EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre

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2,2',6,6'-TETRABROMO-4,4'-ISOPROPYLIDENE DIPHENOL (TETRABROMOBISPHENOL-A or TBBP-A)
Part II – Human Health

CAS No: 79-94-7

EINECS No: 201-236-9

Summary Risk Assessment Report

2006 **22230 EN**

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2006

United Kingdom

The risk assessment of 2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol (tetrabromo-bisphenol-A or TBBP-A) has been prepared by the United Kingdom on behalf of the European Union.

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PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance 2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol (tetrabromobisphenol-A or TBBP-A) that has been prepared by the United Kingdom in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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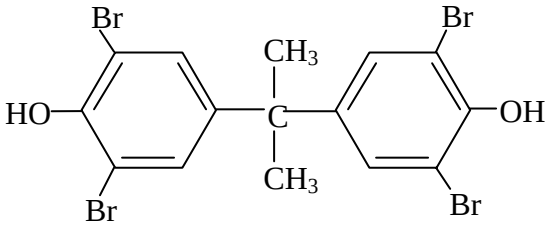
TABLES

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.

Tetrabromobisphenol-A (TBBP-A) is a white crystalline powder at 20°C and 101,325 Pa. The physico-chemical properties of TBBP-A are summarised in **Table 1.1**.

1.2 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties of commercial TBBP-A

Property	Value
Chemical formula	$C_{15}H_{12}Br_4O_2$
Molecular weight	543.9 g/mole
Bromine content	58.8% by weight
Melting point	178°C; 181-182°C
Boiling point	~316°C (decomposes at 200-300°C)
Relative density	2.12; 2.18

Table 1.1 continued overleaf

Table 1.1 continued Physico-chemical properties of commercial TBBP-A

Property	Value
Vapour pressure	< 1.19 10^{-5} Pa at 20°C 6.24 10^{-6} Pa at 25°C
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
Log octanol-water partition coefficient (log Kow)	5.90
Flammability	Not applicable - flame retardant
Autoflammability	Decomposes at 200-300°C
Explosive properties	None
Oxidising properties	None
Acid dissociation constants (pKa)	pKa_1= 7.5 pKa_2 = 8.5
Henry's Law constant	< 0.1 Pa m^3/mole at 20-25°C
Conversion factor	1 ppm = 22.6 mg/m^3 at 20°C

1.3 CLASSIFICATION

1.3.1 Current classification

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

1.3.2 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

TBBP-A is imported into the EU and is used as both a reactive flame retardant (where it is chemically bonded into the polymeric material), and additive flame retardant in plastics. The main uses as a reactive flame retardant are in epoxy and polycarbonate resins. The main uses as an additive flame retardant are in acrylonitrile-butadiene-styrene (ABS) resins and phenolic resins. In addition, tetrabromobisphenol-A is used as an intermediate in the production of other reactive and additive flame retardants.

The current total amount of TBBP-A produced worldwide is estimated at 150,000 tonnes/year. TBBP-A is produced by the bromination of bisphenol-A in the presence of a solvent. The production process is largely conducted in closed systems.

TBBP-A (approximately 13,800 tonnes/year in the EU) is used in a range of consumer goods as a flame retardant. However, since the level of the free residual monomer is very low, consumer exposure to TBBP-A is likely to be insignificant.

Emissions to the environment can occur both to the atmosphere (as vapour and as dust) and waste water. Sources of release include flame retardant production sites, epoxy and polycarbonate resin production sites and polymer processing sites. In addition emissions to the environment could also occur from finished articles (e.g. plastic components) during their use and at disposal.

3 ENVIRONMENT

(to be added later)

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 EXPOSURE ASSESSMENT

Occupational 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.

Six occupational scenarios have been identified:

(1) Addition of TBBP-A powder to mixes of polymer compounds.
(2) Production of laminates for printed circuit boards.
(3) Recycling of computers and electrical equipment.
(4) Assembly of printed circuit boards.
(5) Offices containing electronic equipment.
(6) Recycling of plastic housings.

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 $\mu g/m^3$.

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.

Consumer Exposure

TBBP-A (approximately 13,800 tonnes/year in the EU) is used in a range of consumer goods as a flame retardant. However, since the level of the free residual monomer is very low, consumer exposure to TBBP-A is likely to be insignificant.

Humans exposed via the environment

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 $7.8 \cdot 10^{-5}$ 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 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.

Combined Exposure

Given that consumer exposures are negligible calculation of combined exposure is not necessary.

4.1.2 Effects assessment: hazard identification and dose (concentration) – response (effect) assessment

The available data indicate that TBBP-A is absorbed in humans (given that it has been detected in serum samples from both occupational and non-occupational groups). There is also evidence that once absorbed, TBBP-A and/or its metabolites can be excreted in humans via breast milk (0.01-11 μg/kg lipid from 3 studies).

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. The toxicokinetics following inhalation and dermal exposure have not been investigated. TBBP-A is largely non-respirable (4% particles < 15 μm) and therefore a relatively small proportion of particles may be expected to reach the deep lung following inhalation. The majority of the particles will deposit in the nasopharyngeal region of the respiratory tract and then be swallowed, while the remainder are likely to be exhaled. It is estimated that approximately 75% of TBBP-A particles will be absorbed 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 that dermal absorption is likely to be low. A default value of 10% is therefore assumed for dermal exposure.

Information is available on distribution, metabolism and excretion following exposure via the oral route only. TBBP-A is metabolised by glucuronide conjugation and to a lesser extent sulphate conjugation (accounting for around 30% of the administered dose). Excretion of TBBP-A and its metabolites is predominantly in the faeces (around 95% of the administered dose) with minimal excretion in urine (< 1%) at 72 hours after dosing. Although the general systemic distribution of TBBP-A and/or its metabolites from 4 hours after administration onwards appears to be very low, there is little information on the fate of TBBP-A and/or its metabolites between being absorbed and appearing in the faeces 72 hours post-dosing.

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, 50 g/kg and 10 g/kg, respectively. 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.

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

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 treatment-related, toxicologically significant systemic effects. In a 90-day rat study conducted in accordance with GLP and OECD guidelines no toxicologically significant effects were seen following oral exposure to 100, 300 or 1,000 mg/kg TBBP-A. A decrease in serum T4 levels was observed in all treated males on days 33 and 90 and on day 33 only in all 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 thyroid stimulating hormone (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 gland. In the absence of changes in other parameters of thyroid homeostasis in a species (the rat) that is very sensitive to perturbations in thyroid hormone levels, these decreases are not considered to be adverse. The same decreases in T4 levels were seen in the 100 and 1,000 mg/kg groups of the F_0 and F_1 generations in the 2-generation rat study. However, again, given that there was little impact on other parameters associated with the disruption of thyroid homeostasis in the rat, it is deemed that the decreases observed are not toxicologically significant. In the only conventional repeated dermal exposure study, in which rabbits were dosed with up to 2,500 mg/kg, no toxicologically significant treatment-related effects were apparent.

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. 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 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.

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 toxicity studies, which involved traditional morphological examination of the foetuses. No evidence of developmental toxicity was seen at doses up to 2,500 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 dams 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. A statistically significant decrease in the thickness of the parietal cortex was observed in F2 pups of the 1,000 mg/kg group on PND 11, however, the same effect was not present in these pups on PND 60. Also, no microscopic changes were 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.

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 the 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 up to 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. In view of this, it can be concluded that these kidney effects are likely to be the consequence of the unconventional direct gavage administration of very high doses of TBBP-A to newborn rats, which appear to be more susceptible than young and adult rats to the nephrotoxic effects of TBBP-A. This effect should be considered of potential concern to human infants exposed via the environment.

4.1.3 Risk Characterisation

4.1.3.1 Human health (toxicological properties)

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.

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.

Humans exposed via the environment

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.

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.

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/day. 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 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.

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

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

The only physicochemical hazard identified for TBBP-A is that, in common with many organic materials, the finely powdered material is a significant dust explosion hazard. 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 physicochemical properties is low.

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.

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.

5.2.2 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.