liver damage" and "questionable kidney damage" were reported at 1,000 mg/kg and moderate liver and kidney damage at 2,000 mg/kg and 4,000 mg/kg (no details were given regarding the nature of the damage nor on the numbers of animals affected). The absence or presence of pathology at 500 mg/kg and below was not documented, but it is presumed that in the absence of reporting, no effects were seen. Given that no other studies, including studies conducted to current regulatory standards, and/or using higher dose levels, have reported liver or kidney toxicity, this isolated finding is considered not to be reliable.

Overall, the results of these studies indicate that the acute oral toxicity of TBBP-A is very low and the oral LD_{50} in the rat is greater than 50,000 mg/kg (50 g/kg).

Mouse

Thirty male and thirty female CD1 mice were administered gavage doses of 1,000, 1,585, 2,512, 3,980, 6,308 and 10,000 mg/kg of TBBP-A in corn oil (five mice of each sex per dose level) (International Research and Development, Corporation, 1978a). During the 14-day observation period no deaths occurred. No other details were provided.

In a second study in mice (Israel Institute for Biological Research, 1978), male mice of the Ness Ziona strain were administered doses of 2,900, 3,600, 4,500, 5,600, 7,000 mg/kg TBBP-A in polyethylene-glycol by gavage. Each dose was administered to six mice. No animal died and no other toxic signs were observed during the 14 day study period. No other details were provided.

Overall, the results of these studies indicate that the acute oral toxicity of TBBP-A is low and the oral LD_{50} in mice is greater than 10,000 mg/kg (10 g/kg).

Dermal

In an acute dermal toxicity study which was well reported and conducted in accordance with GLP, a dose of 2,000 mg/kg TBBP-A was applied to the abraded skin of 10 New Zealand rabbits (5 male and 5 female) (Pharmakon Laboratories, 1981b). The compound was slightly moistened with physiological saline and was applied occlusively. After a 24-hour exposure period, slight erythema and oedema were observed in one male animal. No deaths occurred, no other signs of toxicity were observed in any rabbit during the 14-day observation period, and at terminal necropsy no visible lesions were evident.

In a poorly reported study, a dose of 200 mg/kg was applied to the clipped backs of 10 female rabbits (strain not stated) (Leberco Laboratories, 1958b). No details were given as to whether the test substance was moistened or whether a vehicle was used to ensure good skin contact or on whether or not the application site was occluded. At the end of the 24-hour exposure period all animals had a definite erythema. However, at the end of the 48-hour observation

period the appearance of all animals was normal, all animals survived this period and no other signs of toxicity were reported. No other details were provided.

TBBP-A was applied to the clipped abdominal skin of 4 groups of four albino rabbits/sex (strain not stated) (Hill Top Research, Inc., 1966). The skin of two rabbits in each group was abraded. The substance was moistened with corn oil and applied semi-occlusively as a paste at doses of 1,000, 2,150, 4,640 and 10,000 mg/kg. The exposure period was 24 hours and the observation period 14 days. Two animals died, one with intact skin from the 1,000 mg/kg group on day 13, and one with abraded skin from the 4,640 mg/kg group on day 6, but in the absence of a dose response relationship these mortalities are not considered to be treatment related. Whereas 6/7 of the surviving animals in the two lower dosage groups gained body weight, 5/7 of the surviving animals in the two higher dosage groups lost weight. At the end of the 14-day observation period the animals were sacrificed. No other information regarding signs of toxicity or of any gross or histopathological examination was reported.

Overall, the results of these studies indicate that the acute dermal toxicity is low and that the dermal LD_{50} is greater than 10,000 mg/kg (10 g/kg).

Intraperitoneal

In a poorly reported study TBBP-A [^{14}C] was administered via the intraperitoneal route to 60 female Wistar rats in a single dose of 250 or 1000 mg/kg in an olive oil vehicle (Szymanska et al., 2001). Sixteen blood samples per animal were collected from the tail vein, however, it was not reported at what time points these samples were collected. At 1, 4, 12, 24, 48 and 72 hours after exposure 4 animals from each dose group were decapitated and tissues including the liver were selected for examination. Although in the text there was no mention of a control group of animals, control data were presented graphically in the results section. Besides the determination of metabolic parameters (see Section 4.1.2.1) L-γ-glutamyltransferase (γ-GT) activity was determined in the serum, and haeme oxygenase activity (HOx), total content of cytochrome P450, protein content and the level of glutathione (GSH) were determined in liver tissue.

Compared to control values, at 4 hours post administration there was a statistically significant increase (1.3 fold from the analysis of the graphical data) in the hepatic GSH level in the 250 mg/kg group. However, by 24 and 48 hours there was a slight although non-significant decline in the level in both the 250 and 1,000 mg/kg group. At 12 and 24 hours post administration the activity of haeme oxygenase was statistically significantly higher (1.9 fold from analysis of the graphical data) in the 1,000 mg/kg group and at 24 hours it was higher in both the 1,000 mg/kg and 250 mg/kg groups (2.6 fold and 3 fold respectively, from analysis of the graphical data). In both dosage groups the levels had returned to normal by 48 hours. (It should be noted that in a repeat dose oral study conducted by the same authors, no effect on oxygenase activity was observed at doses up to 1,125 mg/kg). Only minor changes were observed in the γ-GT activity in the serum, protein content in the microsomes and total hepatic P450 cytochrome content.

In a poorly reported study which has been cited in the oral dosing section additional groups of 4-6 male Wistar rats were administered a single dose of 500-1,000 mg/kg TBBP-A via the intraperitoneal route (Szymanska, 1995). As with the oral dosing, animals were sacrificed at 2, 4, 12, 24, 48, 72, and 120 hours post injection and serum glutamate-pyruvate transaminase (GPT), L-γ-glutamyl-transferase (γ-GT) activity and triglyceride (TG) levels, liver glutathione

(GSH) and malondialdehyde (MDA) levels were determined. As with oral dosing no adverse findings were reported.

Summary of acute toxicity

No information is available on the effects of single exposure in humans. However, from the studies in animals the 1-hour LC_{50}, oral LD_{50} and dermal LD_{50} values are in excess of 1.3 mg/l, 50 g/kg and 10 g/kg, respectively. Furthermore, no toxicologically significant signs of systemic toxicity were evident following exposure via any route. As such, it can be concluded that TBBP-A is of low acute toxicity by all routes of exposure.

4.1.2.3 Irritation

Skin

0.5g TBBP-A, moistened with 0.5ml of corn oil, was applied occlusively to an intact area of skin and an abraded area of skin on each of 6 albino rabbits for 24 hours (Hill Top Research, Inc., 1966). At 24 and 72 hours post-application animals were observed for signs of erythema and oedema. No evidence of irritation was observed at either site in any animal.

Similarly, in a second dermal irritation study 6 New Zealand White rabbits (3 males and 3 females) were given 0.5 g TBBP-A (Pharmakon Laboratories, 1981f). The test substance was slightly moistened with physiological saline and applied occlusively for 24 hours to two abraded and two non-abraded sites on each animal. At 24 and 72 hours post-application animals were observed for signs of erythema and oedema. There was no evidence of irritation.

In a further skin irritation study the dorsolateral trunk of 6 albino rabbits was clipped free of hair and 0.5 g TBBP-A was applied to 3 animals with intact skin and 3 animals with abraded skin (Israel Institute for Biological Research, 1978). The exposure was occlusive for 24 hours. At 24 and 72 hours after the application of the test material the skin was observed for signs of irritation (erythema and oedema) and was scored using the Draize Scale. No signs of irritation were seen at the intact skin sites. For the animals with abraded skin the mean score for oedema was 1 and 0 at 24 and 72 hours, respectively, and the mean score for erythema was 0 and 0.3 at 24 and 72 hours, respectively.

In a well-conducted 3 week dermal toxicity study, TBBP-A (applied as a paste in physiological saline) was administered to the backs of New Zealand White rabbits at dose levels of 0, 100, 500 and 2,500 mg/kg/day, 6 hours/day, 5 days/week (International Research and Development Corporation, 1979). Each group consisted of 4 male and 4 female animals. The skin of 4 rabbits per group was abraded twice each week. It was unclear from the study report whether the application was occlusive or non-occlusive.

Signs of dermal irritation were scored before and after each daily application period. At the 100 mg/kg dose on day 3, very slight erythema was elicited in one of the animals with abraded skin and one of the animals with intact skin; it persisted for a total of 5 observations in the animal with abraded skin and 4 observations in the animal with intact skin. At the 500 mg/kg dose a very slight erythema was evident in all animals, generally appearing on day 2 and persisting for 1-3 days. At the 2,500 mg/kg level very slight erythema was observed in 6/8 rabbits. In most rabbits it appeared on day 1 and was intermittent persisting for "several days" in 2 rabbits, and 10 days in 1 rabbit.

In a very briefly reported range finding study TBBP-A was applied undiluted to intact and abraded abdominal skin of a single rabbit and as a 10% solution in Dowanol DPM (Dipropylene Glycol Monomethyl Ether) to intact and abraded abdominal skin of a second rabbit (Biochemical Research Laboratory, 1958). A 10% solution was also applied to intact skin on the ear of the second rabbit. Where the skin was abraded, the test material was applied on three consecutive days; where it was applied to intact skin it was done so on 10 consecutive days. No further information regarding the study design was documented.

The undiluted material had no effect on the intact skin. Although the test report concluded no irritant effect on the abraded skin the test data presented indicated the presence of scabbing and scarring; although it is not clear, it is probable that these were a direct consequence of the abrasion procedure rather than TBBP-A treatment. The 10% solution applied to the intact skin on the ear of the one animal caused an "erratic" hyperaemia during week 1, and exfoliation during week 2. The ear returned to normal within 14 days. The 10% solution also caused a slight to moderate hyperaemia and exfoliation during week 2 when it was applied to the intact abdominal skin. The test report concluded that "essentially" no irritation was observed following application to the abraded skin. However, as with the undiluted material the test data presented indicated the presence of scabbing and scarring; again, although it is not clear, it is probable that these were a direct consequence of the abrasion procedure.

In Section 4.1.2.6, as part of a 28 day dermal toxicity study investigating the potential of TBBP-A to induce "bromacne", 1,000 mg TBBP-A in 1 ml Polylan was reported to be the maximum dose at which irritation did not occur in a preliminary dermal irritation study. No other details of this preliminary study have been reported.

Overall, it can be concluded that TBBP-A is not irritating to the skin.

Eye

In a well-reported and well-conducted study 100 mg TBBP-A was applied to the conjunctival sac of the right eye of 6 (3 males and 3 females) New Zealand White rabbits (Pharmakon Laboratories, 1981c). The eyes were examined at 1, 24, 48 and 72 hours and 7 days post application. In four animals slight conjunctival redness (grade 1) was observed at 1 hour but not at 24 hours. No other signs of ocular irritation were observed at any other time point.

In another well-reported study, 100 mg of TBBP-A was inserted into the conjunctival sac of the right eye of 6 male albino rabbits (Israel Institute for Biological Research, 1978). Prior to the application of the test material the eyes were stained with fluorescein to ensure the absence of pre-existing corneal lesions. At 24, 48, 72 hours and 7 days post application the grade of ocular reaction was recorded. Eyes were also examined after 72 hours and 7 days using fluorescein staining. Soon after the instillation of the test material (exact time not stated) slight lacrimation and conjunctival erythema was observed. These signs had completely disappeared by 24 hours. However, at 48 hours there was a mean score 0.17 for conjunctival redness, 0.3 for conjunctival chemosis and 0.17 for iridial irritation. At 72 hours mean scores were 0.17 for conjunctival chemosis and iridial irritation. All scores were 0 at day 7.

In a study conducted in 1966, 100 mg of TBBP-A was inserted into the left eye of six albino rabbits (Hill Top Research, Inc., 1966). The eyes were examined for signs of irritation at 24, 48 and 72 hours. There was a mean score of 1.5, 0.5 and 0.5 for conjunctival erythema at 24,

48 and 72 hours respectively. A second set of 6 animals was tested. The mean score for conjunctival erythema was 0.8, 0.17 and 0 at 24, 48 and 72 hours, respectively.

The potential of TBBP-A to cause eye irritation was also assessed in a study in which 3 mg of test substance was applied to the conjunctival sac of the left eye of 3 New Zealand White rabbits (International Bio-Research, Inc., 1967a). The animals were examined for signs of eye irritation, within 5 minutes of application, and then at 1 hour, 4 hours and daily for 7 days post application (fluorescein was used to facilitate detection of lesions of the cornea). No signs of corneal, iridial or conjunctival irritation were observed.

In a very briefly reported range finding study, TBBP-A undiluted and as a 10% solution in water was inserted into the right and left eye of two rabbits (one rabbit per test condition) (Biochemical Research Laboratory, 1958). The right eye of each animal was washed (when this was done was not documented) and the left eye remained unwashed. In both the washed and unwashed eyes the undiluted material caused a very slight immediate conjunctivitis (grade 2 which diminished to a grade 1 within 1 hour, and disappeared within 48 hours). In both the washed and the unwashed eyes the 10% solution caused "slight pain", conjunctivitis and "corneal damage" for 3 days. Eyes were completely normal within a week.

Overall, it can be concluded that TBBP-A is not irritating to the eye.

Respiratory tract

The only evidence in relation to irritation of the respiratory tract comes from a 14-day inhalation study (see Section 4.1.2.6 for further details of the study). However, in this study, given the high exposure concentrations used, and the lack of chemical reactivity of the molecule, signs of irritation are interpreted as being most likely to be due to mechanical irritation resulting from exposure to very high dust concentrations (International Research and Development Corporation, 1975).

Summary of irritation

No studies in humans are available regarding TBBP-A's potential to cause skin or eye irritation or sensory irritation of the respiratory tract.

The weight of evidence from animal studies indicates that TBBP-A is not a skin irritant or eye irritant.

The only evidence in relation to irritation of the respiratory tract comes from a 14 day inhalation study. However, in view of the high concentrations used and lack of chemical reactivity of the molecule, these signs are more likely to be a direct consequence of mechanical irritation rather than chemical-induced irritation. As such, TBBP-A is not considered to be irritating to the respiratory tract.

4.1.2.4 Corrosivity

From the data presented in the preceding text it is evident that TBBP-A is not a corrosive agent.

4.1.2.5 Sensitisation

Studies in animals

In a well-reported skin sensitisation study TBBP-A (0.5 g, moistened with ethanol) was applied occlusively to the shaved flanks of 10 female Hartley guinea pigs (Pharmakon Laboratories, 1981e). The test area was divided into 3 application sites; these were dosed on a rotating basis. The animals received 9, 6-hour inductions (applications every other day, 3 times a week for 3 weeks). The treatment sites were examined at 7, 24 and 48 hours post dosing. Concurrently, a positive control group consisting of a further 10 females was treated with 1.0% 2-4-dinitro-chlorobenzene in 80% ethanol. The control group was subjected to the same treatment regime as the test group. The study report did not document the use of a negative control group.

Fourteen days after the last induction animals were challenged using the same concentrations of TBBP-A and 2,4-dinitro-chlorobenzene as had been used for induction. In addition to the substances being applied to the induction site they were applied to a second site, the location of which was not stated but was presumably distinct from the induction site. Forty eight hours after the first challenge animals received a second challenge. After each challenge, treated sites were observed at 7, 24 and 48 hours. Any skin reactions observed at challenge were compared to those observed at induction.

A positive response was elicited at the first and second challenge in the positive control group. No irritation was elicited at either induction or challenge in the group exposed to TBBP-A.

Although this study can be criticised for its absence of a negative control, the fact that the result of the study was negative would tend to diminish the importance of this criticism. Moreover, the validity of the negative result is supported by the performance of the positive control and the fact that animals received 9 induction doses of the undiluted test substance and two challenge doses were applied, factors which would tend to enhance the potential for detecting a sensitisation response.

In a reasonably well reported, but unconventional study the potential of TBBP-A to cause skin sensitisation in 12 male albino guinea pigs was evaluated (International Research and Development Corporation, 1978b). The guinea pigs were divided into 2 groups, a treatment group of 8 animals and a positive control group of 4 animals. The test substance (0.1% TBBP-A in 0.9% sodium chloride solution) or positive control substance (0.1% 2,4-dinitro-1-chlorobenzene in a 0.9% sodium chloride solution) were injected intradermally into a shaved area on the right flank. Rather than using a separate group of animals, the negative control (0.9% sodium chloride solution) was injected into a shaved area on the left flank of all 12 animals. The test and control substances were injected every other day (3 times a week) until each animal had received 10 inducing doses. At 24 and 48 hours post injection, the injection sites were scored for the diameter and the intensity of any erythema and the height of any oedema.

Two weeks following the final inducing dose, a challenge dose was administered intradermally (from the study report it was unclear whether or not the challenge concentration was the same as the induction concentrations). Reactions to the challenge dose were scored after 24 and 48 hours. The substance was considered to be a sensitiser in an animal if the score at challenge was greater than the average score for the 10 inducing doses.

Three treated animals showed a mild skin reaction at the induction site, no treated animal showed a skin reaction at the challenge site. In contrast, all animals receiving 2,4-dinitro-1-chlorobenzene had erythema and oedema at the challenge site which was greater than that observed at the induction site. Skin reactions were negative in all animals at the induction and challenge sites of sodium chloride solution alone. Although the result of this study is negative, the possibility that it is a false negative cannot be excluded. The test substance failed to provoke skin reactions in all but three animals at induction; to maximize the ability of the test substance to elicit a reaction, the dose at induction should be sufficient to elicit an irritant response.

Studies in humans

In a modified Draize multiple insult test, approximately 3 to 5 mg of TBBP-A (50-70% concentration) was applied occlusively to the upper arm of 54 human volunteers (International Research and Development Corporation, 1978d). The TBBP-A was mixed with water to produce a 'thick slurry' which was applied as a paste every other, or every third day (total application period 48-72 hours), for a total of 10 applications. The same site was used for each application. Any residual material present at the end of an application period was wiped off, and the site was examined for the presence of a skin reaction. Ten to fourteen days after the 10^{th} application the subjects were re-exposed to the test material for 48 hours. A different site (location not stated) was used for this challenge dose. The site was then examined for skin reactions at 48 and 72 hours post application.

During the induction phase, 1 subject had either a low grade erythema or a 'questionable' reaction following applications (a 'questionable' reaction was defined as one whose presence was questionable or one which was not considered to be a true irritant reaction). In addition 3 other subjects had 'questionable' reactions. Following the challenge phase, 1 subject had a low-grade erythema when the patch was removed. However, this was thought by the authors of the study to be an irritant reaction aggravated by the tape. Overall, the results of this study demonstrate that TBBP-A was not a skin sensitiser in these 54 subjects.

Respiratory sensitisation

No data are available.

Summary of sensitisation

The available studies in humans, from a multiple insult test, do not provide any evidence that TBBP-A is a skin sensitiser. In addition, despite widespread occupational use of TBBP-A, there are no case reports of skin sensitisation. Similarly, despite its widespread occupational use there are no case reports of respiratory sensitisation.

Although both animal studies possess methodological weaknesses it is considered that the sensitisation potential has been adequately tested. Thus, from the studies in animals TBBP-A is not considered to be a skin sensitiser. No animal studies have investigated the respiratory sensitisation potential of TBBP-A, although the absence of significant skin sensitisation potential and the generally unreactive nature of TBBP-A suggest that it would not be a respiratory sensitiser.

Taking all of the strands of evidence into account, it is considered that the sensitisation potential of TBBP-A has been adequately examined. TBBP-A is considered not to be a skin or respiratory sensitiser in humans.

4.1.2.6 Repeated dose toxicity

Studies in animals

Inhalation

In a 14 day inhalation study rats (strain not stated) were whole body exposed for 4 hours/day, 5 days/week for 2 weeks to an atmosphere containing TBBP-A dust at concentrations of 2, 6 or 18 mg/l (particle size information was not documented) (International Research and Development Corporation, 1975). A control group of animals was exposed to air only using the same regime. Each of the 4 groups (3 treatment groups and the control group) consisted of 5 male and 5 female animals. Prior to, throughout and immediately following the exposure period animals were observed for changes in behaviour and appearance. On day 14, blood and urine samples were obtained from the animals in the control and 6 and 18 mg/l groups for clinical chemistry and urinalysis, all animals were sacrificed and necropsied, and a wide range of tissues were prepared for histopathology from the 6 and 18 mg/l groups.

In the 6 and 18 mg/l groups, excessive salivation and a clear nasal discharge were observed in all animals, and nasal porphyrin discharge and excessive lacrimation were observed in most animals. These observations showed a dose dependent pattern; in the 2 mg/l group excessive salivation was the only adverse sign, occasionally observed in approximately 50% of the animals. Overall, given the lack of chemical reactivity of the TBBP-A molecule, these effects are most likely to be due to mechanical irritation caused by high dust concentration. No animal died during the study, body weight and food consumption were similar for control and treatment groups and there were no treatment-related changes in haematological, clinical chemical and urinary parameters.

At gross necropsy no compound-related lesions were observed. Although decreases in mean absolute (86%, 87% and 87% of control values at 2, 6 and 18 mg/l, respectively) and relative liver weights (84%, 82% and 83% of control values at 2, 6 and 18 mg/l, respectively) were reported in females only, of all three treatment groups, there was no dose-response relationship. In addition, only the decreases in relative weight were statistically significant. Similarly the mean absolute weight and relative weight of the thyroid and parathyroid were slightly increased in all three male treatment groups; however, this was not statistically significant or dose related, and thus considered to be of no toxicological significance. No substance-related histopathological lesions were observed in the liver, thyroid and parathyroid or any other examined tissue.

Overall, there is no evidence for treatment-related systemic toxicity up to the highest dose of 18 mg/l. Some evidence of local irritation` of the eyes and the upper respiratory tract, probably as a consequence of mechanical irritation caused by the very high dust concentration, was seen at all dose levels.

Oral

In a study conducted in accordance with GLP and OECD guidelines the sub-chronic toxicity of TBBP-A was evaluated (MPI Research, 2002a). Rats were administered daily gavage doses of 0, 100, 300 or 1,000 mg/kg/day TBBP-A in corn oil for 13 weeks; these dose levels were selected on the basis of data from previous studies. The 100 and 300 mg/kg groups consisted of 10 animals per sex, and the 0 and 1,000 mg/kg groups of 15 animals per sex (5 animals per sex in the latter 2 groups were evaluated over a six week post-treatment period). Animals were observed daily for survival, injury and availability of feed and water. Detailed physical/clinical and neurobehavioral evaluations and measurements of body weights and food consumption were made weekly. A detailed functional observational battery (FOB) was conducted pre-test and at week 12. Motor activity (MA) was also assessed at week 12. Ophthalmoscopic examinations were conducted pre-test, at 13 weeks and at the end of the post-dose recovery period. Other evaluations conducted at the latter two times were haematology, clinical chemistry, urinalysis, organ weights and pathological examinations (macroscopic and microscopic). Thyroid hormone levels were also evaluated in animals at day 33 (~ 5 weeks), 13 weeks and at the end of the recovery period.

During the study five female animals died, 2 in the control group and 3 in the 1,000 mg/kg group. A fourth female in the 1,000 mg/kg group was euthanised in extremis. Necropsy findings for animals in the 1,000 mg/kg group suggested that the deaths were the result of dosing injuries, rather than being substance-related. All other animals survived to the scheduled termination; however, 6 female rats (2 in the control group, 1 in the 100 mg/kg group, 1 in the 300 mg/kg group and 2 in the 1,000 mg/kg group) died soon after the final bleed. In the absence of a dose response relationship these deaths are also not considered to be treatment-related.

No neurobehavioural effect of treatment with TBBP-A was evident from the weekly evaluations and from the FOB evaluations. No toxicologically significant effects of treatment were evident from the MA evaluations, and there was no effect on body weight gain. For one or more treatment groups there were a number of weeks during the treatment period where the food consumption was statistically higher than the controls; this was transient, and unrelated to the dose level and hence is considered unrelated to treatment. No treatment-related effects were evident from the ophthalmoscopic evaluation.

In the haematological evaluations, the only difference seen between test and control animals was that platelet counts were statistically significantly lower in the 1,000 mg/kg males (by 17%) at the termination of the study. However, at the end of the recovery period levels in the control group and treated groups were similar, and no differences were seen in female animals at any time. It is concluded that the isolated difference in platelet count was not caused by TBBP-A.

In clinical chemistry analysis, at study termination total bilirubin values in the 1,000 mg/kg males and females and the 300 mg/kg females were statistically significantly higher (2-3 fold) than in the controls. Serum alkaline phosphatase (ALP) levels in the 1,000 mg/kg females were also statistically significantly higher (1.7 fold) than in the controls. However, bilirubin and ALP levels in the control and treated groups were comparable at the end of the recovery period. In view of the absence of differences between the test and control groups in other clinical chemistry markers of liver toxicity (e.g. aspartate aminotransferase (AST), alanine aminotransferase (ALT)) and the absence of evidence of liver damage on histopathological examination (see below), it is concluded that the clinical chemistry parameters did not

represent a toxic response. There were no differences between the groups in the urinalysis parameters.

Results of thyroid hormone analysis revealed serum TSH and T3 levels were similar between control and treated animals at all time points in both males and females. In males, a statistically significant decrease in mean serum T4 levels (as measured in ng/dl) is reported at all dose levels on both day 33 (5.0, 3.7, 3.4 and 3.4 for the 0, 100, 300 and 1,000 mg/kg groups, respectively) and day 90 (5.0, 3.3, 2.6 and 3.0 for the 0, 100, 300 and 1,000 mg/kg groups, respectively). However, it is noted that these decreases occurred in the absence of a dose-response relationship. Following the 30-day recovery period serum T4 levels were similar between control males and males of the top dose group. In females, a statistically significant decrease in mean serum T4 levels was reported on day 33 in all treated animals (4.3, 3.3, 3.2 and 3.3 for the 0, 100, 300 and 1,000 mg/kg groups, respectively). Again it is noted that this decrease occurred in the absence of a dose-response relationship. By day 90, mean serum T4 levels were similar between control and treated females; and following the 30 day recovery period, the levels were similar between control and top dose females.

Statistically significantly lower absolute spleen weights (by 15% and 18%) in the males of the 300 and 1,000 mg/kg/day groups, respectively, compared to the controls. However, absolute spleen weights were similar in control males and males of the 1,000 mg/kg/day group following the 30 day recovery period. No differences were observed in relative spleen weights between treated and control animals and no treatment-related effect on female spleen weights were reported. In addition, microscopic examination of the spleen revealed no treatment-related findings. Given this, it is likely that these changes in male spleen weights are chance findings of no toxicological significance. A statistically significantly higher mean relative epididymis weight (by 13%) was reported, compared to controls, in the 300 mg/kg/day group. However, a similar increase was not seen in the top dose group and no treatment-related effects were reported following microscopic examination. Consequently, this is likely to be a chance finding of no toxicological significance.

No other statistically significant changes in organ weights (including liver and thyroid/parathyroid) were reported in treated males and females. Microscopic examination (including liver, thyroid, parathyroid and pituitary) revealed no significant treatment-related findings were reported in either males or females.

The only finding of significance in this study is the decrease in serum T4 levels in treated males on days 33 and 90 and on day 33 only in treated females. However, there was no dose response relationship associated with the finding and it did not persist in females; there were no statistically significant changes in serum levels of TSH or T3 in animals of either sex; and macroscopic and microscopic examination revealed no treatment-related changes in the liver, thyroid, parathyroid or pituitary. The decrease in male serum T4 levels persisted from day 33 through to day 90; if this were to be considered a toxicologically significant event, it would be expected that other parameters of thyroid homeostasis would be affected over this time period given the sensitivity of the rat to perturbations in thyroid hormone levels. However, clearly this is not the case.

The study authors have suggested a possible mechanism to explain the decreased serum T4 levels. TBBP-A has been shown to displace T4 from transthyretin (TTR) (a major T4 binding protein in the rat *in vitro.* If this occurred *in vivo,* once displaced, T4 would be available for metabolism and elimination leading to a reduction in T4 levels. However, *in vivo* TBBP-A has not been demonstrated to bind to TTR (Meerts et al., 1999). In addition, increased

metabolism and elimination of T4 should have produced changes in the liver, which were clearly not detected. Therefore, this suggestion is not considered to be a valid explanation for the changes observed.

At present, there is no mechanistic explanation for the decreases in serum T4 levels reported. However, given the lack of a dose response relationship and the absence of any other relevant thyroid-related effects, these decreases are not considered to be adverse. Therefore, this study showed no clear toxicologically significant adverse effects up to the highest dose tested, 1,000 mg/kg/day.

In a well-conducted 90-day study Sprague Dawley rats received dietary doses of 0, 0.3, 3, 30 or 100 mg/kg/bw/day TBBP-A (The Dow Chemical Company, 1975). The 0 and the 3 mg/kg groups consisted of 21 male and 21 female animals; the remaining three groups consisted of 7 male and 7 female animals. (The 0 and the 3 mg/kg groups were larger groups because they contained a recovery group of 12 animals per sex).

Animals were observed several times per week for changes in appearance and behaviour. Body weight and food consumption were also regularly monitored. On day 86, blood and urine samples were collected for determination of haematological and urinary parameters from the control and the 100 mg/kg group.

On day 90 after being fasted overnight, 7 rats/sex/group were weighed and killed. All animals killed underwent gross pathological examination. In five animals/sex/group organs were weighed and a wide range of tissue sections were examined for histopathological alterations. Tissue specimens of liver, kidney, skeletal muscle, fat and serum were collected from the remaining 2 rats/ sex/group for bromine analysis (see Section 4.1.2.1 for the results). From the 0 and the 3 mg/kg group on days 10, 20, 30 and 60 a further 2 rats/sex were killed and specimens collected from the same tissues for bromine analysis. The twelve remaining rats (i.e. 6/sex) in the 0 and 3mg/kg group were placed on a recovery diet of control feed; of these animals, 2 rats/sex/group were killed on day 100, 2 on day 111 and 2 on day 132. Specimens of liver, kidney, skeletal muscle, fat and serum were collected from these animals for the determination of bromine levels. Liver and kidney weights were determined in all animals killed for the analysis of bromine levels (no technical details of the methods used for the bromine analysis were reported).

There were no treatment related mortalities. No changes in appearance or behaviour were observed throughout the study. There were no significant differences in body weight and no treatment-related differences in food consumption between the control and treatment groups. A slight, statistically significant reduction in the packed cell volume of female rats in the 100 mg/kg group was observed. However, this was still within the normal range for the Sprague Dawley rat and is therefore considered not to be of toxicological significance (there was also a slight reduction in the red blood cell count in this group, although this was not statistically significant). Compared to the control animals a statistically significant decrease (by 17%) in serum glutamic pyruvic transaminase was also evident in the female group receiving the 100 mg/kg dose; in the absence of associated pathology this is not considered to have any physiological or toxicological significance. No treatment related gross pathological changes or histopathological lesions were observed.

Overall, no adverse effects were seen in this study following repeated dietary exposure to doses of TBBP-A up to 100 mg/kg.

In a limited 28 day study rats (strain not stated) were administered dietary doses of 0, 1, 10, 100 and 1,000 ppm TBBP-A (~ 0.07, 0.7, 7.2 and 75 mg/kg/day in males, respectively , and 0.07, 0.77, 7.4 and 72 mg/kg/day in females respectively) (International Research and Development Corporation, 1972). Each group consisted of 25 male and 25 female animals. After 4 weeks of compound administration and at 2, 6 and 12 weeks post-administration 5 male and 5 female animals from each group were sacrificed and subjected to gross pathological examination. Histopathological examination was limited to the liver, kidney and thyroid sections in animals sacrificed at 4 weeks. Bromine analysis was also performed at 4 weeks on liver and fat specimens obtained from the control rats and the rats in the 1,000 ppm group (see Section 4.1.2.1.; no technical details of the methods used for the bromine analysis were reported).

During the study there was an absence of treatment related signs of toxicity and at necropsy no treatment related lesions (gross or microscopic) and/or organ weight variations were observed.

In a poorly reported study gavage doses of TBBP-A were administered daily to male Sprague-Dawley rats for 4 weeks (Sato et al., 1996). Six groups of 3 male animals were administered doses of 0, 0.1, 0.3, 1.0, 3.0, 10 mg/kg (the 'low dose' experiment) and six groups of 3 animals were administered doses of 0, 10, 30, 100, 300 and 1,000 mg/kg (the 'high dose' experiment); Dimethyl sulfoxide (DMSO) was used as the vehicle. The body weight of each animal was measured daily. Blood was taken at 2-4 day intervals up to day 16 and the hematocrit value was determined. After 4 weeks the animals were sacrificed and blood was collected. Blood urea nitrogen concentration and cholinesterase activity were measured, and the kidneys and liver were weighed. In the high dose experiment clotting time and cholesterol concentration were also measured. No histopathology was conducted.

In the high dose experiment a statistically significant decrease in body weight gain was observed after day 11 in the 1,000 mg/kg group (in excess of 15%), and a statistically significant dose related decrease in body weight gain in all groups at day 28. From the graphical data it was evident that the latter ranged from approximately 10% in the 10 mg/kg group to 25% in the 1,000 mg/kg group. In the low dose experiment, a statistically significant decrease in body weight gain was reported after day 20, at 0.3, 1.0 and 10 mg/kg. From the graphical data it was evident that the reduction in all three groups was approximately 15%. No reductions in food consumption and water intake were observed. No toxicologically significant differences in organ weights, no mortality and no clinical signs of toxicity were reported to have occurred during the study.

After 2 or 6 days statistically significant reductions in the hematocrit value in the 10 to 1,000 mg/kg groups were apparent, but then recovery was observed at doses below 300 mg/kg. However, it should be noted that these reductions were not dose related and the values were within the normal range for rats. They are therefore not considered to be of toxicological significance. No other toxicologically significant effects were observed.

Overall, from the results of this study it is evident that the only potential toxicologically significant effect was a reduction in body weight at 0.3 mg/kg and above. However, this finding is not consistent with other studies. Moreover, in view of the poor reporting of the study its findings should set aside in favour of the more robust studies and transparent data.

A study was conducted with the aim of evaluating the influence of TBBP-A on the liver of animals on repeated exposure, with special attention to any effect on heme metabolism

(Szymanska et al., 2000). The study was performed using Wistar rats. A pilot study was performed in which male and female animals (group sizes not stipulated) were administered daily gavage doses of 375, 750 and 1,125 mg/kg TBBP-A for 7 days. However, the results were not informative. In the main study female animals (4 to 5 per group) were administered daily gavage doses of 10, 50 and 250 mg/kg TBBP-A for 7, 14, 21 and 28 days. The control animals (3 to 4 per group) were either given sunflower oil by gavage or were untreated. Animals were sacrificed 24 hours after the last dose.

The indices for hepatotoxicity that were used were: alanine aminotransferase (ALT), triglyceride (TG) and L-γ-glutamyl-transferase (γ-GT) levels in the serum; total content of cytochrome P-450 in the liver; levels of glutathione (GSH) and malondialdehyde (MDA) in the liver. The measures of disturbances in heme synthesis used were: urinary excretion of porphyrins (octa-, hepta-, hexa-, penta-, and tetracarboxyporphyrins); indirect measures were: activity of 5-aminolevulinate synthase (ALA-S), 5-aminolevulinate dehydratase (ALA-D), urinary excretion of 5-aminolevulinic acid (ALA-U). Catabolic activity was measured by hepatic heme oxygenase activity (HOx). Liver histology was also evaluated using light microscopy.

In the main study, although slight differences between the groups in urinary and haematological parameters were observed they were not dose-related nor of statistical or toxicological significance.

A tendency for increasing urinary porphyrin concentration was evident, although in a rather irregular fashion; only one observation can be made with confidence: with the exception of tetracarboxyporphyrin, all porphyrins were statistically significantly elevated at 14 days in the 250 mg/kg group (by 30-45% in comparison with the controls). However, by 21 days levels approximated those of the control. As such, it is considered to be a chance finding (if it were a real effect it would be expected to remain). No other statistically significant changes were reported in the other parameters measured for determining disturbances in heme synthesis, catabolic activity or indices of hepatotoxicity, Histopathological examination apparently showed no necrotic changes; no other details were provided.

In a poorly reported study from which little information can be extracted, the hepatotoxic potential of a number of different brominated flame-retardants was evaluated, one of which was TBBP-A (Szymanska, 1995). Groups of 4-6 male Wistar rats were administered 3 to 7 repeated doses (the dosing interval and number of dose levels were not specified) of 500, 2,250 mg/kg TBBP-A via the oral route (and single doses of 500 to 1,000 mg/kg TBBP-A via the oral and intraperitoneal route, see Section 4.1.2.2). Control animals either received no treatment or were dosed with sunflower oil.

Animals were sacrificed 24 hours after receiving the last dose. Serum glutamate-pyruvate transaminase (GPT), L-γ-glutamyl-transferase (γ-GT) activity and triglyceride (TG) levels, liver glutathione (GSH) and malondialdehyde (MDA) levels and ALA-S and ALA-D activity were determined. The liver was also examined for necrotic changes.

There was little reporting of the effects of TBBP-A apart from the fact that γ-GT activity, and levels of TG and GSH were unaffected by treatment. After 3 doses of 1,000 mg/kg an increase in serum GPT activity was evident; however, the magnitude of the response was not reported nor whether this was a statistically significant increase. Serum GPT activity at dose levels above or below 1,000 mg/kg were not reported and so the relevance of this finding in isolation is unclear. After seven doses of 1,100 mg/kg, a 2-3 fold elevation of MDA was

stated to be present in the liver. Again there was no information reported at other dose levels and so the relevance of this finding in isolation is unclear. A further statement indicates that TBBP-A treatment produced a statistically significant decrease in ALA-D activity. However, no other data were presented to support this and so its relevance is unclear.

Given the lack of detail of both methodology and results provided in this study, no definitive conclusions can be drawn from it.

In a poorly reported study to investigate the effect of TBBP-A on the kidneys, daily gavage doses of 10, 50, 250 mg/kg of the compound were administered in sunflower oil to female Wistar rats for 7, 14, 21 and 28 days (the number of animals per treatment group was not stated) (Frydrych and Szymanska, 2001). Two control groups were used, a vehicle (sunflower oil) control and an untreated control. During the 24 hours after the administration of the last dose the animals were placed in metabolism cages and urine samples were collected. When and how the animals were sacrificed was not reported, but it was reported that kidneys and blood were collected. The creatinine and urea concentrations in the serum, the level of GSH in the kidneys, the concentration of urea and protein in the urine and the number of epithelial cells in the urine (Addis count) were determined.

Overall, no dose related or toxicologically significant effects were noted.

It is noted that a 28-day oral study in rats has been undertaken as part of the EU FIRE project. However, the study report is currently not available to the rapporteur.

Dermal

In a well-conducted 3 week dermal toxicity study, TBBP-A (applied as a paste in physiological saline) was administered to the backs of New Zealand White rabbits at dose levels of 0, 100, 500 and 2,500 mg/kg/day, 6 hours/day, 5 days/week (International Research and Development Corporation, 1979). Each group consisted of 4 male and 4 female animals. The skin of 4 rabbits per group was abraded at the application site twice each week. Collars were used to prevent the ingestion of test material (it was unclear from the study report whether the application was occlusive or non-occlusive).

Animals were observed daily for signs of toxicity. Signs of dermal irritation were scored before and after the application period. Body weights were obtained weekly and haematological, clinical chemical and urinary parameters were determined during the pre-test period and at 3 weeks.

In terms of behaviour, appearance and survival there was no evidence of compound related toxicity. There were no significant signs of irritation (for details see Section 4.1.2.3). Changes in body weight were similar for all groups and no treatment related changes in haematological, biochemical and urinary parameters were observed.

At the end of the administration period animals were sacrificed, necropsied and selected tissues from the control and 2,500 mg/kg group were prepared for histopathological examination. No toxicologically significant compound related lesions were evident at necropsy or on histopathological examination.

A repeated dermal exposure study is available which was designed to investigate the potential for “bromacne” (analogous to chloracne) development in the skin (Pharmakon Laboratories, 1981d). In this study, 0.1 ml of a solution of 0.5, 5 or 50% TBBP-A in Polylan was applied to

one ear canal of 3 groups of rabbits (New Zealand White; 2/sex/group), 5 days /week for 4 weeks. The high dose level, 50% TBBP-A in Polylan (1,000 mg TBBP-A in 1 ml Polylan), was reported to be the maximum dose at which irritation did not occur in a preliminary dermal irritation study. The contralateral ear was used as a control to which 0.1 ml of Polylan was applied. The appearance of "bromacne" were recorded prior to the administration of the test material and on days 7, 14, 21 and 28 post-administration. Gross necropsy was performed on all animals at the termination of the study. Apart from one rabbit in the low dose group that exhibited a slight "bromacne" response on day 7, no other responses were recorded in any other animal. Gross necropsy revealed no treatment-related/toxicologically significant observations.

Based on the results of this study TBBP-A is not considered to be an agent that can cause "bromacne". The type of dermal response investigated in this study is not detectable in conventional repeated exposure studies in laboratory rodents, but can be detected using the rabbit ear or the nude mouse models (Klien-Szanto et al., 1991). It is assumed that this study was conducted because of some structural similarity between the TBBP-A and dioxins; dioxins cause chloracne.

Summary of repeated exposure

No information on the effects of repeated exposure to TBBP-A in humans exists. However, its effects have been assessed from repeated exposure studies in rats and rabbits.

Only one repeat dose inhalation study is available. Exposure of rats to concentrations of up to 18 mg/l for 4-hours/day for 14 days, produced no compound related, toxicologically significant systemic effects. Signs of local irritation to the respiratory tract at ≥ 6 mg/l are most likely to be due to the physical effects of inhaling a very dusty atmosphere, given the lack of chemical reactivity of the TBBP-A molecule and are therefore probably not toxicologically significant.

In a 90-day study conducted in accordance with GLP and OECD guidelines no toxicologically significant effects were seen following oral exposure of up to a dose of 1,000 mg/kg. This is supported by the results of other studies.

In the only conventional repeated dermal exposure study, in which rabbits were dosed up to 2,500 mg/kg, no toxicologically significant compound related effects were apparent.

Furthermore, TBBP-A is not an agent that causes "bromacne" (analogous to chloracne).

Views expressed by other Member States

It is noted that one or two Member States expressed concern regarding the significance of the decreases in T4 levels observed in the rat for human health. However, the majority of Member states agreed with the UK position (described above) that these effects are not considered to be adverse.

4.1.2.7 Mutagenicity

Studies *in vitro*

Bacterial/Yeast systems

Reverse mutation assays

In a well-conducted study, 270 chemicals including TBBP-A were tested for their mutagenicity in the preincubation modification of the *Salmonella*/mammalian microsome assay (Mortelmans et al., 1986). Chemicals were tested and evaluated using *Salmonella* strains TA1535, TA1537, TA98 and TA100 with and without Aroclor 1,254-induced rat and hamster metabolic activation systems. The concentrations of TBBP-A used were 0, 100, 333, 1,000, 3,333, 10,000 μg/plate; precipitation, although no cytotoxicity, occurred at concentrations of 1,000 μg and above. Solvent and positive controls with and without metabolic activation were used. TBBP-A gave a negative mutagenic response; the validity of this result was confirmed in a second independent experiment. Appropriate responses were observed with the solvent and positive controls.

TBBP-A was examined for mutagenic activity in the yeast strain *Saccharomyces cerevisiae* D3 and in six strains of *Salmonella typhimurium* (TA92, TA98, TA100, TA1535, TA1537 and TA1538) both in the presence and absence of metabolic activation (The DOW Chemical Company, 1985). No increase in the number of revertant colonies was observed at concentrations of 5, 10, 50, 100, 500 and 1,000 μg/plate and 0.01% and 0.0075% TBBP-A in the bacterial assay and yeast assay, respectively; toxicity, evident as a reduction in the number of colonies, was observed at the higher concentrations. Positive and solvent controls gave the appropriate responses.

TBBP-A gave a negative mutagenic response in the yeast strain *Saccharomyces cerevisiae* D3 and *Salmonella typhimurium* (TA92, TA98, TA100, TA1535, TA1537 and TA1538) at concentrations of 0.1, 1, 19, 100 and 500 μg/plate in dimethyl sulphoxide (DMSO), in both the presence and absence of metabolic activation (Velsicol Chemical Company, 1977).

TBBP-A was negative in a briefly reported Ames test in the *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 at concentrations of 1, 10 and 100 μg/plate in DMSO, in both the presence and absence of metabolic activation (Israel Institute for Biological Research, 1978).

In a second briefly reported Ames test, TBBP-A was negative in the yeast strain *Saccharomyces cerevisiae* D4 and D3 and in the bacterial strains *Salmonella typhimurium* TA1535, TA1537, TA1538, TA92, TA98 and TA100 at concentrations of 0.25, 0.5, 5 and 50 μg/plate in DMSO, in both the presence and absence of metabolic activation (Litton Bionetics, Inc., 1976).

In two further studies, the mutagenic potential of TBBP-A was investigated in the Salmonella assay using strains TA1535, TA1537, TA1538, TA98 and TA100 (Ethyl Corporation, 1981). In the first study, concentrations of 0.005, 0.015, 0.05, 0.15 and 0.5 mg/plate were used and the assay was conducted in triplicate in both the presence and absence of metabolic activation. Appropriate positive and solvent controls were used. No significant increase in the number of revertant colonies was observed. Toxicity was apparent at the higher concentrations and the results of the positive and negative controls were shown to be within the appropriate range.

In the second briefly reported study, no increase in the number of revertant colonies was observed at concentrations of 0.001, 0.003, 0.01, 0.3 and 0.1 mg/plate TBBP-A in both the presence and absence of metabolic activation.

Mammalian chromosome aberration test

TBBP-A has been tested in a well conducted and well reported *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes (HPBL) in both the presence and absence of an Aroclor-induced S9 activation system (BioReliance, 2001). DMSO was used as the solvent (the test substance was soluble in DMSO up to a concentration of 500 mg/ml).

A preliminary toxicity test was conducted in order to establish the concentrations to be used in the main assay. The main assay was performed by exposing duplicate cultures of HPBL to TBBP-A. The cells were exposed for 4 hours in both the presence and absence of the S9 activation system, and for 20 hours in the absence of S9 activation. The highest dose selected for the evaluation of chromosome aberrations induced at least 50% toxicity (as measured by mitotic inhibition). In the 4 hour exposure assays, the following doses of TBBP-A were employed: 0, 6.25, 25, 100 μg/ml without metabolic activation and 0, 3.125, 12.5 and 50 with metabolic activation. For the 20 hour exposure assay doses of 0, 6.25, 25 and 75 μg/ml TBBP-A were used. Cells were harvested at 20 hours. Appropriate positive and solvent controls were used in all assays. A minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid and chromosome type aberrations.

At no concentration of TBBP-A was the percentage of metaphases with structural and numerical aberrations statistically significantly greater than that of the solvent control. The solvent and positive controls gave the expected responses. It can be concluded that in this assay TBBP-A did not exhibit the potential to induce structural or numerical chromosomal aberrations.

Intragenic recombination in mammalian cells

The ability of a number of brominated flame retardants including TBBP-A to induce intragenic recombinations in mammalian cells has been investigated using the *in vitro* Sp5/V79 and the SPD8 recombination assays (Helleday et al., 1999). The clones employed in these assays have a duplication of the *hprt* gene which gives rise to a non-functional HGPRT protein. Both assays assess the ability of test substances to increase the reversion frequency of the mutant gene to the functional *hprt* gene phenotype and thus the ability of test substances to induce intragenic recombinations.

Cells were incubated for 24 hours with TBBP-A at dose levels of 0, 5, 10, 20, 30 and 40 μg/ml in DMSO (final concentration 0.2%) in the SPD8 assay and 0, 10, 20, 40, 70 μg/ml in DMSO (final concentration 0.2%) in the Sp5 assay; at 70 μg/ml, precipitation of the test substance was observed. Cloning efficiency and growth inhibition were assessed as a measure of cytotoxicity.

TBBP-A did not elicit an increase in the number of revertant colonies in either the SPD8 or the Sp5 assay at doses producing some toxicity (30-50% growth inhibition). No data were presented regarding the effects of the positive control, camptothecin (100 nm).

Studies *in vivo*

No data are available.

Summary of mutagenicity

A number of *in vitro* tests using bacterial strains (Ames test) and yeast, with and without metabolic activation, have been performed. TBBP-A has produced consistently negative results. The way in which these studies were conducted was largely compatible with current regulatory guidelines. Similarly, in a well-conducted chromosomal aberration study using human peripheral lymphocytes and in an unconventional *in vitro* recombination assay, TBBP-A tested negative.

No *in vivo* data are available.

Overall, in view of the clearly negative *in vitro* studies, and no structural indications for any genotoxic potential, there are no concerns for genotoxicity.

4.1.2.8 Carcinogenicity

There are no studies available. However, there is no evidence from the available *in vitro* mutagenicity data and no indications from repeated exposure studies (for example, proliferative changes) of concerns for carcinogenicity.

4.1.2.9 Toxicity for reproduction

Effects on fertility

The effects of TBBP-A on reproductive performance and fertility were evaluated in a GLP and OECD compliant 2-generation study (MPI Research, 2002b, 2003). Included in the study was an assessment of the potential developmental neurotoxicity of TBBP-A in the F_2 generation. Sprague-Dawley rats (30 animals/sex/group) were administered 0, 10, 100 or 1,000 mg/kg/day TBBP-A in corn oil by gavage. The F_0 generation was treated during a premating period of 10 weeks and a mating period of 2 weeks. Males and females from each group were randomly paired and co-habited for 2 weeks. Females were also administered the test material during gestation and lactation. F_0 males and females were sacrificed after the mating period and weaning of the F_1 pups, respectively. At weaning, 30 male and 30 female offspring per group were randomly selected for assessment of their reproductive capacity using the same protocol as for the F_0 generation. After selection, the remaining F_1 offspring were sacrificed and subjected to necropsy. At weaning of the F_2 generation, developmental and neurobehavioural assessments (i.e. detailed clinical examinations, motor activity, learning, memory and auditory startle habituation, assessed in 10 pups/sex/group) were performed in addition to neuropathological evaluations (i.e. brain weight and neuropathological evaluation of the brain, spinal cord and peripheral nerves, assessed in 10 pups/sex/group). These data are described under the heading neurobehavioural/ neuropathological studies.

Detailed clinical examinations, body weights and food consumption were recorded regularly throughout the study for the F_0, and retained F_1 and F_2 animals. Sexual maturation (time to vaginal opening and preputial separation) was determined in all retained F_1 animals and all F_2

animals retained for the developmental and neurobehavioural assessments (30 animals/sex/group and 40 animals/sex/group, respectively). After sacrifice, all F_0 and retained F_1 animals were subjected to macroscopic and microscopic examination. The organs examined were the adrenals, brain, gonads (ovary, testis, epididymis), kidney, liver, pituitary, prostate, seminal vesicle with coagulating glands, spleen, thymus, tissue masses, uterus (both horns) with oviducts and cervix and vagina. It is noted that the thyroid was not included in the examination. Reproductive tissues were evaluated microscopically for all F_0 and retained F_1 animals in the control and 1,000 mg/kg groups. Sperm evaluations (motility, caudal epididymal sperm counts and morphology) and a count of primordial follicles were conducted in F_0 and retained F_1 males and F_0 and retained F_1 females, respectively. Serum T_3, T_4 and TSH concentrations were also determined in 10 animals per sex per group in the F_0 and retained F_1 animals several days prior to sacrifice.

In the parental animals from the F_0 and F_1 generations, the only treatment-related effect observed was a statistically significant decrease (7%) in body weight gain during the pre-mating period (week 1-11) evident in the F_1 males at 1,000 mg/kg. No other treatment-related effect was evident in either the F_0 or F_1 generation, based on evaluations of clinical signs of toxicity, estrous cyclicity, reproductive performance (i.e. mating behaviour and fertility), body weight gain, gestation/lactation body weights or food consumption, gestation length, litter data, or on the macroscopic and microscopic evaluations, organ weights, sperm evaluations, and primordial follicle counts.

No treatment-related effect was evident in either the F_1 or F_2 pups with regard to body weights, clinical findings, sex ratios, survival to weaning, macroscopic findings or organ weight data.

In the F_0 generation, statistically significantly lower mean serum T_4 levels were evident in males of the 100 and 1,000 mg/kg groups (4.70, 5.08, 3.90 and 3.38 ng/dl for the 0, 10, 100 and 1,000 mg/kg groups, respectively) and in females of the 1000 mg/kg group (4.23, 3.45, 3.50 and 2.39 ng/dl for the 0, 10, 100 and 1,000 mg/kg groups, respectively). In the F_1 generation, T_4 levels were statistically significantly lower in both sexes in the 100 and 1,000 mg/kg groups (6.29, 5.98, 3.91 and 3.33 ng/dl in males and 5.00, 4.42, 3.40 and 3.41 ng/dl in females for the 0, 10, 100 and 1,000 mg/kg groups, respectively). A statistically significant lower mean serum T_3 level was evident in F_0 generation males of the 1,000 mg/kg group (102.7, 92.8, 97.5 and 83.2 for the 0, 10, 100 and 1,000 mg/kg groups, respectively). No statistically significant decreases in mean serum T_3 levels were observed in F_0 females or at any dose level in either sex of the F_1 generation. Mean serum TSH levels were comparable to controls in both F_0 and F_1 generation males and females at all dose levels.

Given the absence of any effect on TSH levels, no gross or microscopic changes reported in the pituitary and liver (analysis of thyroid tissues was lacking), the mechanism by which decreases in T_4 levels in males and females of the F_0 and F_1 generations and in T_3 levels in top dose F_0 males only, are occurring is unclear. However, it is deemed that the decreases observed are not toxicologically significant given that there was little impact on other parameters associated with a disruption of thyroid homeostasis in the rat. The study authors suggested that the decrease could be a result of induction of hepatic T_4-uridine diphosphate glucuronyl transferase (UDP-GT), the enzyme involved in the removal of circulating T_4. However, the enzyme levels were not measured and there was no change in liver morphology, therefore the basis for this being the mechanism is weak.

Neurobehavioural/neuropathological studies

At weaning of the F_2 generation, 40 male and 40 female offspring per dose group were retained for neurobehavioural investigations. An additional 20 male and 20 female offspring per dose group were retained for neuropathological examination (i.e. brain weight and neuropathological evaluation of the brain, spinal cord and peripheral nerves, assessed in 10 pups/sex/group). All remaining F_2 pups were sacrificed approximately one week after weaning and subjected to necropsy.

Detailed clinical examinations were performed on 10 pups/sex/group on postnatal day (PND) 4, 11, 21, 35, 45 and 60 and no treatment-related findings were reported.

Neurobehaviour - Motor activity

The motor activity of selected F_2 pups (10/sex/group) was assessed on PND 13, 17, 21 and 60, using a Digiscan Activity Monitor equipped with an electronic analyser-recorder. The animals were placed in an activity chamber for 20 minutes and the following activity was recorded: horizontal and vertical activity counts and total distance travelled. In addition, an emotionality assessment was determined recording defecation, urination, rearing, grooming and backing.

On PND 13, there were no statistically significant differences between controls and treated animals in terms of activity or emotionality.

On PND 17, there were no statistically significant differences between controls and treated male animals in terms of activity or emotionality. In females, a statistically significant decrease in horizontal activity was reported in the 15 – 20 minute segment of the test in the 10 mg/kg/day group, and also over the 20 minute period in the 100 mg/kg/day group (though no differences were reported in any of the 5 minute segments). No statistically significant changes were reported at any other timepoint or dose level. No statistically significant differences between controls and treated females were reported for distance travelled, vertical activity or emotionality. Given the lack of any dose response, the fact that the changes in horizontal activity were not accompanied by a decrease in distance travelled and the lack of any response in males, these statistically significant effects are considered to be chance findings and of no toxicological significance.

On PND 21, there were no statistically significant differences between controls and treated animals in terms of activity or emotionality except for the females of the 100 mg/kg/day group. In the 5 – 10 minute segment and over the 20 minute test period as a whole, horizontal activity and distance travelled were statistically significantly reduced. Given the lack of a dose-response relationship and the absence of any response in males, we consider these effects to be chance findings of no toxicological significance.

On PND 60, no data on distance travelled are presented for either males or females. In females, there were no statistically significant differences between controls and treated groups in terms of horizontal and vertical activity and emotionality. In males, there were no statistically significant effects on vertical activity or emotionality. However, in the 0-5 minute segment of the test, horizontal activity was statistically significantly reduced at both 100 and 1,000 mg/kg/day (76% and 70% of control values, respectively), and during the 5 –10 minute segment in the 1,000 mg/kg/day group only (68% of control values). No statistically significant effects were reported at other dose levels or time periods including over the total 20 minute duration of the test. Given that no effects were reported in females and because no

consistent pattern of changes was observed across animals of various ages (PND 13, 17, 21 and 60) and between sexes, the difference seen for males on PND 60 were thought most likely to be chance findings and unrelated to treatment.

Neurobehaviour - Learning and memory – passive avoidance test

Learning and memory were assessed in selected F_2 pups (10/sex/group) using a Step-through Passive Avoidance Test on PND 22 and 60. The test apparatus consisted of light and dark compartments separated by a mechanical door. Each animal was tested once a day for 3 consecutive days. Each animal was initially placed in the light side and allowed to acclimatise for 30 seconds; the barrier was then removed allowing the animal a 3 minute period in which to move to the dark side. The time spent on the light side was recorded for each session. On the first day of the test, any rat that moved from the light to the dark side was administered an electric shock for 3 seconds. On the second and third days, if the animal moved from the light to the dark side, within the 3 minute period, it was not shocked and the time on the light side was recorded. Animals not moving to the dark side within the time period were returned to their cages.

On day 1 of testing of the PND 22 males, the time spent in the light side was relatively short with no statistically significant difference between control and treated groups. On day 2, the males spent longer in the light side (as would be expected), however, the animals in the 1,000 mg/kg/day group spent statistically significantly less time in the light side compared with control animal. On day 3, there was no difference between the control and treated males. The absence of a consistent response on days 2 and 3 suggests that the difference seen on day 2 is unlikely to represent a treatment-related effect on learning. No statistically significant differences were reported in females between control and treated groups.

On day 1 of testing the PND 60 males, statistically significant reductions in the time spent on the light side were reported between controls and all treated groups. However, on days 2 and 3, no differences were reported. The difference on day 1 arose because only 3/10 control animals crossed from the light to the dark side, whereas between 8/10 and 10/10 animals crossed in the treated groups. The unexpected performance of the control animals on day 1 calls into question the reliability of the test system. No statistically significant differences were observed between control and treated females.

Overall, no treatment-related effect on learning/memory was observed in females. In males, although some differences between control and treated animals were noted, there was no consistent pattern across different days of testing and animals of different age (PND 22 and 60), and therefore these differences are not considered to be treatment-related.

Neurobehaviour - Learning and memory – Water M-maze

The same 10 animals/sex/group employed in the passive avoidance test, were analysed for learning and memory in the water M-maze beginning on PND 110. The test consisted of 10 trials/day for 4 consecutive days to assess short-term memory. The animals were then tested again 5 days later (over 10 trials) to assess long-term memory. Each animal had 60 seconds to complete the maze and was analysed for pass/fail, time to completion and number of errors.

Very few animals failed to complete the maze and effectively there was no difference between the control and treated groups. There was no difference between controls and treated

animals in terms of mean times to complete the maze. On each day on which trials took place the mean time to completion was similar across the groups. There were no overall differences between control and treated groups in mean number of errors in the trials on each day of the trial. The data on day 9 were similar to those on day 4 indicating that like the short-term memory, there was no treatment-related effect on long-term memory.

Neuropathology

In the neuropathological segment of the study, 10 F_2 pups per sex per group were randomly selected for the following assessments: investigation of brain weight on PND 60 and neuropathological evaluation of the brain, spinal cord and peripheral nerves on PND 60. In addition, on PND 60, the thickness of the parietal cortex was measured in 10 males of the 0 and 1,000 mg/kg/day groups and 10 and 9 females of the 0 and 1,000 mg/kg/day groups, respectively (MPI Research, 2003). Additionally, 10 F_2 pups per sex per group were selected randomly for sacrifice on PND 11 for neuropathological evaluation and morphometric measurements, the latter comprising of measurements of the thickness of the parietal cortex, hippocampus, the external granular, molecular and Purkinje/internal granular layers of the cerebellum, and thalamus.

Of the morphometric measurements, differences were seen only for the parietal cortex. A statistically significant decrease in the thickness of the parietal cortex was observed in the F_2 pups at 1,000 mg/kg, sacrificed on PND 11 (1.61, 1.56, 1.49 and 1.23 mm in males and 1.60, 1.46, 1.56, 1.33 mm in females at 0, 10, 100 and 1,000 mg/kg, respectively). Although reductions in the thickness were also seen at 10 and 100 mg/kg/day, the differences did not achieve statistical significance and were not thought to represent a dose-dependent response. No histological changes were evident in the parietal cortex, including degeneration, necrosis, cell loss, demyelination, proliferative changes, or changes in neuronal cell density. On PND 60, no difference in the thickness of the parietal cortex was observed between the control and 1000 mg/kg/d groups in either males (2.13 and 2.09 mm, respectively) or females (2.10 and 2.06 mm, respectively).

There was no treatment-related effect on PND 60 brain weights. Furthermore, no microscopic alterations were observed in the brain, spinal cord, nerves and ganglia in PND 60 F_2 animals.

To summarise, a statistically significant decrease in the thickness of the parietal cortex was observed in F_2 pups of the top dose group on PND 11, however, the same effect was not present in F_2 pups of the top dose group on PND 60. Also, there are no microscopic changes reported in these animals on either PND 11 or PND 60. Therefore, the decreased thickness of the parietal cortex is regarded as a transient or chance finding that is unlikely to be toxicologically significant.

Overall, no effects on fertility or development, including neurodevelopment, or any other effects of any toxicological significance were observed in this study up to a dose of 1000 mg/kg/day. Although this dose level did not produce any general toxicity in the parental animals of relevance to humans, nevertheless, it is considered sufficiently high to adequately investigate the potential reproductive toxicity of TBBP-A by the oral route.

It is noted that an additional 1-generation study has been undertaken as part of the EU FIRE project. However, the study report is currently not available to the rapporteur.

Effects on development

Pregnant Wistar rats (22 to 24 per treatment group) were orally administered 0, 280, 830 and 2,500 mg/kg TBBP-A in olive oil, daily throughout gestation, from day 0 (Noda et al., 1985). The doses were established from the results of a preliminary study in which no toxicologically significant effects were observed at the top dose of 2,500 mg/kg.

On gestational day 20, approximately two thirds of the animals were sacrificed. The major organs were observed for gross pathological lesions, and the number of corpora lutea, the number of implants, the number of surviving fetuses, the number of early fetal deaths (reabsorbed or residual placenta) and the number of late fetal deaths (reabsorbed or dead fetus) were also evaluated. The body weights of surviving fetuses were measured, and the sex of fetuses and the presence or absence of external abnormalities was also noted. Approximately half the fetuses were examined for skeletal abnormalities and the remainder examined for visceral abnormalities.

For the animals that were allowed to deliver their offspring naturally, the gestation period was calculated. The number of live and dead offspring, the sex of the offspring and the presence of any abnormalities were noted. Offspring were kept up until weaning on post-natal day 21, during which time the body weight was measured and the state of growth (for example, as seen in the detachment of the ears, hair growth, eruption of lower incisors and eye-opening) and the general state were observed. Surviving pups were then killed and examined for the presence of any skeletal abnormalities. The dams were also killed on day 21 post-partum, and gross pathological examination of their principal organs was conducted and the number of implants was recorded.

There were no toxicologically significant effects in the treated maternal animals throughout gestation. In the early stages of pregnancy in the TBBP-A treated dams there was a slight increase in body weight gain above that of the control animals; by day eight onwards the increase in body weight gain was similar in all groups. In early pregnancy food consumption was significantly reduced in all of the TBBP-A dosed groups, but from mid pregnancy food consumption was increased in the 2,500 mg/kg group. No other differences were evident during the dosing period. With the exception of kidney stones and the resultant deformation of one kidney in one animal in the 830 mg/kg group (clearly not treatment-related), no abnormalities were observed in the dams on gross pathological examination.

TBBP-A had no effect on the length of the gestation period and no toxicologically significant effects on fetal development. In the fetuses examined on gestational day 20, on external observation, examination of the internal organs and skeletal observations, there were no findings of toxicological significance. In the offspring that were delivered normally and reared to day 21, no difference in development was observed between the treated and control groups.

Based on these results TBBP-A did not produce adverse effects on development in the rat at dose levels up to 2,500 mg/kg. Although this dose did not produce maternal toxicity, it is considered sufficiently high to adequately assess developmental toxicity effects by the oral route.

In a second well conducted and well reported developmental toxicity study, gavage doses of 0, 100, 300 and 1,000 mg/kg TBBP-A were administered to pregnant rats (25 per treatment group) daily from gestational day 0 to 19 (MPI Research, 2001). Throughout the dosing period animals were observed for signs of toxicity and body weight gain and food

consumption were monitored. On day 20 they were sacrificed and a necropsy was conducted. Gravid uterine and liver weights and the following parameters were recorded; total number of corpora lutea, uterine implantations, early and late resorptions, viable and non-viable fetuses and fetal sex and weight. Every fetus underwent a gross examination for skeletal and visceral variations and/or malformations.

No treatment-related mortality occurred among the dams; one animal in the 300 mg/kg group died on gestational day 5 but its death was a consequence of a dosing injury. There were no treatment-related clinical observations and no effect was observed on maternal body weight gain and food consumption. The few findings on macroscopic examination in the treated animals were each of low incidence and were considered not to be treatment-related. There was a slight, statistically significantly lower maternal liver weight in the 100 mg/kg group, but in the absence of a similar finding in the 300 and 1,000 mg/kg groups, it was considered to be unrelated to treatment.

There was no effect of treatment on gestational parameters. Similarly, no treatment-related effects were evident on fetal body weight, sex ratios and external fetal observations and visceral and skeletal examination. It can therefore be concluded that at concentrations up to 1,000 mg/kg, TBBP-A had no adverse developmental effects in this study. Although no maternal toxicity was seen at this dose level, again, this top dose is sufficiently high.

Mated female rats were used in a range finding study to determine the dosage levels of TBBP-A for a teratology study (Velsicol Chemical Corporation, 1978). The rats were 15 weeks old at the time of mating. TBBP-A was administered by gavage at dosage levels of 0, 30, 100, 300, 1,000, 3,000 and 10,000 mg/kg/day from day 6 to day 15 of gestation. Five animals were assigned to each group. Animals were observed daily for signs of toxicity. Individual body weights were recorded on gestational days 0, 6, 12, 15 and 20. All animals were sacrificed on gestational day 20 and the numbers of viable and non-viable fetuses, early and late resorptions, total implantations and corpora lutea were recorded.

In animals receiving 3,000 mg/kg or less, survival was 100% and there were no other signs of toxicity. In the 10,000 mg/kg group three animals died; animals also had green, soft stools and an increase in matted hair in the anogenital area. There was also a slight decrease in weight gains between gestational days 6 and 15 for animals in this group. In terms of uterine observations, there were no compound-related differences in the mean number of viable and non-viable fetuses, resorptions, implantations or corpora lutea at any dosage level. Thus, there were no adverse effects on the developmental parameters assessed, up to very high dose levels, including a dose level producing severe maternal toxicity.

In a study assessing developmental neurotoxicity TBBP-A was administered to neonatal male NMRI-mice as a single oral dose on postnatal day 10 (Eriksson et al., 1998, Eriksson et al., 2001). The amount of TBBP-A administered was 0.75 and 11.5 mg/kg. Mice in a control group received 20% fat emulsion vehicle. Each treatment group consisted of mice from 3-4 litters. A spontaneous behavioural test was conducted at the age of 2 and 4 months on eight mice randomly selected from 3-4 different litters (this test measures locomotion, rearing, total activity and all types of vibration within the cage i.e. those caused by mouse movements, shaking (tremors) and grooming). The ability of mice to learn and memorize a spatial navigation task was assessed using a swim maze, at 5 months of age on 16-18 mice randomly selected from 3-4 different litters. No differences in performance were observed with TBBP-A treatment nor were there any clinical signs of dysfunction in treated animals throughout the experimental period compared with the controls.

In a recent, unpublished study (Hass et al., 2003), the developmental neurotoxicity of TBBP-A was investigated according to a test design based on a proposed OECD guideline (TG 426).

Three groups of 20 pregnant rats (Mol:WIST) were administered 0, 50 or 250 mg/kg/d TBBP-A by gavage in peanut oil from gestation day (GD) 7 to postnatal day (PND) 17. The females were monitored daily for signs of toxicity; bodyweights were monitored throughout the dosing period. The expected delivery day of the pups (GD 22) was designated PND 0. Following delivery, pups were counted sexed and checked for anomalies; decedent pups were examined macroscopically, if possible.

Pups were weaned on PND 21 and one male and one female from each litter were randomly selected for the behavioural testing.

Postnatal development was assessed by measuring bodyweight on PND 6 and 13. Anogenital distance was measured at birth. Pups were examined for the presence of either areola or nipples on PND 13 and 14. The age and bodyweight of animals reaching sexual maturation was recorded. Sexual maturation was evaluated by examining vaginal opening in the females and cleavage of the balano-preputial skinfold in the males.

A number of different behavioural tests were undertaken to evaluate motor activity and habituation capability, play behaviour, sweet preference, learning and memory.

The motor activity of the animals was recorded in activity boxes over a 30 minute period at PND 21 prior to weaning, at PND 27 and in adult animals at 12 weeks. In order to assess habituation capability, the 30 minute period was divided into 2 time periods of 15 minutes.

Assessment of play behaviour was performed on PND 31. The animals from each group were placed in pairs and the latency to initiate play behaviour and the number of pinnings was scored.

Learning and memory were evaluated using a Morris water maze. Animals were tested at age 9, 13 and 17 weeks. The animals were tested in 4 daily trials starting from 4 different points, the trial being completed when the animals swam to and climbed onto a submerged platform. If the animal failed to locate the platform within 60 seconds, it was led there. The route the animals took in finding the platform was recorded and the latencies to find the platform, the path lengths and swimming speeds were used as endpoints. The animals were trained until a stable performance was established (over 4 trials/day for 5 consecutive days). To assess memory, 4 weeks after the learning period the animals were tested again over 4 trials for 2 consecutive days, and after a further 4 weeks over 4 trials for 1 day only. The day after this last "memory" test, the platform was placed opposite the original location and the animals were tested again over 4 trials ("reversal learning"). The following day the platform was moved to the centre of the pool and the animals were tested over 4 trials ("new learning").

When the animals were 5 months old they were investigated in the sweet preference test. During testing, animals were given the choice between normal water and water sweetened with 0.25% saccharin for 3 days. Saccharin intake per 100 g bodyweight was recorded.

At the age of 6 – 7 months the animals were investigated in a standard 8 arm radial maze. The arms of the maze were baited with rewards in the form of peanut chops. The animals were tested in 15 daily sessions over 3 weeks (5 sessions/week). The rats were placed in the centre of the maze and allowed to explore until all arms were visited or 10 minutes had passed.

Latency to visit all arms was recorded. In addition the number of errors as defined by visiting an arm on more than one occasion was also recorded.

Gross and histopathological examination was performed on 15 randomly selected male pups (5/group; 1/litter) at PND 15, following weaning (on PND 22) on 10 randomly selected pups/sex/group (1 male/female per litter) and on adult animals (numbers not stated). The following organs were excised and weighed: the left and right testes and the thyroid of PND 15 and 22 males and adults; the brain, left and right epididymes, ventral prostate and seminal vesicles of PND 22 males and adults. Histopathological examination was performed on the testis and thyroid of PND 15 males; the left testis, the left epididymes, thyroid, ventral prostate and seminal vesicles of PND 22 males; and the brain of PND 22 males and females.

Serum T3 and T4 levels were analysed in animals sacrificed on PND 22 (8 – 10/group; 1/litter).

Also in the animals sacrificed on PND 22, brain homogenates were analysed for neurotransmitter levels. These included 5-hydroxytryptamine (5-HT), noradrenaline (NA) and dopamine (DA).

Maternal bodyweight gains during pregnancy, gestation lengths, litter sizes, frequency of neonatal death and birth weights were similar between control and treated animals. No treatment-related effects of exposure were induced on anogenital distances at birth, areolas/nipples on PND 13, or the timing of sexual maturation. At weaning (PND 21), the body weights of the pups were statistically significantly lower in males and females (89 and 88% of control values, respectively) exposed to 50 mg/kg/day but not at 250 mg/kg/day compared to control offspring. At PND 92 a similar finding is reported with the bodyweights of males and females (92 and 92% of control values, respectively) being statistically significant lower than controls in the 50 mg/kg/day group but not in the 250 mg/kg/day group. Given that statistically significant findings only occur at the lowest dose, and on PND 92 they were reduced by less than 10% of control values they are not considered to be a toxicologically significant treatment-related effect.

The latency to initiate play behaviour and the number of pinnings did not differ significantly between the groups. Also, there was no significant difference between controls and treated animals in the sweet preference test.

Motor activity during the entire 30 minute observation period on PND 21 did not differ significantly between treated and control groups in either males or females. However, when the pattern of activity was analysed as two 15-minute segments statistically significant changes are reported in females. During the first segment, there were no statistically significant differences in activity between control and treated animals. During the second segment, activity in the control and 50 mg/kg/day decreased to 17% and 32%, respectively, of that observed in the first segment, while activity in the top dose group remained similar to that in the first segment and was statistically significantly greater than control activity. This indicates a decreased habituation activity in females exposed to 250 mg/kg/day. For males, the 15 minute segment activity analysis provided no evidence of an effect on habituation.

Motor activity during the entire 30 minute period on PND 28 again did not differ significantly between treated and control groups in either males or females. In females, no difference in activity was reported during the first segment of the test. However, during the second segment, there was higher activity in the 250 mg/kg/day group and the 50 mg/kg/day groups compared with controls. The second segment control activity was about 6% of that observed

in the first segment, apparently due to the majority of the females having no activity during this period. For the 50 and 250 mg/kg/day groups, the second segment activity was 35% and 23% of that observed during the first period. The differences from controls were not significant using ANOVA, but were significant using the non-parametric Fisher Chi-square test (the latter test is probably the most appropriate given the obviously non-normal distribution of the results for the controls). This shows reduced habituation activity in females at 50 mg/kg/day and 250 mg/kg/day groups compared with controls, but the absence of dose-response relationship raises the possibility that this may be a chance finding. For males, the 15 minute segment activity analysis provided no evidence of an effect on habituation.

For the adults tested at 12 weeks of age, again no differences were reported between treated and control groups in males, and over the entire 30 minute period no differences between treated and control females. For the females during segment 1, activity in the 50 mg/kg/day group was reduced compared to controls but this did not reach statistical significance, whereas activity in the 250 mg/kg/day group was similar to controls. For the second segment, activity in the 250 mg/kg/day group was higher than that in the control group; mean activity counts (± SEM) were 368 (± 77), 399 (± 49) and 463 (± 38) in the control, 50 and 250 mg/kg/day groups, respectively. The differences between the activity counts for control and 250 mg/kg/day groups was not significant by ANOVA, but significant by Fisher's test. It is not possible to judge from the information currently available which is the more appropriate test. A justification for favouring the Fisher's test is not available in the report. Comparing the changes in activity between the two segments, activities during the second segment were 42%, 61% and 53% of the first segment in the respective groups; this comparison suggests that the 50 mg/kg/day group (rather than the 250 mg/kg/day group) may have displayed the lowest habituation activity.

It can be concluded that the habituation capability on PND 21 in the 250 mg/kg/day females was different to that of the control group. However, for the females there was no firm evidence of an effect on habituation on PND 28 and only weak evidence of an effect in the adults. Also, habituation of the males was not affected at any of the time points.

During the first 5 days of testing using the Morris water maze, statistically significant differences between the control and treated groups in terms of swim length and latency occurred twice. Firstly on day 1, females of the 250 mg/kg/day group showed a statistically significant decrease in swim length and latency to find the platform compared with control animals. Secondly on day 5, males of the 250 mg/kg/day groups showed a statistically significant increase in swim length and latency to find the platform compared with control animals. The swim speed of the animals did not differ between groups of either sex or exposure. The absence of a consistent pattern of differences between the controls and exposure groups indicated that the occasional statistically significant differences arose by chance.

When the trials were undertaken once again to assess memory, a statistically significant increase in swimming length was reported in males of the 250 mg/kg/day group in the first and second of the 4 trials conducted on day 1 of the testing; also latency to find the platform was statistically significantly increased in the second trial. Mean swim length over the 4 trials on day 1 was not significantly different between treated and control animals. No differences were found in females over the 3 days of trials or in males on the second and third day of the trials. Since significant differences were observed only very occasionally, and there was no consistent pattern of changes across the 12 trials it is considered unlikely that these results indicate a treatment-related effect on memory.

No significant treatment-related differences were reported in the "reversal learning" part of this study.

During the "new learning" phase of the testing a statistically significant increase in swim length was reported in females of the 250 mg/kg/day group and in males of the 50 mg/kg/day group in trial 1, but no other differences were reported in trials 2 – 4. These occasional differences did not form part of a consistent pattern and are considered to have arisen by chance. Consequently it can be concluded that there is no clear treatment-related effect on 'new learning'.

When the animals were tested using the radial arm maze there were no statistically significant differences in mean latency between treated and control groups during the trials in week 1, 2 or 3. The mean number of errors decreased over the 3 weeks of the study. Male animals of the 250 mg/kg/day group showed a statistically significant increase in the number of errors compared with controls in weeks 1 (mean ± SD: 4.09 ± 1.34 and 5.13 ± 1.76 for control and 250 mg/kg/day groups, respectively) and 2 (1.13 ± 1.13 and 2.60 ± 1.90) but not week 3. The authors declared these differences to be statistically significant, although the overlapping SDs of the means suggests that this may not be the case if routine parametric statistical tests are used. No significant differences were reported in females. In terms of choosing adjacent arms, there was a statistically significantly lower frequency in males of the 250 mg/kg/day group in week 1 but not among males on weeks 2 and 3 and females throughout the test. Overall, this study provides evidence of a marginal effect on the learning ability and memory of top dose male rats.

No exposure-related effects on either terminal body weight or any of the investigated organ weights were observed in any of the three age groups (PND 15, 22 and adult animals). At PND 15 and PND 22, no treatment-related effects were observed in the brain or any of the investigated reproductive organs during the histopathological examinations.

No exposure-related effects on serum T3 and T4 levels were found in males at PND 22.

The concentrations of NA, DA, and 5-HT in the brains of PND 22 and adult animals did not differ significantly between treated and control animals.

Overall, this study provides limited evidence of changes in the habituation behaviour of female offspring and learning and memory in male offspring in the 250 mg/kg/day group. However, it is not possible to draw definitive conclusions from this study because the size of the reported changes was very small and there was not a convincingly consistent pattern of changes in investigations conducted at different time points. Also, the evidence of developmental neurotoxicity is weakened by absence of consistent changes in the two genders and the lack of histopathological investigations that could provide corroborative findings.

In non-standard studies, Fukuda et al., (2004) investigated the effects of oral administration of TBBP-A in newborn and young Sprague-Dawley rats.

As part of a sighting study, newborn rats (5/sex/group) were administered, by gavage, a suspension of 0, 40, 200 or ,1000 mg/kg/day TBBP-A in 0.5% (w/v) carboxymethylcellulose from days 4–21 after birth. The animals were examined daily for general behaviour and body weight measured twice a week. Following sacrifice at postnatal day 22, haematology and blood biochemistry analyses were performed, and animals were examined macroscopically.

The authors report that at 1,000 mg/kg/day the following occurred (there was no indication of the statistical significance of the results or whether each occurred in males, females or both): diarrhoea, lowering of body weight, decreases in prothrombin time, activated thromboplastin time and haemoglobin, increase in platelet count, lactate dehydrogenase (LDH), glutamate oxaloacetate transaminase (GOT), blood urea nitrogen (BUN), total bilirubin and creatinine, remarkable enlargement of kidneys and slight dilation of the cecum. Statistically significant increases in absolute and relative liver and kidney weights are reported in the 1,000 mg/kg/day for both sexes, however, only data regarding relative weight is provided. The relative liver weight increase was 16 and 18% in males and females, compared with controls, respectively. However, relative kidney weight was reported to increase by over 600% in both males and females. There was no effect of treatment on kidney weight at 200 mg/kg/day.

In the main study, newborn rats (6/sex/group) were administered, by gavage, a suspension of 0, 40, 200 or 600 mg/kg/day TBBP-A in 0.5% (w/v) carboxymethylcellulose from days 4–21 after birth. Animals were sacrificed following the last treatment. Recovery group animals (6/sex/group) were sacrificed at 12 weeks of age (9 weeks without exposure to TBBP-A). General behaviour was observed daily. Body weights were measured twice a week during the dosing period and once a week during the recovery period. Food consumption during 24 h was measured once a week during the recovery period. At day 20 after birth for males and day 21 for females, gait condition, pupillary reflex, auricular reflex, corneal reflex, visual placing reflex, surface and mid-air righting reflexes, and ipsilateral flexor reflex were examined. Fur appearance, incisor eruption and eye opening were examined in all animals from postnatal days 7, 9 and 11, respectively. Testes descent or vaginal opening was observed only in the recovery group from postnatal day 17 or 29, respectively. During the period from days 78-82 after birth, urinalysis was performed. Haematology and blood biochemistry analyses were performed following sacrifice.

The brain, pituitary gland, heart, thymus, liver, kidneys, spleen, adrenal glands, thyroids, lungs, testes, epididymides, prostate, ovaries, and uterus were examined macroscopically (all dose groups) and microscopically (control and high dose group only). Additionally, the trachea, stomach, intestine, pancreas, lymph node, urinary bladder, spinal cord, sciatic nerve, seminal vesicles, bone, and bone marrow were examined microscopically (control and high dose group only).

Diarrhoea occurred sporadically during the treatment period in some males and females in the 200 and 600 mg/kg groups. There were no differences in body weight gain between the control and TBBP-A-treated groups. No definitive changes in physical development or reflex ontogeny were detected in any dose group. Haematological and blood biochemical analysis showed statistically significant decreases in haemoglobin in females and activated thromboplastin time in males, and a statistically significant increase in total bilirubin in both sexes at 600 mg/kg/day, compared with control animals. Again, the absolute and relative kidney weights dramatically increased in both sexes of the top dose group (by 280% in males and 365% in females compared with controls). Relative liver weight increased slightly in top dose males (by 11%).

Histopathological examination revealed polycystic lesions associated with the dilation of the tubules bilaterally from the cortico-medullary junction to the inner cortex in all animals of the 600 mg/kg/day group (described as moderate in females and severe in males) and in 2/6 males (described as slight) of the 200 mg/kg/day group. The lesions were so severe in the 600 mg/kg/day group that the tissue specimen looked like a sponge in gross examinations. In

addition, hyperplasia of the renal tubular epithelium was observed from the cortico-medullary junction to the inner cortex, and the outer cortex was contracted due to the pressure produced by the cysts. Some rats also had marked hyaline casts within tubules and/or regenerating basophilic tubules or suppurative inflammatory reactions. No other microscopic changes were reported apart from centrilobular hypertrophy of the hepatocytes in 3/6 males of the 600 mg/kg/day group.

Following recovery, the absolute kidney weights of top dose animals were still 1.3 times higher than those in the control group (actual data not reported). Histopathological examinations revealed multiple cysts of the kidneys in 1 animal/sex of the 200 mg/kg/day group (described as slight) and in all animals of the 600 mg/kg/day group (described as moderate to severe). These kidneys are reported to have contained reparative changes with interstitial fibrosis.

In the study of young animals, 5-week old rats (5/sex/group) were administered, by gavage, 0, 2,000 or 6,000 mg/kg/day TBBP-A in 0.5% (w/v) carboxymethylcellulose for 18 days. General behaviour was observed daily and body weight was measured twice a week. At the termination of the treatment, animals were sacrificed and the major organs examined macroscopically. In addition, the kidneys were examined microscopically. No changes in general behaviour, body weight or kidney weight were reported. Histopathological examination of the kidneys showed no abnormalities.

These studies show an effect on the kidneys (polycystic lesions associated with the dilatation of the tubules) of newborn rats dosed from day 4 up to day 21 after birth by gavage with 200 and 600 but not 40 mg/kg TBBP-A. However, no similar effect was observed in 5-week old rats administered by gavage 2,000 and 6,000 mg/kg TBBP-A for 18 days and in a comprehensive GLP- and OECD-compliant rat 2-generation study with gavage doses of up to 1,000 mg/kg/day. It is considered that this effect is likely to be the consequence of the unconventional direct gavage administration of very high doses of TBBP-A to such young animals. Therefore, the relevance to human health of this isolated finding is considered questionable.

Summary of toxicity to reproduction

No studies in humans are available.

Information available from a 2-generation reproductive toxicity study in rats indicates that TBBP-A has no toxicologically significant effects on fertility or reproductive performance at doses of up to 1,000 mg/kg.

The effects of TBBP-A on development have been investigated in a pilot range finding study and two standard developmental studies which involved traditional morphological examination of the foetuses. No evidence of developmental toxicity was seen at doses up to 10,000 mg/kg/day in these studies.

In addition, 2 well-conducted developmental neurotoxicity studies have been conducted in the rat and a post-natal developmental neurotoxicity study in the mouse. The rat studies involved exposure of mothers during pregnancy and lactation periods. The first study was part of the 2-generation study and included behaviour and learning/memory tests, specialised neurohistopathology and morphometric examination of the brain. This study provided no convincing evidence of an adverse effect on neurodevelopment at dose levels up to 1,000 mg/kg/day. The second study included behaviour and learning/memory tests,

neurohistochemistry, but no specialised neurohistology. Pregnant rats were administered 0, 50 or 250 mg/kg/day TBBP-A by gavage in peanut oil from gestation day 7 to postnatal day 17 and a neurobehavioural assessment was carried out on weanling rats. The study showed limited evidence of changes in the habituation behaviour of female offspring and learning and memory in male offspring in the 250 mg/kg/day group. However, it is not possible to draw definitive conclusions from this study because the size of the reported changes was very small and there was not a convincingly consistent pattern of changes in investigations conducted at different time points. Also, the evidence of developmental neurotoxicity is weakened by absence of consistent changes in the two genders, the lack of histopathological investigations that could provide corroborative findings, and the lack of any similar findings in the first study at dose levels of 100 and 1,000 mg/kg/day.

In the mouse study, a single exposure to 10 day old neonates, to a relatively low dose, had no effect on behaviour, learning or memory.

In a non-standard study an effect on the kidneys (polycystic lesions associated with the dilatation of the tubules) of newborn rats dosed from day 4 up to day 21 after birth by gavage with 200 and 600 but not 40 mg/kg TBBP-A was reported. However, no similar effect was observed in 5-week old rats administered by gavage 2,000 and 6,000 mg/kg TBBP-A for 18 days and in a comprehensive GLP- and OECD-compliant rat 2-generation study with gavage doses of up to 1,000 mg/kg/day. It is noted that in this 2-generation study the pups might have been exposed to TBBP-A indirectly via lactation. In view of this, it can be concluded that the kidney changes reported by Fakuda et al. (2004) are likely to be the consequence of the unconventional direct gavage administration of very high doses of TBBP-A to such young animals, which appear to be more susceptible than adult animals to the nephrotoxic effects of TBBP-A. This is likely to be due to the immature metabolic capability and/or the immature kidneys of such young animals. A risk characterisation will be conducted for infants exposed to TBBP-A via the environment using the NOAEL of 40 mg/kg/day identified in this study.

Overall, the data do not provide strong evidence of the potential for TBBP-A to act as a developmental toxicant or neurotoxicant.

Views expressed by other Member States

One or two Member States were of the opinion that an effect on neurobehavioural development was observed and that a NOAEL of 50 mg/kg/day could be derived. However, the majority of Member States were in agreement with the position of the rapporteur described above.

4.1.2.10 Other studies

In vitro

Receptor assays

The MCF7 cell line was used in a study to investigate the oestrogenic potential of TBBP-A and other brominated analogues of bisphenol-A (Samuelson et al., 2001). To determine the relative binding affinities (RBA) the ability of the test compounds to compete with 17β [^{3}H]

oestradiol for binding to the oestrogen receptor was measured in MCF-7 cell homogenates and also whole cell cultures.

The RBA of TBBP-A was the lowest of all test compounds (0.004 as compared to 0.05 for bisphenol-A, the compound with the highest RBA of those tested) in the cell homogenate assay. In the whole cell assay the RBA could not be calculated; using serum containing medium, TBBP-A was unable to substitute for 17β [^{3}H] oestradiol and using serum-free medium the three highest concentrations of TBBP-A resulted in cell death (no explanation was given for this), and the lower concentrations were unable to substitute for 17β [^{3}H] oestradiol.

MCF-7 cells were also used to determine the ability of the test compounds to support proliferation. TBBP-A stimulated MCF-7 cells to 27% of the yield of 17β oestradiol. However, TBBP-A demonstrated a potency several orders of magnitude lower than 17β oestradiol: a 10^{-5} M concentration of TBBP-A was required to produce this effect compared to a 10^{-11} M concentration of 17β oestradiol.

All chemicals were also tested for their ability to induce expression of the oestrogen specific proteins pS2 and the progesterone receptor. TBBP-A was the weakest inducer of both proteins (approximately 40% and 25% of the levels induced by 17β oestradiol, respectively). The concentration of TBBP-A which caused expression of these proteins was 10^{-5} M; the concentration of 17β oestradiol which caused expression was not documented therefore it is not possible to draw any conclusions about the relative potency of TBBP-A and 17β oestradiol in this assay.

In a recombinant yeast oestrogen assay the activity of 73 phenolic substances including TBBP-A was assessed (Miller et al., 2001). Yeast cells were transfected with the human oestrogen receptor α (ERα) gene together with oestrogen response elements and the *Lac Z* reporter gene encoding the enzyme β-galactosidase. These cells were incubated in media containing the test chemical and the chromogenic substrate chlorophenol red β-D-galactopyranoside (CPRG). 17β estradiol (as the positive control) and the solvent control (ethanol) were included in each assay; each compound was tested at least twice. TBBP-A did not display any oestrogenic activity.

The oestrogenic activity of polybrominated diphenyl ethers and polybrominated bisphenol-A compounds including TBBP-A was investigated using the human T47D breast cancer cell line stably transfected with an oestrogen-responsive luciferase reporter gene construct (Meerts et al., 2001). The oestrogenic potential of these compounds was evaluated by measuring luciferase activity. Concentrations of 0.05, 0.1, 0.5, 1.0 and 5 μM TBBP-A were used (the rationale for the selection of the top dose is unclear). Each concentration of the test substance was tested in triplicate and each assay was repeated at least twice. At the concentrations tested, luciferase activity induced by TBBP-A was reported as being "less than 1%" (i.e. relative to the maximum luciferase activity induced by 30 pM of 17β oestradiol). Hence, TBBP-A displayed no oestrogenic activity under the conditions of this study.

In a well conducted study the potential for several brominated flame retardants including TBBP-A to compete with the binding of thyroxine (T_4) to transthyretin (TTR) (thyroid hormone-binding transport protein) was assessed in an *in vitro* competitive binding assay using human TTR and ^{125}I-T_4 as the displaceable radioligand (Meerts et al., 2000). At least eight concentrations of TBBP-A, up to 500 nM, were tested. The solvent dimethyl sulphoxide was used as the control.

The relative binding potency of TBBP-A compared to T_4 was determined by dividing the IC_{50} (the concentration of the substance at 50% competition) for T_4 by the IC_{50} of TBBP-A. TBBP-A had a relative binding potency of 10.6 and a maximum competition of 96.5 ± 0.1% at 500 nM.

The results of this study indicate TBBP-A has considerable ability to compete with T4 for binding to TTR *in vitro.*

As part of a larger study, Mariussen and Fonnum (2003) investigated the effects of TBBP-A on the uptake of the neurotransmitters dopamine, glutamate and γ-amino-n-butyric acid (GABA) into isolated rat brain synaptosomes (freshly prepared from the brains of male Wistar rats). In addition, the effect of TBBP-A on membrane potential and vesicular uptake of dopamine was investigated.

TBBP-A showed a concentration-dependent inhibition of neurotransmitter uptake, with IC_{50} (concentration of TBBP-A producing a 50% uptake inhibition) values of 6 μM for glutamate uptake, 9 μM for dopamine uptake and 16 μM for GABA uptake. Kinetic studies with TBBP-A on dopamine uptake indicated that the substance showed a mixed competitive and non-competitive mode of inhibition.

TBBP-A was shown to affect the membrane potential of synaptosomes by its ability to inhibit the uptake of Tetra [^{3}H]phenylphosphonium bromide (a marker used for effects on membrane potential) in a concentration-dependent manner, with an IC_{50} value of 16 μM.

TBBP-A was also shown to inhibit dopamine uptake into isolated rat brain vesicles with an IC_{50} value of 3 μM.

Overall, while this study has shown that TBBP-A causes inhibition of neurotransmitter uptake and affects membrane potential in rat brain synaptosomes *in vitro*, no conclusions can be drawn about extrapolation of these findings to the *in vivo* situation.

Cell proliferation assays

The proliferation of human breast cancer cells (MCF-7 cells) was used as a means of assessing the oestrogenic potential of a number of chemicals including TBBP-A (Körner et al., 1996). 17β-oestradiol at concentrations between 10^{-13} M and 10^{-8} M was used as the positive control; the test compounds were tested at concentrations between 10^{-9} M and 10^{-4} M. TBBP-A clearly stimulated proliferation of the MCF-7 cells. However, as compared to 17β oestradiol the concentration required to obtain a maximum response was four orders of magnitude greater. To determine whether the proliferatory effect was mediated via the oestrogen receptor, cells were also co-treated with $5 \cdot 10^{-6}$M of the antiestrogen Tamoxifen. This co-treatment completely eradicated the proliferatory effect of TBBP-A thus indicating that TBBP-A has some ability to bind to the oestrogen receptor and thereby exhibits some oestrogenic activity in this assay.

Overall, the weight of evidence from *in vitro* screening assays indicates that TBBP-A has no significant oestrogenic potential.

In vivo

The distribution of TBBP-A in the pregnant rat (see Section 4.1.2.1) and the effect of *in-utero* TBBP-A exposure on thyroid homeostasis in dams and offspring have been investigated

(Meerts et al., 1999). Pregnant Wistar rats were orally dosed with 5 mg/kg ^{14}C- ring labelled TBBP-A from day 10-16 of gestation. Control animals received corn oil only. The number of animals/group was not documented. Faeces and urine were collected daily from day 10 of gestation. On gestational day 20, rats were sacrificed via ether anaesthesia. Maternal blood was collected from the *vena cava* and from both the dams and the fetuses a number of tissues and the carcasses were collected for radioactivity measurements, assessed by liquid scintillation counting (the results of this part of the study are reported in Section 4.1.2.1).

The amount of free thyroxine (T_4), the total amounts of T_4 and T_3 and the level of thyroid stimulating hormone (TSH) in the maternal and fetal plasma were measured. Brain type II deiodinase activity and hepatic T4-glucuronidation was measured in both dams and fetuses and *ex vivo* ^{125}I-T_4 competitive binding to transthyretin (TTR) was determined in maternal and fetal plasma. (The latter was done by incubating plasma from the animals with ^{125} I-T_4 prior to PAGE-analysis of samples.)

No effects were observed on maternal body weight, total litter size and the number of resorptions. Compared to control animals, dams exposed to TBBP-A showed a statistically significantly higher thymus to body weight ratio (16.8%). The average fetal weight of exposed animals was also slightly (but statistically significantly) higher than controls (7.3%).

TBBP-A had no effect on the total and free T_4 plasma levels in dams and fetuses, and in the dams it had no effect on the T_3 levels; T_3 was not detected in fetal plasma. Type II deiodinase activity and hepatic T_4 were also unaffected by TBBP-A in both dams and fetuses. There was a non-statistically significant increase in TSH in the dams (22.0 ± 3.7 and 18.0 ± 2 in the treated and control animals, respectively) and a statistically significant increase in TSH in the fetuses (4.9 ± 1.4 and 1.6 ± 1.4 in the treated and control animals, respectively).

The toxicological significance of these findings is questionable given that the study was poorly reported, the documentation of the methodology for fetal (and maternal) plasma sampling was not provided and that the number of animals used in the study was not documented. With respect to the non-statistically significant increase in TSH levels observed in the dams, this effect was not evident in a recent, standard regulatory 90-day oral study and also a standard 2-generation reproductive fertility and developmental neurobehavioural study in the rat and therefore is considered to be an isolated finding rather than a toxicologically significant effect. With respect to the statistically significant increase in TSH levels observed in the fetuses, no comparable data are available from other studies. However, due to the lack of information available on the methodology for fetal plasma sampling and in view of the limitations anticipated with the sampling procedure in the fetus, the reliability of this finding is uncertain.

On PAGE analysis of both fetal and maternal plasma, no ^{14}C-label could be detected on transthyretin. Furthermore, no reduction in ^{125}I-T_4-TTR binding was evident. No firm conclusions regarding these findings can be drawn, given the limitations associated with the study including, the low dose level administered (5 mg/kg) and the short duration of dosing (day 10-16 of gestation). Moreover, samples for *ex* vivo ^{125}I-T_4 competitive binding to TTR were collected on gestational day 20. Given that the results of the toxicokinetic analyses indicate that the majority (79.8%) of TBBP-A and/or its metabolites was excreted in the faeces 48 hours after the final dose (gestational day 18), the absence of competitive binding of TBBP-A to TTR observed in this study may be attributable to the late sampling time.

Overall, *in vitro* studies have demonstrated that TBBP-A has a high potency in competing with T_4 for binding to TTR in animals, however no firm conclusions regarding the affinity of TBBP-A for TTR *in vivo* can be drawn from the limited data available.

4.1.3 Risk characterisation (with regard to the effects listed in Annex 1 of Regulation 1488/94)

The section below, titled "General aspects" provides an overview of the occupational use, exposure and toxicological profile of TBBP-A.

4.1.3.1 General aspects

The total number of persons occupationally exposed to TBBP-A in the EU is not known. The chemical is not manufactured in the EC, but its use is becoming more widespread as a flame retardant in plastics.

HSE has no TBBP-A exposure data on its NEDB (National Exposure Database). No data were available from any other competent authorities and little information was found in published papers – only brief reports of low air concentrations of TBBP-A in computer and other electronic equipment shredding. However, there are more "upstream" uses of TBBP-A that showed potential for higher exposures. In consequence, HSE commissioned a small sampling exercise within the UK to measure total inhalable TBBP-A to cover the main uses of TBBP-A. Two sites were chosen that were involved in the production of polymer products where TBBP-A was incorporated into the finished article, and two sites chosen were involved in the recycling of polymer products.

One of the selected sites added TBBP-A to ABS in an additive manner to represent the mixing of TBBP-A powder and polymers. Another selected site manufactured resin laminates and this represented the reactive inclusion of TBBP-A into a product. The two recycling sites shredded computer parts and this is the major recycling area in which there is potential for TBBP-A exposure.

The majority of the data in this Risk Assessment Report is from this sampling exercise.

Occupational exposure to TBBP-A is discussed in six scenarios.

1. during the addition of TBBP-A powder to mixes of polymer compounds. Data were available from the HSE sampling exercise.
2. during the production of laminates for printed circuit boards. Data were available from the HSE sampling exercise.
3. during recycling of computers and electrical equipment. Data were available from the HSE sampling exercise, and from published literature.
4. during the assembly of printed circuit boards. Data were available from published literature.
5. employees in offices containing electronic equipment. Data were available from published literature.
6. during the recycling of plastic housings. Only modelled data were available.

TBBP-A inhalation exposures varied by several orders of magnitude across the industry sectors. The highest inhalation exposures to TBBP-A were found in the production (loading and mixing) of plastics, with 8-hour time-weighted-averages (TWAs) up to 12,216 $\mu g/m^3$.

At the other end of the range, offices containing computers showed TBBP-A air concentrations of less than 0.001 $\mu g/m^3$. TBBP-A exposures at sites where computers were shredded, or where laminates were manufactured ranged from 0.1 to 75 $\mu g/m^3$.

Overall, the data are sparse, even with the added results from the HSE sampling exercise. Reasonable-worst-case scenarios would have been estimated using the 90th percentile if there had been sufficient data. As data were lacking, professional judgement was used.

All dermal exposures were predicted by using the EASE model. Loading of TBBP-A powder and associated cleaning gave rise to the highest estimates for dermal exposure, but these predictions are subject to very large uncertainties.

In relation to consumers, exposure to TBBP-A has been found to be negligible.

For humans exposed indirectly via the environment, the highest predicted local human intake is for additive flame retardant use in ABS (total human daily intake = 0.19 mg/kg bw/day). The predicted regional human intake is 7.8 · 10-5 mg/kg bw/day.

TBBP-A has been found in samples of human breast milk, indicating that neonates may be specifically exposed to TBBP-A via mother's milk. By comparing the measured cow's milk levels of TBBP-A (Thomsen et al., 2002b) with those estimated by EUSES (very low levels but still higher than the measured ones) and by using these as a surrogate for the levels of TBBP-A in human breast milk (for which only measured levels are available), it can be concluded that the levels of TBBP-A detected in human breast milk are comparable (if not lower) to the very low environmental concentrations of TBBP-A estimated by EUSES. Consequently, neonatal exposure to TBBP-A via lactation is predicted to be very low. Given the very limited nature of this exposure and considering that only 30% of the absorbed dose of TBBP-A is conjugated in adults, it is also concluded that the systemic exposure of neonates to unconjugated TBBP-A (the potentially toxic form) should not differ to too great an extent from the systemic exposure of an adult to unconjugated TBBP-A, even though newborn babies tend to have limited conjugation capability.

In relation to the toxicological profile, the available data indicate that TBBP-A is absorbed in humans given that it has been detected in serum samples of both occupational and non-occupational groups. There is also evidence that once absorbed, TBBP-A and/or its metabolites can be excreted via breast milk.

In experimental animals, toxicokinetic data are available in the rat only. Following oral exposure, 100% of the administered dose of TBBP-A is absorbed from the gastro-intestinal tract. Toxicokinetic studies following inhalation and dermal exposure have not been conducted. With respect to inhalation, the particle size of TBBP-A indicates that very little will be respirable (only 4% < 15 μm) and thus be available for absorption through the lungs. The majority of the particles will deposit in the nasopharyngeal region of the respiratory tract and then be swallowed (a realistic estimate is approximately 70%), while the remainder are likely to be exhaled. Therefore, it is estimated that approximately 75% of TBBP-A particles will be absorbed following inhalation exposure, the majority (70%) through the gastrointestinal tract. Thus, data from oral exposure studies are important for understanding potential health hazards following inhalation exposure. Regarding dermal exposure, the low

water solubility, the high *n*-octanol/water partition coefficient (5.9), and the high molecular weight (>500) of TBBP-A, suggest dermal absorption would be low. In view of this a default value of 10% will be assumed for dermal exposure, as indicated in the Technical Guidance Document (TGD).

Similarly, information is available on distribution, metabolism and excretion following exposure via the oral route only. Once absorbed, little data are available on the distribution of TBBP-A prior to 8 hours post-administration. From this time point general systemic distribution of TBBP-A (and/or its metabolite(s)) appears to be low (based on the tissues analysed). Quantitative measurements in blood indicate very little of the administered TBBP-A and/or its metabolites are present from 4h onwards. It has been postulated that one possible explanation for he low systemic distribution observed is extensive first pass metabolism of TBBP-A; however, if this were the case it would be expected that the majority of TBBP-A would be excreted as a metabolite in the bile, certainly within 24 hours post-administration. The data do not support this. A more detailed investigation would be required to confirm this hypothesis. Enterohepatic recirculation may also be occurring. However, no significant levels of TBBP-A have been detected in the liver and the blood kinetics have not shown the secondary peak typical of enterohepatic recirculation. Also, no analyses of the gastrointestinal tract have been conducted prior to 72 hours. Thus, there is a significant gap about what is known of the fate of TBBP-A between being absorbed and appearing in the faeces.

Analysis of biliary excreta suggests some metabolism occurs (up to 30% of the administered dose), largely by glucuronide conjugation, although limited sulphate conjugation also occurs.

It is noted that one or two Member States expressed concern over the oral absorption of undissolved TBBP-A particles, particularly when administered as a suspension at high dose levels. In the opinion of these Member States, there was some uncertainty as to whether 100% of the administered dose would be absorbed at these higher dose levels, and consequently whether the dosing of particles in suspension will underestimate the toxicity. However, the majority of Member States agreed with the position of the UK rapporteur that, although this concept is important, the data do not allow a quantitative estimate of oral absorption at such high dose levels to be determined. Therefore, it was agreed to assume that 100% of an orally administered dose of TBBP-A is absorbed.

Following oral administration, TBBP-A and /or its metabolites are excreted predominantly in the faeces (approximately 95% of the administered dose) within 72 hours post-administration, with only a small amount (< 1%) being eliminated through the urine. Following intraperitoneal administration, a similar faecal excretion profile is reported, though characterisation of the faecal radioactivity revealed that the majority appeared as unchanged, parent compound.

As the vast majority of TBBP-A is excreted within 72 hours of administration, there is no evidence to suggest that it has the potential to bioaccumulate.

No information is available on the effects of single exposure to TBBP-A in humans. The available studies in animals indicate LC_{50} (1 hour), oral LD_{50} and dermal LD_{50} values in excess of 1.3 mg/l (4-hour LC_{50} > 0.325 mg/l), 50 g/kg and 10 g/kg, respectively. In addition, no toxicologically significant signs of systemic toxicity were evident following exposure via any route. Thus, it can be concluded that TBBP-A is of low acute toxicity by all routes of exposure.

No studies in humans are available regarding the potential of TBBP-A to cause skin, eye or respiratory tract irritation. However, the weight of evidence from animal studies indicates that TBBP-A is not a skin or an eye irritant. With respect to respiratory tract irritation, information is available from a 14-day inhalation study in rats employing high concentrations of TBBP-A. Whole body exposure for 4 hour/day, 5 days/week to an atmosphere containing TBBP-A dust at a concentration of 6 and 18 mg/l resulted in some evidence of local irritation of the upper respiratory tract, however, no effects were observed at a concentration of 2 mg/l. However, in view of the high concentrations used in the study and the lack of chemical reactivity of the molecule, these effects are more likely to be a direct consequence of mechanical irritation rather than chemical-induced irritation. As such, TBBP-A is not considered to be irritating to the respiratory tract.

Data from a modified Draize multiple insult test in humans provide evidence that TBBP-A does not have the potential to cause skin sensitisation. In addition, despite widespread occupational use of TBBP-A, there are no case reports of skin sensitisation. Similarly, there are no case reports of respiratory sensitisation. In animals, negative data are available from two skin sensitisation tests, neither of which were conducted to current regulatory standards and both of which are considered to possess methodological weaknesses. No animal studies have investigated the respiratory sensitisation potential of TBBP-A, although the absence of significant skin sensitisation potential and the generally unreactive nature of TBBP-A suggest that it would not be a respiratory sensitiser. Taking all of the strands of evidence into account it is considered that the sensitisation potential of TBBP-A has been adequately examined. TBBP-A is considered not to be a skin or respiratory sensitiser.

No information on the effects of repeated exposure to TBBP-A in humans exists. However, its effects have been assessed from repeated exposure studies in rats and rabbits.

Only one repeat dose inhalation study is available. Exposure of rats to concentrations of up to 18 mg/l for 4 hours/day for 14 days, produced no compound related, toxicologically significant systemic effects. Signs of local irritation to the respiratory tract at $\geq$ 6 mg/l were most likely to be due to the physical effects of inhaling a very dusty atmosphere.

In a 90-day study conducted in accordance with GLP and OECD guidelines no toxicologically significant effects were seen following oral exposure of up to a dose of 1,000 mg/kg. This is supported by the results of other studies.

In the only conventional repeated dermal exposure study, in which rabbits were dosed up to 2,500 mg/kg, no toxicologically significant compound related effects were apparent.

Furthermore, TBBP-A is not an agent that causes “bromacne” (analogous to chloracne).

It is noted that one or two Member States expressed concern regarding the significance of the decreases in T4 levels observed in the rat for human health. However, the majority of Member states agreed with the UK position (described above) that these effects are not considered to be adverse.

No studies in humans regarding mutagenicity are available. TBBP-A has demonstrated consistently negative results in a range of *in vitro* tests using bacterial strains (Ames test) and yeast both in the presence and absence of metabolic activation. These studies were conducted in a manner largely compatible with current regulatory guidelines. Similarly, in a well-conducted chromosomal aberration study using human peripheral lymphocytes and in an

unconventional *in vitro* recombination assay, TBBP-A tested negative. No *in vivo* data are available.

Overall, the available genotoxicity data indicate that TBBP-A is negative in standard *in vitro* test systems. No *in vivo* data are available, but in view of the negative profile obtained *in vitro* and given that there are no structural indications that TBBP-A would be genotoxic, there are no concerns for this endpoint.

There are no studies in humans or animals available to inform on the carcinogenic potential of TBBP-A. However, there are no indications from the available *in vitro* mutagenicity data and from repeated exposure studies (for example, no target organ toxicity or proliferative changes) to raise concerns for carcinogenicity.

In relation to toxicity to reproduction, no studies in humans are available.

Information available from a 2-generation reproductive toxicity study in rats indicates that TBBP-A has no toxicologically significant effects on fertility or reproductive performance at doses of up to 1,000 mg/kg.

The effects of TBBP-A on development have been investigated in a pilot range finding study and two standard developmental studies, which involved traditional morphological examination of the foetuses. No evidence of developmental toxicity was seen at doses up to 10,000 mg/kg/day in these studies.

In addition, 2 well-conducted developmental neurotoxicity studies have been conducted in the rat and a post-natal developmental neurotoxicity study in the mouse. The rat studies involved exposure of mothers during pregnancy and lactation periods. The first study was part of the 2-generation study and included behaviour and learning/memory tests, specialised neurohistopathology and morphometric examination of the brain. This study provided no convincing evidence of an adverse effect on neurodevelopment at dose levels up to 1,000 mg/kg/day. The second study included behaviour and learning/memory tests, neurohistochemistry, but no specialised neurohistology. Pregnant rats were administered 0, 50 or 250 mg/kg/day TBBP-A by gavage in peanut oil from gestation day 7 to postnatal day 17 and a neurobehavioural assessment was carried out on weanling rats. The study showed limited evidence of changes in the habituation behaviour of female offspring and learning and memory in male offspring in the 250 mg/kg/day group. However, it is not possible to draw definitive conclusions from this study because the size of the reported changes was very small and there was not a convincingly consistent pattern of changes in investigations conducted at different time points. Also, the evidence of developmental neurotoxicity is weakened by absence of consistent changes in the two genders, the lack of histopathological investigations that could provide corroborative findings, and the lack of any similar findings in the first study at dose levels of 100 and 1,000 mg/kg/day.

In the mouse study, a single exposure to 10-day old neonates, to a relatively low dose, had no effect on behaviour, learning or memory.

In a non-standard study an effect on the kidneys (polycystic lesions associated with the dilatation of the tubules) of newborn rats dosed from day 4 up to day 21 after birth by gavage with 200 and 600 but not 40 mg/kg TBBP-A was reported. However, no such effects were observed in 5-week old rats administered by gavage 2,000 and 6,000 mg/kg TBBP-A for 18 days and in a comprehensive GLP- and OECD-compliant rat 2-generation study with gavage doses of up to 1,000 mg/kg/day. It is noted that in this 2-generation study the pups

might have been exposed to TBBP-A indirectly via lactation. In view of this, it can be concluded that the kidney changes reported by Fakuda et al. (2004) are likely to be the consequence of the unconventional direct gavage administration of very high doses of TBBP-A to such young animals, which appear to be more susceptible than adult animals to the nephrotoxic effects of TBBP-A. This is likely to be due to the immature metabolic capability and/or the immature kidneys of such young animals. A risk characterisation will be conducted for infants exposed to TBBP-A via the environment using the NOAEL of 40 mg/kg/day identified in this study.

Overall, the data do not provide strong evidence of the potential for TBBP-A to act as a developmental toxicant or neurotoxicant.

It is noted that one or two Member States were of the opinion that an effect on neurobehavioural development was observed and that a NOAEL of 50 mg/kg/day could be derived. However, the majority of Member States were in agreement with the position of the rapporteur described above.

As a derivative of bisphenol A, the endocrine-modulating potential of TBBP-A has been of interest. The oestrogenic potential of TBBP-A has been investigated in a range of *in vitro* screening assays. Overall, the weight of evidence from these studies indicates that TBBP-A has no significant oestrogenic potential. The potential for TBBP-A to compete with the binding of T_4 to TTR has been investigated both *in vitro* and *in vivo*. The findings of a well-conducted *in vitro* competitive binding assay indicate that TBBP-A has considerable ability to compete with the binding of T_4 to TTR *in vitro*. No reduction in T_4 binding to TTR was observed in maternal and fetal plasma following oral dosing of pregnant rats with 5 mg/kg TBBP-A from day 10 to 16 of gestation. However, no firm conclusions regarding the affinity of TBBP-A for TTR *in vivo* can be drawn given the limitations associated with the data available.

The hazardous properties of TBBP-A have been evaluated to the extent that the minimum data requirements according to Article 9(2) of Regulation 793/93 have been met. Overall, with the exception of potential nephrotoxicity in infants, no other health effects of concern have been identified.

4.1.3.2 Workers

Overall, as no health effects of potential concern to adults have been identified, no risk characterisation has been performed. **Conclusion (ii)** is reached for all endpoints for all scenarios.

The overall conclusion for the occupational risk characterisation is:

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3 Consumers

No health effects of potential concern to adults have been identified and given that consumer exposures are negligible, there are no concerns in relation to any endpoint. **Conclusion (ii)** is reached.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.4 Indirect exposure via the environment

4.1.3.4.1 Regional exposure

The total daily human exposure to TBBP-A via the environment is estimated to be $7.8 \cdot 10^{-5}$ mg/kg/day for regional sources. No adverse health effects of potential concern to adults have been identified and given the low levels of exposure for the regional scenario, these exposures are not considered to be of concern. Therefore, no comparisons between this intake estimate and data from the toxicological studies for endpoints relevant for environmental exposure have been made. **Conclusion (ii)** is reached.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.4.2 Local exposure

The highest local exposure is in the use of TBBP-A as an additive flame retardant in acrylonitrile-butadiene-styrene (ABS) resins during the compounding and conversion processes. Exposure is estimated to be 0.19 mg/kg/day. However, as no health effects of potential concern to adults have been identified, no risk characterisation has been performed. **Conclusion (ii)** is reached.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.4.3 Infants

The only health effect of concern identified for TBBP-A is nephrotoxicity in newborn rats given gavage doses of 200 and 600 mg/kg/day. No effects were seen at 40 mg/kg/d. This effect should be considered of potential concern to human infants exposed via the environment.

Although no such effects were observed via lactation in a comprehensive rat 2-generation study in pups of dams given up to 1,000 mg/kg/day TBBP-A, it is not impossible that exposure of human infants via breast milk could be higher than that observed in the rat. No estimate of the likely total exposure levels to TBBP-A of infants via the environment is available. Therefore, two potential surrogate exposure scenarios have been selected, one based on adult exposure and one on exposure of infants via breast milk.

The first is very much a worst case scenario comparing the highest adult exposure estimate of 0.19 mg/kg/day with the NOAEL of 40 mg/kg/day. This results in a MOS of 210.

In the second scenario, the highest concentration of TBBP-A found in human breast milk of 11 μg/kg fat is compared with the NOAEL of 40 mg/kg/day. This results in a MOS of 10^6, as shown below.

It is assumed that an infant breast feeds for 1 year, and this year of life is subdivided into two periods – 0 to 3 months and 3 to 12 months – reflecting the changing feeding demands of the infant. It is assumed that over the first 3 months the infant has an average weight of 6 kg (data taken from the UK growth charts, published by the Child Growth Foundation, 1995; Freeman et al., in press and Cole, 1994), that the infant ingests 0.8 kg of milk per day, that 100% of the ingested TBBP-A is absorbed and that the breast milk has an average fat content of 3% (assumption). From 3 to 12 months, it is assumed that the infant has an average weight of 10 kg (data taken from same source as above), that the infant ingests 0.5 kg of milk per day, that 100% of the ingested TBBP-A is absorbed and that the breast milk has a fat content of 3%. It is also assumed that the content of TBBP-A remains constant during the breast-feeding period.

Using the following equation and the assumptions detailed above, the average daily uptake of the breast-feeding infant (ADU_{infant}) is estimated for both the 0-3 month and 3-12 month periods of infant life. The resultant uptakes are then summed to generate an average uptake for the infant in mg/kg/day.

$$ADU_{\text{inf }ant} = \frac{C_{milk-fat} xf\,3 xf\,4 xIR_{milk}}{BW_{\text{inf }ant}}$$

where:

$C_{milk\text{-}fat}$	is the concentration of TBBP-A in mg/kg fat in breast milk
f3	is the fraction of fat in breast milk (0.03 kg fat/kg milk)
f4	is the absorbed fraction of ingested TBBP-A (1)
IR_{milk}	is the ingestion rate of milk (kg/day)
BW_{infant}	is the average infant body weight over the exposure period (kg)

TBBP-A uptake during 0-3 months, assuming a concentration of TBBP-A in human breast milk of 11 µg/kg (maximum measured value):

$$ADU_{\text{inf }ant} = \frac{11x0.03x1x0.8}{6} = 0.044x10^{-3}\, mg/kg/day$$

TBBP-A uptake during 3-12 months, assuming a concentration of TBBP-A in human breast milk of 11 µg/kg:

$$ADU_{\text{inf }ant} = \frac{11x0.03x1x0.5}{10} = 0.017x10^{-3}\, mg/kg/day$$

Based on these estimates, the time-weighted year-average uptake of TBBP-A for the first 12 months of life is $0.024 \cdot 10^{-3}$ mg/kg/day. By comparing this estimate with the NOAEL of 40 mg/kg/day, a MOS of $1.7 \cdot 10^{6}$ is obtained.

These MOS values are considered to be sufficient to allow for interspecies and intraspecies differences, and therefore **conclusion (ii)** is reached.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.5 Combined exposure

Consumer exposures are negligible and therefore calculation of the combined exposure is not considered necessary and no risk characterisation has been performed. **Conclusion (ii)** is reached.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

The only physico-chemical hazard identified for TBBP-A is that, in common with many organic materials, the finely powdered material is a significant dust explosion hazard (Grossel, 1988). However, this appears to be well known within the manufacturing industry and it is considered that there are adequate controls for this risk in place. Overall, the risk from physico-chemical properties is low.

The conclusion of the risk assessment for physico-chemical properties is:

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5 RESULTS

5.1 ENVIRONMENT

(to be added later)

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

No health effects of concern have been identified for TBBP-A.

5.2.1.1 Workers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

No health effects of concern to adults have been identified. Therefore **conclusion (ii)** is reached in relation to all endpoints and for all exposure scenarios.

5.2.1.2 Consumers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Given that consumer exposure is negligible **conclusion (ii)** is reached in relation to all endpoints.

5.2.1.3 Humans exposed via the environment

5.2.1.3.1 Regional exposures

No health effects of concern to adults have been identified. Therefore, **conclusion (ii)** is reached for regional exposures.

5.2.1.3.2 Local exposures

No health effects of concern to adults have been identified. Therefore **conclusion (ii)** is reached for all local exposure scenarios.

5.2.1.3.3 Infants

MOS values of 210 and 10^6 have been obtained by comparing the NOAEL for nephrotoxicity in newborn rats with the highest environmental exposure estimate of an adult and the highest

concentration of TBBP-A found in breast milk, respectively. These MOS values are considered to be sufficient to allow for interspecies and intraspecies differences, and therefore **conclusion (ii)** is reached.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2.1.4 Combined exposure

Given that consumer exposures are negligible calculation of combined exposure is not necessary. Therefore **conclusion (ii)** is reached.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2.2 Human health (risks from the physico-chemical properties)

There are no significant risks from physico-chemical properties.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

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ABBREVIATIONS

ABS	acrylonitrile-butadiene-styrene
ADI	Acceptable Daily Intake
ADU	Average Daily Uptake
AF	Assessment Factor
ALP	Alkaline Phosphatase
ALT	Alanine aminotranferease
AST	Aspartate Aminotransferase
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
bfr	Brominated flame retardant
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
BUN	Blood urea nitrogen
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CPRG	Chlorophenol red β-D-galactopyranoside
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
DA	Dopamine
d.wt	dry weight / dw

dfi	daily food intake
DG	Directorate General
DMSO	Dimethyl sulfoxide
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
FOB	Functional Observational Battery
foc	Organic carbon factor (compartment depending)
GABA	γ-amino-n-butyric acid
GLP	Good Laboratory Practice
GOT	Glutamate Oxaloacetate Transminase

GSH	Glutathione
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HIPS	High impact polystyrene
HPBL	Human Peripheral Blood Lymphocytes
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 tonnes/annum)
HSE	Health and Safety Executive
5-HT	5-hydroxytryptamine (Serotonin)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LDH	Lactate Dehydrogenase
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MA	Motor Activity
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category

MITI	Ministry of International Trade and Industry, Japan
MMAD	Mass Median Aerodynamic Diameter
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NA	Noradrenaline
NAEL	No Adverse Effect Level
NEDB	National Exposure Database (HSE)
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidising (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PAGE	Polyacrylamide Gel Electrophoresis
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PC	Personal computer
PCB	Polychlorinated biphenyls
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PND	Postnatal Day
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship

R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RBA	Relative Binding Affinity
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst-Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SCHER	Scientific Committee on Health and Environmental Risks
SD	Standard Deviation
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TG	Triglyceride
γ-TG	L-γ-glutamyl-transferase
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand
TTR	Transthyretin
TWA	Time-weighted average
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum

UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WEEE	Waste Electrical and Electronic Equipment
WHO	World Health Organisation
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

Appendix A Tetrabromobisphenol-A and formation of brominated dibenzo-*p*-dioxins and dibenzofurans

(Appendix A is in reference to the Enviroment part of the risk assessment report, which will be added later)

Much concern has been expressed over the possible formation of brominated dibenzofurans, and brominated dibenzo-*p*-dioxins from certain brominated flame retardants during production, processing, use, accidental fires and disposal (e.g. incineration). This Appendix reviews the known data on tetrabromobisphenol-A on this issue and attempts to draw some conclusions from the data with regards to the environmental exposure.

In the following Sections the general abbreviations used will be:

PBDF - Polybrominated dibenzofuran
PBDD - Polybrominated dibenzo-*p*-dioxin

The following abbreviations will be used in some of the tables in this Appendix:

MBDF	-	Monobromodibenzofuran	MBDD	-	Monobromodibenzo-*p*-dioxin
DiBDF	-	Dibromodibenzofuran	DiBDD	-	Dibromodibenzo-*p*-dioxin
TrBDF	-	Tribromodibenzofuran	TrBDD	-	Tribromodibenzo-*p*-dioxin
TeBDF	-	Tetrabromodibenzofuran	TeBDD	-	Tetrabromodibenzo-*p*-dioxin
PeBDF	-	Pentabromodibenzofuran	PeBDD	-	Pentabromodibenzo-*p*-dioxin
HxBDF	-	Hexabromodibenzofuran	HxBDD	-	Hexabromodibenzo-*p*-dioxin
HpBDF	-	Heptabromodibenzofuran	HpBDD	-	Heptabromodibenzo-*p*-dioxin
OBDF	-	Octabromodibenzofuran	OBDD	-	Octabromodibenzo-*p*-dioxin

Dibenzo-*p*-dioxin and dibenzofuran impurities present in tetrabromobisphenol-A

Kurz (1998) reported the levels of brominated dibenzo-*p*-dioxins and dibenzofurans present in tetrabromobisphenol-A and also a diglycidyl ether derivative of tetrabromobisphenol-A. The results are shown in **Table A1**. No brominated dibenzofurans or dibenzo-*p*-dioxins were found in either of the two flame retardants analysed.

Table A1 Impurities present in tetrabromobisphenol-A and tetrabromobisphenol-A glycidyl ether (Kurz, 1998)

Congener	Concentration (µg/kg flame retardant)	
	Tetrabromobisphenol-A	Tetrabromobisphenol-A glycidyl ether
2,3,7,8-TeBDD	< 0.01	< 0.02
1,2,3,7,8-PeBDD	< 0.02	< 0.05
1,2,3,4,7,8-HxBDD	< 0.05	< 0.1
1,2,3,6,7,8-HxBDD	< 0.05	< 0.1
1,2,3,7,8,9-HxBDD	< 0.05	< 0.1
1,2,3,4,6,7,8-HpBDD		< 0.2
2,3,7,8-TeBDF	< 0.01	< 0.02
1,2,3,7,8-PeBDF	< 0.02	< 0.05
2,3,4,7,8-PeBDF	< 0.02	< 0.05
1,2,3,4,7,8-HxBDF		< 0.1

Table A1 continued overleaf

Table A1 continued Impurities present in tetrabromobisphenol-A and tetrabromobisphenol-A glycidyl ether (Kurz, 1998)

Congener	Concentration (µg/kg flame retardant)	
	Tetrabromobisphenol-A	Tetrabromobisphenol-A glycidyl ether
1,2,3,6,7,8-HxBDF		< 0.2
1,2,3,7,8,9-HxBDF		< 0.2
2,3,4,6,7,8-HxBDF		< 0.2
1,2,3,4,6,7,8-HpBDF		< 0.2
1,2,3,4,7,8,9-HpBDF		< 0.2

Freiberg (1995) carried out an analysis for trace levels of brominated dibenzo-*p*-dioxins and dibenzofurans in tetrabromobisphenol-A. The method used was designed to meet the limit of quantification laid down in the USEPA test rule for these impurities. The results are shown in **Table A2**. Again, no brominated dibenzo-*p*-dioxins of dibenzofurans were found at the limit of quantification required by the test rule.

Table A2 Analysis of tetrabromobisphenol-A according to the USEPA test rule (Freiberg, 1995)

Congener	Limit of quantification (µg/kg flame retardant)	Level found (µg/kg flame retardant)
2,3,7,8-TeBDD	0.1	< 0.1
2,3,7,8-TeBDF	1.0	< 1.0
1,2,3,7,8-PeBDD	0.5	< 0.5
1,2,3,7,8-PeBDF	5	< 5
2,3,4,7,8-PeBDF	5	< 5
1,2,3,4,7,8-HxBDD	2.5	< 2.5
1,2,3,6,7,8-HxBDD	2.5	< 2.5
1,2,3,7,8,9-HxBDD	2.5	< 2.5
1,2,3,4,7,8-HxBDF	25	< 25
1,2,3,6,7,8-HxBDF	25	< 25
1,2,3,7,8,9-HxBDF	25	< 25
2,3,4,6,7,8-HxBDF	25	< 25
1,2,3,4,6,7,8-HpBDD	100	< 100
1,2,3,4,6,7,8-HpBDF	1,000	< 1,000
1,2,3,4,7,8,9-HpBDF	1,000	< 1,000

Ranken et al. (1994) analysed samples of commercial tetrabromobisphenol-A for the presence of fifteen brominated dibenzofurans and dibenzo-*p*-dioxins with the 2,3,7,8- substitution pattern. The analytical method used was a GC-MS method (SIM mode) but extensive sample clean-up was undertaken to allow the brominated furans to be analysed at low limits of detection free from interferences. Several analytical standards were used in the analysis (at least one pure brominated dibenzofuran and dibenzo-*p*-dioxin isomer for each degree of bromination between tetra- and heptabromo). Originally, ten samples of tetrabromobisphenol-A were collected from each of three manufacturers. Seven out of the ten samples from each manufacturer were randomly selected for analysis. None of the fifteen dibenzofurans and dibenzo-*p*-dioxins were detected in any of the samples analysed at concentrations above the limit of quantitation

specified by the USEPA (see **Table A2**). The limits of quantitation varied from 0.1 μg/kg for 2,3,7,8-tetrabromo-*p*-dioxin to 1.0 μg/kg for 2,3,7,8-tetrabromodibenzofuran to 1,000 μg/kg for 1,2,3,4,6,7,8- and 1,2,3,4,7,8,9-heptabromodibenzofuran.

The levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans present in tetrabromobisphenol-A have been determined by Thies et al. (1990). The results are shown in **Table A3**. In these samples, trace amounts of some polybrominated dibenzo-*p*-dioxins and dibenzofurans were found.

Table A3 Levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans present in a commercial tetrabromobisphenol-A (Thies et al., 1990)

Congener	Level (μg/kg)
MBDD	<0.5
DiBDD	<0.5
TrBDD	<0.5
TeBDD	1
2,3,7,8-TeBDD	<0.5
PeBDD	2
HxBDD	5
MBDF	2
DiBDF	1
TrBDF	<0.5
TeBDF	<1
2,3,7,8-TeBDF	<0.5
PeBDF	<2
HxBDF	<14[a]

a) Interference from a co-eluting peak.

The levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans present in technical grade tetrabromobisphenol-A have been reported by Thoma et al. (1986a) and Dumler et al. (1989b). The levels found are shown in **Table A4**. In these samples small amounts of penta- to octabromodibenzofurans were found to be present, but, although individual isomers were not identified in this study, it is clear that the concentrations present are below those required in the USEPA test rule (see **Table A2** for limits).

Table A4 Levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans in technical grade tetrabromobisphenol-A (Thoma et al. (1986a) and Dumler et al. (1989b))

Congener	Level (µg/kg)
TrBDD	nd
TeBDD	nd
DiBDF	nd
TrBDF	nd
TeBDF	nd
PeBDF	1.0
HxBDF	12.2
HpBDF	31.5
OBDF	18.9

Nd Not detected. Detection limit not given.

Brenner and Knies (1993a and 1993b) determined the levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans present in a tetrabromobisphenol-A carbonate oligomer flame retaradant. The method used determined the concentrations of di- to octabrominated congeners. Around 6 ng/kg of tetrabromodibenzo-*p*-dioxins were found in the sample, but these were not 2,3,7,8-substituted. No other polybrominated dibenzo-*p*-dioxins or dibenzofurans were detected in the sample (the detection limits were in the range 0.001 to 0.4 µg/kg for the di- to octabromodibenzo-*p*-dioxins and dibenzofurans).

Summary of levels in tetrabromobisphenol-A

Several studies have investigated the levels of brominated dibenzo-*p*-dioxins and dibenzofurans present in tetrabromobisphenol-A. All studies have indicated that the levels are very low. A few studies have occasionally indicated the presence of small amounts of some congeners. It is possible that the apparent differences between some of the studies in terms of the levels found could be due to the use of improved analytical methods that eliminate possible interferences rather than actual differences in the amounts present. In all cases the concentrations found appear to be below the levels specified in the USEPA test rule.

In terms of the environmental risk assessment, as the effects data used in the assessment has been derived from the commercially supplied product, the results obtained will also account for any toxic impurities present.

Polymer manufacture and use

Bonilla et al. (1990) carried out analysis of the amounts of brominated dibenzo-*p*-dioxins and dibenzofurans present in ABS resin containing tetrabromobisphenol-A both before and after extrusion. In the resin prior to extrusion no brominated dibenzo-*p*-dioxins were found but brominated dibenzofurans were present at a total level of 1.09 µg/kg resin (the brominated dibenzofurans found in the resin were tentatively identified as being 2,3,7,8-substituted). In the resin after extrusion, no brominated dibenzofurans could be detected but the total concentration of brominated dibenzo-*p*-dioxins was 6.16 µg/kg resin. As well as the resin samples themselves, fumes from the extruded plastic were also analysed for the presence of brominated dibenzo-*p*-dioxins and dibenzofurans. The total amount of brominated dibenzo-*p*-dioxins and dibenzofurans present in the fume was 0.006 and 0.020 µg/kg extruded resin respectively.

Thies et al. (1990) looked at the amounts of polybrominated dibenzo-*p*-dioxins and dibenzofurans present in various polymers containing tetrabromobisphenol-A or tetrabromobisphenol-A derivatives produced under normal conditions. The results are shown in **Table A5**.

Table A5 Amounts of polybrominated dibenzo-*p*-dioxins and dibenzofurans in polymers containing tetrabromobisphenol-A or derivatives (Thies et al., 1990)

Congener	Level (µg/kg polymer)		
	ABS with 16% tetrabromobisphenol-A and 6% Sb_2O_3	Polybutylene terephthalate with 10% tetrabromobisphenol-A oligomer and 5% Sb_2O_3	ABS with tetrabromobisphenol-A - bisphenol-A polycarbonate blend (6% copolymerised tetrabromobisphenol-A)
MBDD	< 1	< 0.2	< 0.5
DiBDD	< 1	< 0.2	< 0.5
TrBDD	< 1	< 0.2	< 0.5
TeBDD	< 1	< 0.2	< 1
2,3,7,8-TeBDD	< 1	< 0.1	< 1
PeBDD	< 2	< 0.1	< 1
HxBDD	< 10	< 1	< 1
MBDF	3	4	< 0.5
DiBDF	3	< 0.2	< 1
TrBDF	< 1	< 0.2	< 0.5
TeBDF	< 2	< 0.2	< 1
2,3,7,8-TeBDF	< 2	< 0.1	< 1
PeBDF	< 3	< 0.1	< 1
HxBDF	< 20	< 1	< 10

Brenner and Knies (1993a and 1993b) found no polybrominated dibenzo-*p*-dioxins in three samples of extruded polybutylene terephthalate polymer granulate containing antimony trioxide, glass fibre and around 50% tetrabromobisphenol-A carbonate oligomer, and also in two test articles formed by injection moulding of the resin. The detection limits were in the range 0.01 µg/kg to 17 µg/kg for di- to octabromodibenzo-*p*-dioxin respectively. The levels of polybrominated dibenzofurans found are shown in **Table A6**.

Table A6 Levels of polybrominated dibenzofurans in polybutylene terephthalate containing tetrabromobisphenol-A carbonate (Brenner and Knies, 1993a)

Congener	Level in polymer (µg/kg)				
	Granulate	Granulate	Granulate	Test article	Test article
DiBDF	nd	nd	nd	0.07	0.29
TrBDF	nd	nd	nd	0.2	0.31
TeBDF	nd	nd	nd	0.2	0.17
PeBDF	nd	nd	nd	nd	0.06
HxBDF	0.8	0.4	0.51	2.2	1.5
HpBDF	3.5	0.6	1.6	3.8	1.9

Nd Not detected. The detection limit was not clear.

Fluthwedel and Pohle (1993) reported results of analysis for the presence of polybrominated dibenzofurans and polybrominated dibenzo-*p*-dioxins in various electronic equipment casings and parts. Total levels of between 0.0067 and 4.24 mg/kg were found. Of the 16 samples analysed, 11 exceeded the proposed German limit value of 1 µg/kg for the sum of 4 tetra-/pentabrominated dibenzofurans/dibenzo-*p*-dioxins (maximum level measured 32.7 µg/kg) and the proposed limit value of 5 µg/kg for the sum of 8 tetra- to hexabrominated dibenzofurans/dibenzo-*p*-dioxins (maximum level measured 74.6 µg/kg). The proportion of 2,3,7,8-substituted congeners was around 5.8% of the total. It is not clear if the plastic parts analysed in this study contained tetrabromobisphenol-A. Other flame retardants, in particular the polybrominated diphenyl ethers could have been present in the samples, and so it is not possible to attribute the levels found solely to tetrabromobisphenol-A usage.

Fluthwedel and Pohle (1993) also reported the results of a series of experiments looking at the emissions of polybrominated dibenzofurans from various electronic equipment in use including televisions, printers and monitors. After 3 days sampling, the sum of polybrominated dibenzofurans released was estimated at around 320-1,800 pg/device. Investigations of air levels in a room containing electronic equipment gave a total air concentration of 1.27 pg/m^3 of polybrominated dibenzofurans. It is not known if tetrabromobisphenol-A was present in the electronic equipment used in this study. Again, other flame retardants, in particular the polybrominated diphenyl ethers, are also likely to be present, and so it is not possible to attribute the levels found solely to tetrabromobisphenol-A.

The levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans present in samples of printed circuit board have been determined (Lorenz and Bahadir, 1993). As well as the original printed circuit board sample, samples were also heated in an oven at either 150^{o}C, 200^{o}C, 250^{o}C or 300^{o}C for 30 minutes in order to investigate the effects of thermal stress on the levels found. Under these conditions, no obvious physical changes occurred to the samples at 150^{o}C and 200^{o}C, there was some discolouration of the sample treated at 250^{o}C and carbonisation occurred in the sample treated at 300^{o}C. The results of the analyses are shown in **Table A7**. The results showed that only very low levels of some polybrominated dibenzo-*p*-dioxin and dibenzofuran congeners are present in the original printed circuit board, and that very small amounts of mono- to tribromo congeners appear to be formed when the samples are heated to high temperatures for prolonged periods.

Table A7 Levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans present in printed circuit boards (Lorenz and Bahadir, 1993)

Congener	Concentration present (µg/kg)				
	Original sample	Sample heated at 150^{o}C	Sample heated at 200^{o}C	Sample heated at 250^{o}C	Sample heated at 300^{o}C
MBDD	< 0.05	< 0.05	< 0.05	0.10	0.49
DiBDD	< 0.04	< 0.1	< 0.1	0.16	0.30
TrBDD	< 0.02	< 0.05	< 0.05	0.10	0.09
TeBDD	0.22	0.56	0.33	1.06	0.19
2,3,7,8-TeBDD	< 0.04	< 0.1	< 0.1	< 0.04	< 0.04
PeBDD	< 0.1	< 0.2	< 0.2	< 0.2	< 0.2
HxBDD	< 0.1	< 0.2	< 0.2	< 0.2	< 0.2
HpBDD	< 1	< 3	< 3	< 3	< 3

Table A7 continued overleaf

Table A7 continued Levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans present in printed circuit boards (Lorenz and Bahadir, 1993)

Congener	Concentration present (µg/kg)				
	Original sample	Sample heated at 150°C	Sample heated at 200°C	Sample heated at 250°C	Sample heated at 300°C
OBDD	nd[a]	nd[a]	nd[a]	nd[a]	nd[a]
MBDF	< 0.05	< 0.05	< 0.05	1.68	2.49
DiBDF	< 0.05	0.18	0.26	0.67	0.82
TrBDF	< 0.02	< 0.02	< 0.02	< 0.04	0.13
TeBDF	< 0.05	< 2	< 2	< 0.5	< 2
2,3,7,8-TeBDF	< 0.01	< 0.04	< 0.04	< 0.04	< 0.04
PeBDF	< 0.05	< 0.1	< 0.1	< 0.1	< 0.1
HxBDF	< 0.5	< 1	< 1	< 1	< 1
HpBDF	< 1	< 2	< 2	< 2	< 2
OBDF	nd[a]	nd[a]	nd[a]	nd[a]	nd[a]

a) Not detected. Detection limit not given.

Thies et al. (1990) investigated the concentrations of polybrominated dibenzo-*p*-dioxins and dibenzofurans in the off-gas from a compounding machine where ABS containing tetrabromobisphenol-A was being processed at 180°C, the workplace atmosphere where injection moulding of ABS containing 16% tetrabromobisphenol-A and 6% antimony trioxide was taking place, and in ambient air near to a television cabinet. The results are shown in **Table A8**.

Table A8 Levels of polybrominated dibenzo-*p*-dioxins and furans in air associated with processing of tetrabromobisphenol-A (Thies et al., 1990)

Congener	Level in air (ng/m³)			
	Off-gas from a compounding machine	Workplace atmosphere - injection moulding	15 cm above TV cabinet	2.2 m away from TV cabinet
MBDD	< 8	< 1	< 0.001	< 0.001
DiBDD	< 6	< 1	< 0.001	< 0.002[a]
TrBDD	< 3	< 1	< 0.001	< 0.001
TeBDD	6-8	< 1	< 0.001	< 0.001
2,3,7,8-TeBDD	< 2	< 0.1	< 0.0005	< 0.0005
PeBDD	< 8	< 0.1	< 0.001	< 0.001
1,2,3,7,8-PeBDD	nd	< 0.1	< 0.5	< 0.5
HxBDD	< 20	< 0.1	< 0.008	< 0.008
MBDF	12[a]-13	< 1	< 0.5[a]	< 0.5[a]
DiBDF	12-200	< 1	< 0.1[a]	< 0.1[a]
TrBDF	< 6	< 1	< 0.001	< 0.001
TeBDF	< 4	< 1	0.003	< 0.001
2,3,7,8-TeBDF	< 1	< 0.1	< 0.0005	< 0.0005
PeBDF	< 10	< 1	0.008	< 0.001

Table A8 continued overleaf

Table A8 continued Levels of polybrominated dibenzo-p-dioxins and furans in air associated with processing of tetrabromobisphenol-A (Thies et al., 1990)

Congener	Level in air (ng/m³)			
	Off-gas from a compounding machine	Workplace atmosphere - injection moulding	15 cm above TV cabinet	2.2 m away from TV cabinet
1,2,3,7,8-PeBDF	< 1	< 0.1	< 0.0005	< 0.0005
HxBDF	< 40	< 1	< 0.008	< 0.008

a) Interference from a co-eluting peak.
nd Not determined.

Brenner and Knies (1993a and 1993b) investigated the levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans in workplace air at a facility using a derivative of tetrabromobisphenol-A. In this study samples were taken during extruder production and injection moulding of a polybutylene terephthalate polymer blended with glass fibre, antimony trioxide (3.5%) and tetrabromobisphenol-A carbonate (11%). The levels found are shown in **Table A9**. No 2,3,7,8-substituted polybrominated dibenzo-*p*-dioxins of dibenzofurans were detected in this study.

Table A9 Levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans in air processing of polybutylene terephthalate containing tetrabromobisphenol-A carbonate (Brenner and Knies, 1993a)

Congener	Level in air (ng/m³)					
	Workplace during extrusion	Extruder	Granulator	Workplace during injection moulding	Injection head	Storage area
DiBDD	nd[a]	0.94	nd[a]	nd[b] (< 0.001)	nd[b] (< 0.001)	nd[b] (< 0.001)
TrBDD	nd[b] (< 0.001)	0.07	0.02	nd[b] (< 0.001)	nd[b] (< 0.001)	nd[b] (< 0.001)
TeBDD	nd[b] (< 0.001)	0.08	nd[b] (< 0.001)	nd[b] (< 0.001)	nd[b] (< 0.001)	nd[b] (< 0.001)
PeBDD	nd[b] (< 0.003)	nd[b] (< 0.003)	nd[b] (< 0.003)	nd[b] (< 0.003)	nd[b] (< 0.001)	nd[b] (< 0.004)
HxBDD	nd[b] (< 0.02)	nd[b] (< 0.1)	nd[b] (< 0.02)	nd[b] (< 0.016)	nd[b] (< 0.003)	nd[b] (< 0.058)
HpBDD	nd[b] (< 0.04)	nd[b] (< 0.2)	nd[b] (< 0.02)	nd[b] (< 0.032)	nd[b] (< 0.006)	nd[b] (< 0.116)
OBDD	nd[b] (< 0.08)	nd[b] (< 0.4)	nd[b] (< 0.08)	nd[b] (< 0.064)	nd[b] (< 0.012)	nd[b] (< 0.232)
DiBDF	0.34	0.42	0.23	nd[a]	0.04	0.04
TrBDF	0.11	0.48	0.29	nd[a]	0.012	nd[a]
TeBDF	0.05	0.24	0.17	0.029	0.014	0.02
PeBDF	0.07	0.04	0.02	0.187	0.013	nd[a]
HxBDF	0.05	0.18	nd[a]	0.262	0.039	nd[a]
HpBDF	nd[b] (< 0.04)	nd[b] (< 0.1)	nd[b] (< 0.04)	nd[b] (< 0.013)	nd[a]	nd[a]
OBDF	nd[b] (< 0.08)	nd[b] (< 0.3)	nd[b] (< 0.08)	nd[b] (< 0.026)	nd[a]	nd[a]

a) nd Not detected. The detection limit was not clear.
b) nd Not detected. Detection limit given in ( ).

Summary of levels during polymer manufacture and use

The available data on the levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans associated with the use of tetrabromobisphenol-A in polymers generally show that only very low levels of these impurities are present in, or are emitted from, polymer systems under normal conditions of manufacture or use. Polybrominated dibenzo-*p*-dioxins have been found in only a few of the available studies where elevated temperatures have been used (formation during pyrolysis/combustion is considered in the next Section). Polybrominated dibenzofurans have been found in most studies, but again the levels are low, and the mono- and dibrominated congeners appear to dominate. In particular, it should be noted that the levels of 2,3,7,8-substituted congeners of both polybrominated dibenzo-*p*-dioxins and dibenzofurans are very low and are usually not detectable by the analytical methodologies used.

Pyrolysis studies

Several laboratory studies have been carried out to determine the extent of formation of polybrominated dibenzo-*p*-dioxins and dibenzofurans when tetrabromobisphenol-A (or in some cases a derivative of tetrabromobisphenol-A) is heated or burned at high temperatures. As can be seen, many different experimental designs have been used, with different pyrolysis times, making direct comparison from one experiment to another difficult. However, some of the results may have relevance to the possible formation of these products during accidental fires and incineration and other high temperature processes.

Pyrolysis of tetrabromobisphenol-A and derivatives

Thoma et al. (1986b) studied the pyrolysis of a purified sample of tetrabromobisphenol-A. In the experiment, the flame retardant was heated in open quartz tubes at either 700°C, 800°C or 900°C for 10 minutes. The residue was then analysed by a GC/MS technique, using 1,2,3,4-tetrabromodibenzo-*p*-dioxin as a standard for quantifying both polybrominated dibenzo-*p*-dioxins and dibenzofurans. The results are shown in **Table A10**. No higher bromined products were reported to be formed and the maximum formation of mono- to tribrominated dibenzo-*p*-dioxins and furans was found to occur at 800°C.

Table A10 Pyrolysis of tetrabromobisphenol-A (Thoma et al., 1986b)

Congener	Concentration (mg/kg flame retardant)		
	700°C	800°C	900°C
MBDD	19	129	71
DBDD	32	233	129
TrBDD	11	109	64
TeBDD	1	27	6
MBDF	77	270	182
DBDF	49	623	421
TrBDF	6	236	160
TeBDF	nd	21	16

nd Not detected (detection limit not given).

Thies et al. (1990) determined the levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans in a sample of tetrabromobisphenol-A that had been heated at 240°C or 600°C for 20 minutes in

a BIS-apparatus. Both the solid residue and the gas condensate were analysed. The results are shown in **Table A11**. The levels found in the condensate were much higher in the sample heated to 600°C than in the sample heated to 240°C. Mono- to tetrabrominated congeners dominated the products formed.

Dumler et al. (1989b) carried out pyrolysis experiments with tetrabromobisphenol-A using a DIN-apparatus, a BIS-apparatus and a VCI-apparatus over a temperature range of 300-800°C. It was reported that polybrominated dibenzo-*p*-dioxins and dibenzofurans were formed in mg/kg amounts, and that these were mainly mono- and dibrominated products. Few other details of this study were reported.

It has been reported that 1,3,6,8- and 1,3,7,9-tetrabromodibenzo-*p*-dioxins were formed in pyrolysis experiments using tetrabromobisphenol-A (Ramalingam et al., 1985). Few other details of this study were reported.

Table A11 Levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans present in tetrabromobisphenol-A after heating at 240°C or 600°C for 20 minutes (Thies et al., 1990)

Congener	Level (µg/kg tetrbromobisphenol-A)		
	240°C		600°C
	Condensate	Residue	Condensate
MBDD	< 7	< 7	46,000
DiBDD	< 11[a]	< 14[a]	130,000
TrBDD	< 7	< 7	70,000
TeBDD	< 7	< 7	17,000
2,3,7,8-TeBDD	< 75	< 7	12-15
PeBDD	< 14	< 14	480
1,2,3,7,8-PeBDD	not determined	not determined	21-25
HxBDD	< 70	< 70	330
MBDF	< 7	< 7	18,000
DiBDF	< 11[a]	< 8[a]	40,000
TrBDF	< 7	< 7	60,000
TeBDF	< 14	< 14	7,000
2,3,7,8-TeBDF	< 14	< 7	9-10
PeBDF	< 30	< 30	500
1,2,3,7,8-PeBDF	not determined	not determined	20-50
HxBDF	< 140	< 140	500

a) Interference from a co-eluting peak

Pyrolysis of flame retarded polymers

The pyrolysis of ABS containing tetrabromobisphenol-A has been studied using a horizontal quartz tube reactor (Luijk and Govers, 1992). The sample used had a bromine content of 15.12%, which is equivalent to a tetrabromobisphenol-A content of around 25.7%. The sample (0.1 g) was placed inside a furnace for 20 minutes at temperatures between 400°C and 700°C. A carrier gas (990 ml/minute) was continually passed through the reactor and the volatile products were collected in a cold trap. Nitrogen, a mixture of nitrogen and 5% oxygen or a mixture of nitrogen

10% oxygen were used as the carrier gas. The report indicates that there were problems with the clean-up procedure and interferences in the analyses and so not all samples tested could be analysed for polybrominated dibenzo-*p*-dioxins and dibenzofurans. However, it was reported that the pyrolysis experiments predominantly yielded lower brominated dibenzofurans, and that the yields appeared to increase in the presence of oxygen. The results are shown in **Table A12**. The paper indicates that the concentrations reported should be considered as estimates due to a lack of analytical standards for the congeners found. No 2,3,7,8-substituted congeners were found in any samples.

Table A12 Pyrolysis of ABS containing tetrabromobisphenol-A (Luijk and Govers, 1992)

Congener	Yield (µg/kg polymer)											
	Nitrogen atmosphere				Nitrogen + 5% air atmosphere				Nitrogen + 10% air atmosphere			
	400	500	600	700	400	500	600	700	400	500	600	700
MBDD	nd	nd	2	na	1	3	5	100	nd	6	6	5
DiBDD	nd	0.5	5	na	1	15	250	225	2	70	225	75
TrBDD	0.05	0.5	2	na	1	15	145	35	5	40	220	30
TeBDD	nd	nd	nd	na	nd	nd	3	nd	1	2	6	nd
PeBDD	nd	nd	nd	na	nd	nd	nd	nd	nd	nd	nd	nd
MBDF	10	50	10	nd	10	5	10	200	nd	20	265	130
DiBDF	35	30	170	840	25	40	925	2,250	55	190	1,550	2,400
TrBDF	6	11	50	50	3	15	200	230	15	15	220	420
TeBDF	4	13	80	50	10	50	100	15	20	15	70	85
PeBDF	13	15	30	nd	10	50	50	4	nd	20	35	35

nd Not detected. The detection limit not given.
na Not analysed due to analytical interferences.

In a study by Dumler et al. (1989a), polymers containing one of several brominated flame retardants, including tetrabromobisphenol-A and tetrabromobisphenol-A bis(2,3-dibromopropyl ether), were pyrolysed at either 600 or 800°C in three different oven designs (DIN-apparatus, BSI-apparatus and VCI-apparatus). The polymer samples were in granulate form and the sample size was 1-5 g in the DIN- and BSI-ovens and 20-50 mg in the VCI-oven. No information on the pyrolysis time was given. After pyrolysis, analysis (GC/MS) was carried out for PBDDs and PBDFs in both the pyrolysis gases and the solid residues and the yield of these products was estimated on a mass of flame retardant basis (e.g. mg PBDF/kg flame retardant). The analyses were carried out using GC-MS in SIM mode with external standards of one isomer of each brominated congener of dibenzofuran and dibenzo-*p*-dioxin. The following combinations of tetrabromobisphenol-A, derivatives and polymers were tested:

Epoxy laminate/tetrabromobisphenol-A.

Epoxy laminate/copper/tetrabromobisphenol-A.

Polybutylene terephthalate/tetrabromobisphenol-A.

Polycarbonate/tetrabromobisphenol-A.

Polypropylene/5.9% tetrabromobisphenol-A bis(2,3-dibromopropyl ether)/1.5% polystyrene.

The experiments with tetrabromobisphenol-A indicated that polymers containing the flame retardant generated only small quantities of polybrominated dibenzo-*p*-dioxins and dibenzofurans, with the yields ranging up to a few mg/kg polymer. Only mono- to tribrominated congeners were found. The experiments with the tetrabromobisphenol-A bis(2,3-dibromopropyl ether) derivative showed only very low or not detectable amounts of polybrominated dibenzo-*p*-dioxins and dibenzofurans were formed, with no significant differences being seen between the two temperatures studied. When detected, the products again were mainly mono- to tribrominated dibenzo-*p*-dioxin or dibenzofuran congeners.

Hutzinger et al. (1989) reported the results of very similar pyrolysis studies (possibly even the same experiments as Dumler et al. (1989a)) using an epoxy laminate containing tetrabromobisphenol-A and these results are reproduced in **Table A13**. In these tests, samples of the polymer were pyrolysed for ten minutes at 800°C in each of the three ovens. Analysis for brominated dibenzofurans and dibenzo-*p*-dioxins was carried out by GC-MS in SIM mode, quantification being made by comparison with dioxin and furan congeners of every bromination degree (except for pentabromodibenzofuran which used pentabromodibenzo-*p*-dioxin as standard and hexabromodibenzofuran and all other higher dioxins and furans which were quantified with hexabromodibenzo-*p*-dioxin).

Table A13 Results of polymer pyrolysis experiments at 800oC (Hutzinger et al., 1989)

PBDD/ PBDF	Level (µg/kg polymer)		
	DIN-apparatus	BIS-apparatus	VCI-apparatus
MBDD	680	3,100	10,080
DiBDD	4	77	1,860
TrBDD	2	58	nd
TeBDD	nd	nd	nd
PeBDD	nd	nd	nd

Table A13 continued overleaf

Table A13 continued Results of polymer pyrolysis experiments at 800oC (Hutzinger et al., 1989)

PBDD/ PBDF	Level (µg/kg polymer)		
	DIN-apparatus	BIS-apparatus	VCI-apparatus
HxBDD	nd	nd	nd
HpBDD	nd	nd	nd
MBDF	5,060	5,010	21,000
DiBDF	23	190	780
TrBDF	3	160	810
TeBDF	nd	81	4,910
PeBDF	nd	29	nd
HxBDF	nd	nd	nd
HpBDF	nd	nd	nd

nd Not detected. Detection limit not given.

Thies et al. (1990) looked at the amounts of polybrominated dibenzo-*p*-dioxins and dibenzofurans present in various polymers containing tetrabromobisphenol-A or tetrabromobisphenol-A derivatives after heating at 240^{o}C for 20 minutes in a BIS-apparatus or at 600^{o}C for 20 minutes in a BIS-apparatus or at 600^{o}C for 10 minutes in a DIN-apparatus. The concentrations present in both the residue and gas condensate were determined. The results are shown in **Table A14**.

Lahaniatis et al. (1991) studied the formation of 2,3,7,8-tetrabromodibenzo-*p*-dioxin and 2,3,7,8-tetrabromodibenzofuran during the pyrolysis of several epoxy resin/tetrabromobisphenol-A formulations. The experiments were carried out at 400-800^{o}C using a BIS apparatus. Around 100 mg of the sample was pyrolysed for 10 minutes with an air flow of 500 ml/minute and the products formed were analysed by GC-ECD using external standards and by GC-MS (SIM mode) using ^{13}C-labelled 2,3,7,8-tetrabromodibenzofuran or dibenzo-*p*-dioxin as internal standard. The samples tested were an epoxy resin containing 6% tetrabromobisphenol-A with 5% antimony trioxide and copper oxide, an epoxy resin containing 6% tetrabromobisphenol-A and copper oxide, and an epoxy resin containing 6% tetrabromobisphenol-A and copper. The results are shown in **Table A15**. Clausen et al. (1987) reported similar findings that tetrabromobisphenol-A in epoxy resins showed no tendency to form polybrominated dibenzo-*p*-dioxins and dibenzonfurans under similar thermolytic conditions, even in the presence of antimony trioxide.

Table A14 Amounts of polybrominated dibenzo-*p*-dioxins and dibenzofurans in polymers containing tetrabromobisphenol-A or derivatives (Thies et al., 1990)

Congener	Level (µg/kg polymer)											
	ABS with 16% tetrabromobisphenol-A and 6% Sb_2O_3				Polybutylene terephthalate with 10% tetrabromobisphenol-A oligomer and 5% Sb_2O_3		Polycarbonate with 10% copolymerised tetrabromobisphenol			ABS with tetrabromobisphenol-A - bisphenol-A polycarbonate blend (6% copolymerised tetrabromobisphenol-A)		
	240°C		600°C		240°C	600°C	240°C		600°C	240°C		600°C - BIS-apparatus
	Condensate	Residue	Condensate - BIS-apparatus	Condensate - DIN-apparatus	Condensate + residue	Condensate - BIS-apparatus	Condensate	Residue	Condensate - BIS-apparatus	Condensate	Residue	Condensate
MBDD	< 5	< 5	7	< 7	< 2	< 2	< 5[a]	< 60[a]	485	< 5	< 5	< 6
DiBDD	< 5	< 5	70-350	< 7	< 2	2	< 2	< 5	7,240	< 5	< 5	< 50[a]
TrBDD	< 5	< 5	40-200	< 7	< 2	< 1	< 2	< 2	345	< 5	< 5	< 70[a]
TeBDD	< 10	< 40[a]	10-60	< 14	1.2	< 15	< 2	< 5	165	< 5	< 5	50
2,3,7,8-TeBDD	< 10	< 30[a]	< 5[a]	< 7	< 1	4	< 0.2	< 0.5	<3	< 5	< 5	< 6
PeBDD	< 10	< 30	< 35	< 35	< 2	< 7	< 0.2	< 10	80	< 10	< 10	< 20
HxBDD	< 50	< 50	< 70	< 70	< 2	< 35	< 5	< 20	18	< 50	< 50	< 100
MBDF	< 5	70	< 50[a]	< 7	13	17	10	50	1,110	< 5	< 30[a]	< 50[a]
DiBDF	< 5	30	670-1,430	70	10	80	5	31	3,500	< 5	7	210
TrBDF	< 5	< 5	370-530	70	< 2	10	< 2	< 5	770	< 5	< 5	150
TeBDF	< 10	< 10	40-130	< 14	< 5	3	< 2	< 5	70	< 10	< 10	12
2,3,7,8-TeBDF	< 10	< 10	< 15[a]	< 7	< 1	2	< 0.5	< 0.5	< 16[a]	< 10	< 10	< 10[a]
PeBDF	< 20	< 30	< 35	< 35	< 2	< 7	< 5	< 10	33	< 20	< 20	< 20
HxBDF	< 100	< 100	< 100[a]	< 70	< 2	< 35	< 10	< 20	22	< 100	< 1	< 100

a) Interference from a co-eluting peak

Table A15 Formation of 2,3,7,8-tetrabromodibenzofuran and dibenzo-*p*-dioxin from pyrolysis of various polymer/flame retardant formulations (Lahaniatis et al., 1991)

Polymer sample	2,3,7,8-TeBDD (mg/kg polymer)			2,3,7,8-TeBDF (mg/kg polymer)		
	400°C	600°C	800°C	400°C	600°C	800°C
Epoxy resin/6% tetrabromobisphenol-A/ 5% Sb_2O_3/ CuO	nd	nd [6.0][a]	nd [4.4][a]	nd	nd	nd
Epoxy resin/6% tetrabromobisphenol-A/ CuO	nd	nd [3.4][a]	nd [2.0][a]	nd	nd	nd
Epoxy resin/6% tetrabromobisphenol-A/ Cu	nd	nd [5.3][a]	nd [4.0][a]	nd	nd	nd

nd Not detected, detection limit 0.01 mg/kg.

a) 2,3,7,8-Tetrabromodibenzo-*p*-dioxin was not detected in these samples. The figure given in brackets indicates the concentration of 1,3,6,8-tetrabromodibenzo-*p*-dioxin and/or 1,3,7,9-tetrabromodibenzo-*p*-dioxin found in the sample.

IPCS (1995) reported the results of unpublished studies by Satoh and Sugie (1993) investigating the pyrolysis of ABS containing either tetrabromobisphenol-A, or EP-type or EC-type brominated epoxy oligomer derivatives of tetrabromobisphenol-A. In the study the polymer samples were heated to 600°C and the gas and ash were collected and analysed for the presence of 2,3,7,8-substituted polybrominated dibenzo-*p*-dioxins and dibenzofurans. The experiments using ABS with tetrabromobisphenol-A yielded around 0.9 µg/kg of 2,3,7,8-substituted brominated dibenzo-p-dioxins (including some penta- and hexabrominated congeners) and around 22 µg/kg of 2,3,7,8-substituted brominated dibenzofurans. The ABS with the EP-type and EC-type brominated epoxy oligomers yielded respectively < 0.5 µg/kg and 0.5 µg/kg of 2,3,7,8-substituted brominated dibenzo-*p*-dioxins and < 4 µg/kg and < 4 µg/kg of 2,3,7,8-substituted brominated dibenzofurans.

Wichmann et al. (2002) recently investigated the formation of polybrominated dibenzo-*p*-dioxins and dibenzofurans in a series of pyrolysis/combustion experiments in a laboratory-scale incinerator from a variety of polymer systems flame retarded with tetrabromobisphenol-A (both as an additive and reactive flame retardant). The incinerator system used consisted of a furnace containing a quartz tube through which a constant flow of gases (both air and hydrogen bromide) was maintained. The temperature in the combustion zone was 600°C and the gas had a retention time in the combustion zone of 3-4 seconds. The polymer samples used in the test included both brominated and non-brominated epoxy resin mixed with polyethylene. The samples were pulverised before being placed in the combustion tube (0.5 g was used for each polymer) and combusted for ten minutes (the experiments with phenolic resins were carried out for 30 minutes owing to its slow smouldering combustion under the conditions used), followed by a further 10 minutes with the furnace switched off. The air flow rate through the tube was set at 1 l/minute and the flow rate of HBr (when used) was 80 ml/minute. The HBr was used to simulate the effect of a more constant concentration of HBr in the combustion zone (as may be found during actual incineration processes) during the experiment as experiments with tetrabromobisphenol-A alone under similar conditions had indicated that most of the bromine in the molecule had been released (resulting in flow rates of HBr of up to 167 ml/minute) during the first 60 seconds of the experiment. The condensed products, combined from both the combustion tube and the gas stream, were analysed for the presence of polybrominated dibenzo-*p*-dioxins and furans using a GC-MS method. The results of the experiment are shown in **Table A16**.

Table A16 Formation of polybrominated dibenzo-*p*-dioxins and furans from various polymers at 600°C (Wichmann et al., 2002)

Polymer system	Comment	Amount of PBDD		Amount of PBDF	
		mg/kg polymer	mg/kg TBBP-A	mg/kg polymer	mg/kg TBBP-A
Polyethylene incorporating non-brominated epoxy resin	HBr used in gas flow. Ignition occurred.	11.1	-	1.06	-
Polyethylene incorporating non-brominated epoxy resin and TBBP-A as an additive	Bromine content of polymer 3.6%. Ignition occurred.	0.14	2.17	0.97	15.3
Polyethylene incorporating brominated epoxy resin	Bromine content of polymer 3.6%. Ignition occurred.	0.16	2.5	1.08	17.1

In the experiments with the flame-retarded polyethylene, mostly low brominated dibenzofurans were formed with the monobromodibenzofuran congeners being predominant. However, the experiments with the non-flame-retarded polyethylene using a HBr atmosphere resulted in a predominance of tri- and tetrabromodibenzo-*p*-dioxins. The paper concluded that the predominance of brominated dibenzofurans seen in the experiments with flame-retarded polyethylene could probably be attributed to formation from the tetrabromobisphenol-A component (either as an additive or reactively bound into the polymer) of the polymer. However, it should be borne in mind that the effect of different HBr concentrations on product distribution, particularly the predominance of dioxins over furans, was not investigated in detail. Experiments with polyethylene or epoxy resin (both non-flame- retarded) alone in a similar HBr atmosphere yielded a total polybrominated dibenz-*p*-dioxin/furan concentration of 8.47 mg/kg polymer for polyethylene and 18.1 mg/kg polymer for the epoxy resin. In this case a predominance of hexa- to octabromodibenzofuran congeners was formed from the polyethylene and a predominance of di- to tetrabrominated dibenzofurans.

Other experiments

Fluthwedel and Pohle (1993) compared the levels of polybrominated dibenzofurans and dibenzo-*p*-dioxins in combustion residues of electronic equipment from both laboratory studies and real fires. The analysis looked at both the total levels formed and the sum of the levels for the congeners prescribed under the German Dioxin Ordinance (which gives a limit of 2 µg/kg for the sum of eight 2,3,7,8-substituted congeners). The results of the analysis are shown in **Table A17**. In the test fire results, 2,3,7,8-substituted congeners accounted for around 3.1-8.7% of the total congeners found in the fire residues and 2.6-5.2% of the total congeners found in the soot deposits. In real fires, the proportion of 2,3,7,8-substituted congeners was around 5.4% of the total for the fire residues and 8.7-19.9% of the total for the soot deposits. The results show that the levels found in real fires are around 2-3 orders of magnitude lower than those seen in laboratory studies, although a direct comparison is not possible as few experimental details are reported in the paper. In particular, it is probable that flame retardants other than tetrabromobisphenol-A were also present in the materials tested.

Table A17 Comparison of polybrominated dibenzofuran and dibenzo-*p*-dioxins formed during combustion in laboratory tests and real fires (Fluthwedel and Pohle, 1993)

		Fire residues		Soot deposits on walls	
		Total PBDD/F (µg/kg)	PBDD/F as in GefStoffV (µg/kg)	Total PBDD/F (µg/m²)	PBDD/F as in GefStoffV (µg/m²)
Test fires	min	1,310	22	6,220	64
	max	8,700,000	116,540	1,610,000	26,310
Real fires	min	1	1	134	17
	max	107,000	1,148	13,100	149

The results of an unpublished study by Neupert and Pump (1992) into the combustion residues at a large-scale fire involving plastics containing tetrabromobisphenol-A has been reported by IPCS (1995). The fire occurred in a storage area of a plastics production plant in Germany, and involved a large quantity of polycarbonate and polybutylene terephthalate as well as around 180 tonnes of polybutylene terephthalate that was flame retarded with tetrabromobisphenol-A or tetrabromobisphenol-A derivatives. The maximum concentration of 2,3,7,8-substituted polybrominated dibenzo-*p*-dioxins and dibenzofurans (in total eight tetra-, penta- and hexabrominated congeners were analysed for) found in samples of the burnt polybutylene terephthalate material and in ash/slag samples was 0.5 µg/kg. Three soil samples collected from a distance of 1,340 m, 1,460 m and 1,740 m from the fire were also analysed and the concentrations found were <0.5-1.0 ng/kg.

Summary and conclusions from pyrolysis experiments

From the available information it is clear that polybrominated dibenzo-*p*-dioxins and dibenzofurans are formed in the pyrolysis experiments with tetrabromobisphenol-A and its derivatives. The main products formed appear to be the mono- to tribrominated congeners and the yield of these products is generally up to a few tens of mg/kg polymer. Tetrabrominated congeners are also formed in some experiments at lower levels, and higher brominated congeners are found only occasionally. The amounts of 2,3,7,8-substituted congeners formed are very low, frequently below the analytical limit of detection. Since many different test systems have been used, it is difficult to compare directly the results from one test system to the other. It is not possible to relate these findings directly to the likely behaviour of tetrabromobisphenol-A during actual fires or controlled incineration.

Disposal

It has been estimated that in England, Wales, Germany, France and Spain, approximately 63% of old personal computers are disposed of to landfills, 22% are incinerated and 15% are subject to recycling (WWF, 1998). In the United Kingdom, it is thought that currently the vast majority of electrical and electronic equipment is disposed of to landfill or is incinerated. Recycling of equipment is in its infancy and is not currently carried out to a significant extent. A Proposal for a draft Directive on Waste Electrical and Electronic Equipment (WEEE Directive) was adopted on June 13, 2000 by the European Commission. This sets future targets for reuse and recycling this type of equipment. This means that the current disposal practices may change in the future.

When considering the disposal of articles containing tetrabromobisphenol-A, it should be born in mind that they will be mixed with other waste prior or during disposal. As a result, their contribution to formation of hazardous products (e.g. halogenated dibenzo-*p*-dioxins and furans) as to be considered along with the contribution from all other sources.

Incineration

The chlorine and bromine loads of municipal solid waste incinerator feeds have been estimated by various sources and were summarised by Hardy (1997). Chlorine is the most abundant halogen present in municipal solid waste and a typical concentration of 0.7% wt. (i.e. 7 g/kg) has been given. A study of the chlorine content of municipal wastes in the United Kingdom found that the chlorine level was in the range 5-15 g/kg (Clayton et al., no date). The refuse was broken down into various types and these are shown in **Table A18**.

Table A18 Chlorine content of municipal wastes (Clayton et al., no date)

Refuse type	% of total refuse	Chlorine content (% by weight)
Paper	33%	0.37%
Plastic film	3%	2.69%
Dense plastic	3%	6.79%
Textiles	4%	0.70%
Miscellaneous combustibles	5%	2.44%
Putrescibles	20%	0.67%
<10 mm fraction	10%	0.32%
Ferrous metals	7%	nd
Non-ferrous metals	1%	nd
Miscellaneous non-combustibles	5%	nd
Glass	9%	nd

Bromine is present at much lower concentrations than chlorine in municipal waste, and typical bromine levels of around 15 mg/kg (Hardy, 1997) and 20-90 mg/kg of the total waste (Wilken et al., 1990) or 1-4% (Buser, 1987) and 1-15% of the total chlorine (Hardy, 1997) have been reported.

Several studies have looked at the effect of the total bromine load in waste on the formation of halogenated dibenzo-*p*-dioxins and furans and the results are summarised below.

Ten Berge (1995) reported data on the halogen contents on dioxin emissions (as TCDD-equivalents) from municipal waste incinerators in the Netherlands. The results are shown in **Table A19**, and show no relationship between the bromine level in the waste and the dioxin emissions from the incinerators.

Table A19 Bromine and chlorine levels of waste at municipal incinerators in the Netherlands

Waste incinerator	Bromine content of waste (g Br/tonne)	Chlorine content of waste (g Cl/tonne)	Bromine content of waste (% of total Cl)	Dioxin emission from incinerator (µg TEQ/tonne)
A	8.4	2,982	0.28%	28
B	33	3,684	0.90%	262
C	15.6	3,700	0.42%	45
D	9.6	5.274	0.18%	507
E	5.4	1,920	0.28%	42
F	5.4	4,284	0.13%	277

Similarly, Öberg et al. (1987) found very little difference in the amounts of chlorinated dibenzo-*p*-dioxins and furans formed at an industrial waste incinerator (afterburner temperature 1,000-1,030^{o}C) in Sweden when high loads of bromine were present. Low levels of monobromochloro dibenzo-*p*-dioxins and furans were found in the cleaned flue gas.

A study by Söderström and Marklund (2001 and 2002) compared bromine and chlorine in their ability to form halogenated dibenzo-*p*-dioxins and furans during co-combustion of tetrabromobisphenol-A or other brominated flame retardants (hexabromocyclododecane and decabromodiphenyl ether) as a source of bromine with municipal solid waste. The results showed that, using either a bromine source or chlorine source alone, more brominated dibenzofurans are formed than chlorinated ones under equal combustion conditions. The co-combustion of bromine- and chlorine-containing waste resulted in the formation of mixed chloro-bromo products. The results also indicated that under normal combustion conditions, the flame retardants were completely destroyed and that no differences could be seen between the three flame retardants studied in the formation of halogenated dibenzo-*p*-dioxins and furans. The report concluded that it is likely to be unfavourable to co-combust (batchwise) large amounts of bromine with municipal solid waste due to the increased formation of halogenated dibenzo-*p*-dioxins and furans.

Tange et al. (2001) reported the results of studies to investigate the effect of different bromine loads on the formation of halogenated dibenzo-*p*-dioxins and furans using a small-scale model grate combustion furnace. The materials tested included printed wiring board mixtures, TV backplates and other mixed electronic waste typically found at dismantlers. The actual brominated flame retardants present were not given. In the experiments the amount of electrical and electronic equipment in the waste feed was artificially increased to 20-25% of the total feed, resulting in increased bromine levels in the feed of up to 2,750 mg/kg compared with the typical levels in waste of around 30-100 mg/kg. The formation of bromine-containing dibenzo-*p*-dioxins and especially furans was found to increase with increasing bromine input into the reactor feed, but appeared to reach a constant level at bromine loads of ~500-1,000 mg/kg. The major products found contained 1 bromine atom/molecule and it was shown that the total load of halogenated dioxins remained almost constant during the experiments despite the increased load of bromine-containing material. Overall it was concluded that the formation of halogenated dibenzo-*p*-dioxins and furans was dependent on the products of incomplete combustion and if the burnout of the reactor is optimised, the amounts of halogen present in the fuel had no significant influence on the amounts of halogenated dibenzo-*p*-dioxins or furans formed.

During incineration, it is well known that the halogenated dibenzo-*p*-dioxins and furans are formed in the cooler post combustion zone of the waste incinerator via *de novo* synthesis. The relative proportions of bromine to chlorine in most waste prior to incineration indicates that the

major dibenzo-*p*-dioxins and furans formed will contain chlorine only, with mixed bromine/chlorine containing species (most likely containing 1 bromine) making only a very minor contribution. The amounts of bromine only containing dibenzo-*p*-dioxins and furans will be similarly small (Buser, 1987; Hardy, 1997). In addition to this, European Regulations exist on the design of municipal incinerators in order to minimise the formation of chlorinated dibenzo-*p*-dioxins and furans (EEC, 1989a and 1989b) during incineration. Proper incinerator design should also reduce the potential for release to the environment from the brominated dibenzo-*p*-dioxins and furans.

Landfill

A large proportion of waste containing tetrabromobisphenol-A may ultimately end up in landfill. The waste for landfill is likely to be of a similar composition to that considered above for incineration. Once in the landfill, the potential for formation of halogenated dibenzo-*p*-dioxins and dibenzofurans is likely to be small unless a landfill fire occurs. Although these fires are unintentional, they are known to occur and the temperature in a landfill fire can reach up to 800^{o}C (FRS, 1998). As high temperatures are involved, there is the possibility for formation of halogenated dibenzo-*p*-dioxins and furans under these conditions. However, the residence time of the substance in a landfill fire is likely to be much longer than found in the laboratory pyrolysis studies that have been carried out and so it is not possible to say anything about the extent of formation under these conditions.

Summary of disposal

Disposal of tetrabromobisphenol-A-containing products by both incineration and landfill has the potential to lead to the formation of polyhalogenated dibenzo-*p*-dioxins and dibenzofurans. In both cases, tetrabromobisphenol-A will act as one of a number of sources of halogen and so its presence will contribute to, but will not be the major source of, the formation of these products. Control measures are already in place for municipal and hazardous waste incinerators to minimise the formation of chlorinated dibenzo-*p*-dioxins and dibenzofurans, and these same control measures should also reduce the potential for release to the environment of polybrominated dibenzo-*p*-dioxins and dibenzofurans.

Recycling

Plastics

The concentration of polybrominated dibenzo-*p*-dioxins and furans present in air and plastics during grinding and milling of printed circuit board waste containing tetrabromobisphenol-A has been studied by Lorenz and Bahadir (1993). The waste studied was a mixture of printed circuit board waste derived from punch processes, basic plate material containing copper and faulty printed circuit boards. The tests were carried out in a pilot granulation plant containing a hammer mill and impact grinder. The hammer mill was equipped with a separation cyclone and a vibration filter unit and the samples were supplied to the mill either by conveyor belt or by hand. The impact grinder was equipped with a separation cyclone and a six-element filter, and samples were supplied by screw conveyor. The plant was designed to separate the metal-containing fraction from the plastic fraction, and to reduce the amount of waste.

The test with the hammer mill was carried out over a 180-minute period. During the first 35 minutes, the hammer mill was operated at the maximum permissible load rate, during which time 400 kg of shredded material was produced and the temperature of the hammer mill and shredded material reached 90^{o}C and 100-120^{o}C respectively. In total, 1,486 kg of shredded

material was produced over the 180-minute period. The shredded material from the mill was immediately bagged and then introduced to the impact grinder. The impact grinder was operated continuously for 180 minutes. During this time, 1,440 kg of shredded material was produced and the temperature of the grinder increased from 30°C to 180°C.

During the test, air particulate samples were collected near to the hammer mill and impact grinder. These samples, along with samples of the shredded material, were analysed for the concentrations of polybrominated dibenzo-*p*-dioxins and furans. The results of this analysis are shown in **Table A20**.

Table A20 Levels of polybrominated dibenzo-*p*-dioxins and furans in air and shredded material at a pilot printed circuit board shredding plant (Lorenz and Bahadir, 1993)

Congener	Printed circuit board (µg/kg)	Hammer mill		Impact grinder		Separated waste	
		Air (ng/m³)	Shred (µg/kg)	Air (ng/m³)	Shred (µg/kg)	Metal fraction[a] (µg/kg)	Plastic fraction[b] (µg/kg)
MBDD	< 0.05	< 0.05	< 0.04	< 0.1	< 0.05	< 0.04	< 0.05
DiBDD	< 0.04	< 0.04	< 0.3	< 0.08	< 0.1	< 0.04	< 0.1
TrBDD	< 0.02	< 0.02	< 0.02	< 0.02	< 0.05	< 0.01	< 0.05
TeBDD	0.22	< 0.05	0.67	< 0.02	0.73	0.03	0.58
2,3,7,8-TeBDD	< 0.04	< 0.02	< 0.04	< 0.02	< 0.02	< 0.01	< 0.05
PeBDD	< 0.1	< 0.1	< 0.4	< 0.05	< 0.2	< 0.02	< 0.2
HxBDD	< 0.1	< 0.1	< 0.2	< 0.1	< 0.2	< 0.02	< 0.2
HpBDD	< 1	< 2	< 3	< 2	< 3	< 0.3	< 3
OBDD	nd[c]	nd[c]	nd[c]	nd[c]	nd[c]	nd[c]	nd[c]
MBDF	< 0.05	< 0.05	< 0.06	< 0.1	0.05	< 0.04	0.32
DiBDF	< 0.05	< 0.04	< 0.1	< 0.08	< 0.1	< 0.02	0.23
TrBDF	< 0.02	< 0.02	< 0.02	< 0.02	< 0.1	< 0.01	< 0.2
TeBDF	< 0.05	< 0.04	< 0.4	< 0.02	< 0.2	< 0.1	< 0.2
2,3,7,8-TeBDF	< 0.01	< 0.02	< 0.04	< 0.02	< 0.04	< 0.01	< 0.04
PeBDF	< 0.05	< 0.03	< 0.2	< 0.03	< 0.1	< 0.01	< 0.1
HxBDF	< 0.5	< 0.2	< 1	< 0.2	< 1	< 0.1	< 1
HpBDF	< 1	< 0.4	< 2	< 0.4	< 2	< 2	< 2
OBDF	nd[c]	nd[c]	nd[c]	nd[c]	nd[c]	nd[c]	nd[c]

a) Metal fraction of the shredded and separated waste. This had a metal content of 97.3%
b) Plastic fraction of the shredded and separated waste. This had a metal content of 4.1%
c) Not detected. The detection limit for the octabromo congeners was not given

No polybrominated dibenzo-*p*-dioxins or furans were detected in the air samples. The levels present in the shredded samples were also very low, and appear to be mainly related to contamination of the starting printed circuit board material rather than the grinding/milling process.

Meyer et al. (1993) and van Riel (1995) reported the levels of polybrominated dibenzo-*p*-dioxins and dibenzofurans ABS containing tetrabromobisphenol-A with respect to the German Dioxin

Ordinance. The results are shown in **Table A21**. The limits under the Regulations are 1 µg/kg for the sum of isomers 1-4 and 5 µg/kg for the sum of isomers 1-7 (higher limits of 10 µg/kg for the sum of isomers 1-4 and 60 µg/kg for the sum of isomers 1-7 applied until 15 July 1999; van Riel, 1995). The study looked at virgin granulate material, granulate after recompounding and recompounded and remoulded material. All three materials were shown to meet the German Dioxin Ordinance. Similar results were obtained for reprocessing of a polycarbonate/ABS blend containing tetrabromobisphenol-A polycarbonate as a flame retardant (Meyer et al., 1993).

Table A21 Levels of brominated dibenzofurans and dibenzo-p-dioxins in ABS containing tetrabromobisphenol-A both before and after recycling (van Riel, 1995; Meyer et al., 1993)

No	Isomer	Level (µg/kg polymer)		
		Virgin granulate	Recompounded granulate	Recompounded and remoulded material
1	2,3,7,8-TeBDD	< 0.05	< 0.05	< 0.05
2	1,2,3,7,8-PeBDD	< 0.05	< 0.05	< 0.05
3	2,3,7,8-TeBDF	< 0.05	< 0.05	< 0.05
4	2,3,4,7,8-PeBDF	< 0.2	< 0.2	< 0.2
5	1,2,3,4,7,8-HxBDD + 1,2,3,6,7,8-HxBDD	< 0.05	< 0.05	2
6	1,2,3,7,8,9-HxBDD	< 0.05	< 0.05	< 0.05
7	1,2,3,7,8-PeBDF	< 0.05	< 0.05	0.4
Sum 1-4		< 1	< 1	< 1
Sum 1-7		< 5	< 5	< 5

Meyer et al. (1993) also studied the levels of polybrominated dibenzofurans and dibenzo-*p*-dioxins (as per the German Dioxin Ordinance) in ABS containing tetrabromobisphenol-A newly moulded parts (first processing) and parts that were reground and subsequently reprocessed. The results are shown in **Table A22**. The levels of polybrominated dibenzofurans and dibenzo-*p*-dioxins were below the detection limit of the method in all samples analysed and showed that the plastic still met the requirements of the German Dioxin Ordinance even after multiple reprocessing steps.

Table A22 Levels of polybrominated dibenzofurans and dibenzo-*p*-dioxins in ABS during processing and reprocessing (Meyer et al., 1993)

PBDD/PBDF	Concentration (µg/kg or ppb)				
	1st Processing	2nd Processing	3rd Processing	4th Processing	5th Processing
2,3,7,8-TeBDD	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
1,2,3,7,8-PeBDD	< 0.2	< 0.1	< 0.1	< 0.1	< 0.1
2,3,7,8-TeBDF	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
2,3,4,7,8-PeBDF	< 0.2	< 0.1	< 0.1	< 0.1	< 0.1
1,2,3,4,7,8-HxBDD + 1,2,3,6,7,8-HxBDD	< 0.3	< 0.5	< 0.5	< 0.5	< 0.5
1,2,3,7,8,9-HxBDD	< 0.3	< 0.5	< 0.5	< 0.5	< 0.5
1,2,3,7,8-PeBDF	< 0.2	< 0.1	< 0.1	< 0.1	< 0.1

A further investigation of the recyclability of commercially available ABS containing tetrabromobisphenol-A (and also ABS containing a brominated epoxy oligomer) has recently been carried out by Imai (2003). The flame-retarded plastic samples were subjected to a sequence of extrusion steps in which the material was extruded at 210°C, pelletized and then dried, and then re-extruded, pelletized and dried. This recycling sequence was repeated four times and after the last recycling step the material was analysed for the polybrominated dibenzofurans and dibenzo-*p*-dioxins prescribed in the German Dioxin Ordinance. The results of these analyses are shown in **Table A23** for ABS containing tetrabromobisphenol-A and show that none of the prescribed polybrominated dibenzofurans and dibenzo-*p*-dioxins were detetected (the detection limits used in this study are around 10 times lower than those required in the German Dioxin Ordinance). Identical results were obtained for the ABS sample containing the brominated epoxy oligomer. In addition, the mechanical strength, melt flow rate and the fire safety rating of both plastics was determined after each recycling step. Even after four recycling passes these properties in the recycled material were similar to those in the virgin material.

Table A23 Levels of polybrominated dibenzofurans and dibenzo-*p*-dioxins in ABS containing tetrabromobisphenol-A during repeated extrusion and pelletization (Imai et al., 1993)

PBDD/PBDF	Concentration after four recycling steps (µg/kg or ppb)
2,3,7,8-TeBDD	< 0.01
1,2,3,7,8-PeBDD	< 0.03
2,3,7,8-TeBDF	< 0.02
2,3,4,7,8-PeBDF	< 0.04
1,2,3,4,7,8-HxBDD + 1,2,3,6,7,8-HxBDD	< 0.08
1,2,3,7,8,9-HxBDD	< 0.08
1,2,3,7,8-PeBDF	< 0.04

The information available on the levels of polybrominated dibenzofurans and dibenzo-*p*-dioxins in plastics containing tetrabromobisphenol-A indicates that the levels are well below those prescribed in the German Dioxin Ordinance, even after repeated recycling.

At present there is little recycling of thermoplastics containing tetrabromobisphenol-A in the EU. Recycling of many plastics is currently at the experimental stage. This picture, however, may change in the future. Products such as epoxy resins, where tetrabromobisphenol-A is used reactively, cannot easily be recycled by re-melting, instead recycling can theoretically be achieved by depolymerisation back to the starting monomers. This type of recycling is not routinely carried out, and, as it is essentially a chemical process, would appear to have little potential for formation of polybrominated dibenzo-*p*-dioxins and dibenzofurans.

Metals

Except for precious metals, the only other non-ferrous metals that are of economic importance for recycling are aluminium, copper, lead and zinc (Richardson, 1996). Of these, recycling of copper from printed circuit boards is likely to be the main processes that is associated with tetrabromobisphenol-A use.

Harless et al. (1989) detected bromochlorinated dibenzo-*p*-dioxins and furans (containing 1 bromine) in ash from a secondary copper furnace in the United States, but these were found at

much lower concentrations (6-27 times lower) than the chlorinated dibenzo-*p*-dioxins and furans. In this study, the source of bromine was not identified.

Little information is reported on the potential for formation of brominated dibenzo-*p*-dioxins and furans from metal recycling as a result of use of tetrabromobisphenol-A flame retardants. However, since the process again involves relatively high temperatures, the potential for formation of these compounds exists if plastic containing halogen enters into the recycling process along with the metal. Again, tetrabromobisphenol-A is unlikely to be the only source of halogen in these processes. The possibility for formation of chlorinated dibenzo-*p*-dioxins and furans during, for example, secondary copper production is well known and various emission control techniques, similar to those used in incinerators, can be used to reduce the emissions of these compounds to the environment (HMIP, 1994).

Summary of recycling

The available information shows little or no potential for formation of polybrominated dibenzo-*p*-dioxins and dibenzofurans during the recycling of plastics containing tetrabromobisphenol-A.

Formation of polybrominated dibenzo-*p*-dioxins and furans could, in principle, occur during recycling of metals if plastic containing tetrabromobisphenol-A enters into the recycling stream. However, similar to the case with incineration, other sources of halogen are also likely to be present, and emission control techniques can be used in the process.

Conclusions

The conclusions here only consider the processes which may lead to a significant release of decomposition products to the environment. The available information indicates that the levels of these products in tetrabromobisphenol-A itself, and polymers (either virgin or recycled) containing tetrabromobisphenol-A, are low.

From the available information it is clear that tetrabromobisphenol-A can form small amounts of mono- to tribrominated dibenzo-*p*-dioxins and dibenzofurans in laboratory studies when heated to high temperatures. This means that the same or similar products have the potential to be formed in processes where high temperatures are reached during disposal and recycling. Such processes could include waste disposal (incineration or landfill (where fires could occur)), or recycling of plastics or metals contaminated with plastics. In addition, actual fires involving articles containing the flame retardant could also be considered similarly.

In the case of incineration, landfill, metal recycling and accidental fires, the tetrabromobisphenol-A flame retardant is likely to represent a small part of the total halogen available in the process. The available information indicates, particularly in the case of waste incineration and landfill, that chlorine is the prevalent halogen present, and that the main dioxin and furans formed are chlorinated analogues. Monobromo-polychloro analogues have been found, but generally at lower concentrations than the analogues containing chlorine only. This indicates that the majority of the halogenated dioxins and furans in these processes are likely to be formed by *de novo* synthesis. Thus the amounts of halogenated dibenzo-*p*-dioxins formed in these processes are likely to be a function of the total amount of halogen present, to which tetrabromobisphenol-A will make a contribution, rather than solely on the amount of tetrabromobisphenol-A present. The available laboratory studies using tetrabromobisphenol-A cannot distinguish between *de novo* synthesis and direct formation of the brominated dibenzo-*p*-dioxins and furans. It is, therefore, theoretically possible that direct formation of these products could also occur during incineration etc, followed by halogen exchange to give the

mainly chlorinated species. In the case of accidental fires, many other toxic products may also be formed, for example polycyclic aromatic hydrocarbons, which will also contribute to the overall toxicity of the fire products (Spindler, 1997). These products are not related to the presence of tetrabromobisphenol-A.

It should also be noted that halogenated dioxin and furan formation from some of these processes is well known and emission control technology is available for incinerators and metal recycling, that can be used to reduce the amounts of these substances formed in the process to acceptable levels. However, it may be possible that metal recycling and incineration could take place at installations without suitable emission reduction equipment. As landfill fires and other fires are considered to be accidental, no such emission control technology exists for these.

Overall, for disposal by incineration and landfill, metal recycling and accidental fires, it can be concluded that tetrabromobisphenol-A, as a source of bromine, can contribute to the formation of halogenated dibenzo-*p*-dioxins and furans generated during such processes but it is not possible to quantify the amounts or assess the environmental significance of these products.

The available information for recycling of flame retarded plastics indicates that there is little or no increase in the amounts of brominated dibenzofurans and dibenzo-*p*-dioxins formed. Low levels of these products have also been measured in processed plastics, although in all cases the levels are well below those specified in the German Dioxin Ordinance. The recycling of many plastics is still at an experimental stage and is not currently routinely carried out at present. In terms of the environment, the potential for environmental exposure to these substances from plastics processing and recycling appears to be lower than for some of the other processes mentioned above.

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Appendix E Consideration of degradation to bisphenol-A

(Appendix E is in reference to the Enviroment part of the risk assessment report, which will be added later)

Introduction

As discussed in Section 3 of the risk assessment, which will be added later, there is some evidence that tetrabromobisphenol-A can degrade to give bisphenol-A under certain anaerobic conditions, and that bisphenol-A is stable under these same conditions. This has so far been demonstrated conclusively only for marine or saline environments, but it is not possible to rule out that this could also occur in freshwater anaerobic sediments or other anaerobic systems. This Appendix considers the concentrations of bisphenol-A that could arise from this process if it does occur in the environment. The estimation methods used are relatively crude and the concentrations obtained should be considered as very much worst case tentative estimates.

Sediment

In the Technical Guidance Document, the sediment compartment is considered to consist of 90% anaerobic and 10% aerobic conditions. Thus, in theory 90% of the tetrabromobisphenol-A present in sediment has the potential to degrade to give bisphenol-A. Assuming that 90% of the tetrabromobisphenol-A in sediment can undergo this type of reaction, and 1 mole of tetrabromobisphenol-A gives 1 mole of bisphenol-A, the maximum concentrations of bisphenol-A that could be formed under these conditions are shown in **Table E1**. These figures are speculative as it is not certain that this reaction occurs in freshwater sediment, and the calculations do not take into account the rate of the reaction. This possible reaction is considered further in the Risk Characterisation.

Table E1 Estimated maximum concentrations of bisphenol-A that could potentially be formed by anaerobic degradation of tetrabromobisphenol-A in sediment

Scenario		Estimated concentration of tetrabromobisphenol-A in sediment (mg/kg wet wt.)[a]	Estimated maximum concentration of bisphenol-A in sediment (mg/kg wet wt.)
Production of tetrabromobisphenol-A	Example calculation	180-512	68-193
Use as an intermediate in the production of derivatives	Example calculation	231-659	87-249
Reactive flame retardant use	Manufacture of epoxy and/or polycarbonate resins	0.55-1.56	0.21-0.59
	Processing of epoxy resins	$4.5 \cdot 10^{-3}$-0.013	$1.7 \cdot 10^{-3}$-$4.9 \cdot 10^{-3}$
	Processing of polycarbonate resins	$4.5 \cdot 10^{-3}$-0.013	$1.7 \cdot 10^{-3}$-$4.9 \cdot 10^{-3}$

Table E1 continued overleaf

Table E1 continued Estimated maximum concentrations of bisphenol-A that could potentially be formed by anaerobic degradation of tetrabromobisphenol-A in sediment

Scenario			Estimated concentration of tetrabromobisphenol-A in sediment (mg/kg wet wt.)[a]	Estimated maximum concentration of bisphenol-A in sediment (mg/kg wet wt.)
Additive flame retardant use	ABS	Compounding	14.6-41.4	5.5-16
		Conversion	0.67-1.89	0.25-0.71
		Combined compounding/ conversion	15.2-43.3	5.7-16
	Phenolic resin	Compounding	2.95-8.41	1.1-3.2
		Conversion	0.14-0.39	0.053-0.15
		Combined compounding/ conversion	3.09-8.79	1.2-3.3
Regional sources			$6.6 \cdot 10^{-3}$-0.019	$2.5 \cdot 10^{-3}$-$7.2 \cdot 10^{-3}$

a) Values taken from main risk assessment report.

Soil

Of interest to the assessment of the soil compartment is the possible formation of bisphenol-A during anaerobic sludge digestion. If this did occur, then it is possible that the bisphenol-A formed would be applied to agricultural land with the digested sludge.

In order to try to assess the significance of this process a rough estimate has been made of the maximum possible concentration of bisphenol-A that would be present in soil if it was formed from tetrabromobisphenol-A during sludge digestion. The calculation assumes that all the tetrabromobisphenol-A present in sludge (values taken from the EUSES printout in Appendix B) is converted to bisphenol-A on a molar basis, and that when the sludge is applied to agricultural soil, bisphenol-A will be susceptible to biodegradation in the aerobic conditions present. The resulting concentrations in soil have been estimated with EUSES using the appropriate physico-chemical properties and degradation rates for bisphenol-A. These values are shown in **Table E2** and are taken from the Risk Assessment Report for bisphenol-A (ECB, 2002). The resulting concentrations are shown in **Table E3**. These figures are speculative as it is not certain that this reaction occurs during anaerobic sludge digestion, and the calculations do not take into account the rate of the reaction.

Table E2 Properties of bisphenol-A (ECB 2002)

Property	Value
Vapour pressure	$5.3 \cdot 10^{-6}$ Pa at 25°C
Water solubility	300 mg/l
Log Kow	3.4
Biodegradability	readily biodegradable
Rate constant for degradation in soil	0.0231 d^{-1} (half-life 30 days)

Table E3 Estimated maximum concentrations of bisphenol-A in soil that could potentially result from application of sewage sludge

Scenario			Estimated concentration of tetrabromobisphenol-A in sewage sludge (mg/kg dry weight)	Estimated maximum concentration of bisphenol-A in sewage sludge (mg/kg dry wt.)	Estimated maximum concentration of bisphenol-A in agricultural land (30 day average) (mg/kg wet wt.)
Production of tetrabromobisphenol-A	Example calculation		$1.40 \cdot 10^{4}$-$1.57 \cdot 10^{4}$	$6.59 \cdot 10^{3}$	7.0
Use as an intermediate in the production of derivatives	Example calculation		$1.81 \cdot 10^{4}$-$2.02 \cdot 10^{4}$	$8.48 \cdot 10^{3}$	9.0
Reactive flame retardant use	Manufacture of epoxy and/or polycarbonate resins		42.3-47.4	19.9	0.021
	Processing of epoxy resins		0.052-0.058	0.024	$2.5 \cdot 10^{-5}$
	Processing of polycarbonate resins		0.052-0.058	0.024	$2.5 \cdot 10^{-5}$
Additive flame retardant use	ABS	Compounding	$1.13 \cdot 10^{3}$-$1.27 \cdot 10^{3}$	533	0.57
		Conversion	51.6-57.8	24.2	0.026
		Combined compounding/ conversion	$1.19 \cdot 10^{3}$-$1.33 \cdot 10^{3}$	558	0.59
	Phenolic resin	Compounding	230-258	108	0.11
		Conversion	10.3-11.6	4.87	$5.2 \cdot 10^{-3}$
		Combined compounding/ conversion	240-269	113	0.12

European Commission

EUR 22161EN **European Union Risk Assessment Report**

2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol (tetrabromobisphenol-A or TBBP-A), Part II – Human Health, Volume 63

Editors: S.J. Munn, R. Allanou, K. Aschberger, O. Cosgrove, S. Pakalin, A. Paya-Perez, G. Pellegrini, B. Schwarz-Schulz, S. Vegro.

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Environment and quality of life series

The report provides the comprehensive risk assessment of the substance tetrabromobisphenol-A. It has been prepared by the United Kingdom in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

Part I – Environment

This part of the evaluation considers the emissions and the resulting exposure to the environment in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined.

This part of the evaluation will be added later.

Part II – Human Health

This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. The scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment for tetrabromobisphenol-A concludes that there is no concern for workers, consumers and for humans exposed via the environment.

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European Chemicals Bureau (ECB)

European Union Risk Assessment Report

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