Australian Government

Department of Health

National Industrial Chemicals Notification and Assessment Scheme

Tetrabromobisphenol A

Priority Existing Chemical Assessment Report

Assessment No. 42

May 2020

National Industrial Chemicals Notification and Assessment Scheme

NICNAS

Web: www.nicnas.gov.au

Email: info@nicnas.gov.au

Phone: 1800 638 528

Phone: 61+ 2 857878800

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1 Preface

The Minister for Health (then Health and Ageing) declared, by notice in the Chemical Gazette of 7 June 2005, tetrabromobisphenol A (TBBPA), CAS No. 79-94-7, to be a Priority Existing Chemical (PEC) under Division 5 of the Industrial Chemicals (Notification and Assessment) Act 1989 (the ICNA Act).

Within 28 days of this declaration, importers of TBBPA were required to apply in the approved form for the chemical to be assessed. By notice in the Chemical Gazette, the Director of NICNAS required all persons who introduced the chemical during the period beginning 12 months before the date of the notice and ending 12 months after that date, to provide information about the chemical. Under section 56(2) of the ICNA Act, only persons who had applied for the assessment of chemical (the Applicants) could introduce the chemical into Australia during the assessment period of the chemical.

Ten Applicants (and other users of TBBPA) provided information about the chemical, such as the properties of the chemical, the quantities of the chemical that had been, or were proposed to be imported or manufactured (including handling and storing and methods of manufacture), uses or potential uses of the chemical and other matters specified under Section 58 of the ICNA Act.

The human health and environment risk assessment was then conducted and this report was prepared by officers in the Office of Chemical Safety (OCS) within the Australian Government Department of Health, in accordance with the ICNA Act. Officers from the Australian Government Department of Agriculture, Water and the Environment (DoAWE) contributed to the environmental sections of this report.

In accordance with the ICNA Act, publication of this report revokes the declaration of this chemical as a PEC. Therefore, introducers wishing to introduce this chemical in the future do not need to apply for assessment. However, introducers need to be aware of their duty to provide any new information to the Director, as required under Section 64 of the ICNA Act.

From 1 July 2020, the Industrial Chemicals Act 2019 (the IC Act) replaces the ICNA Act. Section 100 of the IC Act obliges introducers of TBBPA to provide any additional information about TBBPA that has become available to them, to the Executive Director of the Australian Industrial Chemicals Introduction Scheme (AICIS).

For the purposes of Section 78(1) of the ICNA Act, copies of NICNAS assessment reports (including this and other PEC reports) are freely available from the NICNAS website. Hard copies are available free of charge from NICNAS from the following address:

GPO Box 58, Sydney, NSW 2001, AUSTRALIA
Tel: +61 (2) 8577 8800; Free call: 1800 638 528

You can find more information on the NICNAS website.

Acronyms and abbreviations

Acronym / abbreviation	Meaning
ABS	acrylonitrile butadiene styrene
ADG	Australian Dangerous Goods
AICS	Australian Inventory of Chemical Substances
ATSDR	Agency for Toxic Substances and Disease Registry
BAEP	Brainstem auditory evoked potential
BAF	bioaccumulation factor
BCF	bioconcentration factor
BFR	brominated flame retardants
$BMDL_{10}$	dose at which the change in response is likely to be less than 10%
BMF	biomagnification factor
bw	body weight
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations (US)
CTD	characteristic travel distance
decaBDE	commercial decabromodiphenyl ether
DoAWE	Australian Government Department of Agriculture, Water and the Environment
dw	dust weight or dry weight

Acronym / abbreviation	Meaning
EC	European Commission
EC_{10}	concentration at which effects were seen in 10 % of subjects
EC_{50}	median effective concentration
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECOSAR	Ecological Structure Activity Relationship (USEPA software program)
ESD	Emission scenario document
EURAR	European Union Risk Assessment Report
FSANZ	Food Standards Australia New Zealand
GC	gas chromatography
GC-MS	gas chromatography – mass spectrometry
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GM	geometric mean
HIPS	high impact polystyrene
LD_{50}	median lethal dose
LOAEL	low observed adverse effect level
LOEC	lowest observed effect concentration
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
K_{ow}	octanol/water partition coefficient

Acronym / abbreviation	Meaning
kPa	Kilopascal
LDPE	low-density polyethylene
OECD	Organisation for Economic Cooperation and Development
ng	Nanogram
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NTP	National Toxicology Program
PBFR	polybrominated flame retardants
PBT	persistent, bioaccumulative and toxic
PCB	polychlorinated biphenyls
PEC	predicted environmental concentration; Priority Existing Chemical
pentaBDE	commercial pentabromodiphenyl ether
PNEC	predicted no effect concentration
PNW	Post natal week
POP	persistent organic pollutant
QSAR	quantitative-structure-activity relationship
STP	sewage treatment plant
The Act	Industrial Chemicals (Notification and Assessment) Act 1989
TWA	time-weighted average

Acronym / abbreviation	Meaning
US EPA	United States Environmental Protection Agency
VECAP	Voluntary Emissions Control Action Programme
WWTP	waste water treatment plant

2 Overview

2.1 Background

The Minister for Health (formerly Health and Ageing) declared tetrabromobisphenol A (TBBPA), CAS No. 79-94-7, a Priority Existing Chemical (PEC) for full risk assessment under the Act by notice in the Chemical Gazette of 7 June 2005.

TBBPA is one of many polybrominated flame retardants (PBFRs). In 2001, NICNAS published a preliminary PEC assessment of PBFRs as a group (NICNAS, 2001). This was because there was concern over the widespread use of flame retardants in household and industrial situations. As a result, NICNAS published a report focusing on occupational, public and environmental exposure to PBFRs. The report recommended that a full risk assessment be conducted once testing of these chemicals was completed internationally.

A second 'Call for Information' conducted by NICNAS in November 2016 indicated that only two companies were importing TBBPA, either for their own use or for distribution to local manufacturers. Other companies that had been previously importing TBBPA informed NICNAS that they had ceased to import and use TBBPA. Many articles, such as TV sets and computer housings, that had previously contained significant amounts of TBBPA as a flame retardant, no longer contained the chemical. This resulted in a significant decrease in the total volume of TBBPA being introduced into Australia for the year 2015-2016.

2.2 Manufacture and importation

TBBPA is not manufactured in Australia. It is imported into Australia as a pure chemical, in powder form, or as an additive or reactive component in semi-finished products and in finished articles.

In the year 2015-16, nearly 15 tonnes of pure (99 %) TBBPA powder was imported into Australia for use in the manufacture of vinyl ester and acrylonitrile butadiene styrene (ABS) resins. In the same period ~4 tonnes of TBBPA was also imported in formulated products, mainly ABS resins containing <17 % of TBBPA as an additive ingredient. These resins are used at approximately 10 worksites for injection moulding to produce electrical and electronic fittings, such as electrical housings and junction boxes.

2.3 Uses

The main use of TBBPA is as a reactive flame retardant in epoxy resins for printed circuit boards in computers, telecommunications equipment, industrial controls and automotive electronics. TBBPA is also used as an additive flame retardant for low energy applications such as plastic housings for electrical and electronic equipment, mainly computer monitors and printers. It is also used in the manufacture of ABS resins and phenolic resins.

In Australia, TBBPA is mainly used as a reactive flame retardant in the manufacture of vinyl ester resins and as an additive flame retardant in the manufacture of polystyrene resins. When used as a reactive intermediate, TBBPA becomes covalently bound in the polymer and does not leach out. TBBPA constitutes approximately 10-22 % of the final resin composition. As an additive flame retardant, TBBPA is added to polymers during production of articles 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.

2.4 Health effects

TBBPA is rapidly absorbed from the gastrointestinal (GI) tract. Studies in rats indicated that 100 % of the administered oral dose of TBBPA is absorbed from the GI tract with approximately 50 % being excreted in the bile after 24 hours. Dermal absorption is very low.

The majority of administered TBBPA and/or its metabolites is excreted in the faeces. Limited tissue distribution and systemic distribution via the blood suggests that TBBPA does not bioaccumulate. A study using pregnant Wistar rats indicated no significant transfer of TBBPA or its metabolites from maternal circulation to the foetus.

Examination of the bile revealed three metabolites of TBBPA: diglucuronide ester conjugate, glucuronic acid/sulfate ester diconjugate and monoglucuronic acid conjugate, constituting approximately 31% of the total administered dose.

TBBPA has low acute toxicity following all routes of exposure. It is not a skin, eye or respiratory irritant and not a skin sensitiser.

In repeat-dose toxicity studies, adverse effects were not observed in rats or rabbits following either inhalation or dermal exposure. In 2 subchronic oral studies, no adverse effects were observed at exposures up to 1000 mg/kg body weight (bw)/day.

TBBPA was not mutagenic in vitro in bacterial and yeast mutagenicity assays with and without metabolic motivation. It did not:

- cause structural or numerical chromosome aberrations in genotoxicity studies in Chinese hamster lung and human peripheral lymphocytes
- induce other genotoxic endpoints in Chinese hamster cell lines.

In vivo, TBBPA was negative in a peripheral blood micronucleus assay in mice. The results combined indicate that TBBPA is not genotoxic.

In a carcinogenicity study, rats were orally treated with TBBPA. Incidences of adenoma and adenocarcinoma of the uterus in the high dose group of rats were higher than those in the vehicle control group. Testicular tumours were observed in male rats; however, there was no dose-related trend nor pair-wise statistical significance, and the total incidence of all groups (4/200) in the study was within the historical control range (0-4 %). In addition, there were no supportive observations of precursor lesions in the testes. In male mice, the incidence of multiple hepatocellular adenomas was significantly increased in the 500 mg/kg bw/day group and the incidences of hepatoblastoma and hepatocellular carcinoma or hepatoblastoma (combined) in males dosed at 250 mg/kg bw/day were significantly greater than those in the vehicle controls. The liver adenomas in male mice at the high dose were

within the historical control range and there were no observations of supportive precursor lesions. No evidence of carcinogenicity was found in female mice.

A mode of action (MoA) leading to uterine tumour induction in rats by TBBPA is unclear. TBBPA is not genotoxic. The most likely mode of action is via decrease in oestrogen elimination by high doses of TBBPA, resulting in higher serum oestrogen levels. High serum oestrogen may cause mutations in the tumour suppressor gene (Tp53), subsequently leading to tumour formation in the uterus.

Based on these observations, TBBPA is classified, according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), as a Category 2 carcinogen - Suspected of causing cancer (H351).

In several reproductive and developmental studies, no effects upon fertility or reproduction were observed at doses up to 1000 mg/kg bw/day. No treatment-related effects were seen on gestation parameters or on foetal development at doses up to 1000 mg/kg bw/day TBBPA in well-conducted developmental or teratology studies in rats.

In developmental neurotoxicity studies in rats, no adverse effects upon neurodevelopment were observed at doses up to 1000 mg/kg bw/day. In a single exposure protocol with neonatal mice, no effects were observed upon behaviour, learning or memory.

There is some evidence that TBBPA causes developmental toxicity in rats. A study found neurodevelopmental effects on the auditory system following treatment with TBBPA at doses that are not maternally toxic. An adequate supply of thyroid hormone levels is necessary for normal development of the auditory system. Therefore, studies have argued that the observed developmental effects on the auditory system were a result of treatment-related changes in thyroid hormone levels, particularly during the period from gestational day (GD) 17 to postnatal day (PND) 14 (Lilienthal, 2006). The rat thyroid system is known to have a greater sensitivity to some chemicals and physiological perturbations than that of humans given the absence of thyroid binding globulin in rat serum. Therefore, there is insufficient evidence to recommend classifying TBBPA as a developmental toxin in humans.

Toxicity data generated in newborn animals indicated a higher sensitivity during early life stages. In a study of newborn rats, relative kidney weights were significantly increased in both sexes treated with TBBPA compared to the controls. Histopathological examination of the kidneys indicated polycystic lesions associated with dilation of tubules that occurred bilaterally from the cortico-medullary junction to the inner cortex. A no observed adverse effect level (NOAEL) of 40 mg/kg bw/day was established in this study.

This NOAEL (40 mg/kg bw/day) was used for the purpose of risk characterisation in vulnerable groups. TBBPA is not considered to be bioaccumulative and there is no evidence to suggest that it is found in potentially toxic levels in breast milk. Therefore, there is no cause for concern for developmental effects via lactation.

2.5 Public exposure and health risk

TBBPA is used in consumer articles as a reactive as well as an additive flame retardant. Consumers may be exposed to TBBPA when using products that have the chemical in additive form where it may diffuse out. Exposure to TBBPA is expected to be mostly by the dermal route, although exposure through inhalation and oral exposure could also occur.

Potential sources of dermal exposure to TBBPA are household electrical and electronic appliances and decorative laminates treated with TBBPA. Estimates of dermal exposure from this source indicated very low exposure and, therefore, low risk to adults as well as children.

Indirect exposure to TBBPA may occur through the environment via consumption of food and drinking TBBPA-contaminated water and inhalation of indoor and outdoor air carrying TBBPA particles. Exposure from these routes was estimated to be very low, resulting in low risk of adverse effects.

Exposure in toddlers and infants could also occur via breast milk and by ingestion or inhalation of dust/soil. International data on concentrations of TBBPA in household dust showed great variability. Exposure via this route was highest in toddlers, but below levels that could lead to unacceptable risk. Australian data on TBBPA levels in breast milk are not available. Oral exposure of infants to TBBPA was estimated using TBBPA levels in breast milk reported in a UK study. The risk to infants was estimated to be low via this route.

Overall, the available information indicates that, although public exposure will be widespread, it is at a very low level. The risk characterisation indicates that the risk of adults and children being exposed to levels of TBBPA that would lead to health effects noted in repeat-dose animal studies is very low. This is under normal conditions of consumer use.

2.6 Occupational exposure and health risk

The extent of occupational exposure to TBBPA depends on the nature of the work and the different use patterns. Exposure to workers handling TBBPA was estimated based on exposures during:

- transport;
- storage;
- repacking;
- resin and product manufacture;
- use of end products; and
- during recycling of articles containing TBBPA.

The risk to workers of acute adverse health effects, such as inhalation toxicity, skin, eye and respiratory irritation and skin sensitisation, is low. A NOAEL of 42 mg/kg bw/day was selected from a repeated exposure study for risk assessment. A NOAEL for exposure via the inhalation route was not available to determine inhalation risk to workers separately.

To determine risk from dermal exposure, modelled dermal exposure data were converted to internal dose using the dermal absorption values for TBBPA. Total exposure was determined as the sum of the internal dose estimated from dermal, oral and inhalation exposure.

Risk characterisation indicated that, for all tasks, the risk of adverse effects to workers was low as evident from high margins of exposure (>100).

Risk to workers handling semi-finished and end use products is low, as:

- these products contain TBBPA at very low concentrations; and
- the chemical is either incorporated into a plastic matrix or fixed onto fibres.

Workers handling polystyrene resin products containing TBBPA during activities such as cutting and machining for manufacturing shaped products can also be exposed to TBBPA. However, the concentration of the chemical in these products is very low, and the risk of adverse health effects from inhalation or dermal exposure is not expected to be of concern.

Risk of carcinogenicity to workers is considered very low. The most significant carcinogenic effect of TBBPA is the incidence of uterine tumours in female rats at high TBBPA doses and following prolonged exposure. The proposed mechanism suggests that there is an exposure level below which no effect occurs (Section 12.2.5 Summary). Worker exposure to powdered TBBPA is only intermittent – a few days every month. In addition, worker inhalation and dermal exposure to TBBPA is estimated to be very low at these workplaces and dermal absorption of TBBPA is also very low (6 %).

2.7 Environmental effects

The available toxicity data indicate that TBBPA has low acute toxicity to most organisms. However, laboratory studies show that TBBPA can cause adverse chronic reproductive and developmental effects in some fish, amphibian and earthworm species. For example, a 35-day lowest observed effect concentration (LOEC) of 0.31 mg/L was determined for fish embryo survival, and at concentration at which effects were seen in 10% of subjects at 56 days (EC10) of 0.12 mg/kg-soil was reported for earthworm reproduction. The chronic reproductive effects on earthworms are significant because they occur at concentrations that have been detected in some soils internationally. Soils amended with biosolids from Melbourne's Western Treatment Plant are also predicted to have concentrations of TBBPA that are harmful to earthworms. The chronic effects seen in fish only occur at levels that are much higher than those detected in the environment.

TBBPA has been detected in a range of aquatic, terrestrial and avian species at low concentrations. However, the available environmental monitoring data, laboratory data and modelling results indicate that it does not bioaccumulate in organisms (including plants) or biomagnify in the food chain.

TBBPA is persistent under some environmental conditions. Laboratory studies show that it is degraded by microorganisms in anaerobic soil and sediment, but it has been shown to be persistent (half-life >6 months) in aerobic soil and sterilised soil (containing no microorganisms). Environmental monitoring shows that TBBPA can persist over many years in some soils and sediments. Degradation and sorption in soil and sediment are the major routes for TBBPA dissipation in the environment.

In summary, TBBPA has chronic toxicity to several organisms at low concentrations and can be persistent in the environment under some conditions, but has not been demonstrated to be bioaccumulative. Accordingly, TBBPA is classified as 'P', 'Not B', and 'T'.

2.8 Environmental exposure

Australian monitoring data are limited but TBBPA has been detected at low levels (0.13 µg/kg dry weight (dw)) in sediment collected from the Parramatta River which is in an urban/industrial area.

International monitoring data indicate that TBBPA is detected at low levels in air, water, soil and sediment in remote and urban locations, but can be present at higher concentrations in soil and sediment near brominated flame retardant manufacturing facilities and e-waste recycling facilities. For example, in the UK, sediments collected from remote and urban locations contained TBBPA at concentrations of <0.1 – 10 µg/kg, while sediment collected near a brominated flame retardant manufacturing facility contained up to 9753 µg/kg of TBBPA.

The main sources of TBBPA emissions to the environment are from industrial facilities that handle and process TBBPA, and through release from articles that contain TBBPA.

Information supplied by industry indicated that TBBPA processing in Australia occurs exclusively in Melbourne. For the purposes of this assessment, all processing facilities were assumed to be located in the industrial region to the west of Melbourne. Wastewater discharged from these facilities is expected to be the most significant source of TBBPA release to the Australian environment. This wastewater was assumed to be captured by the Western Treatment Plant. The available evidence shows that TBBPA efficiently partitions to biosolids in wastewater treatment plants leading to low concentrations in effluent and significant concentrations in the biosolids. TBBPA that is sorbed to biosolids may not biodegrade (i.e. it may persist in the biosolids), so application of biosolids to agricultural soils may result in significant concentrations of TBBPA in the amended soil. Monitoring data are not available on the concentration of TBBPA in biosolids from the Western Treatment Plant, but the modelled concentration of TBBPA in biosolids from the Western Treatment Plant is 1.25 mg/kg. The estimated concentration in biosolid-amended agricultural soil is 8.3 µg/kg dw. These modelled concentrations are about 6 – 10 times higher than typical concentrations of TBBPA in international data on biosolids, so the modelling appears to be somewhat conservative. Nevertheless, these conservative values are considered to be appropriate for quantitative risk estimation.

Releases from articles containing TBBPA are expected to be diffuse, occurring throughout the lifecycle of the article(s). TBBPA released from articles is expected to partition to soil and sediment and result in low concentrations based on international monitoring data.

2.9 Environmental risks

Soil-dwelling organisms are the only group of organisms identified as potentially being at risk from TBBPA exposure in the Australian environment. These organisms are potentially exposed to significant concentrations of TBBPA when biosolids from the Western Treatment Plant are applied to agricultural soils. The estimated concentration of TBBPA in these amended soils is 8.3 µg/kg, based on the modelled concentration of TBBPA in the biosolids at the Western Treatment Plant (see above). The estimated 'no-effect' level for soil-dwelling organisms is 0.5 µg TBBPA/kg soil, based on chronic toxicity observed in earthworms. Since the modelled concentration of TBBPA in biosolid-amended soil is significantly higher than this no-effect level, organisms living in these soils are potentially at risk.

3 Recommendations

Background

This section provides recommendations arising from the assessment of TBBPA. Recommendations are directed principally at regulatory bodies and importers and formulators of TBBPA and TBBPA products. Implicit in these recommendations is that best practice is implemented to minimise occupational and public exposure and environmental impact.

TBBPA has low acute toxicity following all routes of exposure. It is not a skin, eye or respiratory irritant and not a skin sensitiser.

In repeated-dose toxicity studies, adverse effects were not observed in rats or rabbits following either inhalation or dermal exposure. TBBPA is not genotoxic and has no adverse effects on reproduction and fertility. There is some evidence that TBBPA causes developmental toxicity in rats, although these effects were not significant enough to warrant classification based on these effects.

In a carcinogenicity study, incidences of adenoma and adenocarcinoma of the uterus were observed in rats at high doses. Testicular tumours were observed in male rats; however, there was no dose-related trend nor pair-wise statistical significance, and the total incidence of these tumours in all groups (4/200) in the study was within the historical control range (0-4 %).

In male mice, the incidence of multiple hepatocellular adenomas was significantly increased at very high doses of TBBPA, as were the incidences of hepatoblastoma and hepatocellular carcinoma or hepatoblastoma (combined) at higher doses. No evidence of carcinogenicity was found in female mice.

The most likely mode of action is via decrease in oestrogen elimination by high doses of TBBPA, resulting in higher serum oestrogen levels. High serum oestrogen may cause mutations in the tumour suppressor gene (Tp53), subsequently leading to tumour formation in the uterus. This indicates that there is likely to be a dose threshold below which TBBPA does not cause uterine tumours.

Based on these observations, TBBPA is classified as a carcinogen, with a GHS classification of "Category 2" Carcinogen - Suspected of Causing Cancer (H351).

TBBPA has low acute toxicity to most organisms, but causes adverse effects on reproduction and development in some fish, amphibian and earthworm species. The chronic reproductive effects on earthworms are significant because they occur at concentrations that have been detected in some soils internationally. Soils amended with biosolids from Melbourne's Western Treatment Plant are also predicted to have concentrations of TBBPA that are harmful to earthworms. The chronic effects seen in fish only occur at levels that are much higher than those detected in the environment.

TBBPA has been detected in a range of aquatic, terrestrial and avian species at low concentrations. However, the available environmental monitoring data, laboratory data and modelling results indicate that it does not bioaccumulate in organisms (including plants) or biomagnify in the food chain.

TBBPA is persistent under some environmental conditions. Laboratory studies show that it is degraded by microorganisms in anaerobic soil and sediment, but it has been shown to be persistent (half-life >6 months) in aerobic soil and sterilised soil (containing no microorganisms). Environmental monitoring shows that TBBPA can persist over many years in some soils and sediments. Degradation and sorption in soil and sediment are the major routes for TBBPA dissipation in the environment.

In summary, TBBPA has chronic toxicity to several organisms at low concentrations and can be persistent in the environment under some conditions, but has not been demonstrated to be bioaccumulative. Accordingly, TBBPA is classified as 'P', 'Not B', and 'T'.

Occupational health and safety

Recommendation 1 (to Safe Work Australia)

Classification

Based on the assessment of the available hazard data and in accordance with the Globally Harmonized System of Classification and Labelling of Chemicals (UNECE, 2013), TBBPA is determined to be hazardous and is classified as:

- H351 Suspected of Causing Cancer – Category 2

Environmental Hazards

- H400 Acute Toxicity Category 1
- H410 Chronic Toxicity Category 1

The GHS classification of TBBPA under the is provided in Appendix 1 along with the signal words and hazard statements.

Recommendation 2. Hazard communication (to Industry)

MSDS and label amendments

It is recommended that importers and employers take note of the hazard classification, and amend Material Safety Data Sheets (MSDS), labels and training material, paying particular attention to the following points:

- inclusion of the health hazards, risk and safety phrases as contained in Recommendation 1
- that according to the ADG code, based on its environmental toxicity, TBBPA falls under Class 9. Packaging Group III and UN Number 3077 (environmentally hazardous substance).

Recommendation 3 (to industry)

Based on the assessment findings, powdered or granulated TBBPA should be handled under local exhaust ventilation. Workers should wear face masks, gloves and overalls to reduce exposure to TBBPA.

Recommendation 4 (to government): Compliance with State and Territory legislation

It is recommended that the state and territory occupational health and safety authorities review uptake of the new information in the MSDS and labels, and the safety measures recommended in this assessment.

Environmental safety

Recommendation 5 (to the Melbourne Water Western Treatment Plant)

TBBPA may reach ecologically significant levels in soils amended with biosolids from the Melbourne Water Western Treatment Plant if the levels of TBBPA in the biosolids are as high as those estimated in Section 11.4. It is recommended that TBBPA concentrations be monitored in biosolids generated at the Melbourne Water Western Treatment Plant, and at any other Australian treatment plants serving highly industrialised areas. This would allow refinements to calculations of local predicted environmental concentrations (PECs) so that an informed decision can be made as to whether the sludge is suitable for land application.

Recommendation 6 (to government)

It is recommended that TBBPA be added to the list of organic contaminants that are routinely monitored in sewage treatment effluent and surface waters in Australia.

4 Secondary Notification

This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical based on changes in certain circumstances. Under Section 64 of the Act, the notifiers, and any introducers of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (the Inventory).

Therefore, the Director must be notified in writing within 28 days by the notifiers or introducers:

- under Section 64(1) of the Act if:
    - additional toxicological information becomes available on TBBPA, or degradants of TBBPA
    - additional information has become available to the person about adverse effects of degradants of TBBPA on occupational health and safety, public health, or the environment.

  Or

- under Section 64(2) of the Act if:
    - the chemical (TBBPA) is to be used for any other purpose than those purposes disclosed to the Director through the call for information to industry (2017);
    - the amount of chemical being introduced by a notifier has increased, or is likely to increase, significantly;
    - the chemical has begun to be manufactured in Australia.

The Director will then decide if reassessment (secondary notification and assessment) is required.

From 1 July 2020, the Industrial Chemicals Act 2019 (the IC Act) replaces the ICNA Act. Section 100 of the IC Act obliges introducers of TBBPA to provide any additional information about TBBPA that has become available to them, to the Executive Director of the Australian Industrial Chemicals Introduction Scheme (AICIS).

5 Introduction

5.1 Declaration

The Minister declared tetrabromobisphenol A (TBBPA), CAS No. 79-94-7, a Priority Existing Chemical (PEC) for a full risk assessment under the Act by notice in the Chemical Gazette of 7 June 2005.

The (then) Australian Government Department of Sustainability, Environment, Water, Population and Communities and non-government organisations nominated TBBPA along with other polybrominated flame retardants (PBFRs) for priority review. This was due to widespread use and potential adverse effects from the chemicals on the environment and human health.

At the time that TBBPA was declared as a PEC, its use had increased significantly in Australia giving rise to potentially increased levels of exposure to the public, workers and the environment. However, a more recent call in the Chemical Gazette (NICNAS, 2016), for information on the import and use of TBBPA revealed many Australian companies that had imported TBBPA before, either in a pure form or as a component, have stopped bringing it into Australia. In most brands of TV sets and electronic housings, TBBPA been has replaced by other flame retardants. Many of these companies also indicated that there were no plans of importing TBBPA in the future.

5.2 Objectives

The objectives of this assessment are to:

- characterise the chemical and physical properties of TBBPA
- determine the human health and environmental hazard of TBBPA
- assess the potential for environmental, occupational and public exposure to TBBPA in Australia
- determine the risk of adverse effects to the environment, workers, and the general public from exposure to TBBPA; and
- make recommendations for minimising environmental, occupational and public health risk, and take appropriate hazard communication measures (where applicable).

While several derivatives of TBBPA are available in Australia, it is not the objective of this assessment to determine the risk of these to human health or environment.

5.3 Sources of Information

5.3.1 Industry

In accordance with the Act, introducers of TBBPA and those wishing to introduce TBBPA while the chemical was a PEC had to apply for assessment and supply information. Those formulating TBBPA in Australia and introducers of articles using TBBPA also had to supply information. NICNAS sought:

- information on quantitites introduced
- information on uses of the chemical
- information on the methods used for storing, handling, manufacturing and disposing of TBBPA
- copies of Safety Data Sheets (SDS), labels, and unpublished studies on TBBPA relevant to human health and environmental effects.

5.3.2 Literature review

To enhance efficiency and avoid duplication, this assessment has used assessments carried out by the European Union and the International Programme on Chemical Safety.

For the human health assessment, the primary reference source was a published European Union Risk Assessment Report (EURAR) on TBBPA (EURAR, 2006). For the environmental assessment, the primary reference material was the EURAR on TBBPA (EURAR, 2008). International experts peer-reviewed the draft environmental EURAR on TBBPA. It was discussed at the 20th SIDS Initial Assessment Meeting (SIAM) of Screening Information Data Sets (SIDS) program under the Organisation for Economic Cooperation and Development (OECD). NICNAS staff used the Environmental Health Criteria (EHC) monograph 172 on TBBPA and derivatives (EHC, 1995) and the EHC monograph 192 on Flame Retardants (EHC, 1997) as additional sources of information.

NICNAS staff completed a comprehensive literature search for data published since 2003 to ensure that those studies published after the last literature search conducted for the EURARs were covered. Where the original studies were not sighted but described in detail in the EURAR reports, these have been indicated with an asterisk (*) in this report. Where necessary NICNAS staff reviewed original studies, in particular for critical studies.

5.4 Applicants

Following the declaration of TBBPA as a PEC on 7 June 2005, 10 companies applied for assessment. These applicants supplied information on the:

- properties
- import quantities
- uses of TBBPA
- methods used in the handling, storing and disposal of TBBPA.

Some applicants also provided unpublished studies on TBBPA through the Brussels based Bromine Science and Environmental Forum (BSEF, 2006).

In November 2016, NICNAS conducted a second 'Call for Information' to obtain the latest data on the volume of TBBPA being imported and used in Australia (NICNAS, 2016). In response to this call, only 2 companies reported importing TBBPA, either for their own use or for distribution to local manufacturers. Other companies that had been previously importing TBBPA advised NICNAS that they had ceased to import and use TBBPA. Many articles that had previously contained significant amounts of TBBPA as a fire retardant, such as TV sets and computer housings, were now reported to be free of the chemical. This resulted in a significant decrease in the total volume of TBBPA being introduced into Australia for the year 2015-2016.

Following is the list of applicants:

Amtrade International Pty Ltd

Level 8, 580 St Kilda Road

Melbourne, VIC 3004

Brenntag Australia Pty Ltd

260 - 262 Highett Road

HIGHETT, VIC 3190

Epson Australia Pty Ltd

3 Talavera Road

NORTH RYDE, NSW 2113

Hexion Specialty Chemicals Pty Ltd

2 - 8 James Street

Laverton North, VIC 3026

LG Electronics

2 Wonderland Drive

EASTERN CREEK, NSW 2766

Marchem Australasia Pty Ltd

558 – 562 Geelong Road

Brooklyn, VIC 3012

Martogg Group (trading as) Kantfield Pty Ltd

185-195 Frankston-Dandenong Road

DANDENONG, VIC 3175

NSW Department of Environment and Conservation

59-61 Goulburn Street

SYDNEY, NSW 2000

Plastral Pty Ltd

130 Denison St

HILLSDALE, NSW 2036

Samsung Electronics Aust. Pty Ltd

3 Murray Rose Avenue

SYDNEY OLYMPIC PARK, NSW 2127

6 Background

6.1 Overview of flame retardants

Flame retardants are chemicals that inhibit or reduce the spread of fire when added to combustible material such as clothes and plastic casings. There are over 175 different types of flame retardants, which are generally divided into classes that include:

- halogenated organic (usually brominated or chlorinated)
- phosphorus-containing
- nitrogen-containing
- inorganic flame retardants.

The brominated flame retardants (BFRs) represent a major industry, involving high-production chemicals with a wide variety of uses. This is mainly because of their low cost and high performance efficiency.

The basic mechanisms of flame retardancy vary depending on the specific flame retardant and substrate. Flame retardants can be additive or reactive. Additive flame retardants are added to a polymer without bonding or reacting with the polymer. For instance, they could be mixed into plastics before, during, or after polymerisation and dispersed evenly throughout the product, but not chemically bound to it.

As they are not chemically bonded, additive flame retardants sometimes tend to bleed out of a product and vaporise or collect at the surface. This process is known as 'blooming', resulting in the gradual loss of flame retardancy. The degree (i.e. rate) at which blooming may occur is dependent on a number of factors. These include:

- size and shape of the flame retarding molecule/polymer
- geometric structure of the plastic matrix
- stability of the flame retarding molecule/compound.

Flame retardants are also released in plastic dust by breakdown of articles in which they are incorporated. Laundering of materials treated with additive flame retardants can result in gradual leaching. Physical wear and tear over time can also displace flame retardants applied as surface coatings.

In contrast with additive flame retardants, reactive flame retardants undergo reactions that chemically bind them to the raw materials that are used in the final product and the original molecule is no longer present. This prevents the retardants from bleeding out of the polymer, resulting in the product's retention of its flame retardant property. As the original molecule is no longer present, breakdown of the structure of the article does not release the flame retardant.

The choice of a given flame retardant depends on the type of application, and their suitability is subject to variables such as:

- the material to be flame-retarded
- the fire safety standards with which the product must comply
- cost considerations

- recyclability.

For materials that are being flame-retarded, the effects on the physical properties of the end product and the effects on the product during mixing and transformation need to be considered. For additive flame retardants, compatibility with the polymer or the textile being treated is important as it avoids their migration to the surface. Migration of flame retardants to the surface of polymers or articles (blooming) results in the reduction of the product's flame retardant property. Exposure considerations at each life cycle stage of the flame-retardant chemical need to be taken into account, including:

- during production and transport of raw materials
- manufacturing
- assembling of semi-finished products
- use of end products and service life
- waste disposal
- recycling or incineration (OECD, 1994).

6.1.1 Mechanism of action of brominated flame retardants

Solid materials burn when a heat source increases the internal kinetic activity of molecules in the material. They start to decompose into shorter chain molecules that eventually vaporise into flammable gases (i.e. pyrolysis). These gases react with oxygen (O_2) in the air and burn. Heat from this combustion causes further pyrolysis and further combustion in an ongoing cycle. Highly reactive free radicals (for example $H^{\bullet}$, $OH^{\bullet}$, $R^{\bullet}$, $O^{\bullet\bullet}$ and $OR^{\bullet}$) are released during pyrolysis and help sustain a fire by propagating a radical chain reaction, releasing large quantities of energy into the flames.

Flame retardants can act in various ways to interfere with combustion during a particular stage of this process, for example during heating, decomposition, ignition or flame spread. They can decrease the ignition capacity by:

- increasing the capacity of the product to withstand heat or (once a fire has already begun)
- reducing the tendency of the fire to spread by reacting with the product and forming a less flammable char or non-combustible gaseous layer.

Brominated flame retardants mainly act by hindering the ignition or combustion process through interfering with the free radical mechanism in the gaseous phase of the combustion process. When brominated flame retardant compounds absorb enough heat, they release bromine (Br•) as a free radical. Br• free radicals are heavy and low-energy radicals, and they react with the flammable gaseous hydrocarbon molecules to give HBr. The HBr then reacts with the high-energy H• and •OH radicals to give water (H_2O) and the much lower energy Br• radicals, which are then available to begin a new cycle of H• and •OH radical removal. The reaction of the bromine with the reactive radicals interferes with the propagation of chain reactions and withdraws energy from the combustion–propagation mechanism. The exothermic processes stop and the system cools down, and the supply of flammable gases is reduced or suppressed.

The effectiveness of halogenated flame retardants depends on the quantity of the halogen atoms they contain and also, very strongly, on the control of the halogen release. For

instance, because chlorine (another halogen) is released over a wider range of temperatures than bromine, it is then present in the flame zone at lower concentrations and so is less effective. Bromine is released over a narrow temperature range, thus resulting in optimal concentrations in the flame zone.

6.1.2 Classes of flame retardants

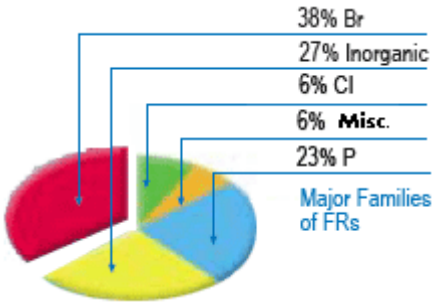
Chemicals used as flame retardants can be classified into 4 main classes:

- inorganic (including antimony, aluminium, boron, magnesium and tin compounds)
- halogenated
- organophosphorous (primarily phosphate esters, chlorinated phosphate esters)
- nitrogen-based products.

Bromine and chlorine are the only halogens used in flame retardant compounds with commercial significance, the former being more important due to its greater flame retarding efficiency.

A major producer of flame retardants made the graph below. It provides an indication of the relative global market proportions of the main classes of flame retardants.

Major families of flame retardants (ICL Industrial Products, 2013)



Key: Br=bromine-based; Cl=chlorine-based; P=Phosphorous-based

Halogenated flame retardants can be further divided into 3 classes based on chemical structure:

- aromatic
- aliphatic
- cycloaliphatic.

They can also be subdivided based on whether they are chlorine- or bromine-containing (eg brominated flame retardants, or BFRs).

In general, among the BFRs, those in the aromatic group tend to be the most thermally stable. They may be processed in thermoplastics at fairly high temperatures without the use of stabilisers and at very high temperatures with stabilisers.

Aliphatic compounds tend to break down more easily and are more effective at lower temperatures. They usually require thermal stablilisers for processing as they are less temperature-resistant (IPCS, 1997).

6.2 International Perspective

TBBPA is the most commonly used brominated flame retardant in the world. It is used mainly as a reactive flame retardant in printed circuit boards found in electrical devices (BSEF, 2006). TBBPA may also be used as an additive flame retardant in acrylonitrile-butadiene-styrene (ABS) and in high-impact polystyrene (HIPS). HIPS is used in automotive parts and plastic housings of appliances (Hakk, 2001; ICL 2012; ICL, 2013).

According to a report by Ryunosuke et al. (2010), 'about 120000 tonnes/year of TBBPA are consumed worldwide, of which 75% is used in Asia, 15% in the USA and 9% in Europe'. As a comparison, in 1999, a study estimated use of TBBPA at 21600 tonnes in the USA and 85900 tonnes in Asia. About 13800 tonnes/year of TBBPA is used in Europe and ~40000 tonnes of TBBPA and its derivatives in Japan each year (Nagayama, 2000; EURAR, 2006). With annual manufacture of TBBPA exceeding 1 million pounds (450 tonnes) in the USA (120 million pounds (55000 tonnes) in 2011), the USA listed it as a High Production Volume (HPV) chemical.

The use of TBBPA is restricted or prohibited in Argentina, Canada and the United Arab Emirates (Galleria Chemica, 2019). In the US, several states and section 8(b) of the chemical inventory of the Environmental Protection Agency (EPA) Toxic Substances Control Act (TSCA) list TBBPA as a 'chemical of concern'. Manufacturers and importers of TBBPA must provide the EPA with copies of unpublished health and safety studies (Haneke, 2002). On 1 April 2016, the governor of Washington state signed the Engrossed Substitute HB 2545 'The toxic-free kids and families act' into law. It restricted the use of 5 flame retardants (FRs), including TBBPA in an additive form, in children's products as defined under RCW 70.240.010 as well as in residential upholstered furniture (State of Washington, 2019). This legislation took effect on 1 July 2017.

The chemical is also listed in a number of voluntary standards, including the International Zero Discharge of Hazardous Chemicals (ZDHC) Manufacturing Restricted Substances List, International Apparel & Footwear International RSL Management Group (AFIRM) - Restricted Substances List, US Banned Lists of Chemicals Cradle to Cradle Certified Product Standard - Banned list of chemicals for technical nutrients.

The IPCS published a general review of flame retardants, including TBBPA, in 1997 (EHC 192, 1997). The German Chemical Society Advisory committee on existing chemicals (BUA) published a report on TBBPA in 2003. The former European Chemicals Bureau published the human health section of the EURAR on TBBPA in 2006. In its conclusion, it identified no health effects of concern for any exposure scenarios and consequently recommended no further testing or risk reduction measures. The environmental section of the EURAR was published in 2007. International experts peer-reviewed the human health and environmental hazard assessment sections of the draft EURAR on TBBPA. Recommendations were agreed to at the 20th OECD SIAM (TBBPA SIAP, 2005). The EU Risk Assessment on TBBPA was finalised and published in the EU Official Journal on 18 June 2008. The assessment identified an environmental risk for soil, sediment, and aquatic organisms when TBBPA was used in the processing stage with ABS plastics.

TBBPA was registered under the EU regulatory framework for Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) in 2010. The European Chemicals Agency (ECHA) administers REACH. Companies were required to report to ECHA the uses, properties and risks of substances registered under REACH (REACH, 2015). The EU has also conducted human health and environmental risk assessments of TBBPA (EURAR, 2006, 2008).

In 2009, the European Food Safety Authority (EFSA) issued a call for data on brominated flame retardants including TBBPA. The panel on contaminants in the food chain (CONTAM Panel) of EFSA delivered its scientific opinion on TBBPA and its derivatives in food in 2011. The CONTAM Panel evaluated the results from the analysis of TBBPA in 652 food samples spanning the period 2007 to 2010 and reported them to be less than the limit of quantification (LOQ).

Since a general population exposure estimate was not possible, the CONTAM Panel estimated worst case scenario intake estimates for adult fish consumers and toddler high cow's milk consumers. They identified a $BMDL_{10}$ of 16 mg/kg bw/day for thyroid hormone changes from a 28-day study as the critical reference point. Due to uncertainties and limitations in the database, they concluded that it was inappropriate to use this BMDL to establish a health based guidance value. Therefore they used a margin of exposure (MOE) approach for the health risk assessment of TBBPA.

In view of the large MOEs, the CONTAM Panel concluded that current dietary exposure to TBBPA in the European Union does not raise a health concern. Also, exposure of infants via human milk does not raise a health concern. Additional exposure, particularly of young children, to TBBPA from house dust is unlikely to raise a health concern. The CONTAM Panel recognised that there is a need for information on production volumes, use, chemical characteristics, occurrence in food and toxicity of TBBPA derivatives.

The International Agency for Research on Cancer (IARC) has classified TBBPA as 'probably carcinogenic to humans (Group 2A carcinogen)' (IARC, 2018). They based this on their conclusion that 'there is inadequate evidence in humans for the carcinogenicity of tetrabromobisphenol A and there is sufficient evidence in experimental animals for the carcinogenicity of tetrabromobisphenol A'.

Health Canada and Environment Canada published TBBPA screening assessment reports in November 2013. The assessments concluded that TBBPA does not constitute a danger to human health based on current exposure estimates (Health/Env Canada, 2013).

On 20 March 2015, Denmark included TBBPA in the EU Community Rolling Action Plan (CoRAP) for evaluation. CoRAP further studied substances identified according to risk-based criteria developed by ECHA and member states competent authorities. TBBPA was selected as a CoRAP substance based on:

- its potential to cause endocrine disruption
- its known carcinogenic/mutagenic/reprotoxic properties
- exposure
- aggregated tonnage (REACH, 2015).

Effective 27 October 2017, the California State Office of Environmental Health Hazard Assessment (OEHHA) added TBBPA to the list of chemicals known to the State of California

to cause cancer for purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) (OEHHA, 2017).

6.3 Australian Perspective

NICNAS staff conducted a preliminary PEC assessment of polybrominated flame retardants (PBFR), including that of TBBPA. The focus was on use patterns and potential exposure. NICNAS published the report in 2001 (NICNAS, 2001). The report recommended a full risk assessment following completion of testing under the OECD Program.

In October 2004, NICNAS called for information under Section 48 of the Industrial Chemicals (Notification and Assessment) Act 1989 to determine the most consumed PBFRs in the country. The survey found that while TBBPA was not manufactured in Australia, the importation of TBBPA more than doubled in 2003-04 compared to 1998-99. TBBPA was also the second most used PBFR, with approximately 70 tonnes being imported in 2003-04. The Minister declared TBBPA a Priority Existing Chemical for full risk assessment on 7 June 2005.

TBBPA is currently listed in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia) as an environmental hazard with the risk phrases:

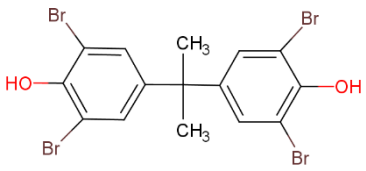
- R50 'Very toxic to aquatic organisms'
- R51 'Toxic to aquatic organisms'
- R52 'Harmful to aquatic organisms'
- R53 'May cause long-term adverse effects in the aquatic environment'.

The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) does not list TBBPA.

7 Chemical Identity and Composition

7.1 Chemical identity

Chemical identity information

IUPAC name	**2,2′,6,6′-tetrabromo-4,4′-isopropylidenediphenol**
CAS No:	79-94-7
SMILES	C(C1cc(c(O)c(c1)Br)Br(c1cc(c(O)c(c1)Br)Br)(c)C.
Synonyms	TBBPA; TBBA; phenol, 4,4'-(1-methylethylidene)bis(2,6-dibromo-); 2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol; 2,2',6,6'-tetrabrom-4,4'-isopropylidendiphenol; 2, 2-bis (4'-hydroxy-3',-5'-dibromophenyl) propane; bis(phenol, 2,6-dibromo), 4,4'-(1-methylethylidene); bisphenol A, tetrabromo-; 3,3',5,5'-tetrabromobisphenol A
Trade name	BA 59; BA 59P; Bromdian; CP 2000; FG 2000; Fire Guard 2000; Firemaster BP 4A; Flame Cut 120G; Flame Cut 120R; FR 1524; GLCBA 59P; NSC 59775; PB 100; RB 100; Saytex CP 2000; Saytex RB 100; Saytex RB 100PC.
Molecular formula	$C_{15}H_{12}Br_4O_2$
Molecular weight	543.9
Structural formula	

7.2 Impurities and Additives

Australian industry has indicated that commercial TBBPA imported into the country has a purity of approximately 99%. The EHC (1995) reported that the purity of commercial TBBPA is 98.5%. The impurities were water at 0.1%, hydrolysable bromine at 0.006% and ionic bromine at 0.01%. Penta- (31 μg/kg), hexa- (12 μg/kg) and octa-brominated dibenzofurans (19 μg/kg) were also present in commercial TBBPA at trace amounts. There are no additives in commercial TBBPA. The bromine content of commercially available TBBPA is 59 % (Great Lakes, 2003).

7.3 Physical and chemical properties of tetrabromobisphenol A

Commercial TBBPA is a fine white to off-white crystalline powder. Information on vapour pressure, water solubility and environmental partitioning are discussed further below. Due to its application as a flame retardant, it is assumed to not have flammability properties (ATSDR, 2004).

7.3.1 Physical properties

Table 1 – Summary of physicochemical properties of TBBPA

Property	Value	Reference
Physical state	White crystalline powder with phenolic smell	Albemarle, 2001 Great Lakes, 2003
Boiling point	~250°C (decomposes)[a]	DSBG, 2003
Melting point	181 – 182°C	EHC, 1995; DSBG, 2003
Specific gravity	1.76 – 2.18 g/cm^3	Great Lakes, 2003
Water Solubility (mg/L @ 25^{0}C)	0.24 (non-buffered reagent water) 0.148 (pH 5.0) 1.26 (pH 7.0) 2.34 (pH 9.0) Pure water (pH 6.71): 0.063 (21 °C)	MacGregor and Nixon, 2002
Vapour pressure (Pa)	<1.19×10^{-5} Pa at 20°C [c] 8.04×10^{-6} Pa at 25°C	Lezotte and Nixon, 2001
Granulometry	31.8 – 52.2 µm[b]	Inveresk, 2001
Partition coefficient (Log K_{ow})	5.90 ± 0.03	MacGregor and Nixon, 2001; USEPA, 2015a; EURAR, 2008; Health/Env Canada, 2013
Log Koc	5.75	EPIWin v3.11

Property	Value	Reference
Henry's Law Constant	0.014 – 0.054 Pa m^3/mole	EURAR, 2006
Dissociation constant (pKa)	pKa_1 = 7.5 pKa_2 = 8.5	WHO/IPCS, 1995

[a] This is considered to be the decomposition temperature rather than the actual boiling point temperature. Based on the chemical structure the Syracuse Research Corporation's MPBPWIN program (Ver. 1.28) estimated a boiling point of 486 °C (EURAR, 2006). Thermal degradation of TBBPA commences at around 185 °C, and becomes important above 230 °C (Marsanich, 2004).

[b] Approximately 4 % of the particles had an aerodynamic diameter of <15 μm.

[c] TBBPA releases Br_2/HBr gases as it decomposes at temperatures >200 °C (EURAR, 2006). This reaction accounts for its flame retardant property.

TBBPA has two acid dissociation constants of pKa_1 = 7.5 and pKa_2 = 8.5 (EHC, 1995). This means that in environments with pH values greater than 7-8, TBBPA will be present in the ionised form (EURAR, 2006). Under lower pH conditions TBBPA will be present in an undissociated form. For conversion of units for TBBPA dust in air, 1 ppm (TBBPA in air) = 0.02 mg/L under standard conditions (EHC, 1995).

7.3.1.1 Water Solubility

MacGregor and Nixon (2002) determined the water solubility of TBBPA in water at 25°C using the generator column method with water buffered at pH 5.0, 7.0 and 9.0 and non-buffered reagent water. The test followed OECD Test Guideline (TG) 105 as well as EPA OPPTS 830.7860 and they conducted it according to good laboratory practice (GLP).

The test substance was a composite of 3 commercial samples. Analysis of the composite sample showed a purity of 99.17 % TBBPA. In the pH 5.0 buffered solution, the mean concentration of TBBPA from both the high and low flow rate tests was 0.148 mg/L (total range of 1.25-1.28 mg/L). In the pH 7.0 buffered solution, the mean concentration of TBBPA from both the high and low flow rate tests was 1.26 mg/L (total range of 1.25-1.28 mg/L). In the pH 9.0 buffered solution, the mean concentration of TBBPA from both the high and low flow rate tests was 2.34 mg/L (total range of 2.03-2.51 mg/L). Finally, in the non-buffered reagent water, the mean concentration of TBBPA from the high and low flow rate tests was 0.24 mg/L (total range of 0.236-0.243 mg/L).

Other international chemical reviews have been undertaken for TBBPA including those by the US EPA, EU and Health/Env Canada (EURAR, 2008; Health/Env Canada, 2013; USEPA, 2015a). The US EPA has reviewed available data for determining the water solubility of TBBPA. Its review recommends use of solubility of 4.16 mg/L at neutral pH at 25°C. Reports from a chemical manufacturer originally reported these data in 1978. The EU and Health Canada reviews indicate use of the value listed above, 0.24 mg/L, a value from more recent

assessments. The EU risk assessment notes that the assessment of fate is not particularly sensitive to the chosen water solubility value.

Solubility of TBBPA appears to increase as pH increases, with the solubility at pH 9.0 (2.34 mg/L) being almost 20 times that at pH 5.0 (0.128 mg/L). TBBPA could exist in an ionised form at higher environmentally relevant pH values. Consequently, the water solubility would be expected to be dependent on the pH of the water and the results seem to confirm it.

An assessment of water solubility at various pH values was undertaken (Kuramochi et al., 2008). The solubility of TBBPA was:

- 0.171 mg/L at pH 3
- 4.15 mg/L at pH 7.6
- 30.5 mg/L at pH 8
- 228 mg/L at pH 8.5
- 1510 mg/L at pH 8.9
- 27900 mg/L at pH 9.5.

These data show an effect on water solubility by changing the pH as the molecule ionises.

7.3.1.2 Vapour Pressure

The vapour pressure of TBBPA was determined at ambient temperature using a spinning rotor gauge (SRG) (Lezotte and Nixon (2001). The study was performed according to GLP and followed OECD TG 104 and EPA OPPTS 830.7950. The test substance was a composite of 3 commercial samples. Analysis of the composite sample revealed a purity of 98.9 % TBBPA. The mean vapour pressure measure of TBBPA was determined to be $<1.19x10^{-5}$ Pa.

The US EPA chemical review recommends use of a value of $<1x10^{-6}$ mm Hg @25°C which is close to the value listed above (USEPA 2015a).

The EU and Health Canada reviews recommend the value determined by the SRG method, $<1.19x10^{-5}$ Pa (EU 2008; Health/Env Canada 2013).

In considering the long range transport potential of TBBPA, Wania (2003) report a vapour pressure of $8.04x10^{-6}$ Pa @ 25°C. The report estimated the value using gas chromatography (GC) retention times, but provided no actual experimental details.

Based on the scale of Mensink et al. (1995), TBBPA is classed as very slightly volatile.

7.3.1.3 Octanol/Water Partition Coefficient

The n-octanol/water partition coefficient (K_{OW}) of TBBPA was determined at 25°C using a column elution method (MacGregor and Nixon, 2001). The test followed EPA OPPTS 830.7560 and was conducted according to GLP. The K_{OW} of TBBPA was calculated to be $7.97x10^{5}$, or log K_{OW} = 5.90.

All of the more recent chemical reviews also recommend the use of this value for log K_{OW} – 5.9 (EU 2008; Health/Env Canada 2013; USEPA 2015a).

As observed in the water solubility study above, solubility is dependent on pH of the water, and dissociation may be expected in the environmental pH range. Therefore; it could be

expected that as pH increases, log K_{OW} may decrease. In this study, the pH of the reagent water is unclear, although it appears to be the same as that the above solubility study used for the unbuffered reagent water.

In the assessment of water solubility at various pH values described above, the authors used measured solubilities in calculating K_{OW} (Kuramochi et al., 2008). The modelled log K_{OW} values for TBBPA were:

- 6.53 at pH 3
- 4.75 at pH 7.5
- 3.00 at pH 8.1
- 1.25 at pH 9.2
- -0.293 at pH 10.2
- -0.769 at pH 11
- -1.22at pH 11.8.

This confirms the change in log K_{OW} as pH increases.

7.3.1.4 Dissociation

WHO (1995) reports 2 acid dissociation constant (pKa) values for TBBPA of 7.5 and 8.5. This is consistent with the observation that TBBPA has different solubilities at different pH values, and with 2 acidic hydrogen atoms in the structure.

Health Canada's review includes reference to another study assessing dissociation Kuramochi et al., 2008). The pKa1 and pKa2 from this study were 6.79 and 7.06. These values indicate that ionisation is likely at environmental concentrations. All of the published international reviews recommend using the WHO values for dissociation (EU 2008; Health/Env Canada 2013; USEPA 2015a).

7.3.2 Chemical properties

The basic structure of TBBPA consists of 2 hydroxyphenyl rings linked by a carbon bridge with bromine substitution at the 3, 3', 5 and 5'-position relative to the carbon bridge.

TBBPA contains 58.7 % bromine. When pyrolyzed in open quartz tubes for 10 minutes, TBBPA produces polybrominated dibenzo-p-dioxins (PBDDs) and -furans (PBDFs) at 700°C. When used as a flame retardant, TBBPA contains <0.01-0.05 µg/kg PBDDs and <0.01-0.02 µg/kg PBDFs.

Chromatographic methods coupled with mass spectrometry (MS) or other detectors can detect TBBPA. Gas chromatography (GC) and GC/MS are used after conversion of TBBPA to the diethyl derivative by ethylation.

8 Manufacture, Importation and Use

8.1 Manufacture

TBBPA is produced by the bromination of bisphenol A in the presence of a solvent. This reaction may be conducted:

- in the presence of a hydrocarbon solvent only or
- with water, 50 % hydrobromic acid or aqueous alkyl monoethers.

When methanol is used as the solvent, methyl bromide is formed as a by-product. The production process is largely conducted in closed systems (WHO/IPCS, 1995).

TBBPA is not manufactured in Australia or Europe. It is produced in the USA, Israel, China and Japan. A study estimated global production volume in 2004 to be more than 170000 tonnes per year (Health/Env Canada, 2013). Current global production volumes of TBBPA are not available.

8.2 Consumption, Import and Uses

The main use of TBBPA is as a reactive flame retardant in epoxy resins for printed circuit boards in computers, telecommunications equipment, industrial controls and automotive electronics (Carignan et al., 2015). TBBPA is also used as:

- an additive flame retardant for low energy applications such as the plastic housing for electrical and electronic equipment, mainly computer monitors and printers
- in the manufacture of acrylonitrile-butadiene-styrene (ABS) resins and phenolic resins.

A breakdown of use worldwide indicated that around:

- 70 % is used for epoxy resins in printed circuit boards
- 15 % is used additively in styrene resins for casing materials
- 10 % is used for the production of derivatives
- 5 % is used as an additive for other polymers and thermoplastic polyesters (Leisewitz, et al., 2000).

NICNAS obtained information on the amounts and uses of commercial grade TBBPA and TBBPA-containing formulations imported into Australia in 2003-04 and 2015-16 from importers and companies who have used these substances or products. In Australia, TBBPA is imported:

- as a pure chemical (technical or commercial grade) for further use in the plastics industry
- as an additive or reactive component in semi-finished products
- in finished articles.

Australian manufacturers of articles containing TBBPA either:

- obtain the chemical from local suppliers to formulate or

- purchase formulations for injection moulding parts in electrical equipment.

8.2.1 Technical/commercial grade TBBPA

Technical or commercial grade TBBPA is imported into Australia in powder form (purity ≥99 %) under brand name FR 370 (ICL Industrial products). Imported TBBPA is packed in 25-kg polyethylene-lined paper bags, usually in 1000 kg quantities (40 bags per pallet), shrink-wrapped with a polyethylene 'stretch wrap' or in 500 kg bags. Containers of the powder arrive by sea freight and are transported by road to warehouses and stored on pallets and, in most cases, resold and distributed to customers via local transport. Estimated quantities of imported TBBPA for the years 2003-04 and 2015-16 are shown in Table 2.

Some 90 % of the total use of TBBPA is as a reactive intermediate in the manufacture of epoxy, vinyl ester and polycarbonate resins. The main application of TBBPA in epoxy resins is in printed circuit boards. As a reactive intermediate, it is covalently bound in the polymer and does not leach out. However, the polymer will also contain a very small portion of unreacted TBBPA as a result of excess TBBPA added during the production process. As this unreacted TBBPA is not bound to the polymer, it represents a fraction that can leach out from the polymer matrix into the environment and subsequently result in exposure of animals and humans.

In one formulation, TBBPA constitutes approximately 10 - 22 % of the final resin composition. For incorporation of TBBPA in resins, such as vinyl resin, a base polyester resin is charged to the reactor, TBBPA is then added and the mixture blended with other additives to form vinyl ester resin with styrene present as a reactive diluent. The mixture is decanted into an appropriate container. The vinyl ester resin products are packaged into Intermediate Bulk Containers (IBCs), drums and pails. They are then used in the manufacture of fibreglass composites, such as pipelines and storage tanks, particularly in the mining and building industries where flame retardant properties are required.

TBBPA is used as an additive flame retardant in the manufacture of acrylonitrile butadiene styrene (ABS) resins, high impact polystyrene (HIPS) and phenolic resins. It is considered as an alternative additive flame retardant to octabromodiphenyl ether in ABS. When used as an additive flame retardant, TBBPA is generally used with antimony oxide (Hakk, 2001). When used as an additive flame retardant, TBBPA is added to polymers during production of articles to impart flame retardant properties. It does not react chemically with the other components of the polymer. As a result it may leach out of the polymer matrix.

Polystyrene resins manufactured in Australia are used mainly in the manufacture of electrical housings, such as electrical cabinets for roller door housing, and in the manufacture of some safety signs. It has been reported that less than 10 workplaces in Australia currently handle this resin owing to performance reasons.

Imports of TBBPA in Australia, either as pure form or in intermediates, such as polymers, pellets, or in products, have declined considerably in recent years. In the year 2015-16, approximately 15 tonnes of pure (99 %) TBBPA was imported and used in the manufacture of vinyl ester and ABS resins (see Table 2).

8.2.2 TBBPA imported as component in imported plastic resins

TBBPA is also imported as ABS latex formulated products (Polylac 765 series, and specifically Polylac PA756A natural and Polylac PA756B white). ABS resins containing <17 % of TBBPA as an additive ingredient are imported into Australia in 25 kg polyethylene bags. Occasionally 1000 kg bulk sacks of woven polypropylene are used. Import quantities of TBBPA are given in Table 2. These resins are used at approximately 10 worksites for injection moulding to produce electrical and electronic fittings, such as electrical housings and junction boxes.

Table 2 – Comparison of quantities of commercial grade TBBPA and TBBPA in ABS resins imported into Australia in 2003-04 and 2015-16 (tonnes)

TBBPA	2003-04	2015-16
TBBPA – technical grade chemical	50.5	14.7
TBBPA imported as additive ingredient in plastic compounds (ABS resins)	6	4.64
Total	56.5	19.34

8.2.3 TBBPA as a component in imported articles

8.2.3.1 Resins

A study estimated that about 70 % of TBBPA produced world-wide was incorporated in epoxy resins and used in printed circuit boards in computers, telecommunications equipment, industrial controls, automotive electronics and the high-end consumer electronics (Leisewitz et al., 2000).

There are 2 main types of reinforced laminated printed circuit boards that are commonly used. These are glass fibre reinforced epoxy resin (designated FR4) and cellulose paper reinforced phenolic resin (designated FR2). The FR4-type laminate is by far the most commonly used and is typically made by reaction of around 15-17 % TBBPA in the epoxy resin. Its TBBPA content has been estimated to be at around 0.42 kg/m^2. This type of laminate is typically used in computers, television sets and telecommunications equipment (EURAR, 2006). In 2008, TBBPA was used to make the epoxy resin base material in more than 90 % of FR4 boards, while alternative flame-retardant materials were used in only 3-5 % of FR4 boards (USEPA, 2015b).

The FR2-type laminates contain TBBPA at around 0.036 kg/m^2, but in this case it acts as an additive flame retardant. These types of laminates are used in printed circuit boards in low energy applications such as remote controllers for televisions (EURAR, 2006).

Epoxy resins containing TBBPA are also used to encapsulate certain electronic components such as plastic/paper capacitors, microprocessors, bipolar power transistors, and metal oxide

varistors. The concentration of TBBPA in the resins for encapsulation is relatively low, reported as around 2 % or 90 g/m^2 (Danish EPA, 1999).

8.2.3.2 Electrical and electronic housing

Electrical and electronic equipment housing is usually made from styrene copolymers or blends containing styrene copolymers. The most common copolymer used is ABS, and TBBPA is commonly used as the flame-retardant ingredient for ABS (Posner & Boras, 2005; Leisewitz et al., 2001; EURAR, 2006). Other polymeric materials containing TBBPA that are used for fabrication of electronic housings include combinations such as:

- PC/ABS (polycarbonate/ABS blends)
- SB (styrene-butadiene)
- HIPS (high impact polystyrene)
- PPE/HIPS (a blend of polyphenylether and HIPS).

Typical levels of TBBPA in medium to high-impact ABS are between 17.6 and 22 %, and in high impact polystyrene the concentration of TBBPA is about 14 % (EURAR, 2006). TBBPA-containing ABS housing components are used in articles such as personal computers, laptops, keyboards, scanners, printing and copying machines, telephones, audio & video devices, refrigerators, garden tools and medical electronic equipment. In automobiles, these materials can be found in dashboards, engine components, interiors, grill work and heating/ventilation systems (OECD, 1994; Posner & Boras, 2005).

TBBPA is reportedly replacing PBDEs in some electronic housing applications in Northern Europe (Leisewitz et al., 2001; Posner & Boras, 2005; Danish EPA, 1999). This is especially the case for computer casings and for television casings (Leisewitz, 2001). For television sets, there has been a shift away from the use of ABS to PC/ABS and especially HIPS, where decaBDE has traditionally been the preferred flame retardant.

In addition to printed circuit boards and electronic housing, polymeric materials that contain TBBPA are used in lighting, some other parts of electrical and electronic appliances and machines, wiring and power distribution, and building materials.

8.2.3.3 Volume of TBBPA in imported articles

The amounts of TBBPA reported by industry in imported articles is assumed to be incomplete. Under the Act, NICNAS is not able to issue a mandatory call for information to importers of articles. In Australia, TBBPA is mostly imported as reacted ingredient in finished articles, such as circuit boards.

It is assumed that greater amounts of TBBPA are contained in imported articles than in locally produced articles, as this class of articles is mostly imported. In this category, TBPPA was used in printed circuit boards and power units of televisions, computers and accessories (for example printers, monitors, hard drives), and electronic devices (for example digital cameras, audio devices, mobile phones). In the additive category, TBBPA was used in home electrical appliances (for example in the casings of refrigerators, microwave, oven, washing machines, vacuum cleaners and in control boxes of air-conditioners) and in electronic devices (for example car and home audio devices).

For the year 2015-16, less than 5 tonnes of TBBPA was imported as a component of ABS resins. All companies that had previously reported importing TBBPA in products such as refrigerators, television sets and air conditioners, advised NICNAS that their articles no longer contain TBBPA. The actual amount of TBBPA in imported articles for the period 2015-2016 is, therefore, considered to be significantly reduced from previous years.

8.2.4 Other uses of TBBPA Overseas

Other potential uses of TBBPA, not reported to occur in Australia but identified by manufacturers of TBBPA and in overseas reports, include use as a flame retardant in the following applications:

- transportation devices
- sports or recreation equipment
- lighting fixtures and signs (EURAR, 2006)
- in simulated marble floor tiles
- bowling balls
- glass-reinforced panels
- furniture parts
- sewer pipe coupling compound
- automotive patching compounds
- buttons
- furniture parts
- wood and leather articles
- paints
- adhesive and binding agents
- military applications
- vacuum cleaners
- coffee machines
- telephones
- for enhancing corrosion resistance in unsaturated polyesters used in chemical processing equipment (Health/Env Canada, 2013).

In the most recent survey conducted by the State of Washington in the USA, the following uses of TBBPA were reported:

- surface coating flame retardant in artists' accessories
- synthetic polymer flame retardant in powered 'viewing toy'
- 'toy/games variety packs' and in powered toy vehicles
- flame retardant in textiles in baby car/booster seats
- baby carriers
- baby play pens/dens and baby swings
- stabiliser in clothing accessories
- a component of plastic resin or polymers in toys (State of Washington, 2015).

Articles of these types containing TBBPA have to be considered likely to also be brought into Australia even if not reported under the NICNAS voluntary call for information on TBBPA in articles.

9 Public exposure

9.1 Method for assessing exposure

Public exposure includes direct consumer exposure through use of articles and indirect exposure via the environment. Consumer exposure is assessed based on the typical scenarios that a consumer may encounter. Exposure through the environment is assessed based on measured or predicted data of TBBPA in the different environmental compartments and in food and drinking water.

Public exposure to a chemical is not uniform across a population. Some groups or individuals may have higher potential exposures because:

- they live in the vicinity of industrial sources or
- they exhibit some dietary habits or age-specific behaviours that may increase their exposure (for example inadvertent soil ingestion among young children through mouthing of objects or hands).

In this assessment, where relevant, exposures are estimated separately for adults and children. Exposures to children are estimated for three representative age groups in line with the approach of Food Standards Australia New Zealand (FSANZ, 2005):

- infants (9 months)
- toddlers (2 years)
- older children (12 years).

Public exposure is estimated by using a 'reasonable worst-case' approach, in which estimates are based on worst-case, or unlikely but plausible, exposure scenarios. It is believed that this approach will address practically all exposures within a population. There may still be uncertainties associated with such exposure estimates, although care has been taken to address them.

Actual measured data are always preferred in exposure assessment. Where Australian data are not available, overseas data will be used. Modelled data will only be used if measured data are not available.

9.2 Direct Exposure

9.2.1 Sources of Exposure

TBBPA is used primarily as a reactive intermediate in epoxy resins used mainly in printed circuit boards. When used in this manner, TBBPA becomes covalently bound in the polymer and will not normally be available for public exposure. TBBPA is also used as an additive flame retardant in some products, for example in styrene-based resins for casing materials. When used as an additive flame retardant, TBBPA is physically added into the articles rather than being chemically combined. It is thus possible for the chemical to diffuse out of the treated articles to a limited extent.

For the general population, exposure to TBBPA is possible from inhalation of ambient air and dermal contact with the compound, primarily in products made from polymers incorporating the TBBPA in additive form. Ingestion of TBBPA is also a possible exposure route. In commercial drinking water stored in reusable polycarbonate containers, studies detected TBBPA as well as brominated derivatives of the ^{13}C-bisphenol A (BPA). TBBPA is used predominantly in electronic equipment, including data processing equipment. Consumers who use these treated products may be directly exposed to the chemical.

This Section will focus on those consumer products in which TBBPA is present as an additive flame retardant (for example, casings for electrical and electronic appliances).

Consumer end-products containing TBBPA as an additive flame retardant are either manufactured in Australia or imported from overseas. Only a relatively small amount (approximately 4 tonnes per year) of imported TBBPA (technical grade) is used as additive flame retardant in polystyrene resins and phenolic resins. The following imported products are likely to contain TBBPA:

- housing of electronic equipment (for example, computers, televisions, digital cameras, audio system and mobile phones)
- housing of home electrical appliances (for example, refrigerators, air-conditioners, microwave ovens and vacuum cleaners)
- decorative laminates used in interiors of public buildings (for example, elevator linings, hospital furniture and doors, partitions, public corridors and hallways).

In response to the recent NICNAS call for information on the volume of TBBPA imported in pure form or as a component in articles, many companies reported that their imported articles do not now contain TBBPA. These include TV monitors, microwave ovens and vacuum cleaners. However, for the purpose of risk assessment, it is assumed that some of the articles being used by the general public are old and still contain the chemical.

9.2.2 Oral

It is unlikely that materials detached from treated articles will be ingested. The types of TBBPA-containing consumer articles are not considered likely to be mouthed by young children. Thus, consumer exposure through direct ingestion is considered to be negligible.

9.2.3 Inhalation

Due to its low vapour pressure (6.2×10^{-6} Pa at 25°C), significant emission of TBBPA as vapour from treated articles is not expected.

Low emissions from treated articles are demonstrated by many recent overseas studies, i.e. printed circuit boards of a TV set (de Boer et al., 1998), printed circuit board of a personal computer [reaction products of TBBPA detected] (Wolf et al., 2000), indoor air of an electronic recycling plant (Sjodin et al., 2001), computer monitors (Ball and Herrmann, 2002; Herrman et al., 2003), and part of a personal computer housing (Kemmlein et al., 2003).

In a study reported by de Boer et al. (1998) TBBPA was not detected in the air inside or surrounding a TV set in which the flame retardant was present in the printed circuit board at a concentration of 266 mg/kg. They analysed air samples by using the GC/MS method.

An emission test was conducted for individual parts of a television set (Wolf et al., 2000). In this test, 100 mg of an epoxy resin printed circuit board was placed in a flask where it was heated to about 100°C and nitrogen gas was passed through it at a flow rate of 0.2 L/min. Release of brominated substances into the carrier gas was not detected by using the analytical method GC/MS; this was attributed to the fact that the flame retardant (TBBPA) in the circuit board is reacted into the polymer matrix.

Airborne TBBPA levels in various indoor locations was measured (Sjodin et al., 2001). Very low readings were recorded: in offices with two to three computers, the mean level was 0.036 ng/m^3 (range = <0.01 – 0.07 ng/m^3, n=4); in a computer repair workshop, the levels were 0.031 ng/m^3 and 0.038 ng/m^3 (n=2); and in a teaching hall where a large number of computers were running, the levels were 0.035ng/m^3 and 0.15 ng/m^3 (n=2).

Emissions of TBBPA even from computer monitor housings where the flame retardant was present in an additive form, were negligible (Ball and Herrmann, 2002). Air levels of TBBPA measured in the enclosed chamber varied between 0.1 and 2.0 ng/m^3; air levels of TBBPA measured in the office investigation peaked at 2.3 ng/m^3 (during the first day) before falling slowly to between 0.1 and 0.2 ng/m^3. Wipe samples from the test chambers showed a maximum TBBPA value of 569 µg/m^2 at the bottom of the sampling area, but particles were seen beforehand and this may have represented contamination from the housing.

TBBPA concentrations in UK homes, offices, public spaces and outdoors were measured (Abdallah et al., 2008). The average, minimum and maximum concentrations were: UK homes – 16, 9 and 22 pg/m^3, offices – 16, 4 and 33 pg/m^3, public spaces – 26, 17 and 32 pg/m^3, outdoors – 0.8, 0.7 and 0.9 pg/m^3, respectively.

In a study determining the emission of a range of flame retardants (Kemmlein et al., 2003), part of a computer casing (containing ~10 % TBBPA) was placed in a 0.02-m^3 emission test chamber under standard climatic conditions (temperature = 23°C, relative humidity = 50 %). After 150 days of testing, a small amount of TBBPA was found adsorbed on the interior surfaces of the chambers (concentration: 356 ng/m^2 of interior surface), but the chemical was not detected in the chamber atmosphere. A low emission rate of 0.4 ng/m^2/h was calculated.

An emission study of computer monitors was conducted in Germany (Herrman et al., 2003). Two monitors that contained about 12.5 % TBBPA in the casings were placed separately in emission chambers for 140 days. Another monitor containing <0.1 % TBBPA in its casing was used as the control and was treated in a similar manner. Inside the chambers, the monitors were switched on in an active mode during the whole test period. The emission chambers had air exchange rates of 2 per hour and were kept at a temperature of 20-30°C. Levels of airborne TBBPA emitted from the two monitors were found to be very low, starting from 1.2 ng/m^3 on day 1 and falling slowly to about 0.8 ng/m^3 towards the end of the test period. Less than 0.05 ng/m^3 (detection limit) was found emitted from the control during its 219 days of test, indicating that TBBPA was not even emitted from the other electronic parts (e.g. printed circuit boards in these monitors, which were found to contain 5-7 % bromine in a reacted form). TBBPA was also detected on the interior surface of a test chamber after 140 days of testing; however, this was probably due to contamination from the monitor casing. An office experiment was also performed, by running one of the test monitors in an office for 117 days. The air concentration of TBBPA near the monitor was found to be 2.3 ng/m^3 on day 1, slowly falling to 0.1-0.2 ng/m^3 by day 117.

Computers and home electrical appliances are widely used in the indoor environment. Given the low vapour pressure of TBBPA, and its very low emission from treated articles, consumer exposure through inhalation is considered to be negligible. Any attempt at quantitative assessments will result in disproportionately high errors because of the small exposures anticipated.

9.2.4 Dermal

McPherson et al. (2004) reported the presence of trace amounts of TBBPA in dust swiped from surfaces of computers in public buildings in eight states in the USA. TBBPA concentrations ranged from <0.006 to 2.4 pg/cm^2.

Occasional or infrequent skin contact with TBBPA-treated products (for example, electronic devices, home electrical appliances, decorative laminates used in interiors of public buildings) should result in negligible dermal exposure, typically less than 1 ng/kg/day.

9.3 Indirect Exposure

9.3.1 Source of exposure

TBBPA is a ubiquitous environmental contaminant that is observed in both abiotic and biotic matrices. Many channels can release and distribute it in the environment:

- release into the atmosphere or wastewater from its industrial uses and disposal
- emission from TBBPA-treated articles
- leaching and emission, such as from landfill.

TBBPA can migrate from soil and sediment into the aquatic and terrestrial food chains, with higher concentrations in the lipid portion of food.

Indirect exposure of humans to TBBPA through the environment may occur by:

- consumption of food and drinking water
- inhalation of air
- ingestion of soils (particularly by children) that are contaminated with the chemical.

Quantitative exposure assessment will be conducted for each of the following scenarios:

- inhalation exposure from outdoor and indoor air/dust;
- oral exposure from the consumption of food;
- oral exposure from the ingestion of soil and indoor dust due to hand-to-mouth behaviour, particularly in children; and
- oral exposure of infants to the chemical from consumption of breast milk

Indirect exposure through dermal contact, for example with soil, can occur. However, this type of indirect exposure is considered to be negligible.

9.3.2 Indoor exposure

9.3.2.1 Inhalation exposure from dust

Due to the low volatility of TBBPA, inhalation exposure from the indoor air environment is considered to be almost solely from TBBPA in dust. Inhalation exposure to TBBPA may be estimated if the concentration of TBBPA in dust and the amount of dust in the air are known. TBBPA has been found in dusts collected in houses and offices in many countries. In a study of dust in offices from the European Parliament building, concentrations in 9 out of 16 samples were reported to be between 5 and 47 ng/g (Leonards et al., 2001). Abdallah et al. (2008) reported TBBPA concentrations (average, min, max) in homes to be 87, below the limit of detection (<LOD) and 382 ng/g dust; in offices 49, <LOD and 140 ng/g dust and in cars 6, <LOD and 25 ng/g dust. Information from various studies is summarised in Table 3. There are no Australian studies on indoor dust level of TBBPA.

The studies typically used a vacuum cleaner to collect dust from the floor of the house or office with high pressure liquid chromatography (HPLC) or GC/MS used to determine TBBPA concentrations. There were differences in particle sizes of the dusts reported in the studies analysed, as well as reported results of each study (for example pooled or individual samples).

Table 3 – Measured levels of TBBPA in dust in houses and offices

Location	Sampling Period	No. of Samples	TBBPA (ng/g) dust	Reference
Belgium	2008	43 homes	419	D'Hollander et al., 2010
		10 offices	212	
Belgium	2008	18 houses	146	Geens et al., 2009
		2 offices	73	
Germany	Not reported	5 houses	59 [2.9 – 233]	Kopp et al. (2012)
United States	2006-2007	10 buildings	20 – 938	Batterman et al., 2010
Japan; Hokkaido	2007	House 1	490	Takigami et al., 2007
		House 2	520	

Location	Sampling Period	No. of Samples	TBBPA (ng/g) dust	Reference
Japan; Interior of used TV	2005 (Manuf'd 1989-98)	TV 5	$2.4x10^5$ [$5.5x10^3$ - $6.8x10^5$]	Takigami et al., 2008
		Front cabinet 5	$2x10^4$ [240- $6.7x10^4$]	
		Rear cabinet 5	$19x10^6$ [120 - $97x10^6$]	
China	2012	2 homes	95-97	Wang et al., 2013
UK Day-care centre and Primary School	2007-2008	43	17-1400	Harrad et al., 2010
UK	2006-2007	35 houses	87 (LOQ–382)	Abdallah et al., 2008
		28 cars	6 (LOQ–25)	
		20 Offices	49 (LOQ–140)	
UK – 10 regions	Oct-Nov, 2002	Houses; detected in 4 of 10 pooled samples	190 – 340	Santillo et al., 2003

Mean concentrations of TBBPA in indoor dust from homes, offices, cars and public microenvironments ranged widely and were highest in the UK study (Harrad et al., 2010).

In a study by Harrad et al. (2010), the mean and 95th percentile concentrations of TBBPA in dust from classrooms were:

- 200 ng/g in primary schools
- 460 ng/g in day-care centres.

The maximum concentration was 1400 ng/g dust.

In a study by Harrad and Abdallah (2011), the concentration of TBBPA in dust from the 4 seats in 5 different cars ranged from <0.2 to 16 ng/g dust, with a median of 2 ng/g dust. TBBPA concentrations in the dust from the front seats were usually higher than those in dust

from seats in the rear. As a worst case scenario, the highest measured TBBPA in dust in homes (1400 ng/g) will be used for exposure and risk assessment.

The worst-case estimate of the amount of dust in indoor air is based on the maximum permissible level of particles in indoor air of 90 μg/m^3, as recommended by Australia's National Health and Medical Research Council (NHMRC, 2003). Considering the TBBPA levels in dust from the investigations by Harrad et al. (2010), the maximum concentration (1400 ng/g) TBBPA concentrations in dust are equivalent to TBBPA concentrations of 0.126 ng/m^3 in air as the reasonable worst-case levels.

9.3.2.2 Estimation of inhalation exposure

In estimating inhalation exposure to indoor dust, the following assumptions are made:

- 75 % of the inhaled dust will be retained in the respiratory tract and 25 % will be exhaled (enHealth, 2002);
- the ventilation rates for infants, toddlers, children and adults are 0.8, 3.8, 15 and 22 m^3/day, respectively (NHMRC, 2003);
- indoor air exchange rate is negligible
- the time spent indoors is 20 h/d for both adults and children in Australia (NHMRC, 2003);
- the bioavailability for inhalation exposure is 100 %.

The size distribution of dust particles containing TBBPA is unknown. The Environmental Health Committee publication 'Environmental health risk assessment guidelines for assessing human health risks from environmental hazards' (enHealth, 2003) states that half the inspirable dust particles will be sufficiently small to reach the pulmonary alveoli. It is assumed as a worst-case scenario that all the retained dust particles containing TBBPA are available for absorption, either within the lungs or in the gastrointestinal tract following mucociliary clearance.

The exposure arising from the inhalation of TBBPA in indoor air is estimated by using the method and equation provided at Appendix 2, and the results are presented in Table 4.

9.3.2.3 Estimation of oral exposure from ingestion of indoor dust

The ingestion of dust or soil is a potential source of human exposure to chemicals. Adults may ingest soil or dust particles that adhere to food, cigarettes or their hands. The potential for exposure via this route is greater for young children because they are more likely to ingest soil than adults as a result of behavioural patterns during childhood. Inadvertent dust ingestion among young children may occur through mouthing of objects or hands.

Deliberate dust or soil ingestion is defined as pica and is considered to be relatively uncommon. As such, pica behaviour will not be considered in this assessment.

The enHealth Council has reviewed the relevant studies on soil ingestion behaviour and recommended the following soil ingestion rates:

- negligible for infants aged 0 to <1 years
- 100 mg/day for children aged 1 to <5 years
- 50 mg/day for children aged 5 to 15 years

- 25 mg/day for adults (enHealth, 2003).

These values were applied to indoor dust in the estimation of oral exposure.

The soil ingestion rates cited by the enHealth Council as well as the US EPA in their exposure factors handbooks are intended to represent ingestion from a combination of soil and dust, without distinguishing between these two sources. The recommended default values are called "soil" which also include "dust tracked into the indoor setting, indoor settled dust, and air suspended particulate matter that is inhaled and swallowed" (enHealth, 2003).

In the estimation of oral exposure via ingestion of TBBPA in dust, the following assumptions are made:

- a reasonable worst-case TBBPA concentration of 1.4 µg/g dust (day care centre) for the general population (see Table 3).
- dust/soil ingestion factors in Australians are based on the information from enHealth (enHealth, 2003).
- on average, both adults and children spend 20 h/d indoors (enHealth, 2003). The source of indoor exposure is solely from dust.
- average bodyweights for infants, toddlers, children and adults are 5.8, 12.9, 46.9 and 70 kg, respectively.
- ingestion rate is 0, 100, 50 and 25 mg/day for infants, toddlers, children and adults, respectively.
- the bioavailability via oral exposure is 100 %.

The exposure arising from the ingestion of soil or dust due to hand-to-mouth behaviour can be estimated by using the method and equation provided at Appendix 2.

9.3.2.4 Total indoor exposure

The combined worst case exposure estimates for the indoor environment for the general public are represented in Table 4.

Table 4 – Estimate of indoor exposure from inhalation of dust and ingestion of soil/dust

Exposed group	Exposure to TBBPA (ng/kg bw/day)		
	Inhalation exposure	Oral exposure (ingestion of dust)	Total exposure
Infants (9 months)	0.011	Negligible	0.011
Toddlers (2 years)	0.023	9.04	9.063
Children (12 years)	0.025	1.244	1.269
Adults	0.025	0.417	0.515

The estimation shows that the ingestion of dust is the major contributor to exposure. Thus, the highest level is seen in toddlers (2 years) followed by children (12 years).

9.3.3 Outdoor exposure

9.3.3.1 Inhalation exposure from dust

No Australian monitoring data are available for TBBPA in air. Xie et al. (2007) analysed TBBPA in outdoor air samples from a rural site in northern Germany, over the Wadden Sea and offshore in the Northeast Atlantic Ocean. They found comparable concentrations of TBBPA at the northern German site (<0.04 to 0.85 pg/m^3) and over the Wadden Sea (0.31 to 0.69 pg/m^3). TBBPA concentrations over the Northeast Atlantic Ocean ranged from <0.04 to 0.17 pg/m^3, with the highest concentration present in a sample they collected at the West Norwegian coast. This indicated an input source from land to ocean. TBBPA was present primarily in the particulate phase rather than in the vapour phase.

As stated in Section 11 of this report, a local predicted environmental concentration in air (PEC_{air}) value of 13 pg/m^3 for TBBPA was calculated using worst-case assumptions that all processing occurs in either of Australia's two major cities, Melbourne and Sydney. For exposure estimate, a PEC_{air} of 13 pg/m^3 will be used.

9.3.3.2 Estimation of inhalation exposure

In estimating inhalation exposure of the public to TBBPA in outdoor air, the assumptions are the same as that for estimating the inhalation exposure to indoor dust with the additional assumption that the time spent outdoors is 4 h/d (enHealth, 2003).

The exposure arising from the inhalation of TBBPA in outdoor air is estimated by using the method and equation provided at Appendix 2, and is presented in Table 5.

9.3.3.3 Oral exposure from ingestion of soil

No Australian monitoring data are available for TBBPA in soil. As stated in Section 11, a one-year predicted environmental concentration in soil (PEC_{soil}) of 2.8 µg/kg soil was calculated for the case of agricultural soils amended with sewage sludge.

The 10-year accumulation level is 28 µg/kg (or 28 ng/g) soil and is considered as the reasonable worst-case value. It is expected that urban soils would show lower TBBPA levels than amended agricultural soil.

9.3.3.4 Estimation of oral exposure

In estimating oral exposure of the public to TBBPA in outdoor soil, the assumptions are the same as those for estimating the oral exposure to TBBPA in indoor dust with the additional assumption that the time spent outdoors is 4 h/d (enHealth, 2003).

The exposure arising from the ingestion of dust and soil from hand-to-mouth behaviour is estimated by using the method and equation provided at Appendix 2, and is presented in Table 5.

9.3.3.5 Total outdoor exposure

The combined exposure estimates from outdoor environment are presented in Table 5.

Table 5 – Estimate of outdoor exposure from inhalation of dust and ingestion of soil/dust

Exposed group	Exposure to TBBPA (ng/kg bw/day)		
	Inhalation exposure	Oral exposure (ingestion of dust)	Total exposure
Infants (9 months)	Negligible	Negligible	Negligible
Toddlers (2 years)	0.00007	0.107	0.1071
Children (12 years)	0.00008	0.015	0.0151
Adults	0.00008	0.005	0.0051

9.4 Exposure from food consumption

Dietary intake of a chemical is estimated by combining food consumption data with the concentration of the chemical in the food. There are no Australian total TBBPA dietary studies available. Total TBBPA dietary intakes for the Australian population are estimated from the international studies wherein the dietary exposures to BFRs were estimated based on total diet studies analysed for these compounds.

In 2011, the European Commission asked EFSA to deliver a scientific opinion on TBBPA and its derivatives in food. EFSA analysed data on TBBPA in 652 food samples submitted by 4 European countries (Ireland, Norway, Spain and the UK) (EFSA, 2011). These results covered the period from 2003 to 2010. In order, the categories were:

- 'Fish and other seafood (including amphibians, reptiles, snails and insects)' (n=465)
- 'Meat and meat products (including edible offal)' (n=49)
- 'Animal and vegetable fats and oils' (n=41)
- 'Milk and dairy products' (n=40)
- 'Eggs and egg products' (n=27).

Overall, the food consumption data EFSA gathered in the Comprehensive Database are the most complete that are currently available in the EU. All analytical results on TBBPA were reported as less than the limit of quantification (LOQ) (in general ≤ 1 ng/g wet weight). Therefore, a meaningful exposure assessment for the general population was not possible.

To indicate the possibility of health concerns with respect to dietary exposure to TBBPA, EFSA made a worst case intake estimate for 2 specific groups of the population. They considered adult high fish consumers and high cow's milk consumers (toddlers). They substituted the concentration levels of TBBPA in fish and in cow's milk by the maximum LOQ reported for those food categories of 1 ng/g and 0.65 ng/g wet weight, respectively.

In order to make a rough estimation of the dietary exposure to TBBPA for high fish consumers, a daily consumption of 2.6 g/kg bw of fish meat was used. This value was identified as the highest 95th percentile for consumers of fish only, retrieved from the Comprehensive Database

For a rough estimation of the dietary exposure to TBBPA for high consumers of liquid cow's milk (for example toddlers), a daily consumption of liquid milk of 85.7 g/kg bw was used. This value was identified as the highest 95th percentile for consumers of cow's milk. The resulting "upper bound" intake estimate was 2.6 and 55.7 ng/kg bw/day TBBPA from fish and milk, respectively (EFSA, 2011).

In China, Shi et al. (2009) reported the results of a total dietary survey (TDS) they carried out in 2007 comprising 662 food items they collected from local markets, groceries and rural households, and aggregated into 13 food groups. From these, they analysed 4 food groups of animal origin for TBBPA. They were:

- eggs and egg products
- aquatic food
- milk and milk products
- meat and meat products.

They detected TBBPA in about 70 % of the samples. They found the highest levels in the aquatic food group, followed by the meat and meat products group. They found the lowest concentrations in eggs and egg products. The total estimated daily intake of TBBPA was:

- 0.232 ng/kg bw/day (lower bound, LB)
- 0.256 ng/kg bw/day (medium bound, MB) or
- 0.280 ng/kg bw/day (upper bound, UB).

The contribution of the food groups to the estimated daily intake were:

- 52 % from meat and meat products
- 30 % from aquatic food
- 10 % from milk and milk products
- 8 % from egg and egg products.

In the Netherlands, a study estimated the dietary exposure to TBBPA through the analysis of food samples (n=91) including dairy products, meat, animal fat, eggs and vegetable oils (de Winter-Sorkina et al., 2003). The consumption data were from the third Dutch National Food Consumption survey. The authors estimated mean medium bound dietary exposure at 0.04 ng/kg bw/day. They noted that the high percentage of non-detects may have introduced uncertainties in the exposure estimates.

The UK Food Standards Agency estimated the dietary exposures to BFRs and related compounds in UK consumers (Food Standards Agency, 2006). This study analysed 19 composite samples of food groups collected during the 2003 UK Total Diet Survey for polybrominated diphenyl ethers (PBDEs) and brominated dioxins. However, it concluded that this was an insufficient sample to obtain results of good quality for TBBPA. Thus, the study re-measured these compounds in samples from the 2004 UK Total Diet Survey. Foods they analysed included various fruits and vegetables, dairy products, meats, cereals and oils. They presented upper bound estimates for 'average level consumers' and 'high level consumers' of various food groups and they derived a total dietary exposure from a distribution of the individual consumer's consumption patterns across all foods.

The UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) issued an assessment on organic chlorinated and brominated

contaminants in shellfish, farmed and wild fish. They analysed composite samples of 47 species of farmed and wild fish and shellfish consumed in the UK for, among others, TBBPA (COT, 2006).

The total dietary exposure was estimated by using the consumption data from the 2000-01 National Diet and Nutrition Survey. The estimated intake of TBBPA from the non-fish part of the diet was taken from the 2004 total diet study (TDS) where TBBPA was found <LOD (generally 0.36 µg/kg wet weight) in all the food groups and the intake was estimated at 1.5 ng/kg bw/day (COT, 2006). For the fish part of the diet, a consumption of 140 g of mackerel, identified as the species containing the highest TBBPA concentrations (0.21 µg/kg fresh weight), was considered. It resulted in a total daily intake (non-fish part plus fish part of the diet) of 1.6 ng/kg bw/day, less than in the hypothetical scenario above (EFSA, 2011). This calculation assumed a body weight of 60 kg. For children (different age groups covering from 4 to 18 years old), the estimated upper bound average dietary intake ranged from 3.7 to 1.3 ng/kg bw/day. For toddlers (different age groups covering from 1.5 to 4.5 years old) it ranged from 7.0 to 4.6 ng/kg bw/day. These estimates were considerably below the TDI of 1 mg/kg bw/day the COT recommended in 2004.

Table 6 – Dietary TBBPA intake for different countries as reported in the literature

Country, year	Estimation	TBBPA (ng/kg bw/day)		Reference
China, 2007	LB	0.232		Shi et al., 2009
	MB	0.256		
	UB	0.280		
The Netherlands, 2002	MB	0.04		De Winer-Sorkina et al., 2003
	LB	0.04		
UK, 2003-04	UB	Toddlers (1.5-4.5 years)	7.0	COT, 2006
		Children (4-18 years)	3.7	
		Adults	1.6	

LB - lower bound, MB - medium bound, UB - upper bound.

As the studies presented used different methods to estimate dietary exposure, the results from these studies cannot be compared directly to each other. Some of these methods are conservative and tend to overestimate exposure (EHC, 2009). It can be seen from the table that the UK estimates gave the highest TBBPA dietary intakes.

Collection of the food consumption data in the UK and Australia use similar methods, with both the UK's National Diet and Nutrition Survey and Australia's National Nutrition Survey conducting dietary recall interviews and collecting self-completion questionnaires in

accordance with internationally accepted principles. In addition, the UK study gives estimates for all of the age groups being considered in this assessment, including infants (1–6 months) for which exposure is considered to be via breast milk. Thus, the exposure estimate from COT (2006) is chosen with the "high-level consumer" values taken as the reasonable worst-case intake estimates, respectively, of TBBPA from food in Australia.

9.4.1 Oral Exposure to infants from the consumption of breast milk

9.4.1.1 Breastfeeding in Australia

Results from Australia's National Health Survey show that in 2014-15, 92 % of infants aged 0-3 years had, at some stage, obtained nutrition from breast milk (ABS, 2015). The proportions of children still being breastfed declined in progressively older age groups.

The 2006–07 Longitudinal Study of Australian Children showed that:

- 88 % of children were being fully breastfed (breastfeeding with no other food or fluid intake) at discharge
- 56 % 3 months later
- 46 % 4 months later
- 28 % 5 months later
- 14 % 6 months later (AIFS, 2008).

The Australian Health Ministers' Conference (2009) reported that Australia is comparable with other OECD countries in relation to duration of breastfed infants being up to 3 months. In this report, a fully breastfed infant's duration of 6 months is selected as a conservative approach for exposure estimation.

The daily intake of breast milk by infants in Australia is not available. The NHMRC (2003) has recommended average intakes of fully breastfed infants at 710 mL/d for 0 to 2 months and 800 mL/d for 3 to 8 months. A higher volume of 850 mL/d is also cited in the WHO report (WHO, 1985). The Child-specific exposure factors handbook from US EPA:

- indicated that the weighted average daily breast milk intake for infants aged 1 to 6 months ranges from 702 to 765 mL/d
- indicated that the upper percentile values (mean plus 2 standard deviations) for the same age groups are 1007 to 1059 mL/d (USEPA, 2002)
- recommended the above 2 figures are adopted for oral exposure estimation via breast milk in infants.

The US EPA recommendations are based on the weighted averages of several studies and are similar to the values ECETOC (2001) reported for Swedish infants.

9.4.1.2 TBBPA levels in breast milk

Measured data of TBBPA concentrations in breast milk in Australia are not available. A number of overseas studies have been conducted to determine the levels of TBBPA in breast milk. These studies have been reviewed and are summarised in Table 7. The reported TBBPA levels in breast milk are quite consistent between Japan and Germany. The highest reported mean value of 4.1 ng/g lipid weight (Cariou et al., 2008) is taken as the worst-case TBBPA concentration in breast milk, and will be used for exposure estimate.

A recent study reported TBBPA in breast milk from first-time mothers in Greater Boston, Massachusetts, USA (Carignan et al., 2015). Human milk samples were analysed by liquid chromatography coupled with electrospray ionisation mass spectrometry (LC-ESI-MS)/MS and TBBPA was detected in 35 % of the analysed samples, with concentrations ranging from the LOQ of 0.030 to 0.55 ng/g lipid weight.

Table 7 – TBBPA levels in lipid component of human breast milk from overseas studies

Location	Study subjects	N	Mean	Range	References
			ng/g lipid wt.		
Germany	4 subjects (age 25-37)	4	N/A	0.29-0.94 (2 samples <LOD)	Kemmlein, 2000, quoted in EURAR, 2006
Norway	1 pooled sample from 20 mothers	1	N/A	0.067	Thomsen et al., 2002a
France	Samples collected in 2004-06	34	4.1	0.06-37.3	Cariou et al., 2008
France	Collected in 2005	23	0.17 (median)	0.03-9.4	Antignac et al., 2006
Norway	Pooled samples (each pool from 10-12 mother)	N/A	N/A	0.01-01	Thomsen et al., 2003
Japan	36 mothers (age 21-33). Samples pooled in 9 groups	9	0.37	0.18-0.94	Ohta et al., 2004
China	1237 samples pooled into 24 lots	24	0.933	<LOD-5.1	Shi et al., 2009
US	First time mothers		N/A	0.03-0.55	Carignan et al., 2015

A study also detected dimethyl-TBBPA semi-quantitatively in pooled samples of human milk from Norway in concentrations of approximately 0.1-1.1 ng/g lipid. The source of the compound was not identified, but two explanations were offered by the authors (Thomsen et al., 2003):

- dimethyl-TBBPA has been infrequently used as a flame retardant, or
- it may be the product of biological methylation.

The body weights of infants between the ages 1 to 6 months are the averaged values of the 50th percentile figures for both males and females using USA data (USEPA, 2002). These figures are similar to Australian data collected from 1933 to 1985 compiled by Gracey and Hitchcock in 1985 (Lester, 1994).

Based on the average breast milk intake volumes, the average body weights (7.3 kg) and the density of human milk (1.03 g/mL), the breast milk intake rate of infants 1 to 6 months old is:

- 139 g/kg bw/day (typical scenario) or

- 194 g/kg bw/day (reasonable-worst case scenario).

Table 8 – Estimation of oral exposure levels to TBBPA via breast milk in 1-6 month old infants

Case	TBBPA (ng/g lipid wt.)	Lipid content	Intake rate (g/kg bw/day)	Bioavailability	Oral exposure (ng/kg bw/day)
Typical case	4.1	4 %	139	100 %	22.8
Reasonable worst-case	4.1	4 %	194	100 %	31.8

Exposure arising from breast milk consumption is estimated in the fully breastfed infants age group of 1-6 month (Appendix 2).

Due to the decrease of breast milk intake as seen in surveys resulting from the introduction of other food, the age group of 9 months is not included in the estimation.

Summary of exposures

The exposure estimates are in Table 9. As shown in the table:

- the overall public exposures using a worst case approach are quite low, all less than 0.05 μg/kg bw/day
- the majority of the exposure comes from the consumption of food.

A typical exposure estimate would be even lower.

Table 9 – Summary of daily exposure of the public

Route	TBBPA exposures (ng/kg bw/day) (Reasonable worst-case values)			
	Infants (1-6 months)	Toddlers (2 years)	Children (12 years)	Adults
Exposure from consumer products				
Oral	Negligible	Negligible	Negligible	Negligible
Inhalation	Negligible	Negligible	Negligible	Negligible
Dermal	Negligible	Negligible	Negligible	Negligible
Exposure from the environment				

Route	TBBPA exposures (ng/kg bw/day) (Reasonable worst-case values)			
	Infants (1-6 months)	Toddlers (2 years)	Children (12 years)	Adults
Total indoor exposure	0.01	9.06	1.27	0.442
Total outdoor exposure	Negligible	0.1071	0.0151	0.0051
Food consumption (COT, 2006)	Negligible	7	3.7	1.6
Breast milk consumption	31.8	-	-	-
Total	31.81	16.17	4.99	2.05

9.5 Biological Monitoring Data

9.5.1 Measured data – TBBPA in blood

Biological monitoring provides a means to assess exposure and health risk to the public. It entails measurement of the concentration of a chemical determinant in the biological media (for example, blood, or urine) of those exposed. It is an indicator of the uptake of a substance. Biological monitoring can assist in the determination of total body concentration and in detecting past exposure.

A number of overseas studies have been conducted to determine the levels of TBBPA in human blood. These studies have been reviewed and are summarised in Table 10. It is not possible based on these data to determine the specific sources of the TBBPA exposure, or to determine the actual exposure levels of the individuals.

Table 10 – Summary of biological monitoring studies on blood levels of TBBPA

Study reference	Study subjects	N	Serum TBBPA (ng/g lipid wt.) Mean	Comment
Nagayama et al., 2000	24 volunteers (12 males, 12 females, age: 37-49) in Japan in 1998	14	1.4 0.9 (median) Range: <LOD - 3.7	The limit of detection (LOD) was not reported. 6 samples were below LOD.
Nagayama et al., 2001	54 volunteers (27 males, 27 females, age: 37-49) in Japan in 998.	54	2.4 (median) Range: <LOD - 12	LOD was not reported.
Thomsen et al., 2002b	Archived serum from patients in hospitals in Norway (40-50 years old men) between 1977 and 1999.	1	<LOD	Serum pool of 34 patients. LOD is about 0.07-0.27 ng/g lipid wt.).
	Serum pool: 1981	1	<LOD	Serum pool of 17 patients.
	Serum pool: 1986	1	0.44	Serum pool of 24 patients.
	Serum pool: 1990	1	0.42	Serum pool of 20 patients.
	Serum pool: 1995	1	0.59	Serum pool of 19 patients.
	Serum pool: 1999	1	0.65	Serum pool of 29 patients.
	Archived serum (as above) from 8 groups sampled in 1998 in Norway.			
	Group 1: 0-4 years	1	0.71	Serum pool of 14 patients

Study reference	Study subjects	N	Serum TBBPA (ng/g lipid wt.) Mean	Comment
	Group 2: 4-14 years	1	0.40	Serum pool of 10 patients.
	Group 3: 15-24 years, female	1	0.40	Serum pool of 10 patients.
	Group 4: 15-24 years, male	1	0.56	Serum pool of 13 patients.
	Group 5: 25-59 years, female	1	0.34	Serum pool of 12 patients.
	Group 6: 25-59 years, male	1	0.65	Serum pool of 11 patients.
	Group 7: >60 years, female	1	0.42	Serum pool of 13 patients.
	Group 8: >60 yrs, male	1	0.31	Serum pool of 10 patients.
Jakobsson et al., 2002	19 computer technicians in a hospital in Sweden. Only 10 serum samples were analysed.	10	<0.54 (median) Range: <0.54-1.8	Only 4 samples had TBBPA above the limit of quantification (0.54 ng/g lipid wt.).
Hayama et al., 2004	5 healthy male volunteers in Japan.	5	1.2 Range: 1.0 - 1.5	pg/g in serum converted to ng/g lipid wt, assuming serum lipid level of 0.6 %.

Serum lipid of Norwegian subjects (n=29) contained a mean concentration of 0.65 ng/g lipid (cohort from 1999).

Serum of Japanese subjects (n=5) contained 7 pg/g lipid.

Adipose tissue of subjects in New York City (n=20) contained 0.05 ng/g lipid.

10 Occupational Exposure

10.1 Method for Assessing Exposure

10.1.1 Sources of Exposure

TBBPA is not manufactured in Australia. Australian industry imports TBBPA for further formulation for industrial uses or in formulated products and finished articles. Occupational exposure to TBBPA may occur during:

- transport
- storage
- repacking
- formulation of products
- resin manufacture
- use of end products containing TBBPA
- recycling of articles containing TBBPA.

In assessing occupational exposure to chemicals, it is preferable to use measured exposure data (IPCS, 2000). Studies are conducted to measure worker exposure to the chemical while performing different tasks. The median and the 90th percentile values are used to represent the typical and reasonable worst-case estimates, respectively.

In the absence of measured data, modelled data are used for certain worker scenarios, using the Estimation and Assessment of Substance Exposure (EASE) model (UK HSE). The EASE model, developed by the UK Health and Safety Executive (HSE) is a general-purpose predictive model for workplace exposure assessments. Daily exposures are predicted as a range of exposure values derived from databases of measured exposures from workplace environments based on a standard 8 h working day (enHealth, 2003). The model considers dermal and inhalation exposures to substances, which may be present as solids, liquids, gases or vapours. EASE is able to consider a wide range of workplace activities, including maintenance and sampling procedures, and can also account for some risk management measures (e.g. use of local exhaust ventilation). It is acknowledged that the EASE model takes a conservative approach and is likely to overestimate exposure (Creely et al., 2005).

The EASE model assumes that the operator spends a full shift (8 h) working at different sites and is exposed to the raw TBBPA. Since the majority of work processes involving potential exposure to TBBPA do not fit this assumption, the estimates need to be adjusted based on each use scenario and process description.

The sources of TBBPA exposure at workplaces can be divided into direct and indirect sources. The highest occupational exposure to TBBPA occurs as a result of direct exposure. However, indirect exposure to workers may also occur via environmental sources such as air and water. These environmental sources are not unique to workplace environments and are considered to be comparable to other environmental settings such as in the home. Therefore, assessment of occupational exposure will focus on direct exposure to TBBPA within the workplace, and indirect exposure to TBBPA via environmental compartments is addressed in the public exposure section.

10.1.2 Routes of exposure

During occupational use of TBBPA powder and TBBPA-containing end-use products, the main exposure routes are dermal and inhalation, although ocular exposure may occur. Occupational exposure by the oral route is unlikely under normal circumstances. However, accidental ingestion may occur due to hand contamination with TBBPA. Oral exposure may also occur from ingestion of non-respirable particles deposited in the upper respiratory tract following mucociliary clearance.

Inhalation route

At standard conditions, TBBPA is a solid with a low vapour pressure of $<1.19 \times 10^{-5}$ Pa at 20°C (Lezotte and Nixon, 2001). Therefore, inhalation exposure to TBBPA as vapour is unlikely. In the workplace TBBPA is used in powdered form, with a median diameter of 31.81-52.20 μm, with approximately 4 % of the particles having an aerodynamic diameter of <15 μm (*Inveresk, 2002). Inhalable dust particles are considered to be those with a diameter of less than 100μm (ECB 2003). Respirable dust particles, which are small enough to enter the alveoli of the lungs, have a diameter of less than 10μm (enHealth, 2003). The inhalable dust, which is not respired, is likely to either be coughed or sneezed out, or swallowed, with the latter being most likely. Poorly water-soluble particles, such as TBBPA particles, are not readily absorbed from the respiratory tract. Therefore, the inhalable fraction of dust minus the respirable particles needs to be taken into account in the oral ingestion assessment (enHealth 2003).

It is assumed that most of the airborne TBBPA dust will be in the inhalable range, with a small percentage available for absorption in the lungs. Worker exposure to TBBPA via dust inhalation is possible when handling TBBPA powder.

Oral route

Direct occupational exposure to chemicals via the oral route is not usually expected unless poor hygiene practices, such as hand-to-mouth activities, are observed**.** However, as stated, airborne TBBPA particles that are inhaled and not respired into the lungs are either swallowed and absorbed by the gastrointestinal tract or coughed or sneezed out of the body. According to the EURAR report on TBBPA, an estimated 70 % of inhaled particles are deposited in the upper respiratory tract and are available for oral ingestion (EURAR, 2006).

Dermal route

Dermal exposure may occur when workers manually handle TBBPA powder, or semi-finished or end-use products that contain TBBPA. The degree of dermal absorption is considered to be low for TBBPA due to its high molecular weight and high log K_{ow} (ECB, 2003). The EURAR and the Canadian assessment have used a dermal absorption estimate of 1.6 %. But a more recent study (Knudsen et al., (2015), discussed in detail in Section 12, has indicated that a 6 % dermal absorption parameter may be more appropriate. This more conservative value will be used in this assessment.

10.1.3 Measured and modelled data

In the estimation of occupational exposure, it is preferable to use measured data for each of the work scenarios. If both personal and static sampling data are available, personal sampling data are selected for estimation.

For this assessment, no measured data were available from Australian industry. Limited studies measuring airborne concentrations of TBBPA during occupational use have been conducted in the European Union (EURAR, 2006). These data have been used to evaluate the exposure occurring in Australian workplaces.

For scenarios where measured data are not available, exposure modelling was conducted using the EASE (Estimation and Assessment of Substance Exposure).

10.2 Assessment of exposure

10.2.1 TBBPA as a reactive flame retardant

The major use of pure TBBPA powder imported into Australia is as a reactive flame retardant in vinyl ester resins. Workers may be exposed to TBBPA during the manufacture of the flame retardant vinyl ester resins.

When used as a reactive flame retardant, TBBPA acts as a monomer and is incorporated into the polymer structure during the polymerisation reaction. Once the TBBPA has been incorporated into the vinyl ester resin, it is chemically bound and no longer exists as free TBBPA. However, there may be very small amounts of unreacted TBBPA in the vinyl ester resin. According to the EURAR report, the amount of free residual monomer is likely to be less than 1000 ppm or 0.1 % (EURAR, 2006). The major scenario for occupational exposure is handling of the raw TBBPA powder during the manufacture of vinyl ester resin.

The manufacture of TBBPA-flame retarded vinyl ester resin is undertaken at a single site in Australia. According to the applicant, the process is semi-enclosed, with manual handling only occurring during charging of the reactor and packing of the resin product into drums.

The charging of the reactor involves manual handling of 25 kg bags of TBBPA powder. Hoists and trolley trucks shift these bags around the floor of the worksite and lift them to the charge chute, where they are cut open and the contents poured into the chute. It takes a single operator up to 1 hour to charge each batch. This task is carried out for 3 hours a day, for approximately 26 days a year. A total of 5 workers are assigned to this work area. There is no extraction hood associated with the chute, but the reactor is under a vacuum and acts as an extraction system. The operators wear protective clothing including safety glasses and leather or chemical resistant gloves.

The packing process is semi-automated, with operators required to take 3 samples per batch for quality control. However, at this stage of the process the TBBPA is already covalently bound in the vinyl ester resin and therefore exposure will be minimal.

10.2.2 TBBPA as an additive flame retardant

TBBPA is also used in the polymer industry as an additive to impart flame retardant properties to polystyrene and unsaturated polyester resins. TBBPA is added after polymerisation occurs and does not react with the resin. Thus, it is not chemically bound to the polymer. Workers in the polymer industry may be exposed to TBBPA during compounding of flame-retardant resins.

The compounding process of TBBPA-containing polystyrene is semi-enclosed, with manual handling of TBBPA occurring when the powder is weighed out and loaded into the ribbon blender. The powder is weighed out manually into plastic bags. A single worker carries out this task for a maximum of 40-50 minutes per day for approximately 10 days per year. The weighed-out powder is transported to the ribbon blender, where 2-4 workers per shift load powders into the blender. The charging of the blender with TBBPA is carried out for a maximum of 40-50 minutes per day approximately 10 days per year. Dust extraction systems are in operation at the weigh station and blenders, and workers are required to wear personal protective equipment (PPE) including a cartridge type full respirator, disposable gloves, and disposable overalls.

Manufacture of the phenolic resin is conducted in a closed reactor, with manual handling of the TBBPA powder occurring only when it is added to the reactor via an open floveyor system.

TBBPA is used as an additive flame retardant for the production of polystyrene resin at one site in Australia at a concentration of 5-6 % of the final formulation.

10.2.3 Exposure scenarios

Exposure to TBBPA is assessed based on occupational scenarios. This is a useful approach for quantifying exposure, which is achieved by the measurement or estimation of the amount of TBBPA that comes into contact with the worker and the frequency/duration of contact. These are subsequently linked together to estimate exposure or dose. The occupational exposure to TBBPA is assessed based on four scenarios:

- exposure from handling TBBPA powder;
- exposure from handling semi-finished products containing TBBPA;
- exposure from the use of end-products containing TBBPA; and
- exposure from recycling components containing TBBPA.

Workers involved in the importation, transportation and storage industries may accidentally be exposed to TBBPA if packaging is faulty or broken.

10.2.4 Assumptions in exposure estimations

In order to conduct quantitative estimates of occupational exposure, a number of assumptions were made to facilitate the calculations. They include:

- as a worst-case scenario estimate, it was assumed that all airborne TBBPA particles are smaller than 100 μm and are capable of being inhaled (inspirable).
- 4 % of TBBPA particles in air are respirable
- 70 % of TBBPA particles in air are orally ingested after inhalation
- the respiratory rate for an average worker is 1.3 m^3/hour (ECB, 2003)
- surface area of hands and forearms for dermal exposure is 1000 cm^2
- bodyweight for average workers is 70 kg
- inhalation absorption = 100 %
- dermal absorption = 6 %

According to the OECD guidance document (OECD, 2003), when estimating occupational exposure levels, the median and 90th percentile values are selected for a typical and reasonable worst-case situation, respectively.

Exposure was estimated based on typical and worst-case scenarios with the worker not using PPE. The use of PPE is expected to reduce the exposure depending on the efficiency and correct use of the equipment.

10.3 Exposure from handling TBBPA powder

10.3.1 Estimation based on measured data

Australian industry provided no exposure monitoring data. However, measured data from overseas are available.

UK data (1)

UK Health and Safety Executive (EURAR, 2006) described in detail a typical compounding system for PBFRs, where TBBPA powder is added to an extruder for the production of an ABS masterbatch.

The loading task involved slitting the sacks of TBBPA and tipping the powder into the open hatch of the mixer. The mixer, housed in a downdraught booth, has an inlet hatch that requires the operator to stand on a raised platform. Weighed raw materials are manually tipped into the open hatch before the lid is closed and locked. The addition of TBBPA and the mixing of masterbatches at this site takes place for a full shift, but usually only for 1 or 2 days a month. Personal and static samples were collected during loading and mixing, as well as during the extrusion process, and TBBPA air concentration levels are shown in Table 11.

Table 11 – TBBPA air concentrations, UK study (EURAR, 2006)

Sample Point	Sample Type	TBBPA (9.5 h shift) ($\mu g/m^3$)	TBBPA (8 h TWA) ($\mu g/m^3$)
Work Task			
Loading/mixing	Personal	10000	12000
Supervisor/mixing	Personal	170	200
Sampling Area			
Mixer/extruder	Static	120	-
Storage	Static	8	-

UK data (2)

In 2002, the UK HSE visited one resin mixing plant and sampled for TBBPA. They described the mixing process as follows:

1. for addition of the TBBPA, two 1-tonne bags of TBBPA powder are manoeuvred above the hatch of reaction vessel by a mechanical hoist.
2. the drawstring bottom of the bags is opened manually to release TBBPA into the vessel. The addition takes about 15 minutes.
3. the empty bags are rolled up manually for disposal.

The operator wears protective glasses, boots, cotton gloves and a disposable respirator during TBBPA addition. The air concentration of TBBPA at the resin-mixing plant was measured from a personal sampler to be 75 μg/m^3 (8-hour TWA).

German data

A German study reported measured data from 2 plants in Germany (EURAR, 2006).

Plant A has an ABS compounding facility. At the hopper, samples were taken during the emptying of bags containing TBBPA into several hoppers. Emptying of big bags (no information on bag size is available) lasts between 30-45 minutes per day. No local exhaust ventilation (LEV) was provided at the filling site but disposable respirators were worn.

At plant B, operators were sampled when they added big bags of TBBPA into the hopper. The work also included cleaning the hopper area. The hopper was filled with 15-25 bags per shift. LEV was not provided but disposable respirators were worn. Measured levels of TBBPA in air from both plants are shown in Table 12.

Table 12 – TBBPA air concentrations in Germany study (EURAR, 2006)

Plant	Work Task	Sampling Duration (minutes)	TBBPA (μg/m^3)
A	Hopper-emptying bags	10	1520
A	Hopper-emptying bags	23	1470
A	Hopper-emptying bags	8	350
B	Hopper operator	100	1600
B	Hopper operator	50	900

Estimation based on the combined measured data

The measured data from the UK plant were much higher than those from the German site. The HSE survey report indicated possible reasons for the increased exposure to TBBPA, including:

- the large quantities of TBBPA being added to the plastic batches
- a poorly designed booth at the master batch mixer
- poor practices observed at other addition stages.

Occupational exposure for an Australian scenario is estimated from measured data from the German study. The sample sizes in all three studies are small; therefore, the measurements from the personal monitoring samples during the loading/mixing task (i.e. emptying bags of TBBPA into the hopper) at all four sites (n=9) were pooled, and the median and 90th percentile values used to determine the typical and worst-case concentrations respectively.

The duration and frequency of handling TBBPA powder varies in Australian companies. For the reasonable worst-case scenario, exposure estimation is based on assumptions that a worker handles TBBPA powder 3 hours per day for 56 days per year. Inhalation and oral exposure estimates are presented in Table 13.

Table 13 – Estimated exposure of Australian workers to TBBPA when handling powdered TBBPA

Exposure type	TBBPA air concentration (μg/m^3)	Duration (hour/day)	Frequency (day/year)	Inhalation exposure (μg/kg/d)	Oral exposure (μg/kg/d)
Typical exposure	1470	3	56	3.28	57.3
Worst-case exposure	1600	3	56	3.57	62.4

Based on the pooled data and using calculations shown in Appendix 1, the:

- estimated typical inhalation exposure for a worker handling TBBPA is 3.28 μg/kg/day
- reasonable worst-case inhalation exposure (highest recorded) is 3.57 μg/kg/day
- estimated typical oral exposure for a worker handling TBBPA is 57.3 μg/kg/day
- reasonable worst-case oral exposure is 250 μg/kg/day.

10.3.2 Estimation based on modelled data (EASE)

At the industry sites, the highest occupational exposure occurs when workers weigh and add TBBPA powder to the reactor or mixer. The inhalation and dermal exposure to TBBPA during the weighing and adding processes is selected for EASE modelling estimation.

The EASE scenario of dry manipulation of inhalable dust was used to model the inhalation exposure to TBBPA during the addition of the powder to the reactor. Assuming that the solid is non-aggregating, the full-shift concentration was estimated by EASE modelling to be 2-5 mg/m^3 with LEV present, and 5-50 mg/m^3 without LEV present.

The dermal exposure during the addition of TBBPA to the extruder was also modelled using the EASE program. Non-dispersive use and intermittent direct handling of a 'dusty' solid was used to represent powder addition to the extruder. The predicted dermal exposure was estimated to be 0.1-1 mg/cm^2/day.

The exposure levels in the presence and absence of LEV are used for the estimations of the typical exposure and the reasonable worst-case exposure, respectively. Since these values are derived from full-shift exposure levels, duration of 3 hours per day and frequency of 56 days per year are used for further estimation.

Table 14 – Exposure to TBBPA via oral ingestion, inhalation and dermal contact based on EASE modelling (when handling powdered TBBPA)

Exposure type	TBBPA air conc. (μg/m^3)	Duration (hr/day)	Frequency (day/year)	Inhalation exposure (μg/kg/d)	Oral exposure (μg/kg/d)	Dermal exposure (μg/kg/d)
Typical exposure (with LEV)	2000-5000	3	56	4.46 – 11.1	78-195	32.1-321
Worst-case exposure (without LEV)	5000-50000	3	56	11.1 – 111.4	195-1195	

The calculated internal exposures from measured exposure values are in reasonable agreement with those obtained from EASE estimates (lower end) for typical and worst case exposures. Oral and inhalation exposures calculated from measured values are used for risk assessment.

Measured dermal exposure values are not available. Values obtained from EASE estimates for dermal exposure are used for risk assessment. The EASE model estimates dermal exposure to a dusty substance to be in the range of 0.1-1 mg/cm^2/day. Based on a dermal exposure area of 1000 cm^2 and 6 % dermal absorption, the systemic dose arising from dermal exposure to TBBPA is calculated to be 32.1-321 μg/kg bw/day, using equations in Appendix 1.

10.4 Exposure from handling semi-finished products containing TBBPA

Worker categories in this scenario include:

- printed circuit board workers
- electric/electronic product assemblers/repairers
- laminate manufacturers
- plastic moulders
- other workers handling semi-finished products containing TBBPA.

TBBPA concentration in semi-finished products ranges from less than 0.5 % in circuit boards and phenolic resin to <17 % in ABS based products.

10.4.1 TBBPA as a reactive flame retardant in semi-finished products

When TBBPA is used as a reactive flame retardant, the occupational exposure to TBBPA in semi-finished products is restricted to the residual TBBPA monomer content.

The amount of residual TBBPA monomer in resins is uncertain. According to the EURAR report on TBBPA, the amount of free residual monomers is likely to be less than 1000 ppm or 0.1 % (EURAR, 2006). Other estimates predict this value to be even lower.

One study has measured the amount of free TBBPA extracted from printed circuit board filings (Sellström and Jansson, 1995). A small sample of the filings (0.5 g) was extracted with 10 mL of water containing NaOH (0.01 M) and NaCl (0.2 M) for 20 hours. The amount of unreacted TBBPA extracted was 0.7 μg per gram circuit board, corresponding to about 4 μg free TBBPA per gram of TBBPA used in the circuit board. Based on information from the manufacturer, the printed circuit board was assumed to contain 8-12 % bromine, so that the amount of TBBPA used in its manufacture would have been 14-20 %. Therefore, the residual TBBPA monomer content was concluded to be between 3.5 to 5 ppm. The authors state that the extraction process used would probably only extract the fraction of acidic compounds present within the filings. This is likely to result in an underestimation of the residual TBBPA content.

The amount of residual TBBPA was also estimated from the known values of the residual bisphenol-A content in similar resins. The EU risk assessment report of bisphenol-A indicates that the maximum residual monomer content of bisphenol-A in epoxy resins is 1000 ppm (EURAR, 2006). The curing process would reduce this value even further. The EU risk assessment report of TBBPA confirms this with reported information from industry, which indicated that the residual monomer content of some epoxy resin products is <200 ppm (or <0.02 % w/w) (EURAR, 2006).

TBBPA is used as a reactive flame retardant in FR4 type laminates used in the production of printed circuit boards. These laminates contain low amounts of unreacted TBBPA, assumed here to be 0.02 % by weight. The laminates are not manufactured in Australia, but rather are either imported as the base material or as part of complete circuit boards. The highest potential for worker exposure occurs during the assembly of printed circuit boards, and is expected to be very low.

There are some sites in Australiathat use the FR4 type laminates as a base material. The assembly of printed circuit board on the production line is an automated or semi-automated process with limited manual handling required. Although no industry data for TBBPA exposure were submitted to NICNAS, both inhalation and dermal exposures to TBBPA during this process are expected to be low based on:

- the low concentration of TBBPA monomer in the printed circuit board
- limited handling during assembly of printed circuit board.

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10.4.2 TBBPA as an additive flame retardant in semi-finished and finished products

Although TBBPA is an additive component, which is normally added after polymerisation, it is incorporated in the polymeric matrix at low percentages. Inhalation, oral and dermal exposures to TBBPA during this process are expected to be low.

TBBPA in phenolic resin

Phenolic resin containing TBBPA is used in the production of decorative laminates. Industry supplied no information on the process of laminate manufacture or on occupational exposures.

The manufacture of laminates typically involves impregnating paper with a phenolic resin and then compressing multiple sheets of the treated paper in a hydraulic press to form the laminate. To impregnate the paper with the phenolic resin the paper is drawn between 2 rollers, one of which applies a thin coating of resin to one side of the paper. After giving the resin time to soak in, the paper is passed through drying ovens and then cut into sheets.

The manufacturing process is generally an enclosed process so that inhalation exposure will be minimal. Dermal exposure may occur during addition of the resin at the beginning of the process. However, due to the low concentration of TBBPA in the phenolic resin (between 0.1-0.4 %) this exposure is likely to be minimal. Occupational exposure may result from laminate board cutting (manual or automated). However, due to the low concentration of TBBPA in the resin, this exposure is likely to be minimal.

TBBPA in ABS

Acrylonitrile butadiene styrene (ABS) copolymer masterbatch pellets, containing <17 % TBBPA is imported into Australia. It is then sold to approximately 10 plastics manufacturers who use the masterbatch for injection moulding applications.

The injection moulding process is generally conducted in a closed or semi-closed system. The masterbatch pellets are poured into a hopper and are then heated to form a molten thermoplastic. This is then injected under high pressure into a steel mould. Once the plastic has cooled and solidified, the mould is opened and the plastic product removed. High temperatures are involved in the process, which could lead to the generation of TBBPA vapour, as well as decomposition products. However, the heating process is carried out in a closed vessel, so the exposure is minimised. There is the possibility of dermal exposure to the masterbatch pellets when loading the hopper, and to the finished plastic product when it is removed from the mould. However, the TBBPA is encapsulated in the polymer matrix, so dermal exposure to TBBPA is minimal.

10.4.3 Estimation of inhalation exposure based on measured data

UK data

In 2002, the HSE measured worker exposure to TBBPA at a laminates manufacturing company. The workers at this facility are involved in manufacturing and processing of copper/resin laminates which are used for production of printed circuit boards. The epoxy

resin used for manufacture of the laminates contained reacted TBBPA (EURAR, 2006). At the resin mixing plant, TBBPA is added to the resin at a concentration of 25 % by weight.

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 TBBPA has been reactively incorporated into the resin, so little should be available for either dermal, oral or inhalation exposures. The laminated sheets are mostly cut by automatic guillotines. However, some manual cutting is also performed onsite. On the treatment lines, operators routinely collected air samples for quality control purposes by grinding up small portions of the composite material. This was undertaken on a small bench fitted with an extractor.

Both static and personal samples at the treater line and guillotine sites were collected. TBBPA air concentrations are shown in Table 15.

Table 15 – TBBPA air concentrations in UK study

Area/task	Sample type	TBBPA (μg/m^3, 8-h TWA)
Treater line plus quality control (QC) sampling	Personal	4.6
Treater line plus QC sampling	Personal	0.2
Guillotine (cleaner)	Personal	0.6 (0.9 μg/m^3 over 5.5 h)
Treater line	Static	0.01
Treater line	Static	0.003
Guillotine	Static	Below detection
Lamination	Static	0.7

Swedish data

A published study measured the air concentration of TBBPA in a Swedish factory involved in the assembly of printed circuit boards (Sjodin et al., 2001). It took 6 static measurements in areas of the factory where components were soldered onto the circuit boards. The TBBPA concentrations ranged from 0.00011-0.00037 μg/m^3.

Estimation of inhalation and oral exposure

Since TBBPA concentrations at the circuit board assembly sites were about 10-fold less than the lamination sites, the UK data are selected to estimate inhalation exposure for workers handling semi-finished products containing TBBPA.

At the lamination sites, only three personal samples are available and low levels were detected from the static samples. The level of 0.6 μg/m^3 is selected for the typical exposure, and 4.6 μg/m^3, as a reasonable worst-case exposure. It should be noted that uncertainties are associated with these levels due to the limited amount of available measured data for this scenario. Workers are assumed to work 8 hours per day and 5 days per week. It is also assumed that oral exposure may result from the inhalation of particulate TBBPA.

Table 16 – Estimated exposure of Australian workers to TBBPA when handling semi-finished products containing reactive TBBPA

Exposure scenario	Air conc. (μg/m^3)	Duration (hour/day)	Frequency (day/week)	Inhalation exposure (μg/kg/d)	Oral exposure (μg/kg/d)
Typical exposure	0.6	8	5	0.003	0.06
Worst-case exposure	4.6	8	5	0.027	0.48

10.5 Exposure from the use of end-products containing TBBPA

Many employees in Australia work in offices or other places equipped with computers, printers, photocopiers and other end-use products containing plastic components flame-retarded with TBBPA. There is the potential for TBBPA-containing dust from these plastics to become airborne. TBBPA vapour emissions from end-products are likely to be minimal due to the low vapour pressure of TBBPA.

The stability of ABS resins has been investigated over a range of temperatures (Luijk and Govers 1992). Very low levels of TBBPA were detected above 200 °C., Air levels of TBBPA in offices containing large numbers of computers were measured (Sjödin et al., 2001). Four static samples had a mean value of 3.6 x 10^{-8} mg/m^3 [range 1 - 7 x 10^{-8} mg/m^3]. Wolf et al. (2000) demonstrated no releases of brominated compounds from an epoxy resin printed circuit board containing TBBPA. EURAR (2006) reported studies where no TBBPA was detected in the air inside or surrounding a television set or computer monitor casing. This was for cases where the flame retardant was present in printed circuit boards (reactive form) or monitor casings (additive form) (De Boer et al., 1998; Ball and Hermann, 2002). For the latter, an office experiment tested release from monitor usage under simulated 'real life' conditions. The monitor casings contained 12 % TBBPA and the circuit boards within them contained between 4 % and 8 % TBBPA. Air levels of TBBPA measured in the enclosed chamber varied between 1 x 10^{-7} mg/m^3 and 2.0 x 10^{-5} mg/m^3. Air levels of TBBPA the study measured in the office investigation peaked at 2.33 x 10^{-5} mg/m^3 before falling slowly to between 1 and 2 x 10^{-7} mg/m^3. TBBPA levels between 0.1 to 2.3 ng/m^3 were measured in an enclosed chamber that housed computers (Ball and Herrmann, 2002).

Wipe samples from the test chambers showed a maximum TBBPA value of 0.57 mg/m^2 at the bottom of the sampling area, but particles were detected beforehand and may have represented contamination from the housing (EURAR 2006). These data indicate that there is potential for exposure to very low levels of TBBPA in areas with close proximity to operating computers and monitors.

TBBPA air concentrations in office environments are low and similar to those found in residential houses. In a Swedish study, Sjödin et al. (2001) reported a mean TBBPA concentration of:

- 0.036 ng/m^3 in 6 office microenvironments containing computers
- 0.09 ng/m^3 in 2 teaching halls
- 0.035 ng/m^3 in 2 computer repair facilities.

In the same study they found that TBBPA was present primarily in the particulate phase rather than in the vapour phase. Therefore, the exposure to TBBPA from end-use products is expected to be low and this issue is addressed in the public exposure section.

Dermal contact with TBBPA-containing circuit boards is not expected in workers except in the case of IT specialists. People working in the IT industry may have extensive dermal contact, particularly on the fingers, with hard plastic computer and electronic casings, and other plastic components during operation of TBBPA-containing end-use products. Since TBBPA is incorporated into the polymer matrix within these products and minimal absorption of TBBPA occurs through the skin (6 %), dermal exposure is considered to be negligible.

10.6 Exposure from recycling activities

Occupational exposure from recycling activities is expected to occur during recycling of circuit boards. The recycling of printed circuit boards is carried out at one site in Australia. The boards are manually separated from other electronic waste and sent overseas for processing. No shredding operations are carried out in Australia.

There are no models for estimating exposure during recycling of circuit boards. No Australian measured data were available for this exposure scenario. However, dermal exposure to TBBPA during dismantling of circuit boards with tools is expected to be low as TBBPA is bound within the resin and dermal absorption for TBBPA is very low.

Air samples taken from Swedish and UK factories where computers, printers and monitors are dismantled and printed circuit boards are shredded indicated very low potential of worker exposure to airborne TBBPA. Concentrations of TBBPA in the range 5.8 – 29.7 ng/m^3 were detected in air samples at plants for the recycling of electronic equipment (Bergman et al., 1999; Sjodin et al., 2001).

10.7 Biological monitoring data

Only a limited number of studies have been conducted to determine the levels of TBBPA in biological samples from workers.

The TBBPA plasma levels of 3 different occupational groups (electronics dismantlers, circuit board producers and laboratory personnel) were compared in Norway (Thomsen et al., 2001). In each occupational group, 5 people were sampled. The study considered laboratory

personnel, a non-occupationally exposed group. Although some computer work was involved in their daily routines, the authors expected their exposure to be no greater than for the general population. They found the highest levels amongst the electronics dismantlers (Table 17).

Table 17 – TBBPA plasma levels in 3 occupational groups

Occupation	Range (ng/g lipid weight)	Mean (ng/g lipid weight)	Converted internal dose (ng/kg)
Electronics dismantlers	0.64-1.8	1.3	0.48
Circuit board producers	Not detectable – 0.8	0.54	0.2
Laboratory personnel	Not detectable – 0.52	0.34	0.13

Grimvall et al. (1997) indicated that the average lipid weight in human blood is about 5 g/L and a total blood volume of 5.2 L is assumed for an adult (enHealth 2003). Assuming the TBBPA levels in plasma represent the total TBBPA in vivo, the mean TBBPA data are then converted into internal doses. The highest internal dose is seen in electronics dismantlers, followed by the circuit board producers.

Summary

The estimated internal doses from inhalation, oral and dermal exposure are listed in Table 18. The exposure from handling end-use products containing TBBPA is estimated to be low and not included in the table. The inhalation and oral exposure levels from the other three scenarios are estimated from measured data, and dermal exposure is calculated based on the EASE model estimates.

Table 18 – Summary of internal doses from TBBPA occupational exposure (µg/kg bw/d)

Scenario	Exposure	Oral exposure	Inhalation exposure	Dermal exposure	Total exposure
Handling powder	Typical	57.3	3.28	32.1-321	92.7 - 382
	Worst-case	62.4	3.57		98.1 - 387
Handling semi-finished products	Typical	0.06	0.003	Very low	0.063
	Worst-case	0.48	0.027		0.507
Recycling (dismantling)	Worker exposure during dismantling circuit boards is expected to be very low as TBBPA is bound within the resin and dermal absorption for TBBPA is very low. Shredding of circuit boards does not occur in Australia.				

According to exposure estimates, the internal dose of TBBPA for workers from highest to lowest is:

- during manual handling of TBBPA powder at the beginning of resin production
- handling semi-finished products
- working at recycling sites.

For workers handling TBBPA powder:

- exposure from oral exposure is highest
- inhalation and dermal routes contribute almost equally to occupational exposure.

Dermal exposure is significant during manual handling of TBBPA powder, but is much lower in other scenarios. The EASE prediction of dermal exposure for workers handling TBBPA powder is probably an overestimate since:

- TBBPA powder is unlikely to readily adhere to the skin surface
- the dermal absorption rate may be lower than 6 % without the presence of a suitable solvent.

For workers handling semi-finished products and recycling TBBPA products, occupational exposure is mostly by oral exposure via inhalation.

Uncertainties in exposure estimation arise from the use of analogue data where no measured data are available. Furthermore, the use of overseas data to estimate occupational exposure levels at Australian worksites also gives rise to exposure uncertainties.

11 ENVIRONMENTAL EXPOSURE

The environment is potentially exposed to TBBPA during all stages of the life cycle of the chemical. The stages can be summarised as follows:

- production of the chemical (not relevant for this assessment as no production occurs in Australia)
- processing/formulation (site specific, point source releases)
- use (point or diffuse release depending on use pattern)
- disposal.

Very few Australian environmental monitoring data are available for TBBPA so, in its absence, a semi-quantitative approach will be taken for the exposure assessment. The environmental concentrations that result from the release of TBBPA to sewer from industrial processes will be estimated using the OECD approach for estimating releases of chemicals in the plastics industry (OECD, 2009); other releases will be treated qualitatively.

In the following sections, references not sighted directly have been indicated with an asterisk (*). These references are treated in the TBBPA environmental assessment reports published by Health/Environment Canada (2013), USEPA (2015) and EURAR (2008) and the summaries provided herein are based on these reports.

11.1 Quantifying Release

Manufacture, importation and use figures are in Section 8 of this report. TBBPA is imported into Australia in three main forms:

- as a pure chemical (technical or commercial grade) for further use in the plastics industry
- as an additive component in plastic compounds and other semi-finished products
- as a component (either reacted or as an additive) in retail goods like computers, home electrical and electronic equipment.

Technical or commercial grade TBBPA (purity ≥ 98 %) is imported into Australia in powder form for use:

- mainly as a reactive flame retardant in the manufacture of epoxy resins, vinyl ester resins and polycarbonate resins
- to a lesser extent as an additive flame retardant in the manufacture of polystyrene resins, acrylonitrile butadiene styrene (ABS) resins and phenolic resins.

Mean importation rates for 2003-04, 2004-05 and 2005-06 for technical TBBPA are around 27 tonnes per annum. Importation of TBBPA in 2015-16 was 19.34 tonnes. Of this, 14.7 tonnes was imported as a raw material and 4.64 tonnes was imported as an additive ingredient in ABS resin. Based on information provided to NICNAS, it is assumed that:

- 90 % (13.23 tonnes) of the TBBPA introduced as a raw material is used as a reactive intermediate in the manufacture of epoxy, vinyl ester and polycarbonate resins
- the remaining 10 % (1.47 tonnes) is introduced for use as an additive flame retardant.

The OECD Emission Scenario Document (ESD) for estimating releases of chemicals used in the plastics industry will be referred to as appropriate in this section (OECD, 2009).

11.1.1 Local release estimation

Local releases will result from manufacturing resins using raw TBBPA and from processing these resins into products. The available information indicates that most of the TBBPA introduced into Australia is used in resin manufacturing and resin processing facilities in Melbourne.

11.1.1.1 Technical/commercial grade TBBPA

Raw material handling

The ESD assumes emissions of dust to be removed or settle, and losses will be to solid waste or waste water as a result of wash-down. The emission factors used below incorporate this assumption. The ESD assumes that no TBBPA dust leaves the factory by diffuse emissions. That is, all of the raw chemical is either incorporated in plastics or ends up in a waste stream. However, international soil monitoring data around plastics factories shows that some TBBPA does escape such facilities, mostly as dust (see Section 11.2.5 and Section 11.2.6). Such emissions will be treated separately.

The ESD considers 2 scenarios for release of particulates of different particle size:

- powders >40 µm
- powders <40 µm.

The scenario for powders <40 µm was chosen for consistency with the human health component of the risk assessment where it is assumed that all particulates are respirable (<10 µm in size).

There is some ambiguity in the release factors (F) used in the ESD. For example:

- $F_{handling, water}$ is given as '(0.1 + 0.5) = 0.6 % to solid waste/water'. This is interpreted as 0.1 % to solid waste and 0.5 % to waste water.
- $F_{handling, air}$ is given as 0 %.
- Tthe value of $F_{handling, waste}$ for particles of size <40 µm is 1 % and is attributed to solid waste residue in import bags. This is unreasonably high and a factor of 0.1 % (as used for powders >40 µm) will be used instead.

The additional factor of 0.1 % from $F_{handling, water}$ is added to $F_{handling, waste}$.

For powders of particle size <40 µm the corresponding emission factors used to calculate release from raw materials handling are therefore:

- $F_{handling, water}$ = 0.5 % to wastewater
- $F_{handling, air}$ = 0 %
- $F_{handling, waste}$ = 0.1% + 0.1 % = 0.2 % to solid waste

Annual releases from raw materials handling are predicted to be:

- air: None
- waste water: 0.005 × 14700 kg = 73.5 kg
- solid waste: 0.002 × 14700 kg = 29.4 kg

11.1.1.2 Compounding (formulation)

This section pertains to releases that occur when TBBPA is combined into resin or plastic as either an additive or reactive component.

Particles are again assumed to be <40 µm in size and only the 14.7 tonnes of TBBPA introduced as a raw material will be considered. Based on the criteria given in the ESD (p. 98), TBBPA is classified as a low volatility flame retardant.

The corresponding emission factors are as follows:

- for powders of particle size <40 µm, release factors for calculating release during formulation are:
  - $F_{compounding, air}$ = 0.001 %
  - $F_{compounding, water}$ = 0.051 %

Therefore, the annual releases from compounding are predicted to be:

- air: $1 \times 10^{-5} \times 14700$ kg = 0.15 kg
- water: $5.1 \times 10^{-4} \times 14700$ kg = 7.5 kg

11.1.1.3 Conversion (processing)

This section pertains to releases that occur during production of plastic articles from resins or plastics.

Reactive TBBPA

It is assumed that releases from TBBPA used as a reactive flame retardant will be minimal during conversion/processing because the majority of the chemical will be covalently bound within the resin. In the human health component of this risk assessment, it is assumed that only 0.1 % of the TBBPA used as a reactive flame retardant remains unbound. Based on an annual import volume of 13.23 tonnes for use in reactive flame retardants (90 % of 14.7 tonnes), this would leave 13230 kg × 0.1 % = 13.23 kg of unbound TBBPA in the plastic matrix. Only a small fraction of this unbound TBBPA will be released during conversion so the net release of TBBPA from this pathway can be considered to be negligible.

Additive TBBPA

Release that occurs during the conversion stage is considered for the 6.11 tonnes of TBBPA imported annually for use as an additive flame retardant (1.47 tonnes of raw material + 4.64 tonnes imported in finished ABS resins). Conversion processes are assumed to occur in closed systems, at 'small' facilities (processing <750 tonnes of plastic per annum), and at temperatures >200 °C. Small facilities incur an extra multiplicative release factor of 10, and temperatures >200 °C also incur an additional factor of 10.

The standard release factors (before multiplication) for calculating release during conversion are as follows:

- $F_{conversion, air}$ = 0.001 %
- $F_{conversion, water}$ = 0.001 %

Annual releases from conversion are therefore predicted to be:

- air: $1 \times 10^{-5} \times 6110$ kg $\times 10 \times 10 = 6.11$ kg
- water: $1 \times 10^{-5} \times 6110$ kg $\times 10 \times 10 = 6.11$ kg

11.1.1.4 Summary of local releases

Estimated annual releases from handling, compounding and conversion of TBBPA in Australia are in Table 19.

Table 19 – Summary of releases from processing of TBBPA into plastics

Stage of operation	Release (kg per annum)		
	Air	Water	Solid waste
Resin manufacture			
Handling	-	73.5	29.4
Compounding	0.15	7.5	-
End use product manufacture (conversion)			
Conversion, >200°C, <750 t plastic p.a.	6.11	6.11	-
Total	6.26	87.1	29.4

11.1.2 Other releases

TBBPA will also be released to air during the service life of articles in which it is incorporated as an additive flame retardant. TBBPA incorporated as a reactive flame retardant is not released in measurable quantities via volatilisation (Health/Env Canada, 2013 and references therein). Based on the responses to a NICNAS call for information for introduction volumes of TBBPA in articles for the 2004-05 financial year, it is estimated that 509 tonnes of TBBPA was introduced in articles as an additive flame retardant. This is probably an underestimate, as not all importers of electrical goods responded to the NICNAS call for information. Thus the quantity of TBBPA that is imported for manufacturing processes (~ 6 tonnes per annum) is negligible compared to the quantity of TBBPA imported annually in finished articles. As a result, the majority of the TBBPA that is emitted during the service life of articles is reported to be from imported articles rather than articles manufactured in Australia that use imported

raw material or resins. Release from articles will occur through volatilisation or via particulates that form during the degradation of the articles. In both cases, TBBPA will be associated with atmospheric particulates. Released TBBPA will eventually be distributed between soil, wastewater and landfill, depending on the fate of the particulates. It is difficult to quantify the annual release of TBBPA through this mechanism. The model in the ESD gives estimates for emissions over the lifetime of products, but since these lifetimes vary significantly depending on the product, these are not easily converted into annual releases.

TBBPA will also be released from articles during disposal. The majority of the TBBPA released on disposal will be from articles that are imported into Australia. Some of these articles will be disposed of to landfill, and some will be recycled under the National Television and Computer Recycling Scheme.

More than 290000 tonnes of e-waste has been collected and recycled in Australia since 2011. As highlighted in the human health section of this report, articles are usually dismantled in Australia, with the majority of the plastic shipped overseas for further processing. However, sites where e-wastes are stored and processed have been shown to be sources of brominated flame retardants in the Australian environment. Soil near 2 sites in Melbourne had concentrations of decabromodiphenyl ether of 1060 and 13100 µg/kg respectively (McGrath et al., 2016). These are comparable with e-waste recycling facilities in developing countries (McGrath et al. 2017).

Automotive dismantling and metal recycling facilities have also been shown to be a source of brominated flame retardants in the Australian environment (Hearn et al., 2012). Brominated flame retardants have also been detected at high concentrations in Australian landfill soil (McGrath *et al.,* 2016).

11.2 Environmental Fate and Partitioning Behaviour

11.2.1 Physical and chemical properties

The physical and chemical properties of TBBPA have been discussed in Section 7:

- TBBPA dissociates within the environmental pH range and its solubility increases with increasing pH
- water solubilities of 0.148-2.34 mg/L for pH 5.0-9.0 have been reported
- the vapour pressure of TBBPA has been measured as $<1.19 \times 10^{-5}$ Pa (very slightly volatile)
- the Henry's law constant is 1.47×10^{-5} pa m^3/mole, indicating that the chemical is slightly volatile from water
- the octanol-water partition coefficient is high (log K_{OW} = 5.9).

Qualitatively, these data indicate that when released to the environment, TBBPA will partition strongly to organic carbon and is unlikely to volatilise to the atmosphere. Where TBBPA is present in water and the atmosphere, it is most likely to be sorbed to particulate matter.

Level III fugacity modelling by Environment Canada (EC) provides a quantitative picture of the partitioning behaviour of this chemical (Health/Env, 2013). The model predicts that if released to:

- air, EC expected a very small fraction (0.1 %) to remain in air, with the remainder partitioning to soil (97.6 %) and sediment (2.2 %)
- water, EC expected TBBPA to partition to sediment (96.4%) with only a small amount remaining in water (2.8 %)
- soil, EC expected TBBPA to remain in soil (99.8 %).

There is a degree of uncertainty in the values the model predicted due to variations in solubility with increasing pH. However, the results are consistent with the expected behaviour for a chemical with low volatility and high lipophilicity.

11.2.2 Persistence

11.2.2.1 Abiotic degradation

Photolysis

The following results for photolysis experiments are reported in WHO (1995):

The half-life of TBBPA decomposition in water by UV radiation was calculated as 10.2 days in spring, 6.6 days in summer, 25.9 days in autumn, and 80.7 days in winter. Cloud cover lengthened the half-life by a factor of two and water depth also influenced the direct photodegradation (Bayer, 1990). While the measured half-lives are likely to be different under Australian conditions, the results indicate that TBBPA is potentially persistent in water during winter (see Section 14.4).

TBBPA was photodegraded when adsorbed onto the surface of quartz cuvettes (Eriksson and Jakobsson, 1998*). The experiment used UV-light of wavelengths >290 nm both in the absence- and presence-of hydroxyl radicals. TBBPA was found to degrade completely within 5 - 6 days. The major breakdown product was identified as 2,4,5-tribromophenol, which also underwent further degradation under the experimental conditions. A number of other products (at least 20) were also formed and some of these were tentatively identified including di- and tribromobisphenol A, dibromophenol, 2,6-dibromo-4-(bromoisopropylene)phenol, 2,6-dibromo-4-(dibromoisopropylene)phenol and 2,6-dibromo-1,4-hydroxybenzene.

The photochemical transformation of TBBPA and related phenols including tri-bromo BPA has also been studied in water by Eriksson et al. (2004). The pH-dependence of the decomposition rate was also investigated (pH 5.5 – 11). The decomposition rate was six times higher at pH 8 than at pH 6. Identification of the degradation products indicated that TBBPA and tri-bromo BPA decompose via different mechanisms. Three isopropylphenol derivatives (4-isopropyl-2,6-dibromophenol, 2-isopropylene-2,6-dibromophenol and 4-(2-hydroxyisopropyl)-2,6-dibromophenol) were identified as the major degradation products of TBBPA while the major degradation product of tri-bromo BPA was identified as 2-(2,4-cyclopentadienyl)-2-(3,5-dibromo-4-hydroxyphenyl)propane.

Atmospheric Photoxidation

TBBPA has a low vapour pressure which indicates that partitioning to the atmosphere will be minimal and any volatilised chemical is expected to be sorbed to airborne particulate matter. Atmospheric breakdown of volatilised or sorbed TBBPA will occur through reactions with hydroxyl radicals (•OH).

The half-life for TBBPA degradation by hydroxyl radicals is estimated to be 3.62 days based on calculations made with the AOPWIN Program (Atmospheric Oxidation Program for Microsoft Windows) Version 1.91, Syracuse Research Corp. 1988-97.

Stability in Water

Hydrolysis

No data for hydrolysis of TBBPA are available. Based on its molecular structure, the compound is not expected to be hydrolysed under environmentally-relevant conditions.

Volatilisation from water

Based on two reported vapour pressures (<1.19 × 10^{-5} Pa and 8.04 × 10^{-6} Pa), TBBPA is estimated to have a Henry's Law Constant of 2.66 × 10^{-7} atm m^3/mol and 1.8 × 10^{-7} atm m^3/mol respectively. These low values indicate that TBBPA is only very slightly volatile from water and moist soil. Additionally, TBBPA is expected to strongly sorb to suspended material in water and to partition to sediment via deposition of the suspended matter.

11.2.3 Biodegradation

The available data indicate that TBBPA will biodegrade in most, but not all, circumstances. However, biodegradation may be very slow and complete mineralisation limited. These observations indicate that persistent degradants are formed and a limited number of these degradants have been fully characterised.

TBBPA and its degradation products can chemically bind to soil, and the available evidence indicates that this process is reversible (see below). If the process is reversible, the chemical may be slowly released from soil and become available to organisms. This is likely to affect the rate of biodegradation by prolonging the release of 'free' TBBPA which is bioavailable to microorganisms for degradation.

Bisphenol A (BPA) is produced during anaerobic biodegradation of TBBPA (Ronen and Abeliovich, 2000). BPA appears to be formed via stepwise reductive debromination of TBBPA and is the major metabolite (88 % yield). By contrast, BPA is not formed as a major metabolite during aerobic degradation. BPA is a persistent chemical that has exhibited reproductive, developmental and systemic toxicity in animal studies (US EPA – BPA).

11.2.3.1 Aerobic

Ready biodegradation

TBBPA has been tested in a (Japanese) Ministry of International Trade and Industry (MITI) ready biodegradation test (CITI, 1992) at a nominal concentration of 100 mg/L, well in excess of its water solubility. Test media were prepared containing: i) water and test substance (two concentrations), ii) sludge and test substance (two concentrations), iii) sludge and aniline (positive control, 100 mg/L), and iv) a control blank. Activated sludge was added to the relevant test vessels so that the concentration of suspended solids reached 30 mg/L. Test media were stirred and conditions of cultivation included a temperature of around 25°C with cultivation duration of 14 days. Biodegradation was assessed by measuring the biochemical oxygen demand (BOD). The test report states that the test was valid due to greater than 40% and 60% biodegradation of aniline (calculated by BOD) at the 7th and 14th days

respectively. No biodegradation of TBBPA was observed at day 14 (0% by BOD). Therefore, based on this test, it is concluded that TBBPA is not readily biodegradable.

Soil

Schaefer and Stenzel (2006a) investigated the aerobic degradation of ^{14}C-labelled TBBPA (99.6 % purity) over six months in four soils (loamy sand, sandy clay loam, silty loam and silty clay loam). The test was conducted following the OECD TG 307 protocol. The test found that TBBPA was strongly sorbed to soil. At the start of the test, between 1.8 and 6.2 % of the applied TBBPA remained bound to the soil after extraction, but at one month the bound portion increased to between 55.3 % and 83.6 % whereafter the bound fraction remained relatively constant. Sorption was influenced by the soil organic carbon (OC) content with the highest degree of sorption occurring in the soils with the highest organic carbon content. The dissipation half-life in the first month was in the range 5.3 – 7.7 days, but thereafter was much slower. At six months, mineralisation (degradation to CO_2) varied between 17.5 – 21.6 % and unidentified biotransfomation products were detected in the range 3 – 7 %.

The fate of TBBPA in aerobic soils was studied using ^{14}C-labelled TBBPA (Li et al., 2015). The study duration was 143 days and was performed using sandy soil. The dissipation half-life was determined to be 14.7 days. At the end of the study, the authors found that 20 % of the original TBBPA applied to the soil had been mineralised (degraded to CO_2), 67 % was still incorporated into the soil, and some of the original chemical was converted into degradation products (eight unique degradation products identified). The bound residues were found to increase rapidly through the first 35 days and it appeared that these residues were bound to humins. Residues bound to humic or fulvic acids increased through the study until they reached a plateau. The study reported that the major dissipation route was through formation of bound residues, most of which were bound to humins via ester bonds. This reaction may be reversible; if the conditions in the soil change then ester bonds may be hydrolysed and release TBBPA back into the soil.

The fate of ^{14}C-labelled TBBPA in aerobic silty clay soil was investigated (Wang et al., 2017) using soil taken from a rice paddy. The dissipation half-life was reported as 14.6 days, similar to that reported by Li et al. (2015) in sandy soil. The study duration was 93 days. A number of degradation products were identified including two that were methylated. These degradation products represented approximately 10% of the concentration of TBBPA applied to the soil. Bound residues increased throughout the study accounting for approximately 80% of the initially-applied TBBPA. About 85% of these residues were associated with the humin fraction and about 55 % of this was hydrolysable (i.e. TBBPA released by strong alkali conditions). The proportion of bound residues was higher in this fine textured soil than in more coarsely textured soil (sandy). The study also examined the degradation behaviour when clean soil was mixed with soil containing bound residues of TBBPA over the course of 231 days. Some of the bound residues were found to be released back into the soil. While TBBPA was found to dissipate quite rapidly in aerobic soils (degradation half-life (DT50) 14.6 days) by binding to organic carbon fractions in the soil (humins), at least some of the bound fraction bonded through reversible linkages meaning that the chemical may remain available to organisms for much longer periods.

The fate of ^{14}C-labelled TBBPA was studied in soil containing earthworms (*Metaphire guillelmi*; Gu et al., 2017a). Mineralisation decreased from 4% to 2.5% when earthworms were present and dissipation also decreased in the presence of the earthworms. DT50 decreased

from five to four days when earthworms were present. The half-life for the extractable residues was nine days without earthworms and 12 days with earthworms. The earthworms also sequestered some TBBPA so dissipation in soil was decreased even more than was apparent by the direct measurements. When earthworms were present, O-methylation of TBBPA was increased (1 – 15%) and the proportion of soil-bound TBBPA halved. The study noted that the presence of earthworms could have modified the microbial community or the organic carbon fraction in the soil (humin and/or humic acids), which is likely to have limited the proportion of TBBPA that could be bound. The key outcomes of the study were a notable increase in persistence of TBBPA in these conditions, as well as the formation of more of the O-methylated degradation products instead of more polar metabolites.

The fate of TBBPA in soil in the presence of plants was studied by Li et al. (2011) over the course of eight weeks. During the exposure period, TBBPA sorbed to soil resulting in a 90 % decrease in the concentration of 'free' (unbound) TBBPA. The soil was treated with sufficient chemical to reach a concentration of 1 mg/kg dw. The presence of plants did not significantly alter the concentrations of TBBPA in soil versus the control experiment performed in the absence of plants (control treatment – 0.05 mg/kg dw; radish treatment – 0.06 mg/kg dw; cabbage treatment and combined cabbage + radish treatment – 0.03 mg/kg dw). The authors concluded that dissipation of TBBPA was primarily due to sorption to soil rather than due to the presence of the plants or sequestration by the plants. Concentrations of TBBPA were measured at 0.018 mg/kg in cabbage and 0.005 mg/kg in radish. The limited TBBPA that was sequestered by plants was primarily localised in the roots demonstrating that TBBPA was not easily translocated through the plants.

Water/Sediment systems

Biodegradation of ^{14}C-TBBPA (96 % purity) was examined in an aerobic sediment/soil microbial system that was collected from a small brook (Fackler, 1989). The study followed an 'in-house' protocol and was performed according to GLP.

The test systems consisted of 40 mL of sediment (~20 g dw) and 135 mL of river water. TBBPA was prepared in acetone and was applied to the test systems at concentrations of 10, 100 and 1000 µg/L. Each system was incubated under aerobic conditions at 25 °C in the dark for 56 days. A sterile sediment control was also prepared.

At the start of the test, TBBPA accounted for the majority (up to 100 %) of the radioactivity found in the extracts. After 56 days, TBBPA accounted for 44.7 % of the radioactivity in the 10 µg/L system with higher levels found in the 100 and 1000 µg/L systems (64.2 % and 60.8 % respectively). The slower breakdown at higher concentrations can be attributed to lower microbial populations in these test systems. The half-lives for the 10, 100 and 1000 µg/L tests were 53, 69 and 84 days, respectively, while the half-life in the sterile system was approximately 1300 days. These results demonstrate that microbial degradation, rather than physical degradation, is responsible for the breakdown of TBBPA in the test systems.

River sediment from southern Taiwan was used to evaluate aerobic degradation of TBBPA (Chang et al., 2012). Sediment was treated with TBBPA at 50 mg/kg dw. The dissipation half-life ranged from nine to 13 days under the test conditions.

A study of the fate of TBBPA in water/sediment systems using a flume to simulate strong dynamic conditions has been undertaken (Cheng and Hua, 2018). Three racetrack-style flumes were used to investigate the fate of TBBPA under varying hydrodynamic conditions.

One system simulated strong dynamic conditions, one simulated weak dynamic conditions and the third simulated static or still conditions. The study duration was 34 days and samples were collected every three days. Degradation was fastest under strongly dynamic conditions. The DT50 in overlying water was 37 days under still conditions decreasing to 12.6 days under strong dynamic conditions. The DT50 in suspended sediment was 40 days under still conditions decreasing to 12 days under strong dynamic conditions. The DT50 in settled sediments was 35 days under still conditions decreasing to 10 days under strong dynamic conditions. The proportion of TBBPA in the overlying water increased from ~1.5 % to 7 % as the conditions in the flume were more highly disturbed.

11.2.3.2 Anaerobic

Sludge

The rate and extent of primary biodegradation, transformation and mineralisation of ^{14}C-TBBPA (purity 99.6%) was studied in anaerobic digester sludge (Schaefer and Stenzel, 2006b). The study was performed according to the OECD TG 308 protocol. Anaerobic digester sludge from a municipal wastewater treatment plant was used to prepare various test vessels containing both abiotic and biotic systems. Each test vessel contained 100 mL of live or sterile sludge and a suitable mineral salts solution. Test vessels were dosed at a nominal concentration of 50 µg/L TBBPA and incubated at 35°C for up to 120 days.

Very little mineralisation occurred. The mean cumulative total mineralisation (conversion to CO_2) was 1.1% and 0.9% in the biotic and abiotic systems respectively. However, in the biotic system, degradation (incomplete mineralisation) of TBBPA proceeded efficiently (via at least three unidentified intermediates) until BPA was formed. Under the test conditions, BPA proved to be very resistant to further degradation. The half-life for TBBPA degradation in the biotic system was 22 days while the extracts from the abiotic vessels showed very little transformation.

Anaerobic degradation of TBBPA and several other brominated flame retardants in sewage sludge was studied (Gerecke et al., 2006). A DT50 of 0.59 days was determined for TBBPA (i.e. rapid degradation). A sterile control showed negligible degradation of TBBPA. This is consistent with other studies that demonstrate that TBBPA is primarily degraded by microbial rather than physical processes.

A study examined the removal efficiency for TBBPA in sewage treatment processes (Potvin et al., 2012). Four types of treatment systems were evaluated – a full scale conventional activated sludge plant with tertiary treatment (disinfection) and three different pilot-scale membrane bioreactors, each of which had different sludge retention times. All four treatment systems were evaluated using the same influent. The effluent for the full scale conventional plant had a TBBPA concentration of 0.7 ng/L. The various membrane bioreactors had effluent concentrations ~ 6 ng/L with no correlation between effluent concentration and sludge retention time. Removal was expected to occur via sorption and biodegradation. A pilot-scale membrane aerated biofilm reactor was assessed using tap water with TBBPA (125 ng/L) and ammonia only (i.e. no solids). The effluent from this treatment system showed significant removal of TBBPA, which was attributed to biodegradation as there were no solids for sorption to occur. The study reported that for treatment systems with short retention times, sorption to sediment is likely to be the major mechanism of TBBPA removal. For plants with longer retention times, degradation is also a

significant contributor. The study also observed solubilised TBBPA in sewage effluent which indicates that not all of the influent TBBPA is sorbed to particles. Back-calculations using sludge data and comparison with the results in this study indicate that approximately 90 % of the TBBPA may be solubilised rather than adsorbed.

Soils

Schaefer and Stenzel (2006a) studied the anaerobic degradation of ^{14}C-TBBPA (99.6 % purity) over six months in four soil types (loamy sand, sandy clay loam, silty loam and silty clay loam). The study was performed according to OECD TG 307.

Mineralisation of TBBPA under the anaerobic conditions of this study was in the range 2.5 – 8.5% after six months. This is significantly lower than in aerobic studies conducted on the same soil types (17.5 – 21.6 % - described earlier). Approximately 60 % of the applied chemical remained sorbed to soil after six months and degradation was not significant. Several degradants were detected at low levels (≤ 3% of the applied concentration) at the end of the study, but there was insufficient material to fully characterise these degradants.

The fate of TBBPA in soil under sequential anaerobic and then aerobic conditions was studied (Liu et al., 2013). Treated soil was kept under anaerobic conditions for 195 days in one part of the investigation and compared to treated soil kept under anaerobic conditions for 125 days and then under aerobic conditions for 70 days. TBBPA kept under anaerobic conditions was bound to soil (36 % of the initial concentration) or was degraded to bisphenol A (BPA) via reductive dehalogenation with a half-life of 36 days. By the end of 125 days BPA was the sole detectable degradation product (54% of original TBBPA level). Once conditions were changed to aerobic, BPA was rapidly dissipated with a half-life of 11 days – 6% was mineralised and 62% was in the form of bound residues. Under aerobic conditions, much of the residue-bound TBBPA formed during the first 125 days was released and was persistent under the aerobic conditions. The study concluded that degradation under sequential anaerobic/aerobic conditions was not an effective approach for dissipating TBBPA.

Sediment

A 45 day anaerobic study of TBBPA in contaminated soil from an industrial complex in Israel was undertaken (Ronen and Abeliovich, 2000). By day 45, the applied TBBPA was completely debrominated and the results indicated that most of the dehalogenation reaction occurred within 10 days (~85 %). During dehalogenation, intermediate metabolites were detected by HPLC and were identified as tri- and di-brominated BPA. Levels of BPA increased during the study and after 45 days BPA accounted for ~88 % of the initial TBBPA. BPA persisted in the anaerobic slurry and was not degraded even after three months of incubation.

Water/sediment systems

The anaerobic transformation of ^{14}C-TBBPA (99.6 % purity) was studied in two freshwater aquatic sediment systems (Schaefer and Stenzel, 2006c*). The test was based on the OECD TG 308 protocol. TBBPA transformation was observed in the water extracts after day zero. BPA was found at levels >10 % of the initially-applied concentration of TBBPA by the end of the study in both systems. Polar metabolites accounted for <7 % of the initially-applied

concentration of TBBPA in both systems. Three additional degradants (apart from BPA) were identified, but these were not fully characterised.

In sediments, BPA concentrations increased over the duration of the study and accounted for 22.5-55 % of the applied TBBPA by the end of the experiment. Half-lives for TBBPA were determined to be 14.6-16.5 days in water, 28.5-41.8 days in sediment and 23.8-27.5 days for the whole system.

11.2.4 Bioaccumulation

Some of the following discussion on the bioaccumulation potential of TBBPA has been paraphrased from the EC assessment (Health/Env Canada, 2013). These references are marked with an asterisk (*) and have not been independently reviewed for this assessment.

Bioaccumulation of organic chemicals is affected by numerous factors including the lipophilicity of the chemical (log K_{OW}), efficiency of uptake, metabolic transformation, and depuration rate.

The lipophilicity of TBBPA (estimated by log K_{OW}) is strongly dependent on the pH of the aquatic medium in which it is dissolved. At low pH (3.05), log K_{OW} = 6.53; at 'neutral' pH (7.53), log K_{OW} = 4.75, and at high pH (9.18), log K_{OW} = 1.25 (Kumarochi et al., 2008). The results indicate that at low and neutral pH, TBBPA has a higher potential to partition to lipids than it does at high pH where a significant portion of the chemical is dissociated, charged and therefore more soluble in water than in lipids (Health/Env Canada, 2013). In addition, other recent chemical reviews recommend using log K_{OW} = 5.9 for TBBPA because this is a conservative value that represents the high end of TBBPA bioaccumulation potential in surface waters (EURAR 2008; Health/Env Canada, 2013).

EC report measured data on the bioaccumulation of TBBPA in several species of fish, aquatic invertebrates and terrestrial organisms. These data indicate that TBBPA has low to moderate potential for bioaccumulation (Table A.3.1; Appendix 3).

Bioconcentration and elimination of TBBPA has been studied in fathead minnow (Pimephales promelas; Brominated Flame Retardants Industry Panel, 1989c*). The measured bioconcentration factor (BCF) was 1200 L/kg. The estimated BCF, based on uptake and depuration rates, was 1300 L/kg. Radio-labelled TBBPA was rapidly eliminated from fish tissue with a half-life of less than 24 hours. Most of the chemical was eliminated in the first four days and 98 % was eliminated after six days. This study was also reviewed by the EU in 2008 report and BCF was re-calculated because the original report did not exclude metabolites when calculating BCF. The revised value of BCF was much lower (~160 L/kg).

The BCF was also measured in bluegill sunfish (Lepomis macrochirus; Velsicol Chemical Corporation, 1978*). Over the 28 day treatment period, BCF values were determined to be 20 L/kg in edible tissue and 170 L/kg in visceral tissue. The concentration of TBBPA decreased rapidly during the withdrawal period, and was undetectable by day seven in edible tissue and by day 10 in the viscera.

A bioconcentration study in carp (Cyprinus carpio), exposed for eight weeks to TBBPA at concentrations of 80 µg/L or 8 µg/L, demonstrated BCF values in the range 30 – 341 L/kg in the fish exposed to 8 µg/L and 52 – 485 L/kg in the fish exposed to 80 µg/L (CITI, 1992*).

The bioconcentration and elimination of TBBPA was studied in Eastern oysters (Crassostrea virginica; Brominated Flame Retardants Industry Panel, 1989b*). The measured BCF was 720 L/kg, and the estimated BCF, based on uptake and depuration rates, was 780 L/kg. TBBPA was continuously eliminated during the depuration period and the half-life for depuration was estimated to be between three and five days.

A 14-day study demonstrated a clear correlation between organic carbon content (OC) in sediment and bioaccumulation of TBBPA in freshwater midges (Chironomus tentans; Brominated Flame Retardants Industry Panel, 1989e*). BCF values were calculated based on the ratio of TBBPA in the body of insects to the concentration in interstitial water. In sediment with high OC (6.8 %) BCF values were determined to be 240 – 510 L/kg, in medium OC (2.7 %) BCF values of 490 – 1100 L/kg were determined and in the low OC sediment (0.25 %) BCF values were determined to be 650 – 3200 L/kg. The results indicate that TBBPA is more bioavailable in sediments with low OC content and, therefore, more bioaccumulative in these sediments than in sediments with high OC content.

Uptake of TBBPA from soil by earthworms (Eisenia fetida) was investigated (Aufderheide et al., 2003*). The authors concluded that although TBBPA was bioavailable, it did not bioaccumulate in worm tissue over the 28-day exposure period.

Measured bioaccumulation data were compared with predicted values by EC (Health/Env Canada, 2013) using two models: BCFBAF EPIsuite 2008 and CPOPs 2008. Modelling parameters were adjusted to normalise for middle trophic level fish in Canadian waters because it was considered that these fish are most likely to be eaten by other animals. The calculated BCF values were comparable to measured BCF values (BCF = 150 L/kg [BCFBAF EPIsuite model]; and BCF = 348 L/kg [COPs model]). Allowing for metabolic transformation, the predicted bioaccumulation factor (BAF) was 174 L/kg. Thus, BCF and BAF predictions indicate low potential for bioconcentration and bioaccumulation.

A study of TBBPA uptake by zebrafish was undertaken (Liu et al., 2018). Embryos were exposed to 650 µg TBBPA/L for 122 hours (post fertilisation) to assess uptake and accumulation. The study found that the fish sequestered approximately 20 % of the TBBPA they were exposed to and, of that, about 10 % was metabolised. The BCF determined from these data was 160 – 180 L/kg. Exposure was undertaken in triplicate with 400 embryos exposed in each replicate. Three metabolites were detected in fish tissue.

Transfer of brominated flame retardants from adult zebrafish to their eggs was examined (Nyholm et al., 2008). Adult fish were exposed to TBBPA via their diet – freeze dried chironomid to which TBBPA had been added at 10 or 100 millimoles per g dw. Twenty three males and twenty three females were exposed at each treatment with only one replicate. Fish were sampled on days 0, 3, 7, 14, 28, 35 and 42, while egg samples were collected on days 0, 2, 3, 6, 7, 13, 14, 27, 28, 34, 35, 41 and 42. TBBPA was detected in all egg samples after day zero. Female fish were found to have tissue concentrations of approximately 1 nmol/g live weight when exposed to 100 mmol/g feed and 0.2 nmol/g lw when exposed to 10 mmol/g feed. The egg-to-fish concentration ratio was 2 which indicates that bioaccumulation is expected under these conditions. Several other brominated flame retardants were tested and had higher egg-to-fish concentration ratios indicating higher potential for accumulation than TBBPA.

Fish bioconcentration factors were compared between brominated flame retardants and their non-brominated analogues (Hardy, 2004). The study examined bioconcentration factors for 11 brominated flame retardants and their analogues in orange-red killifish (Orizias latipes) and Japanese carp (Cyprinus carpio). Fish were exposed for six to eight weeks with 15 – 20 fish per test concentration. For compounds with high molecular weights (>700 Da) bioconcentration was not observed. The study reported that TBBPA did not bioconcentrate. The measured BCF in this study for TBBPA was 30 – 485 L/kg, which is below the lower limit of concern for chemicals to be considered bioaccumulative (BCF ≥ 2000 L/kg indicates that a chemical is bioaccumulative; EPHC, 2009). Other studies reported here used ^{14}C-labelled TBBPA and found that the TBBPA reached a plateau concentration in three to seven days with a half-life of less than one day and 98 % elimination of the labelled residues at day six.

11.2.5 Australian data on TBBPA levels in biota

No Australian monitoring data are available.

11.2.6 International data on TBBPA levels in biota

Some of the following discussion on the presence of TBBPA in biota has been paraphrased from the EC assessment (Health/Env Canada, 2013). These references are marked with an asterisk (*) and have not been independently reviewed for this assessment.

TBBPA has been detected in various biota including invertebrates, fish, birds and marine mammals (Table A.3.2; Appendix 3).

TBBPA levels were analysed in samples of biota from the Scheldt basin, UK Estuaries and the North Sea (de Boer et al., 2002*; Morris et al., 2004*). The studies measured TBBPA at concentrations of <0.1 – 2.6 µg/kg wet weight (ww) in eel, 5 – 96 µg/kg lw in whelk, <1 – 10 µg/kg lw in sea star, <1 – 35 µg/kg lipid in hermit crab, <97 – 245 µg/kg lw in whiting, 0.07 – 0.28 µg/kg ww in cormorant liver, 0.05 – 376 µg/kg ww in porpoise, 4.5 µg/kg ww in whole sea star and <0.1 – 0.8 µg/kg ww in cod liver. TBBPA was not detected in seal blubber or liver, tern eggs, mysid shrimp, gudgeon or hake liver.

Archived samples of harbour porpoise blubber and cormorant liver were analysed for TBBPA by Morris et al. (2004*). Samples were taken from various locations in the UK. TBBPA was detected in eight out of 25 porpoise blubber samples at concentrations of 0.05 – 376 µg/kg ww, with a mean concentration of 52 µg/kg ww. TBBPA was detected in seven out of 28 cormorant liver samples at concentrations of 0.07 – 10.9 µg/kg ww, with a mean concentration of 2.6 µg/kg ww.

TBBPA was detected in eggs of certain predatory birds from Norway (Herzke et al., 2003*; Herzke et al., 2005*). The species sampled included white-tailed sea eagle (Haliaeetus albicilla; 2 samples), peregrine falcon (Falco peregrinus; 2 samples), golden eagle (Aquila chrysaetos; 2 samples) and osprey (Pandion haliaetus; 2 samples). TBBPA was present in all samples analysed at concentrations ranging from <4 pg/kg ww to 13 pg/kg ww. The highest levels detected were in the osprey egg samples.

The concentrations of TBBPA in blue mussel and cod livers from Norway were investigated (SFT, 2002*). TBBPA was found in all samples analysed (six blue mussel and six cod liver) at concentrations of 0.01 – 0.03 µg/kg ww in blue mussel and 0.08 – 0.16 µg/kg ww in cod liver.

TBBPA was detected in biota across several locations in Norway (Fjeld et al., 2004)* (some of these data are also reported in Schlabach et al. (2004)). The samples analysed included fish from freshwater lakes and rivers including brown trout (Salmo trutta), perch (Perca fluviatilis), pike (Esox lucius), burbot (Lota lota), vendace (Coregonus albula) and smelt (Osmerus eperlanus). TBBPA concentrations in these freshwater fish samples were in the range 0.01 – 0.18 µg/kg ww. Marine fish from sites along the Norwegian coast, including cod (Gadus morhua), flounder (Platichthys flesus) and eel (Anguilla anguilla)), blue mussel and cod liver were also sampled. TBBPA was detected at concentrations of 0.35 – 1.73 µg/kg ww in the cod liver samples (detected in five out of six samples,) but was not detected in the mussel samples (four samples in total).

Levels of TBBPA and its dimethyl ether derivative (a possible metabolite of TBBPA) were measured (Watanabe et al., 1983)* in mussels (Mytilus edulis) from Osaka Bay, Japan. The concentration of TBBPA was below the detection limit (detection limit not given). The concentration of the dimethyl ether derivative of TBBPA was ~ 5 µg/kg ww.

Polybrominated flame retardants were detected in samples of Japanese sea bass and grey mullet (Ohta et al., 2004*). The fish were sampled from Osaka Bay, Japan and the mouth of the Yamato River which flows into Osaka Bay. TBBPA was found in the sea bass samples at concentrations of 3.4 – 23 µg/kg lw. The results for grey mullet were not presented in the paper.

Samples of eel, perch and pike were collected in the greater Berlin area (Germany) and analysed for TBBPA (Asplund et al., 1999). TBBPA was primarily concentrated in the lipids of the animals. The concentrations (expressed on a whole body weight basis) were: 0.045 µg/kg ww and 0.10 µg/kg ww in eel, 0.033 µg/kg ww in perch and 0.021 µg/kg ww in pike tissue.

TBBPA was detected in mysid shrimp (Neomysis integer) at two (out of three) sites in the Scheldt estuary at concentrations of 0.8 – 7.7 µg/kg lw (Verslycke et al., 2005), but was not detected in sediment samples from the same area.

TBBPA was not detected in peregrine falcon eggs (Falco peregrinus) from South Greenland but the dimethoxy derivative of TBBPA was detected in 28 out of the total of 32 samples at concentrations of 0.1 – 940 µg/kg lw (Sørensen et al., 2004; Vorkamp et al., 2005).

A study of TBBPA levels in 30 fish taken from nine UK lakes reported TBBPA concentrations ranging from <0.29 – 1.7 µg/kg lw (Harrad et al., 2009).

TBBPA levels in dolphins and sharks around Florida were investigated (Johnson-Restrepo et al., 2008). TBBPA was detected in all tested organisms. The concentrations of TBBPA were: 0.056 – 8.48 µg/kg lw in dolphin blubber (mean concentration of 1.2 µg/kg lw); 0.035 – 35.6 µg/kg lw in the muscle of bull sharks (mean of 9.5 µg/kg lw); and, 0.495 to 1.43 µg/kg lw in the muscle of Atlantic sharpnose sharks (mean of 0.87 µg/kg lw).

The US EPA chemical review reported that harbour porpoises from the UK were assessed for TBBPA (USEPA, 2015a). Blubber samples contained 0.1 – 418 µg/kg lw TBBPA. For samples collected around the coast of the UK, TBBPA concentrations in blubber ranged from <4 – 35 µg/kg lw. No TBBPA was detected in blubber samples collected from animals originating from the North Sea.

A study of fish tissue concentrations of TBBPA and a range of other flame retardants was undertaken in the Singapore Strait (Zhang and Kelly, 2018). TBBPA was not detected in any of the fish samples collected.

A review of the environmental fate of TBBPA included some data on the concentrations of this chemical in biota (Malkoske et al., 2016). Samples of organisms (predominantly bird species) collected close to e-waste recycling facilities and disposal sites in China were found to have concentrations ranging from 0.23 – 1482 µg/kg lw. White breasted waterhen exhibited the highest concentrations of the tested species (28 – 1,482 µg/kg lw). Concentrations in aquatic species were in the range 0.23 – 1.74 µg/kg lw.

The US EPA chemical review reports that shellfish samples collected from Scotland did not contain detectable levels of TBBPA (USEPA, 2015a). The limit of detection for this work was 0.01 to 0.35 µg/kg ww. In samples collected in the North Sea, concentrations of TBBPA ranged from 5 – 96 µg/kg lw in whelks, <1 – 10 µg/kg lw in sea star, and <1 – 35 µg/kg lw in the abdomen of hermit crabs. TBBPA was not detected in mysid shrimp collected in the Netherlands nor in the majority of starfish collected in the UK (although 4.5 µg/kg ww was detected in one starfish and 205 µg/kg lw in another).

The US EPA chemical review reports results for TBBPA concentrations in a range of fish samples (USEPA, 2015a). TBBPA was detected in fish in a number of studies from China with mean concentrations ranging from 29 – 39 µg/kg dw for whole samples. In samples collected in Japan in 2007, concentrations ranged from <0.03 – 0.09 µg/kg ww with 90 % detection frequency. An earlier study in fish from Japan reported concentrations ranging from <0.03 – 0.15 µg/kg ww with another study reporting concentrations in sea bass of 3.4 – 23 µg/kg lw.

The US EPA chemical review reports results for TBBPA concentrations in samples from birds (USEPA, 2015b). TBBPA was detected in the livers of cormorants from the UK at concentrations of 2.5 – 14 µg/kg lw but was not detected in egg samples collected from the Faroe Islands, the Netherlands or Japan.

Levels of TBBPA in biota from the Chinese Bohai Sea have been investigated (Liu, A et al., 2016). Concentrations of TBBPA ranged from <LOD – 207.3 µg/kg lw but levels >LOD were detected in 87 % of the organisms sampled. The study found a negative correlation between TBBPA concentration and trophic level (higher trophic levels had lower concentrations).

In summary, TBBPA has been detected in biota at concentrations which range from <LOD up to 1482 µg/kg lw. Several samples showed concentrations >100 µg/kg on a whole body weight, or wet weight basis, but most analyses showed levels <10 µg/kg on a whole body weight, or wet weight basis. Measured concentrations were frequently below this level. TBBPA was detected in several higher trophic level organisms but the available evidence does not demonstrate a positive correlation between trophic level and concentration of TBBPA (Table A.3.3; Appendix 3).

11.2.6.1 Conclusion – Bioaccumulation of TBBPA

Laboratory and modelling studies on bioaccumulation of TBBPA and analyses of the chemical in biota indicate that TBBPA has low bioaccumulation potential.

The log K_{ow} of TBBPA varies with pH but if a conservative value is used (log K_{ow} = 5.9), TBBPA is predicted to have bioaccumulation potential. However, laboratory studies show that the chemical can be significantly metabolised and is readily excreted. Laboratory studies and modelled data yield values of BCF and/or BAF which are below the threshold value for TBBPA to be considered bioaccumulative (BAF ≥ 2000 L/kg) and generally indicate that TBBPA has low bioaccumulation potential (measured values are typically <2000 L/kg). Analyses of TBBPA and its metabolites in biota demonstrate that concentrations are highly variable. The available evidence does not demonstrate a positive correlation between concentration and trophic level.

11.2.7 Potential for Long-Range Atmospheric Transport

Long-range transport (LRT) potential is a key property considered when classifying a chemical as a persistent organic pollutant (POP). The Stockholm Convention identifies 3 key criteria for identifying chemicals with LRT potential. These are:

- measured levels of a chemical in locations distant from the source of its release that are of potential concern
- monitoring data that indicate that LRT may have occurred
- fate properties and/or model results demonstrating the potential for LRT (for a chemical that migrates significantly through air, a half-life in air greater than 2 days indicates LRT potential).

LRT potential is not just an intrinsic property of a chemical pollutant. It derives from both chemical properties (intrinsic) and environmental conditions (extrinsic).

Several multimedia transport models have been used to assess the long-range transport potential of TBBPA and the results concluded that TBBPA has low potential to reach remote areas (Wania, 2003). However, the transport behaviour was found to depend on the type of particulate matter to which the chemical was sorbed. Characteristic travel distances (CTD) determined for TBBPA from two models (TaPL3 and ELPOS) were determined to be 516 km and 539 km respectively. While modelled results should be treated with some caution, they can be useful for ranking the LRT potential of chemicals. For example, an additional study estimated the LRT potential of several PBDEs and PCBs using the same models and these results were compared with results obtained for TBBPA (Wania, 2003). The study indicated that the CTD of TBBPA was comparable to various PBDEs ranging from tetra- to deca-brominated diphenylethers, and was much lower than the low- to medium-chlorinated PCBs.

Experimental monitoring data indicate that TBBPA may undergo long-range transport in the environment. TBBPA has been detected in an air sample from Dunai in Russian Arctic and in moss samples collected at two arctic sites in Norway (de Wit, 2006). TBBPA was found in sediment samples from Tromsø Harbor,Norway (de Wit, 2004) and in Atlantic cod from the remote Norwegian Lofoten islands and Varanger peninsula (Nøstbakken, 2018). Samples collected at various latitudes between the Wadden Sea and the Arctic showed concentrations ranging from not detected (ND) to 0.85 pg/m^3 with levels decreasing at increasing latitudes (Xie et al., 2007). Other studies have also found detectable levels of TBBPA in air in the Arctic (Vorkamp and Rigét, 2014).

11.3 Conclusion on Environmental Fate

TBBPA is a lipophilic chemical with a low vapour pressure and is expected to partition primarily to soil and sediment when released to the environment. TBBPA can chemically bind to the humic and fulvic acid components of soils via ester bonds and this is a major mechanism for dissipation when released to soil. However, ester bonds are susceptible to hydrolysis, so the process is reversible and bound TBBPA can be released from soils and become bioavailable.

TBBPA is expected to be abiotically stable and is not readily biodegradable. It may undergo photolysis, but this is not expected to be a significant degradation mechanism in the environment because the chemical tends to partition to sediment and soil where exposure to sunlight is limited. Some mineralisation of TBBPA is evident in biodegradation tests, but under some conditions persistent degradants are formed including the bis-methyl ether derivative and BPA.

The log K_{ow} of TBBPA varies with pH, but using the conservative value log K_{OW} = 5.9, it is predicted that TBBPA may have bioaccumulation potential. However, laboratory studies show that the chemical can be significantly metabolised and is readily excreted by all the organisms tested. Laboratory studies and modelled data find that the bioconcentration/bioaccumulation factor for TBBPA is <2000 L/kg which indicates that TBBPA has low bioaccumulation potential. Monitoring data show that while concentrations of TBBPA in biota are highly variable, the measured levels are generally low; this indicates that TBBPA is unlikely to bioaccumulate. The available evidence does not demonstrate a correlation between concentration and trophic level.

TBBPA has been detected in air and wildlife in remote areas indicating that it may undergo long-range transport in the environment.

11.4 Levels of TBBPA in the Environment

11.4.1 Australian data

Concentrations of brominated flame retardants (BFRs) were measured in sediment samples from the Australian aquatic environment by Toms et al. (2006). Sediment samples were obtained from all States and Territories of Australia. Background concentrations of TBBPA were analysed in sediment samples (sediment cores of 10 cm depth) collected in 2002-03. Sediment samples upstream and downstream of the outfall of sewage treatment plants were collected in 2005 to assess contamination from these potential point sources. All samples were analysed for 26 PBDE congeners and five samples were analysed for TBBPA. The limit of detection for TBBPA was 0.1 µg/kg dw.

The five samples analysed for TBBPA were from:

- Port Darwin (urban)
- upper Brisbane River (remote)
- Canberra (Lake Burley Griffin – urban)
- Parramatta River (industrial/urban)
- Port Jackson (industrial/urban).

The only sediment sample where TBBPA was detected was from the Parramatta River with a concentration of 0.13 µg/kg dw.

11.4.2 International data

Some of the following discussion on international monitoring data has been paraphrased from the EC assessment (Health/Env Canada, 2013). These references are marked with an asterisk (*) and have not been independently reviewed for this assessment.

Air

Studies have detected TBBPA in air and precipitation at industrial, urban and remote locations. The studies reviewed by EC, and studies identified for this assessment, indicate that atmospheric concentrations in the vicinity of TBBPA manufacturing facilities may be millions of times greater than in air at remote locations.

One study detected TBBPA in air samples obtained near 2 organobromine manufacturing facilities at concentrations of 0.028 µg/m^3 and 1.8 µg/m^3 (Zweidinger et al., 1979*). Another study found TBBPA to also be present in air particulates collected near TBBPA manufacturing facilities in Arkansas, USA (DeCarlo, 1979*). However, the concentrations were not reported. Air samples collected at an electronics recycling plant contained a mean concentration of 29.7 ng/m^3 TBBPA (Bergman et al., 1999*).

Concentrations of TBBPA in air in China were surveyed by Liu et al. (2016) and a maximum concentration of 66 – 95 ng/m^3 was reported at a primitive e-waste facility in the Guangdong Province. A concentration of 70 ng/m^3 was measured in one air sample from Dunai (Russian Arctic; de Wit et al., 2006).

Vapour phase and particulate sampling from air in a rural forest area in northern Germany, the Wadden Sea region of the North Sea, and the Arctic Ocean between Svalbard and Greenland was conducted (Xie et al., 2007). TBBPA was detected in most of the samples from the forest area in north Germany with total concentrations of TBBPA in the particulate and vapour phase ranging from below the limit of detection (0.04 pg/m^3) to 0.85 pg/m^3, with an average of 0.48 pg/m^3. The authors suggest that this average may represent the typical background concentration of TBBPA in air over much of northern Germany. Similar concentrations were detected in air over the Wadden Sea close to the heavily industrialised regions of north Germany (0.31 – 0.69 pg/m^3, average = 0.58 pg/m^3). Total concentrations of TBBPA in air samples from the Arctic Ocean ranged from below the detection limit (0.04 pg/m^3) to 0.17 pg/m^3. The highest concentrations were detected off the Norwegian coast and a declining trend with increasing latitude was reported from the near-coast to the open sea. The authors suggest that these results may indicate that TBBPA has the potential for long range transport.

TBBPA has been detected in rainwater in eight of fifty samples obtained from sites in the Netherlands, Belgium and Germany in the range of 0.5 – 2.6 ng/L (Peters, 2003*).

Water

Numerous studies have investigated the presence of TBBPA in the aquatic compartment. These studies indicate that the highest concentrations of TBBPA in water are associated with

wastewater treatment plants in heavily populated regions and in water sampled at (or near) heavily industrialised areas.

It is beyond the scope of this assessment to provide a comprehensive review of the extensive literature on TBBPA in water. The summaries below include several key publications EC (Health/Env Canada, 2013) and EU (EURAR, 2008) have cited as well as several recent publications identified as being of particular value for this assessment. References marked with an asterisk (*) are summarised from EC (Health/Env Canada, 2013) and EU (EURAR, 2008) and have not been independently reviewed for this assessment.

Concentrations of TBBPA have been measured in water upstream and downstream of wastewater treatment plants in Germany (Kuch et al., 2001*). TBBPA was detected in 10 out of 19 effluent samples at concentrations of 0.62-25.0 ng/L. The concentrations in receiving waters ranged from:

- 0.81-20.4 ng/L in the upstream samples (detected in 4 out of 15 samples analysed)
- 1.1-18.8 ng/L in the downstream samples (detected in 3 out of 15 samples analysed).

The detection limit was 0.2 ng/L.

A study in the UK investigated levels of TBBPA in 9 English lakes (Harrad et al., 2009). The concentration of TBBPA in water ranged from 0.14-3.2 ng/L:

- 5 lakes had concentrations between 0.1-0.5 ng/L
- 4 lakes had concentrations above 1 ng/L.

The study determined that approximately 60 % of the TBBPA detected was dissolved in the water and the remainder was attached to particles.

The presence of TBBPA in Taihu Lake in China was investigated (Xu, J et al., 2013). Levels in water ranged from 'not detected' to 1.12 ng/L. Twelve samples were collected but only three had levels above the detection limit. The levels reported were similar to those in UK lake waters discussed above.

A survey of measured environmental concentrations of TBBPA in China was compiled by Liu et al. (2016). Concentrations of TBBPA in water from Lake Chaohu (Anhui Province) were found to be in the range 0.85 – 4.87 µg/L. This lake is in the watershed of a heavily industrialised region.

Twenty three rivers in Sweden were monitored for TBBPA and other flame retardants (Gustavsson et al., 2018). Concentrations up to 62 ng/L were reported with TBBPA being detected in 44 % of the rivers tested. The flux of the various flame retardants was analysed on a daily basis. TBBPA had the largest daily flux of all the flame retardants investigated with 4.6 kg of TBBPA being discharged to the Baltic Sea each day. The rivers with the highest reported concentrations were close to airports although it was not known if there was a link between airports and TBBPA use.

Monitoring of flame retardants in seawater in Korea was undertaken (Gu, S-Y et al., 2017b). Concentrations of TBBPA in seawater ranged from ND to 2.79 ng/L. TBBPA was the flame retardant detected at highest concentrations in water.

Monitoring of TBBPA levels in coastal waters near Qingdao in China was undertaken (Gong et al., 2017). Samples were collected seasonally over a year at six locations. Concentrations ranged from ND to 1800 ng/L (mean 270 ng/L). The method detection limit was 10 ng/L. The mean recovery of TBBPA in spiked samples was 56 %. The highest concentrations were detected in samples obtained near heavily industrialised regions.

TBBPA has been detected in leachate from landfill at a scrap metal facility in Espoo Finland at a concentration of 0.90 µg/L (Peltola, 2002)*. Eleven landfill sites in the Netherlands were monitored and TBBPA was detected in the particulate phase of leachate from these sites at concentrations ranging from <0.3 – 320 µg/kg dw (mean 54 µg/kg dw; Morris et al., 2004).

Levels of TBBPA in leachate from landfill sites in Japan have been measured (Osako et al., 2004)*. Samples were collected at leachate treatment plant(s) associated with each site. Samples were taken before treatment, and in some cases, also after treatment. The landfill sites included five municipal solid waste landfills. In Japan around 80 % of municipal solid waste is incinerated prior to landfill disposal so the landfills were mostly composed of ash, incombustibles and crushed fragments from bulk wastes (including waste electrical and electronic equipment). TBBPA was detected in raw leachate samples from three of the five municipal landfills at concentrations in the range of 0.009 – 0.62 µg/L (the detection limit was 0.001 µg/L). The level of TBBPA in the treated effluent from these sites was much lower (ND – 0.01 µg/L).

Influent and effluent from sewage treatment plants in the United Kingdom and the Netherlands have been tested for TBBPA (Morris et al., 2004). Samples of influents from five sewage treatment plants in the United Kingdom showed that TBBPA was primarily in the dissolved phase with levels in the range of 2.6 – 85 ng/L. Levels of TBBPA in the influent particulate phase were in the range of <3.9 – 21.7 µg/kg dw. Levels of TBBPA in the effluent from the five UK sites were all below the detection limit of 15 ng/L for the water phase and 3.9 µg/kg dw for the particulate phase. Samples of effluents from five sewage plants in the Netherlands contained TBBPA in the particulate phase (3.1 – 63 µg/kg dw, mean 42 µg/kg dw).

Influent and effluent from sewage treatment plants in South Africa have been tested for TBBPA (Chokwe et al., 2012*). Concentrations of TBBPA were 6.6 µg/L in filtered influent, 6.8 µg/L in unfiltered influent and 3.3 µg/L in the effluent.

11.4.2.1 Household and indoor dust

As discussed in Section 9.3, TBBPA has been detected in household and indoor dust and this is likely to represent an additional point of release of TBBPA to the environment. These emissions are expected to be diffuse and are not quantified.

Sediment and soil

The available scientific literature indicates that heavily populated regions and industrial areas have the highest concentrations of TBBPA in sediment and soil. Some of the following discussion has been paraphrased from the EC (Health/Env Canada, 2013) report. These references are marked with an asterisk (*) and have not been independently reviewed for this assessment.

Sediment

Suspended sedimentary material and settled sediments collected from eight locations in Canada and the USA were analysed for TBBPA (Quade, 2003*). Concentrations in the suspended matter were in the range of 0.6 – 1.84 µg/kg dw. The highest concentrations were detected downstream of a Detroit sewage treatment plant (1.84 µg/kg dw) and below the mouth of the Rouge River (1.82 µg/kg dw), which drains a highly industrialised and heavily populated region. TBBPA levels in suspended sedimentary matter were lowest in southern Lake St. Clair (0.6 µg/kg dw) which is upstream of major industry. Samples of settled sediments showed that concentrations were lower in sediment from Lake Ontario than in sediment from the Detroit River.

The levels of TBBPA and its dimethyl ether derivative have been analysed in surface sediments (top 1 cm) near a Swedish plastics factory that used TBBPA (Sellström and Jansson, 1995). The sediments were taken from two locations, one 2 km upstream from the factory and the other 5 km downstream from the factory. The concentration of TBBPA was 34 µg/kg dw in the upstream sediment and 270 µg/kg dw in the downstream sediment.

TBBPA concentrations in sediment samples from Berlin (Germany) were measured (Kemmlein, 2000*). For some sites, sediments from different depths within the core were analysed to obtain information about possible chronological trends in the concentrations. TBBPA was detected in 12 of the 13 areas sampled. Concentrations varied widely with the lowest reported at 0.02 µg/kg ww and the highest at 18.68 µg/kg ww. The depth-dependent analysis indicated that TBBPA was not present in the sediments until the 1970s when the use of flame retardants in plastics and polymers became common.

Sediments from the Scheldt Estuary, the Netherlands, UK and Ireland were examined for TBBPA (Morris et al., 2004). The study detected TBBPA in most samples, with particularly high concentrations detected in the vicinity of an English brominated flame retardant production facility. TBBPA was found to be present in 13 out of 19 samples from the Scheldt basin at concentrations of <0.1 – 67 µg/kg dw (mean 5.4 µg/kg dw), and 14 out of 19 samples from the Western Scheldt at concentrations of <0.1 – 3.2 µg/kg dw (mean 1 µg/kg dw). TBBPA was not detected in eight samples from Dublin Bay, but was detected in three out of four river-sediment samples from Ireland at concentrations of <2.4 – 3.7 µg/kg dw. TBBPA was detected in 10 out of 22 sediment samples from English rivers and estuaries at concentrations of 4.5 – 57.1 µg/kg dw (River Tees), 2 – 5.1 µg/kg dw (River Tyne), up to 9753 µg/kg dw (River Skerne) but was not detected in River Humber, Mersey or Clyde. TBBPA was detected in eight out of nine river sediment samples from the Netherlands at a concentration of <0.1 – 6.9 µg/kg dw (mean 2.2 µg/kg dw). The highest levels from the UK were from the River Skerne (up to 9753 µg/kg dw) which is close to a brominated flame retardant production site.

Sediments from nine English lakes were monitored for TBBPA (Harrad et al., 2009); concentrations ranged from 0.33 – 3.8 µg/kg dw.

Sediments were collected from a river in Paris and TBBPA was detected in all of the sediment samples in the range 0.065 – 0.28 µg/kg dw (Labadie et al., 2010).

Sediment samples were collected across Finland and analysed for TBBPA (Peltola, 2002*). Samples were collected in the summer/autumn of 2000 and were taken from the aerobic

surface layer of the sediments. The detection limit for the method was 0.2 µg/kg dw. TBBPA was not detected in three coastal samples taken around the Gulf of Finland, but was detected at a concentration of 0.4 µg/kg dw in sediment from an urban creek that collects storm water from Helsinki. The highest level found in the study was 21 µg/kg dw in a sediment sample from a storm water trench of a scrap metal facility.

TBBPA levels in sediment samples from various industrial areas in Norway were reported (Fjeld et al., 2004*). The sites sampled included ponds, landfill leachate, and river beds near industrially contaminated sites. TBBPA was found to be present in all of the soil and sediment samples from landfills and industrial sites at concentrations of 0.06 – 6.2 µg/kg dw.

A survey of the levels of TBBPA in sediments from various regions of Japan was carried out by the Environment Agency Japan (1996*). In 1977, TBBPA was not detected in 15 samples analysed (detection limit 1.3 – 7 µg/kg dw). In 1987, TBBPA was detected in 14 out of 66 samples at a concentration of 2 – 150 µg/kg dw.

Sediment samples collected in 1999 from six locations in the coastal area around Osaka Bay (Japan) were analysed for TBBPA (Ohta et al., 2002*). TBBPA was detected in all six samples at concentrations ranging from 0.7 µg/kg dw to 12 µg/kg dw. The highest recorded level was in a harbour surrounded by industrial facilities. A second study examined surface sediments collected in 2003 from seventeen locations around the coastal area of the Setouchi Sea, Japan (Ohta et al., 2004*). TBBPA concentrations ranged from 0.08 µg/kg dw to 5 µg/kg dw. The highest levels were found in an area with numerous chemical factories.

Surface sediments in the Pearl River Delta in China were collected and analysed for TBBPA (Feng et al., 2012). Approximately 100 samples of sediment were collected for this study from the rivers discharging into the Delta and from the Delta itself. Concentrations of TBBPA ranged from 0.06 – 304 µg/kg dw. The highest concentrations were found in areas where e-waste recycling occurs. Recovery in the spiked blanks and matrix samples was 50 %.

Surface sediments and cores were collected from a heavily industrialised area in South China for analysis of flame retardants (Zhang et al., 2009). There was a 100 % detection frequency for TBBPA in the surface sediments, and concentrations ranged from 4 – 230 µg/kg dw. For the deeper sediments, concentrations of TBBPA were much lower ranging from 9 – 18 µg/kg dw. These samples were collected at 60 cm depth which was expected to represent sediments deposited 10 – 15 years prior to the time the samples were taken. Further investigation of the deeper sediments showed that much of the TBBPA was tightly bound to the sediment particles. It is not clear from the study whether these bound residues were available to organisms.

Sediments from Lake Taihu in China have been investigated (Xu, J et al., 2013). Sediments were reported to contain TBBPA at concentrations between 0.056 and 2.15 µg/kg dw. There was no correlation between total organic carbon levels and the measured concentrations of TBBPA.

Sediments in rivers in Korea have been investigated for TBBPA and other flame retardants (Lee et al., 2015). The concentrations of TBBPA ranged from 0.05 to 150 µg/kg dw. Background levels were reported as 3 µg/kg dw in samples taken upstream from heavily populated and industrialised areas. The highest concentrations were in samples taken near an industrial complex manufacturing electronic equipment. Concentrations of TBBPA in

sediments from coastal and offshore locations in Korea were investigated (Gu, S-Y et al., 2017b). Results ranged from ND to 0.62 µg/kg dw.

Sediment samples were collected in the Singapore Strait and analysed for flame retardants and other organic chemicals (Zhang and Kelly, 2018). This location is tropical and the study was designed to investigate the presence of organic pollutants in a tropical marine food web. TBBPA was detected in sediments but not in the biological samples.

A review of the environmental fate of TBBPA was undertaken (Malkoske et al., 2016). In China about half of the water bodies for which data were available had concentrations in sediments above 100 µg/kg dw, while for other countries less than 10 % of water bodies tested had concentrations above this value.

Soil

There is relatively little information in the scientific literature on soil concentrations of TBBPA. However, the available evidence indicates that the highest concentrations of TBBPA in soils are found in the vicinity of TBBPA manufacturing sites and near e-waste facilities.

Soil samples collected close to a brominated manufacturing facility in Arkansas (USA) contained measurable quantities of TBBPA however the concentrations were not reported by the authors (DeCarlo, 1979*). A maximum concentration of 220 000 µg/kg TBBPA in soil (wet or dry weight not specified) was reported by Pellizzari (1978*) near a brominated chemical factory in Arkansas.

A TBBPA concentration of 450 000 µg/kg (wet or dry weight not specified) was reported by Arnon (1999)* in soil samples collected from the upper 15 cm of soil at a heavily contaminated site in Israel. Soil collected near a brominated chemical manufacturing facility in Israel contained TBBPA at a concentration of 0.2 µg/kg dw (Leisewitz, 2001*).

TBBPA was detected in 2 of 11 soil samples from farmlands near an e-waste facility in Beijing, China at concentrations of 0.8 and 5.6 µg/kg dw (Xu et al., 2012). Soil concentrations up to 7.76 µg/kg dw were detected near a TBBPA manufacturing plant in the Shandong Provence, China (Liu et al., 2016). Concentrations of TBBPA have been measured at manufacturing, reformulation, handling and e-waste recycling sites across China and range from 1 – 7700 µg/kg dw with the highest levels reported near a manufacturing site (Malkoske et al., 2016).

In Vietnam, soil concentrations ranged from <0.5-2900 µg/kg dw with the highest concentrations detected at an e-waste recycling site (Malkoske et al., 2016).

In Spain concentrations in soil ranged from 3.4-32.2 µg/kg dw for sites where TBBPA is incorporated into products (Malkoske et al., 2016).

Sewage sludge

In Australia, sewage sludge is applied to soils on farms and cultivated forests, primarily to replace plant nutrients and to improve soil properties (Pritchard et al., 2010). This is an important route by which TBBPA enters soil so it is appropriate to review the available data on the levels of TBBPA in sewage sludge.

Some of the following discussion on the presence of TBBPA in sewage sludge has been paraphrased from EC (Health/Env Canada, 2013) and EU (EURAR, 2008). These references are marked with an asterisk (*) and have not been independently reviewed for this assessment.

No data are available on the levels of TBBPA in Australian sewage sludge.

TBBPA concentrations have been measured in sewage sludge from a treatment plant that received leachate water from a landfill that contained waste from a plastics factory using TBBPA (Sellström and Jansson, 1995). In addition, a sewage sludge sample was also analysed from a treatment plant with no known sources of TBBPA. TBBPA was identified in both samples:

- 56 µg/kg dw in the sludge sample from the treatment plant receiving the leachate
- 31 µg/kg dw in the sludge sample from the 'control' treatment plant.

Sewage sludge samples taken from 22 Swedish municipal wastewater treatment plants between October 1999 and September 2000 contained TBBPA at concentrations of <0.3 µg/kg – 220 µg/kg ww (median 2.0 µg/kg ww; Öberg et al., 2002). Samples with the highest concentrations of TBBPA were collected from a waste water treatment plant that processed waste water from the electronics industry.

Sewage sludge samples from three municipal sewage treatment plants in Stockholm (Sweden) contained TBBPA at concentrations of 5, 10 and 45 µg/kg dw (Sellström et al., 1999)*.

TBBPA has been detected in sewage sludge at concentrations up to 472 µg/kg dw (median 96.7 µg/kg dw) in 15 of 17 treatment plants sampled from Catalonia Spain (Gorga et al., 2013*). The tribromo- derivative was detected in samples from 10 treatment plants (up to 886 µg/kg dw) and the monobromo- derivative was detected in sludge samples from six facilities at concentrations of up to 807 µg/kg dw.

Sludge samples collected from 32 municipal waste water treatment plants in Baden-Württemberg, Germany contained TBBPA at concentrations of 0.6 – 62 µg/kg dw, (mean level 16 µg/kg dw; Metzger and Kuch, 2003*).

TBBPA concentrations were measured in samples of sewage sludge from treatment plants in the UK, Ireland and the Netherlands (Morris et al., 2004). TBBPA was detected in five out of six sewage sludge samples from three treatment plants in Ireland at concentrations of <2.4 – 192 µg/kg dw (mean 95 µg/kg dw). Similarly, TBBPA was detected in sewage sludge samples from all five treatment plants sampled in the UK at concentrations of 15.9 – 112 µg/kg dw (mean 59 µg/kg dw). Samples from the Netherlands had TBBPA in sludge samples from all eight waste water treatment plants at concentrations of 2 – 600 µg/kg dw (mean 79 µg/kg dw). The detection limit of the method used was in the range of 0.1 – 2.4 µg/kg dw).

Municipal sewage sludge from Canadian waste water treatment plants was tested for TBBPA (Lee and Peart, 2002). Samples of both raw sludge (collected from primary sedimentation tanks) and digested sludge (collected from secondary clarifiers) were included in the study. In all, 35 sludge samples taken from 21 municipal sewage treatment plants between 1994 and 2000 were analysed. TBBPA was present in 34 of the samples at concentrations of 2.9 – 46.2 µg/kg dw (detection limit 1 µg/kg).

Sewage sludge from five sewage and waste water treatment plants in the southern Ontario region and seven plants in the USA was tested for TBBPA (Quade et al., 2003*). All of the Canadian facilities used primary and secondary digestion and one used tertiary digestion. The USA facilities used either primary digestion, lime stabilisation or composting. TBBPA was detected in all sludge samples collected from southern Ontario facilities at concentrations in the range 9.04 – 43.1 µg/kg dw. TBBPA was detected in all of the samples from the US facilities at concentrations in the range 2.98 – 196 µg/kg dw.

TBBPA and its possible degradation products have been studied in sewage sludge samples from Canada (Chu et al., 2005). Samples were collected from plants in Windsor, Ontario (Canada). All sludge samples contained TBBPA (2.09 – 28.3, µg/kg dw). The degradation products tri-bromo BPA, di-bromo BPA and in some cases mono-bromo BPA were also identified. BPA was also present in all samples. These results provide indirect evidence that TBBPA can undergo debromination reactions in the environment; however, the detected BPA could also originate from alternative sources.

Sludge from sewage treatment plants and waste water treatment plants in Korea were monitored for brominated flame retardants, including TBBPA (Hwang et al., 2012). Samples were collected from four sewage treatment plants and seven industrial waste treatment plants. The concentration of TBBPA was highest in samples from the sewage treatment plants. Sludge from the industrial waste treatment plants had concentrations ranging between 4 – 144 µg/kg dw, while sludge from the sewage treatment plants ranged from 67 – 618 µg/kg dw.

Concentrations of TBBPA in sewage sludge in China, England, Germany, Ireland, Netherlands, Northern Europe, South Korea and Spain were reviewed (Malkoske et al., 2016). Sludge concentrations ranged from <0.4 – 732 µg/kg dw. Gorga et al. (2013). In addition, the concentrations of TBBPA in sewage sludge were also reviewed. The following concentrations were observed: 2.9 – 7.6 µg/kg dw in Sweden (late 1990s); ND – 220 µg/kg dw in Sweden (2000s); <2 – 600 µg/kg dw in the UK/Ireland (2002); 300 µg/kg dw in Canada (2003); 0.6 – 62 µg/kg dw in Germany (2006); and nd - 1329 µg/kg dw in Spain (2008). All measured concentrations were in the range not detected – 1329 µg/kg dw.

Conclusions relating to measured levels

Air:

TBBPA has been detected in air and precipitation from industrial, urban and remote locations. In general, measured air concentrations are very low with typical concentrations for rural and urban air in the range of 0.5-25 pg/m^3. The available evidence indicates that adsorption to particulates is the major mode for the presence of TBBPA in air. TBBPA has been detected in air at remote locations in the Arctic at concentrations in the range of 0.05-70 pg/m^3. This provides some (limited) evidence that TBBPA may undergo long range transport. The concentrations of TBBPA in the air near TBBPA manufacturing facilities may be much greater than in air at remote locations. For example, measurements of 1.8 µg/m^3 near a US facility and 0.095 µg/m^3 at a Chinese e-waste facility have been reported.

Water

The highest concentrations of TBBPA in water are associated with wastewater treatment plants in heavily populated regions and in water sampled at (or near) heavily industrialised areas. Remote lakes and rivers contain very low levels (often not detected), while lakes and streams near urban areas contain TBBPA at concentrations (typically) in the range of 1-5 ng/L. Waterways near industrialised areas carry higher concentrations of TBBPA, ranging from about 1-100 ng/L.

Although data are somewhat limited, studies have detected TBBPA in effluent from sewage and waste water treatment plants at concentrations up to 6.8 µg/L in the dissolved phase and up to 63 µg/kg dw adsorbed to particulate matter. Concentrations of TBBPA in leachates from landfills (which are often treated at waste water facilities) vary from not detected up to about 1 µg/L.

Sediments

Samples of sediments from Port Darwin (urban), upper Brisbane River (remote), Canberra (Lake Burley Griffin - urban), Parramatta River (industrial/urban) and Port Jackson (industrial/urban) were analysed for TBBPA. The only sediment sample where TBBPA was detected was from the Parramatta River at a concentration of 0.13 µg/kg dw. All other samples had concentrations below the detection limit.

International data for sediment concentrations are available from numerous countries/regions. These data show high levels of TBBPA in sediments near factories producing brominated flame retardants with concentrations up to 9753 µg/kg dw. Generally, in other industrial or urban areas, levels are in the range of 1-500 µg/kg dw. In more remote locations, sediment levels are typically below 1 µg/kg dw.

Soils

International data are available for some soils. Results for soils in most locations were in the range ND-10 µg/kg dw. Soils at sites where TBBPA is manufactured or used, or where e-waste recycling occurs, contain much higher concentrations of TBBPA, up to 7700 µg/kg dw.

Sewage Sludge

No data are available on the levels of TBBPA in Australian sewage sludge. Most of the available data are from Europe and Canada.

TBBPA is detected in most samples of sewage sludge and sludge from waste water treatment plants in Europe, Canada and the USA. Concentrations range from <LOD-1329 µg/kg dw. However, typical concentrations are in the range 5-200 µg/kg dw, with typical mean concentrations in the range 10-100 µg/kg dw. For the risk calculation in this assessment, a concentration of 95 µg/kg dw is assumed for Australian sewage sludge. This is a conservative value based on mean values from Ireland, England, Spain and the Netherlands.

11.5 Predicted Environmental Concentrations

As discussed in the Release Section (Section 11.1), processing of TBBPA, either in its raw state or through resins imported containing the substance, occurs predominantly in Melbourne.

Based on emission factors in the OECD Emission Scenario Document (OECD, 2009), 87.1 kg TBBPA is predicted to be released to sewer annually (see Table 19). It is assumed that all of the TBBPA released during processing is treated in the Melbourne Water Western Treatment Plant.

According to Melbourne Water, the Western Treatment Plant treats about half of Melbourne's sewage, or about 320 million litres per day (Melbourne Water, 2020). In 2013, Melbourne Water produced around 79000 m^3 of biosolids (Ukwatta and Mohajerani, 2015). Assuming a density of 1.5 tonne/m^3, the Western Treatment Plant produces approximately (79000 m^3 × 1.5 tonne/ m^3) / 2 ≈ 59000 tonnes of biosolids each year.

Removal through the sewage treatment plants (STP) is predicted based on the SIMPLETREAT model (Struijs, 1996). This model predicts removal from water through degradation, volatilisation or sorption to sludge and uses parameters of log K_{OW} (5.9) and log H (-1.57 to –2.73 Pa.m^3/mol depending on vapour pressure and solubility). While some primary degradation in sludge may be expected under anaerobic conditions, it will be assumed no degradation will occur during the residence time in the STP. SIMPLETREAT predicts under these inputs that volatilisation to air will be 0 % with sorption to sludge of 85 %.

Assuming 87.1 kg of TBBPA is released to the Western Treatment Plant per year, and that 85 % partitions to the 59000 tonnes of biosolids produced, the predicted concentration of TBBPA in biosolids will be 87.1 × 10^6 mg × 0.85 / (59 × 10^6 kg) = 1.25 mg/kg. This is very high compared to biosolids concentrations found internationally. As reviewed above, typical concentrations measured in biosolids overseas are up to 0.2 mg/kg, with few measurements above this level. This suggests that the release estimates based on the OECD method (OECD, 2009) are conservative by a factor of at least six.

Concentrations of TBBPA in the influent and effluent of the Western Treatment Plant can be calculated in a similar fashion. The Western Treatment Plant treats about 320 ML per day. Assuming that the daily effluent volume, and 87.1 kg of TBBPA is released to the plant over the course of a year, the average concentration in influent will be 87100 g / (3.2 × 10^8 L/day × 365 days) = 7.46 × 10^{-7} g/L = 746 ng/L. Assuming 15 % of this amount remains in effluent after treatment, the approximate concentration in effluent is 0.15 × 746 ng/L = 112 ng/L. Although there are limited measured data on concentrations of TBBPA in STP influent and effluent, the predicted concentration in STP influent of 746 ng/L appears to be well above the highest available measured value in other Western countries of 83 ng/L. Thus the estimated concentration of 112 ng/L TBBPA in effluent from the Western Treatment Plant value is likely to be conservative by a factor of at least nine.

The Western Treatment Plant releases effluent to the ocean. For this release scenario, EPHC 2009 recommends a dilution factor of 10, resulting in a predicted environmental concentration in the ocean around the vicinity of the Western Treatment Plant outfall of 11.2 ng/L. However, as noted above, the estimated effluent concentration, based on the OECD method (OECD, 2009), is likely to be conservative by a factor of ayt least nine. Therefore, the estimate of ocean water concentration near the effluent outfall (11.2 ng/L) is likely to be similarly conservative.

Concentrations in soil amended with biosolids from the Western Treatment Plant are estimated using the model in EPHC 2009. For a single application of biosolids to land, it is assumed that the application rate is 1 kg/m^2/year, biosolids are mixed to a depth of 0.1 m,

and soil bulk density is 1500 kg/m^3. This results in a dilution factor of 150 with respect to the initial concentration in biosolids. A single application of biosolids containing TBBPA at a concentration of 1250 µg/kg would result in a concentration of 8.3 µg/kg.

Multiple applications of biosolids to soil can result in an appreciable build-up of chemicals with long degradation half-lives. For a single application, the fraction remaining at time t is given by $r(t) = \exp(-\ln(2)\ t\ /\ t_{1/2})$ where $t_{1/2}$ is the half-life. For multiple applications separated by time interval Δt, the concentration is given by $C_0(r(\Delta t) + r^2(\Delta t) + r^3(\Delta t) + \ldots)$, where C_0 is the initial concentration from a single application. If the half-life of the chemical is short compared with the application interval, a steady state concentration, slightly above C_0, is reached after a small number of applications. If the half-life is much longer than the application interval, the concentration increases roughly linearly during the initial applications, being approximately $2C_0$ after the second application, $3C_0$ after the third application, and so on. It will take many applications to reach a steady state. The sum $C_0(r(\Delta t) + r^2(\Delta t) + r^3(\Delta t) + \ldots)$ can be evaluated using a geometric series, and approaches the steady state value $C_0(r(\Delta t)\ /\ (1 - r(\Delta t)))$ as the number of applications increases. If the half-life of the chemical is long compared to the application interval (i.e. if $r(\Delta t)$ is nearly one), this can be significantly greater than C_0.

The degradation half-life in soil for TBBPA is difficult to establish from the available data, given that:

- significant amounts of TBBPA become reversibly bound to the humin fraction in soil
- TBBPA may become methylated under some conditions.

Nevertheless, TBBPA and its adducts can be persistent in soil and it is possible that significant amounts may accumulate in soil with multiple applications of biosolids from the Western Treatment Plant. It will be assumed that the concentration of TBBPA in soil amended with biosolids from the Western Treatment Plant will be at least 8.3 µg/kg.

Available monitoring data for TBBPA in Australian sediments indicate that concentrations were generally low or below the limit of detection; however, no data are available for sediments near the outfall of the Western Treatment Plant in Melbourne where significant levels might be expected. In the absence of measured data, it is assumed that the concentration in sediment near the Western Treatment Plant outfall is up to 500 µg/kg dw; this is a conservative estimate based on values found in sediment overseas.

Release of TBBPA from articles is expected to be limited as the majority of the TBBPA used worldwide is incorporated into articles as a reactive flame retardant and will remain bound in the plastic articles in which it is incorporated. Since industrial use of TBBPA only occurs in Melbourne and waste from industrial use of TBBPA is treated by the Western Treatment Plant which releases effluent to the ocean, dispersive release of TBBPA to rivers through an STP is expected to be limited, and a riverine PEC was not calculated.

A PEC in air was determined based on the scenarios in the OECD Emission Scenario Document (OECD, 2009). This is of limited value for the environmental assessment because:

i) effect concentrations for exposure to organisms via the air are not available
ii) any TBBPA released to air is expected to rapidly partition to soil.

Fugacity modelling indicates that TBBPA is unlikely to be present at high concentrations in the atmosphere in the gaseous phase. There are no defined scenarios for predicting air concentrations in Australia. Melbourne covers an area of approximately 7700 km^2. If the atmospheric height is 2000 m, the atmospheric compartment would be of the order of 1.54×10^{13} m^3.

Local release estimations indicated that a total 6.26 kg per annum may be released to the atmosphere (see Table 19, Section 11.1). Assuming processing occurs on 200 days per annum, the daily release is 0.313 kg/day. Assuming all processing occurred in Melbourne, and that this amount of TBBPA is uniformly distributed in the atmospheric compartment, the daily atmospheric concentration would be 2 pg/m^3. This estimate is consistent with measured concentrations of TBBPA in air samples from various urban locations in Europe (see Section 11.4.2 above).

Release of TBBPA to air from manufacturing facilities and e-waste recycling and auto-dismantling facilities also results in high concentrations in the surrounding soil. A PEC in soils surrounding these facilities has not been determined, but concentrations in the mg/kg range have been reported near such facilities overseas, and other flame retardants have been detected at high concentrations near Australian facilities (McGrath et al., 2016)

The predicted environmental concentrations in various environmental compartments are summarised in the table below. In summary, the PEC in the ocean near the outfall of the Western Treatment Plant in Melbourne was calculated using the mass of TBBPA determined to be released to sewer using the method in OECD 2009, assuming 15 % remains in effluent, and diluting by the amount of water treated at the plant each year. The concentration in biosolids from the Western Treatment Plant was estimated assuming 85 % of the TBBPA in influent partitions to biosolids, and diluting by the amount of biosolids produced by the plant each year. This was further diluted by a factor of 150 according to method in EPHC 2009 to give the PEC in soil amended with one application of biosolids from the Western Treatment Plant. The PEC in sediment is a conservative estimate based on monitoring data from overseas.

Table 20 – Predicted Exposure Concentrations for TBBPA

PEC	Concentration
PEC_{ocean}	11.2 ng/L
$PEC_{sediment\ (ocean)}$	0.5 mg/kg dw
PEC_{soil}	8.3 µg/kg dw
PEC_{air}	2 pg/m^3

12 Human Health Hazard Assessment

To enhance efficiency, this assessment has utilised assessments carried out by the European Union and the International Programme on Chemical Safety (IPCS). The European Union Risk Assessment Report on TBBPA (EURAR, 2006) was utilised as reference material for this Section.

A comprehensive literature search was carried out for data published since year 2006 to ensure that studies published after the EU assessment of TBBPA were covered. Studies that were not sighted but described in adequate detail in the EURAR on TBBPA (Part II - Human Health) are indicated with an asterisk (*) in this report. Primary sources of data were consulted where necessary and for critical studies.

12.1 Toxicokinetics

12.1.1 Absorption

In a study investigating the absorption of TBBPA (Hakk et al., 2000), ten male Sprague Dawley (SD) rats were administered a single dose of ^{14}C-TBBPA (2.0 mg/kg bw; 1 μCi/rat) in 0.5 mL peanut oil via gavage. An identical dose was administered to 8 bile duct cannulated male rats. In the cannulated animals, 71 % of the administered dose was excreted in the bile within 72 h, and a further 20 % appeared in the faeces in the period between 24 – 72 h. Considering that the average gastrointestinal transit time in rats is ≈12 h (Takahashi, 1999), it is estimated that 92 % of the dose is absorbed from the gastrointestinal tract. Conservatively, it can be assumed that 100 % of TBBPA is absorbed when administered via the oral route.

In a toxicokinetics study, 20 mg/kg bw ^{14}C-TBBPA was orally administered as a single bolus dose to 4 male Fischer 344 rats. Blood was collected through an indwelling jugular vein cannula at 8, 15 and 30 mins and 1, 2, 4, 6, and 8 h (Kuester, 2007). In another experiment 20 mg/kg bw ^{14}C-TBBPA was intravenously administered to 9 animals and blood was sampled via the jugular vein cannula at 5, 10, 15, 20 and 30 mins and 1, 2, 4, 6, 12, 24 and 36 h. In the oral study, the concentration of ^{14}C-TBBPA appearing in blood was less than 0.1 % of the dose with a maximum concentration (Cmax) of 0.2 μg/mL and an area under the curve (AUC) of 24 μg x min/mL. The initial rate of absorption was rapid with the maximum reached at 30 min following dosing and concentration declining thereafter for up to 2 h. A small increase in absorption at 4 h was observed compared to 2 h and this may indicate entero-hepatic recycling. By comparing the AUC from the intravenous administration (1440 μg × min/mL) with that of the AUC from oral administration (24 μg x min/mL), the systemic bioavailability following oral dosing was estimated to be 1.6 %.

Oral absorption of TBBPA was examined in a study in 10 female SD rats (Brady, 1978). The rats were dosed with ^{14}C-labelled TBBPA (6.5 – 7.6 mg/kg bw in corn oil) by gavage, and urine and faeces were collected as follows: Group 1 (n = 2) – 4 and 8 h; Group 2 (n = 2) – 4, 8, 16 and 24 h; Group 3 (n = 2) – 4, 8, 16, 24, 48 and 72 h. Group 4 consisted of 4 additional animals. In two animals from this group, blood was sampled at 4, 8, 24, 48 and 72 h, and in the other 2 animals, blood was only sampled at 16 h post dosing. Only a very small amount of the administered TBBPA was found in the blood; the maximum being 0.03 % of the

administered dose and this occurred in the 0 – 4 h and 4 – 8 h periods. By the end of 72 h post treatment, 95 % of radiolabelled TBBPA was excreted in faeces. Taking into consideration the findings of the Hakk et al., (2000) study with bile duct cannulated rats, and given the average gastrointestinal transit time in rats is approximately 12 h (Takahashi, 1999), this faecal lag is considered a result of absorption and possibly enterohepatic circulation.

In a briefly reported study, the time course of TBBPA appearing in blood was determined (Sato, 1996). Six male SD rats were orally dosed by gavage with TBBPA (500 mg/kg bw; most likely in DMSO). Blood samples were taken at 1, 2, 4, 6, 12 and 24 h after dosing. TBBPA concentrations were highest in the blood at 1 h at 2750 pg/mL. TBBPA concentrations in the blood decreased to approximately 400 pg/mL at 4 h, and then approached to zero by 24 h. While the sampling was also done at 2 and 12 h, this information was not presented in the graph.

To evaluate dermal absorption of TBBPA, an in vitro study was conducted according to OECD TG 428 to determine the rate and extent of absorption of ^{14}C-TBBPA following topical application to human skin (Roper, 2005). Four samples of full-thickness human breast skin were obtained from patients aged 19 to 49 years. Split-thickness skin membranes (thickness of 400 μm and exposed surface area of 0.64 cm^2) were mounted into flow-through diffusion cells and the skin surface was maintained at 32 °C. The receptor-chamber volume was 0.25 mL and the flow rate of receptor fluid was approximately 1.5 mL/h. The receptor fluid for the barrier integrity assessment was physiological saline. All skin samples with a tritiated water permeability coefficient (k_p) of less than 2.5×10^{-3} cm/h were used to evaluate the test substance. At the conclusion of the barrier integrity assessment the receptor fluid was changed to ethanol: water (1:1 v/v) to allow sufficient solubility of the applied TBBPA. ^{14}C-TBBPA in acetone (6.4 μL containing 1246 μg TBBPA) was applied to the stratum corneum of the exposed skin using a pipette. Receptor fluid was collected hourly from 0 – 8 h and then every 2 h from 8 – 24 h post dose. Receptor fluid samples were mixed with 10 mL scintillation fluid and analysed. At 8 h post dose, the exposed skin was washed according to the "soap + Q-Tip" method. At 24 h post dose the underside of the skin was washed, and the rinse was analysed. The stratum corneum was removed with 25 successive tape strips, and the tapes were analysed by combustion/liquid scintillation counting.

The absorbed dose was 0.7 % (14.6 μg ^{14}C-TBBPA/cm^2) of the applied dose. The highest absorption rate was found to be 1.1 μg ^{14}C-TBBPA/cm^2/h at 10 h post dose. The dislodgeable dose was 62 % of the applied dose with 25 % in skin wash, 2 % in tissue swab, 0.1 % in pipette tips and 34 % in Q-Tips. The stratum corneum was associated with 12 % of the applied dose. The calculated dermal absorption was 1.6 % (32 μg ^{14}C-TBBPA/cm^2).

In vitro and in vivo studies were undertaken to elucidate the dermal absorption of TBBPA (Knudsen et al., 2015). The in vivo study was conducted in female Wistar Han (WH) rats and in vitro study was conducted using split-thickness skin (i.e. epidermis and upper portion of the dermis) from human donors and female WH rats, exposed to TBBPA in a flow-through system.

In the in vitro study, human skin (from 1 male, 2 female Caucasian individuals aged 71–77 years old, dorsal/scapular skin, excised ≤12 h post-mortem) or rat skin were thawed and dermatomed to approximately 300 μm thicknesses and placed in receptor fluid. Four discs were cut from each sample of human skin and 3 from each rat skin.

The mean skin thicknesses of human and rat skin were 294 and 244 µm, respectively. The disks were mounted epidermal side up in the flow-through system and treated with 100 nmol/cm^2 of ^{14}C-TBBPA in 10 µL acetone (1 µCi). Fractions were collected every 6 h until 24 h post-dosing. The epidermal surface was washed six times with 0.5 mL of soap:water to remove unabsorbed chemical. The skin wash fractions were pooled into two vials and mixed with scintillation fluid. The skins were allowed to dry overnight followed by each skin disk being tape-stripped 10 times with clear tape. Each tape strip was placed in a separate vial. Skin washes, body washes, tape strips and receptor fluid were mixed with scintillation fluid and analysed for radioactivity in a liquid scintillation analyser.

Analysis of the receptor fluid in the in vitro experiments demonstrated penetration of radiolabelled TBBPA through both rat and human skin over time. ^{14}C-TBBPA penetration was significantly lower in human skin in each 6 h fraction compared to that in rat skin. Approximately 0.2 % of the dose applied to human skin was recovered in the receptor fluid, whereas approximately 3 % of the dose passed through the rat skin in 24 h. Total dose recoveries (expressed as percent of administered dose) were 99 %.

Table 21 – Recovery of [^{14}C]-radioactivity in various fractions of the in vitro flow-through system at 24 h post-dose

Species	Dose (nmol/cm^2)	Penetrated (%) (receptor fluid)	Absorbed (%) (skin)	Unabsorbed (%) (washes & strippings)
Human[a]	100	0.2 ± 0.006	3.4 ± 1.8	95 ± 3
Rat[b]	100	3.5 ± 0.7	9.3 ± 0.8	86 ± 3

[a]N = 3, performed in quadruplicate; [b]N = 4, performed in triplicate.

In the in vivo study, female WH rats (n = 4 rats/dose group) were prepared for non-occluded dermal application and were topically treated with two doses (100 nmol/cm^2 and 1000 mol/cm^2) of ^{14}C-labelled TBBPA (100 µCi/kg, 400 µL/kg) at the clipped areas. The dosing site was covered with a non-occlusive steel mesh cap attached with polyacrylate glue to prevent ingestion of the test article. Faeces, urine, and cage rinses were collected and analysed at 24 h intervals. Animals were euthanised by CO_2 inhalation after 24 or 72 h and blood was collected by cardiac puncture, dosed skin was excised, and complete necropsies were performed. Skin from the application area was swabbed 10 times using filter paper soaked with acetone, 10 times using a 10 % soap solution, and then tape stripped 10 times using clear tape to maximise recovery of the dose remaining on the surface and in the stratum corneum of the skin.

As observed in the in vitro studies, most of the administered ^{14}C-TBBPA was recovered unabsorbed from the dosing site within 24 h of administration. Doses of 100 nmol/cm^2 and 1000 mol/cm^2 gave similar results in vivo. Continuous exposure over 24 h to TBBPA resulted in 10–20 % of the dose crossing into the skin into systemic circulation at both dose levels. Approximately 14 % of the dose was detected in the skin at the dosing site (absorbed) and 8 % was present in tissues or excreta. In the 100 nmol/cm^2 group, 6 % of the dose was

recovered in faeces with an additional 1–2 % found in the gastrointestinal (GI) tract contents at 24 h. Blood and other tissues contained less than 1 % of the administered doses.

Penetration and absorption, as determined by recovery of ^{14}C-TBBPA in faeces, were continuous between 24 and 72 h (data not shown). By 72 h post-application, faeces or GI tract contents contained approximately 30 % of the administered ^{14}C-TBBPA. GI tract tissues contained <1 % of the dose while 'non-GI tissues' contained approximately 3 % of the dose, most of which was found in the skin collected far from the dosing site.

Table 22 – Recovery of ^{14}C-TBBPA in various fractions from rats

Dose (nmol/cm^2)	Exposure (h)	Penetrated (excreta & tissues, %)	Absorbed (skin, %)	Unabsorbed (washes & strippings, %)
100	24	7.7 ± 2.4	13.6 ± 2.5	80 ± 3
1000	24	5.3 ± 2.7	5.1 ± 3.4	85 ± 8
1000	72	30 ± 10	40 ± 7.2	30 ± 10

Amounts of penetrated, absorbed, and unabsorbed dosed at 72 h significantly higher than amounts measured at 24 h for either dose. Data presented as mean ± S.D., N = 3-4 animals per dose group.

The principles of the parallelogram approach to the dermal exposure assessments were used to estimate a likely level following in vivo human systemic exposures to a relevant dose of dermally-applied TBBPA as described by Ross et al., (2011). Briefly, in vivo human exposure is estimated as a function of in vitro human exposure multiplied by a normalisation factor based on the same dose applied to rat skin in vivo and in vitro.

Estimation of human in vivo systemic exposure relative to the ratio of animal to human absorption (penetrated + absorbed) of dermally applied chemicals:

$$\text{Human}_{\text{in vivo}} = (\text{Rat}_{\text{in vivo}} / \text{Rat}_{\text{in vitro}}) \times \text{Human}_{\text{in vitro}}$$

The authors of the study concluded that based on this parallelogram calculation, up to 6 % of dermally applied TBBPA may be bioavailable to humans exposed to TBBPA.

In a repeat dose dermal study (Yu et al., 2016), not conducted according to OECD guidelines, male Wistar rats were repeatedly exposed by dermal application of 20, 60, 200 and 600 mg TBBPA/kg bw, 6 hours daily for 90 days (details of exposure procedure not provided). Concentrations of TBBPA in serum were determined on the 90th day, and in urine and faeces on days 0, 1, 10, 20, 30, 40, 50, 60, 70, 80 and 90. TBBPA concentrations in serum ranged from 19-427 ng/gm lipids, and increased with dose. The percentage of the TBBPA dose recovered in serum on the 90th day varied from 0.002 % to 0.013 %, and the percentage of the dose excreted in urine varied between 0.004 % to 0.07 %, while 3.3 % to11.2 % of the

dose was recovered in faeces. TBBPA was excreted mainly in faeces and only small amounts were recovered in urine. The results showed that about 3.3 to 11.2 % TBBPA was absorbed dermally under different dosing regimens and very little remained in the blood stream.

These studies indicate that, following oral exposure, close to 100 % of the administered TBBPA is absorbed from the gastrointestinal tract. Based on the in vitro dermal absorption study using human skin, and in vivo rat dermal absorption and the repeat dose dermal absorption study in the rat, the dermal absorption of TBBPA is 6 % of the applied dose.

No studies have been performed to investigate the absorption of TBBPA by the inhalation route.

TBBPA was absorbed and metabolised rapidly in healthy human volunteers receiving a single oral dose of 0.1 mg/kg (Schauer et al., 2006). The chemical was below the limit of detection in all blood samples, at the initial time points of 1, 2, and 4 hours. However, TBBPA-glucuronide was present at all time points, up to 72 hours, with peak concentrations detected between 2 and 6 hours. Traces of TBBPA-glucuronide were also detected in urine samples (Carignan et al., 2015).

12.1.2 Distribution

In the Hakk et al. (2000) study, the rats were sacrificed after 72 h and the following organs were removed for distribution studies: adipose tissue (epididymal), blood, intestines, heart, kidney, liver, lung, spleen, testes and thymus. It was reported that only 2.1 % and 1.0 % of the administered dose was retained in the tissues of the intact and bile-cannulated rat, respectively. The highest retention of radiolabelled TBBPA was found in the small intestine (0.7 %), large intestine (1.0 %) and the lung (0.2 %) in the intact rat. In the bile-cannulated rat, similar distribution was also seen. Radioactivity was also detected in the carcass, kidney and the liver in low amounts. Retention of TBBPA in the adipose tissue, blood, heart, spleen, testes and thymus was below the limit of detection. The higher levels detected in the intestines were probably a result of not removing the faecal contents prior to analysis.

In the Brady (1978) study, the liver, brain, kidney, muscle, fat, skin, spleen and gonads were analysed for radioactivity. Analysis of tissues taken from the Group 1 (i.e. sacrificed after 8 h) animals indicated that a total of 0.73 % of the administered TBBPA was retained in those tissues. The highest levels were found in the liver (0.41 %) and fat (0.07 %). In the Group 2 animals, sacrificed at 24 h, the total TBBPA retained in the analysed tissues was 0.85 %. The highest levels were found in the liver (0.33 %). In Group 3 animals, sacrificed after 72 h, only 0.2 % of administered TBBPA was found in the analysed tissue.

In a TBBPA distribution study (Meerts et al.,1999), pregnant Wistar WU rats were exposed to ^{14}C-TBBPA (5 mg/kg bw in corn oil) orally on gestation days (GD) 10 to 16. Control rats received the vehicle only. On GD 20 the animals were sacrificed and the following tissues were removed for further analysis: liver, skeletal muscle, abdominal fat, placenta, forebrain, kidney, lungs, plasma, spleen, heart, cerebellum, pancreas and thymus. Maternal blood was collected via the vena cava for analysis. Analysis of the tissues determined that 0.83 % of radiolabelled TBPPA was retained in maternal tissue and 0.34 % was retained in foetal tissue four days after the final dose was administered. In the dams, the highest levels of radioactivity were found in the carcass (0.37 % of the administered dose) and liver (0.26 %). In the foetuses, the highest levels of radioactivity were also found in the carcass (0.07 %) and

liver (0.06 %). The study did not investigate the nature of the excreted radioactivity to determine the presence of metabolites.

A bromine analysis was conducted as part of a 90-day repeated dose study in SD rats (Quast, 1975, as cited by EURAR, 2006). Rats received TBBPA (0, 0.3, 3, 30 or 100 mg/kg bw/day) in diet. On day 90, seven animals/sex were sacrificed from each dose group and the following tissue specimens were removed from two animals for bromine analysis: liver, kidney, skeletal muscle, fat and serum. In addition, from the 0 and 3 mg/kg bw/day groups a further 2 rats/sex were sacrificed on each of days 10, 20, 30 and 60, and specimens were collected from the same tissues as above for bromine analysis. Tissue analysis indicated that there were no significant differences in bromine concentrations between the treated groups and the controls, suggesting that there was no accumulation of TBBPA in tissues.

When ^{14}C-TBBPA (either 250 mg/kg bw or 1000 mg/kg bw in olive oil) was administered intraperitoneally (i.p.), the highest levels were retained in fat, muscle, liver, sciatic nerve and adrenals at 1 h (Szymanska et al., 2000; Szymanska et al., 2001). However, by 72 h significant amounts were found only in fat, muscle and red blood cells. Analysis of faeces indicated that about 10 % of radioactivity (administered dose being 250 mg/kg ^{14}C-TBBPA) is due to the metabolite tribromobisphenol A. Gas chromatography analysis indicated that the remainder of the radioactivity in the faeces was in the form of unchanged TBBPA. The authors suggested that gastrointestinal flora may have been responsible for the debromination of TBBPA to tribromobisphenol A. Metabolites in the urine were not identified.

In a poorly reported study, the distribution of TBBPA was determined in both the maternal and foetal mouse tissue (Sundberg, 2004). Pregnant C57 B1 mice were sacrificed on gestation days 14 or 17, 1.5 – 72 h following intravenous administration of ^{14}C-TBBPA in 20 µL DMSO. The total number of animals utilised in the study is unclear. The sacrificed mice were subjected to tape-section autoradiography. While the report did not present any quantitative data, it provided some comments on the distribution of these substances. In the dams, ^{14}C-TBBPA was present in liver tissue at all post-injection times, and also in the uterine luminal fluid and yolk sac epithelium. There was no accumulation in the corpora lutea in the ovaries. Higher relative concentrations of ^{14}C-TBBPA were found in the foetuses than in most maternal tissues. Penetration of ^{14}C-TBBPA to maternal and foetal brains was low.

These results show that TBBPA is initially widely distributed in the body. It has been detected in the lung, kidney, liver, intestines, skeletal muscle, fat, blood, uterine luminal fluid, yolk sac epithelium and the carcass, while in a less reliable study, detection in sciatic nerve and adrenals was also reported. However, by 72 h post treatment no significant retention of TBBPA was observed. While TBBPA was distributed to the foetus of pregnant rats, less than 0.83 % of radiolabelled TBPPA was retained in maternal or foetal tissues four days after the final dose was administered. Overall, it is concluded that the accumulation of TBBPA in tissues is low.

12.1.3 Metabolism

Three metabolites of TBBPA were identified in bile samples 24 h following administration of low amounts of TBBPA in rats (Hakk, 2000). The three metabolites, a diglucuronide ether conjugate of TBBPA, a glucuronic acid/sulfate ester diconjugate of TBBPA and a monoglucuronic acid conjugate of TBBPA, were found in the following proportions as percentages of the administered dose: 12.4 %, 6.9 % and 11.7 %, respectively. No

metabolite of TBBPA could be detected by high performance liquid chromatography (HPLC) in the faeces. The authors of the study suggested that the delay in faecal excretion is possibly due to TBBPA undergoing enterohepatic circulation (Hakk, 2000; 2003). This would involve metabolism by the liver and excretion via the bile, and then deconjugation by intestinal microflora to the parent TBBPA.

In another in vivo study, 6 male SD rats were administered a single oral dose of TBBPA (300 mg/kg bw in corn oil) by gavage (Schauer, 2006). Urine samples were collected at 6 to 12 h intervals and faeces samples were collected 12 hourly. Blood samples were taken at predetermined time points at 3 to 12 h intervals, and analysed by LC/MS-MS. The metabolites, TBBPA-sulfate and TBBPA-glucuronide, were present in the blood. The concentration of TBBPA-sulfate peaked at approximately 700 μMol, 6 h post dosing, and concentrations of TBBPA-glucuronide peaked at 25 μMol, 3 h post dosing. In the urine, TBBPA-sulfate was the predominant metabolite at 0.8 μmol in urine collected between 12 – 24 h post-dose. In faeces, in addition to TBBPA-sulfate and TBBPA-glucuronide, traces of tribromobisphenol A and tribromobisphenol A-glucuronide were seen.

In vitro metabolism of TBBPA was studied using human and rat liver S9 fractions and microsomes (Zalko, 2006). The purchased human liver S9 fractions and microsomes were from pools of 10 males and 10 females. Rat liver sub-cellular fractions were obtained from Wistar rats (3 males and 3 females). ^{14}C-TBBPA was diluted with unlabelled TBBPA (20, 50, 100 or 200 μM) and was incubated for 2 h at 37 °C with 2 mg microsomal protein or 7 mg S9 protein. Qualitatively there were no differences between radio-HPLC profiles obtained with 20 μM or higher concentrations of unlabelled TBBPA. Furthermore, there were no sex or species difference in the HPLC profiles of metabolites. TBBPA mono-glucuronide and glutathione conjugate of 2,6-dibromo-4-isopropylphenol were only present with S9 fraction. Major additional metabolites included hydroxylated isomers of 2,6-dibromo-4-isopropylphenol; 2,6-dibromo-4-(2′,6′-dibromo-1′-hydroxycumyl)-phenoxy-3″,5″-dibromo-4″-hydroxybenzene and 2,6-dibromo-4-(2′,6′-dibromo-1′-hydroxycumyl)-phenoxy-2″-hydroxy-3″-bromo-5″-(2′,6′-dibromo-1′-hydroxycumyl)benzene.

These studies indicate that majority of the administered dose is excreted as the unchanged parent TBBPA molecule in the faeces. In some studies, tribromobisphenol A and tribromobisphenol A-glucuronide were also detected in the faeces. The following metabolites were present in the bile: diglucuronide ester conjugate of TBBPA, glucuronic acid/sulfate ester diconjugate of TBBPA and monoglucuronic acid conjugate of TBBPA.

12.1.4 Elimination and Excretion

In the Hakk et al., (2000) study, described earlier, urine, bile (from bile-duct cannulated rats) and faeces were collected from rats at 24 h intervals for 72 h. In the bile duct cannulated rat, 71 % of administered ^{14}C-TBBPA was excreted in bile and 26 % was excreted in faeces over the 72 h period. In the first 24 h period biliary excretion dominated, with 48.4 % excreted in bile and only 6 % of administered dose excreted in faeces. In the 24 – 48 h and 48 – 72 h periods, 21 % and 1.9 %, and 15.3 % and 5 % were excreted in bile and faeces, respectively. In the intact rat a total of 91.7 % of administered dose was excreted in faeces over 72 h. The time course was 6.6 % within 24 h, 66 % during 24 – 48 h and 19.5 % during 48 – 72 h. In the bile-duct cannulated rats and intact rats, 0.3 % and 0.7 % of the administered dose was excreted in the urine, respectively. Of the proportion of TBBPA excreted in urine, 18 % of TBBPA and/or metabolites was associated with carrier proteins. The authors were not able to

further characterise the protein-bound TBBPA/ TBBPA metabolites given the lack of sensitivity of the methods utilised. The amount of radiolabelled TBBPA appearing as bound to protein in bile was low (less than 0.42 % of administered dose).

In the Kuester et al. (2007) study, following intravenous (i.v.) administration, the concentration-time profile for TBBPA in blood is consistent with a two-compartment model. The half-life for excretion in blood was: $t_{½}$ α = 5 min and $t_{½}$ β = 82 min. The systemic blood clearance (CL) was 2.44 mL/min. Following i.v. administration the predominant route of excretion was in faeces, with 73 % of the radioactivity eliminated within 24 h and another 7 % eliminated by 36 h. Urine excretion was less than 0.5 %. Following single oral bolus doses of 2, 20 or 200 mg/kg ^{14}C-TBBPA, 90 – 95 % of radioactivity was excreted in the faeces within 72 h. At all doses the elimination in urine was less than 1 %. A similar pattern of excretion was seen when 20 mg/kg bw/day ^{14}C-TBBPA was administered orally for 1, 5, or 10 d with faeces accounting for 82, 85 and 98 % of radioactivity, respectively. The radioactivity appearing in urine was negligible. In other experiment with oral administration of 20 mg/kg bw ^{14}C-TBBPA in 2 bile duct cannulated rats, 47 % and 51 % of the administered dose was excreted in the bile within 2 h.

Elimination of TBBPA from blood followed first order kinetics with an elimination half-life of 13 h (Schauer et al., 2006). Only trace concentrations of TBBPA were excreted in the urine. Greater than 80 % of the administered dose was excreted unchanged in the faeces with peak excretion at 24 h post dose.

In the Brady (1978) study, the total amount of TBBPA excreted in faeces in the 0 – 72 h period was 95 % of the administered dose. The maximum amount of TBBPA excreted in urine was 0.32 % and this occurred over the time period 48 – 72 h. The total amount of TBBPA excreted in urine over the 72 h period was 1.03 % of the administered dose. The half-life of TBBPA in blood was 19.9 h and the maximum half-life of TBBPA in any tissue was in fat (71 h).

In the Meerts et al. (1999) study much of the radioactivity (79.8 %) was excreted in the faeces within 48 h after the last dose on GD16. Less than 0.2 % of the administered radiolabelled TBBPA was excreted in urine.

Following i.p. administration of ^{14}C-TBBPA (250 mg/kg bw), 37 %, 61.5 % and 65.5 % ^{14}C-TBBPA was excreted in faeces at 24 h, 48 h, 72 h after administration, respectively (Szymanska et al., 2001). At the higher dose (1000 mg/kg bw), 25 %, 42.8 % and 51 % of the administered radioactivity was excreted in the faeces at these time points, respectively. At both doses approximately 0.3 % of radioactivity appeared in urine by 72 h. For the low dose group (i.e. 250 mg/kg bw), results from blood sampling gave the following amounts of administered dose (radioactivity): 1.8 % (24 h), 4.0 % (48 h) and 3.8 % (72 h). Blood was not analysed in the higher dose group.

In conclusion, TBBPA is excreted predominately in faeces, particularly via the bile, within the first 72 h of dosing. Only a small amount is excreted in urine. In the blood, TBBPA is eliminated quickly with a half-life of 20 h or less.

12.2 Effects on Laboratory Mammals and other Test Systems

In accordance with Australian Government policy of utilising international assessment data where appropriate, this assessment has utilised assessments carried out by the EU and the IPCS.

A comprehensive literature search was carried out for data published since year 2003 to ensure that studies published after the EU assessment of TBBPA were evaluated for relevance for inclusion. Studies that were not sighted but described in adequate detail in the EURAR on TBBPA (Part II - Human Health) are indicated with an asterisk (*) in this report. Primary sources of data were consulted where necessary and for critical studies.

12.2.1 Acute Toxicity

Acute Oral Toxicity

Acute studies on TBBPA conducted by the oral route in rats and mice are summarised in Table 23.

The Dow Chemical Company (1958a)* reported that a necropsy of rats orally exposed to a single dose of 1000 mg/kg bw TBBPA) indicated slight liver damage and questionable kidney damage. The study reported moderate liver and kidney damage with TBBPA doses of 2000 and 4000 mg/kg bw. These pathological findings are in contrast to those reported in other studies, including a limited study in rats conducted to GLP and current regulatory guidelines (Malloroy et al., 1981e), showing no significant pathological effects or toxic effects at similar or higher doses (median lethal dose (LD_{50}) >5000 mg/kg bw). In mice, the studies indicate a very low acute toxicity with a LD_{50} >10000 mg/kg bw.

Studies on the acute toxicity of TBBPA indicated it has low oral toxicity in rats and mice.

Table 23 – Summary of Acute Oral Studies

Species (Strain)	Dosage (Vehicle)	Observations	LD_{50} (mg/kg bw)	Reference
Rats (SD) 5/sex/group	5000 mg/kg bw (0.25 % methylcellulose)	No animals died and no signs of toxicity in 14 d observation period	>5000	Malloroy et al., 1981a; EURAR, 2006
Rats (Wistar) 5/sex/group	50000 mg/kg bw (0.25 % methylcellulose)	Three animals (sex not reported) died within 5 h	<50000	*Great Lakes Chemical Corporation, 2004

Species (Strain)	Dosage (Vehicle)	Observations	LD_{50} (mg/kg bw)	Reference
Rats (strain not reported) 2 females/group	250, 500, 1000, 2000 and 4000 mg/kg bw in corn oil	No animals died, moderate liver and kidney damage at 2 higher doses	>4000	*The Dow Chemical Company, 1958a
Rats (strain not reported)	Not reported	Not reported	>2000	Gustafsson & Wallen, 1988
Rat (CD(SD) 5/sex/group	0 and 2000 mg/kg bw	No deaths occurred in animals treated with 2000 mg/kg TBBPA	>2000	Sudo, 2001a
Mice (CD1) 5/sex/group	1000, 1585, 2512, 3980, 6308 and 10000 mg/kg bw (corn oil)	No deaths observed within the 14 d period	>10000	*International Research and Development Corporation, 1978a
Mice (Ness Ziona) 6 males/ group	2900, 3600, 4500, 5600 and 7000 mg/kg bw (polyethylene glycol)	No deaths observed within the 14 d period. No signs of toxicity were seen	>7000	*Israel Institute for Biological Research, 1978

Acute Dermal Toxicity

An acute dermal toxicity study, carried out according to GLP, was undertaken in New Zealand White rabbits (5 males and 5 females) (Malloroy et al., 1981a). A dose of 2000 mg/kg bw TBBPA moistened with physiological saline was applied under occlusive conditions to abraded skin for a period of 24 h. Slight erythema and oedema were observed in one male on day 1. There was no mortality and no other toxic effects were evident during the 14 d observation period. At autopsy no gross lesions were evident. The dermal LD_{50} for TBBPA was determined to be >2000 mg/kg bw.

In another study, TBBPA (1000, 2150, 4640 or 10000 mg/kg bw) was moistened with corn oil and applied semi-occlusively to the clipped abdominal skin of 4 albino rabbits (sex not reported) per group for 24 h (*Hill Top Research Inc., 1966). The abdominal skin of two animals per group was abraded prior to treatment. One animal with abraded skin in the 4640 mg/kg group and another animal with intact skin in the 1000 mg/kg group died, on days 6 and 13, respectively. No other deaths occurred during the 14 d observation period.

Since the mortality rates were not dose-dependent, these deaths were not considered to be treatment-related. In the two lower dose treatment groups, 6 of the 7 surviving animals gained body weight and in the two higher dose groups, 5 of the 7 surviving animals lost body weight. There was no indication whether the weight losses were biologically significant. No other information was reported in regards to toxicity or histopathology. The dermal LD_{50} was determined to be >10000 mg/kg bw.

In a brief study report, the backs of 10 female rabbits (strain not reported) were clipped and 200 mg/kg bw TBBPA was applied (*Leberco Laboratories, 1958b). There was no mention of whether the application site was occluded or whether a vehicle was used. On day 1 all animals showed erythema. However, by 48 h the skin appearance was normal. No other signs of toxicity were reported and no mortality occurred. In this study the dermal LD_{50} for TBBPA was determined to be >200 mg/kg bw.

Environmental Health Criteria 172 (EHC, 1995), reported an acute dermal study summary provided by the Great Lakes Corporation in 1986. The study was conducted in albino rabbits (sex and strain not reported). TBBPA (3160 mg/kg bw) was applied to the clipped, intact skin and left in contact for a period of 24 h. No animals died and no signs of toxicity or significant pathological lesions were evident. No other information was provided.

The above studies indicate a low acute dermal toxicity for TBBPA. An LD_{50} of >2000 mg/kg bw was determined from what was considered to be a well conducted and reported study (*Malloroy et al., 1981b).

Acute Inhalation Toxicity

In an acute inhalation study, rats (Wistar), mice (NMDI) and guinea pigs (strain not reported) were exposed (whole body) together (i.e. 5 males and 5 females for each species) in a stainless steel inhalation chamber for 8 h to an aerosol of TBBPA (0.5 mg/L) (International Bio-Research Laboratories Inc., 1967b). After exposure, animals were observed for 48 h and then sacrificed to determine pathological changes. No rationale was given for choosing this exposure concentration for the limit test. There was no mortality and no toxic effects were evident within the observation period of 48 h. No pathological lesions were found at necropsy. The median lethal concentration (LC_{50}) was determined to be >0.5 mg/L TBBPA for an 8 h exposure period in rats, mice and guinea pigs.

In an inhalation study, 10 male rats (Dublin strain) were exposed whole body to 1.3 mg/L TBBPA aerosol for 1 h in an inhalation chamber (*Hill Top Research Inc., 1966). TBBPA was aerosolised by bubbling the air intake through molten TBBPA. During the 14 d observation period no mortality occurred and no signs of toxicity were evident. No information was reported on whether necropsy was carried out. The LC_{50} was determined to be >1.3 mg/L TBBPA for a 1 h exposure period.

No information was given in either study as to the droplet size distribution.

A repeated-dose inhalation study in rats (5 animals/sex/group) exposed whole body to 0, 2, 6 or 18 mg/L TBBPA for 4 h/day and 5 days/week for 2 weeks found no mortality or systemic toxic effects (*International Research and Development Corporation, 1975). Hence, the LC_{50} is >18 mg/L TBBPA for a 4 h exposure period.

Evidence from acute and short-term inhalation studies indicate TBBPA has a low acute inhalation toxicity in rats and mice with a 4hr LC_{50} of >18 mg/L in rats.

Intraperitoneal Studies

While TBBPA was dosed via the i.p. route in two rat studies to determine the effects on biochemical parameters (Szymanska, 1993) (Szymanska, 2001), there are no acute intraperitoneal studies designed to establish a LD_{50} value.

In a poorly reported study, 4-6 male Wistar rats per group were i.p. treated at 500 – 1000 mg/kg TBBPA in sunflower oil (Szymanska, 1993). The authors stated that control animals were administered sunflower oil or no injections were given. No mortality was reported. Animals were sacrificed at 2, 4, 12, 24, 48, 72, and 120 h and liver and blood from heart were collected. Levels of triglycerides in serum, levels of glutathione and malondialdehyde in the liver, and activities of glutamate-pyruvate transaminase (alanine transaminase) and L-γ-glutamyl-transferase were determined. No adverse findings were reported.

Outbred IMP:Wist rats (60 females) were administered ^{14}C-TBBPA in olive oil at 250 mg/kg bw and 1000 mg/kg bw via the i.p. route (Szymanska, 2001). After dosing, four animals were sacrificed at 1, 4, 12, 24, 48 and 72 hours. No mortality was reported. At 250 mg/kg bw TBBPA caused a significant increase in hepatic glutathione concentration at 4 h after dosing. However, this effect was not dose-dependent. At 250 mg/kg bw TBBPA, the haem oxygenase activity was significantly increased at 24 h, and at 1000 mg/kg bw TBBPA there was a significant increase at both 12 and 24 h. For both doses, haem oxygenase activity returned to control levels by 48 h. While the haem oxygenase activity was significantly increased at 24 h at both doses, the effect does not appear to be dose dependent. The authors reported that there were no treatment related effects on γ-glutamyltransferase activity in serum, protein content in microsomes or total content of hepatic cytochrome P450, although data were not presented.

12.2.2 Skin and Eye Irritation

Skin Irritation

TBBPA was at most a slight skin irritant. In one skin irritation study, TBBPA (500 mg) was moistened with physiological saline and applied occlusively to two abraded and two intact sites for 24 h on 3 male and 3 female New Zealand White rabbits (Malloroy et al., 1981c). No irritation was observed when the sites were scored at 24 h and 72 h post-application. The study was conducted in compliance with GLP.

TBBPA (500 mg in 0.5 mL of corn oil) was applied occlusively to both intact and abraded skin on the back of 6 albino rabbits for 24 h (*Hill Top Research Inc., 1966). Test sites were scored for erythema and oedema at 24 h and 72 h post-application. No evidence of irritation was observed.

In another study, the dorsolateral trunk of albino rabbits was clipped and TBBPA (500 mg) was applied occlusively to 3 animals with intact skin and a further 3 animals with abraded skin for 24 h (*Israel Institute for Biological Research, 1978). At 24 h and 72 h post-application, the test sites were scored according to the Draize scale. No irritation was observed in animals with intact skin. In animals with abraded skin, the mean score for

oedema was 1 and 0 at 24 h and 72 h, respectively. In the same animals the mean score for erythema was 0 and 0.3 at 24 h and 72 h, respectively.

TBBPA (undiluted) was applied to intact and abraded abdominal skin of a single rabbit (sex and strain not specified) in a briefly reported range-finding study (*Biochemical Research Laboratory, 1958). In a second rabbit, TBBPA (10 % solution in Dowanol DPM) was applied to intact and abraded abdominal skin, and intact skin on the ear. The test material was applied on 3 consecutive days when tested on abraded sites and on 10 consecutive days when tested on intact sites. No other information was reported on the test method. The study reported no irritant effects with undiluted TBBPA on either intact or abraded skin. While the study concluded that essentially no irritation was seen with the 10 % TBBPA solution, "erratic" hyperaemia occurred during week 1 and exfoliation during week 2 when the chemical applied to the intact ear skin. Ear skin returned to normal within 14 days. Slight to moderate hyperaemia and exfoliation also occurred when the 10 % TBBPA solution was applied to the intact abdominal skin.

In a 3-week dermal study in New Zealand White rabbits (described in detail in Section 12.2.3), there was no mortality, and there were no changes in behaviour or appearance as a result of treatment with TBBPA up to a dose of 2500 mg/kg bw/day. At 100 mg/kg bw/day, one animal with intact skin and one animal with abraded skin had very slight erythema for 4 and 5 days, respectively, starting from day 3 of the study. At 500 mg/kg bw/day, very slight erythema was seen in all animals. This slight reaction appeared around day 2 and lasted for less than 3 days. At 2500 mg/kg bw/day a very slight erythema was observed in 6 of the 8 rabbits in the group. This effect was persistent for "several days" in 2 animals and for 10 days in 1 animal.

Eye Irritation

TBBPA is a slight eye irritant. In an eye irritation study (Malloroy et al., 1981d), TBBPA (100 mg) was applied to the conjunctival sac of the right eye of 3 male and 3 female New Zealand White rabbits. The untreated left eye was used as a control. At 1 h post-application slight redness (grade 1) was observed in 4 rabbits. No signs of ocular irritation was observed at 24 h post-application.

TBBPA (100 mg) was applied to one eye of 6 male albino rabbits (*Israel Institute for Biological Research, 1978). After application, the eyes were examined at 24 h, 48 h, 72 h and 7 days. Slight lacrimation and conjunctival erythema were observed soon after application. However, the effects disappeared completely by 24 h. At 48 h the mean score for conjunctival redness was 0.17, conjunctival chemosis was 0.3 and iridial irritation was 0.17. At 72 h the mean score for conjunctival chemosis and iridial irritation was 0.17. At day 7 all scores were 0.

In another study, TBBPA (3 mg) was applied to the conjunctival sac of one eye of 3 New Zealand White rabbits (International Bio-Research Inc., 1967a). No signs of conjunctival, corneal or iridial irritation were found when the animals were examined at 5 min, 1 h, 4 h and daily for 7 days post application.

Irritation of the Respiratory Tract

In a 14-day inhalation study, four groups of rats (5 males and 5 females/ group; strain not reported) were exposed whole body to 0, 2, 6 or 18 mg/L TBBPA for 4 h/day, 5 days/week for 2 weeks (*International Research and Development Corporation, 1975). In the 2 mg/L treatment group approximately 50 % of the animals had occasional excessive salivation. In the 6 and 18 mg/L treatment groups, excessive salivation was observed in all animals, and nasal discharge and excessive lacrimation were observed in most animals. These effects were dose-dependent. No other toxicological effects or histopathological changes indicative of respiratory tract irritation were evident. Given the lack of chemical reactivity of the TBBPA molecule, and in the absence of similar findings in the acute inhalation studies (Section 12.2.1), the observed effects are most likely due to the mechanical irritation from the high dust concentrations used in the study. Therefore, TBBPA is not considered to be an irritant to the respiratory system.

Skin Sensitisation

In a skin sensitisation study conducted, 500 mg of TBBPA was moistened with ethanol and applied occlusively to the shaved flanks of 10 female guinea pigs (Hartley strain) (Malloroy et al., 1981e). For the positive controls, 10 additional animals were administered 2,4-dinitrochlorobenzene (1 % in 80 % ethanol). There was no mention of the use of a negative control group. A total of 9 induction applications (250 mg, applied every other day, 3 times per week for 3 weeks) were made to three application sites on the test area on a rotating basis. Each induction exposure lasted for 6 h. Two weeks after the last induction exposure animals were challenged with TBBPA (500 mg) or 2,4-dinitrochlorobenzene (1 %). At the same time a challenge patch was also applied to a site (exact location of the site not reported) distinct from the induction test area. A second challenge was made 48 h after the first challenge. At the conclusion of each challenge observations were made at 7, 24 and 48 h. Positive responses were reported at the first and second challenge with 2,4-dinitrochlorobenzene (positive control). At induction and subsequent challenges with TBBPA, no reactions were seen.

In one study, TBBPA (0.1 % in 0.9 % sodium chloride solution) was administered intradermally every other day for a total of 10 induction doses into the shaved right flank of 8 male albino guinea pigs (*International Research and Development Corporation, 1978b)(EURAR, 2006). The positive control (0.1 % 2,4-dinitrochlorobenzene in 0.9 % sodium chloride solution) was administered to 4 guinea pigs. A separate negative control group was not utilised, instead 0.9 % sodium chloride solution was intradermally injected into the shaved left flank of all 12 test animals. At 24 and 48 h post administration the sites were scored for signs of erythema and oedema. Two weeks after the last induction dose, a challenge dose (concentration unclear) was intradermally administered. The test substance was considered to be a sensitiser in an animal where the score at challenge was greater than the average score obtained for the 10 induction doses. Only three TBBPA-treated animals had a mild reaction at induction. No reactions were observed at 24 and 48 h post-challenge with TBBPA. No skin reactions were seen with 0.9 % sodium chloride solution at the "negative control" sites.

Overall, the available animal studies suggest that TBBPA is not a skin sensitiser.

Chloracnegenic Activity

TBBPA (0.5, 5, or 50 % in a polyurethane vehicle) was applied at a volume of 0.1 mL to one ear of each rabbit (New Zealand White; 2 males and 2 females/group) once daily for 5 d per week for 4 weeks (Naismith, 1981). The control was 0.1 mL of vehicle applied to the contralateral ear. Observations were made soon after the first application and on days 7, 14, 21 and 28 post-application. A slight comedogenic response (grade 1) was found with one rabbit at the 0.5 % TBBPA dose on day 7. No positive responses were found at higher doses and no gross lesions were observed at any dose at necropsy. These results indicate that TBBPA is not a comedolytic agent.

12.2.3 Repeated Dose Toxicity

Oral Toxicity

Short term studies

The nephrotic potential and toxicokinetics of TBBPA in vivo following single or repeat-dose oral exposure in SD rats were investigated (Kang et al., (2009). Two groups of rats were given TBBPA at 0 (control), 200, 500 or 1000 mg/kg bw doses via oral administration (in corn oil) once (first group) or once daily for 14 days (second group). In the first group, blood and urine samples were collected at several time points between 0.5-30 hours and 6-81 hours, respectively. In the second group, blood samples were obtained every 24 hours after daily dosing and urine samples were collected for 24 hours on each day.

No changes in haematological parameters were observed from single exposure to TBBPA of up to 1000 mg/kg bw. A significant increase in the renal marker of lipid peroxidation, thiobarbituric acid-reactive substances (TBARS), was observed five hours after a single oral dose of 1000 mg/kg bw of TBBPA. In these animals, elevation of superoxide dismutase (SOD) was reported in animals at all dose levels. In the repeat-dose experiment, TBBPA did not affect the serum level of the enzymes tested or markers for oxidative stress in the kidney at all dose levels. In the toxicokinetics study, animals from both single and repeat-dose studies showed dose- and time-dependent increases of TBBPA in the urine. The half-life of TBBPA was between seven and nine hours.

A 14 day oral repeat dose study in male ICR mice (Tada et al., 2007) was conducted to assess TBBPA effects on the liver. Male mice (7 weeks old) were allocated to groups of 7-8 animals and dosed with TBBPA by oral gavage at 0, 350, 700 or 1400 mg/kg bw/day for 14 days.

No treatment-related clinical effects or mortality were observed during the 14 day dosing period. There were no significant differences in haematological parameters and serum biochemistry between control and treatment groups. Decreases in red blood cells (RBC), haemoglobin and total blood count (TBC) values were noted across all treated groups.

The absolute and relative spleen and liver weights all appeared to increase in a dose-dependent manner; however, only the mean absolute liver weight in the high dose group was significantly increased compared to controls.

Histopathology showed an increased incidence of hepatocyte focal necrosis in all treatment groups with incidence in the highest dose group significantly different from the control group. An increased incidence of hepatocyte enlargement was observed in all treatment groups and was significantly different in the middle dose group compared to the control group.

Inflammatory cell infiltration of the liver was significantly increased in all animals for all treatment groups above control frequencies. Although effects were also observed in the kidneys (dilation of renal tubules, cysts and atrophy/necrosis/regeneration of renal tubules) and pancreas (increase of secretory granules) at slightly increased frequencies across treatment groups, these were not significantly different from control.

While a clear dose-response relationship was not observed for enlargement and focal necrosis of hepatocytes in treatment groups, inflammatory cell filtration in the liver appears to be treatment-related. A no observed adverse effect level (NOAEL) was not established in this study.

28-day studies

In a 28-day repeat dose toxicity study, conducted in Wistar rats (Van der Ven et al., 2008), TBBPA was well tolerated and appeared to be of low general toxicity. Groups of rats (10/sex/dose) were fed nominal doses of 0, 30, 100 or 300 mg/kg bw/day TBBPA in their normal diets. Rats were observed during the treatment phase, and at the end of the exposure period (28 days), necropsies were carried out on all rats for organ weights and other analyses.

There were no effects on food intake or body weight in treated rats. Liver concentrations of TBBPA increased in a dose-dependent way. Plasma concentrations of TBBPA, and its two metabolites, TBBPA-glucuronide and TBBPA-sulfate were higher and correlated well with doses in males, although not in females due to incongruity in the 300 mg/kg bw/day dose group. There were no dose-related effects on any organ weights.

Plasma thyroxine (T_4) was decreased significantly and plasma triiodothyronine (T_3) was increased in both sexes of treated rats, although no TBBPA-induced histopathological changes were noted in the thyroid, based on follicle size and cell activation (cell and nuclear hypertrophy and cell vacuolization).

The high correlation between external dose and concentrations of TBBPA and/or its metabolites in the liver and in the plasma confirms the bioavailability of the compound. The increases of liver concentrations appeared to level off above doses of 100 mg/kg bw/day, suggesting saturation of absorption and/or increased elimination. The presence of TBBPA in control animals, albeit at low concentrations, suggests background exposure through the control diet or from other ambient sources.

In a study to investigate the effect of TBBPA on kidney function, female Wistar rats were treated with 10, 50, 250 mg/kg bw/day of TBBPA by gavage for 7, 14, 21 and 28 days (number of animals per treatment group not stated) (Frydrych and Szymanska, 2001). Control rats were given sunflower oil (vehicle). During the 24 hours after the administration of the last dose, the animals were placed in metabolism cages and urine samples were collected. Rats were sacrificed at 7,14, 21 and 28 days and kidneys and blood were collected. Creatinine and urea concentrations in the serum, the level of glutathione in the kidneys, concentration of urea and protein in the urine and number of epithelial cells in the urine (Addis count) were determined. No dose related or toxicologically significant effects were noted.

In a study considered to be poorly reported, TBBPA (0, 10, 30, 100, 300 or 1000 mg/kg bw/day in DMSO) was administered daily by gavage to 3 male SD rats per dose group for 4 weeks in the "high dose" experiments (Sato, 1996). In addition, TBBPA (0, 0.1, 0.3, 1, 3 or 10

mg/kg bw/day in DMSO) was administered daily by gavage to 3 male rats per dose group for 4 weeks in the "low dose" experiments. Body weight was measured daily and blood was taken at 2-4 d intervals. At the end of the treatment period rats were sacrificed and whole blood was collected.

There was no mortality during treatment. In the "high dose" groups (10-1000 mg/kg bw/day) the body weight gain was significantly reduced (by 12-25 %), with a dose-response relationship, in all treatment groups compared to the controls. In the "low dose" experiments, the body weight gain was significantly reduced in the 0.3, 1 and 10 mg/kg bw/day dose groups, but not in the 0.1 and 3 mg/kg bw/day groups. Given that a decrease in food and water consumption was not observed even at the 1000 mg/kg bw/day dose group, the authors suggested a possible decrease in the efficiency of nutrition intake or organ injury.

There was significant reduction in clotting time at 10 mg/kg bw/day TBBPA and higher doses. Relative kidney weights were significantly increased at 10, 30 and 300 mg/kg bw/day, but without a dose-response relationship. Relative liver weight was slightly but significantly reduced in only the highest dose group. Given the reduction in relative liver weights were less than 10 % compared with the controls this is not considered to be of biological significance. No other gross or histopathological changes were reported. The only toxicologically relevant effects found in this study were the reduction in body weight gain and reduction in clotting times. However, these observations are not supported by other well-conducted studies (including a study done according to OECD guidelines and GLP) described below. A NOAEL of 1000 mg/kg bw/day was established in this study.

90-day studies

In a 90-day study, SD rats (9 per dose group) received TBBPA (0, 0.3, 3, 30 or 100 mg/kg bw/day) in diet (Quast, 1975*). The 0 and 3 mg/kg bw/day groups included 12 additional males and 21 females as a recovery group. Blood and urine samples were collected from the control group and the highest dose group on day 86. On day 90, seven males and females from each dose group were sacrificed and histopathological examinations were conducted on a range of tissues.

No mortality related to treatment was observed. There were no changes in appearance or demeanour, and there were no significant changes in body weights or food consumption in treated animals compared to the controls. There were no gross or histopathological changes. Significantly reduced serum glutamic pyruvic transaminase (alanine transaminase) was observed in the females of the highest dose group. In the absence of corresponding histopathological changes, such as in the liver, or clinical symptoms, this is not considered to be of toxicological relevance. Overall, no adverse toxicological effects were found up to the highest dose tested. A NOAEL of 100 mg/kg bw/day TBBPA was assigned based on no adverse effects seen at the highest dose tested.

In a 90-day study conducted according to OECD TG 408 and GLP, the toxicity of TBBPA was investigated in CD [Crl: CD (SD) IGS BR] rats (Schroeder, 2002*, as cited by EURAR, 2006). The animals were administered 100, 300 or 1000 mg/kg bw/day TBBPA or vehicle (corn oil) by gavage daily. Five animals per sex from the control group and the highest dose group were observed over a six-week recovery period. A detailed functional observational battery (FOB) was conducted before treatment and during week 12. Motor activity was evaluated

during week 12. Ophthalmoscopic examinations were conducted before treatment and during week 13, and again at the conclusion of the recovery period. Haematological, clinical chemistry, urinalysis, organ weight and pathological examinations were also conducted.

While several mortalities occurred during the study, these were scattered among the groups and were considered to be due to injuries from the gavage procedure and not related to TBBPA toxicity. There were no treatment-related clinical or functional observations, neurobehavioural changes, ophthalmological changes or body-weight changes in animals at any dose. The platelet count in males at 1000 mg/kg bw/day was statistically significantly lower than the controls by 17 %; however, this effect was transient with the platelet counts being similar to the controls by the end of the recovery period. Platelet counts in treated females were comparable to controls. Bilirubin values were significantly elevated by 2-3-fold in the two highest dose treated groups compared to the controls. Serum alkaline phosphatase levels were also statistically significantly elevated by 1.7-fold in females at 1000 mg/kg bw/day compared to the controls. The elevated bilirubin values and serum alkaline phosphatase levels returned to control values at the end of the recovery period.

The absolute spleen weights in the males were statistically significantly lower in the 300 and 1000 mg/kg bw/day dose groups (weight decrease of 15 % and 18 %, respectively) than the controls at the end of the treatment period. The absolute spleen weights after the recovery period were similar to the controls. No other treatment-related organ weight changes or histopathological changes were observed.

In the absence of clear dose-response relationship, the transient decrease in platelet counts observed in males in the high dose group is not considered to be a treatment-related effect. The elevated bilirubin values and serum alkaline phosphatase levels were considered not to be toxicologically significant given that no histopathological effects were seen in the liver or any other tissue and as these were fully reversible. Furthermore, other liver enzymes such as serum aspartate aminotransferase (aspartate transaminase) and serum alanine aminotransferase (alanine transaminase) were within control values. Overall, no adverse toxicological effects were observed up to a concentration of 1000 mg/kg bw/day TBBPA. A NOAEL of 1000 mg/kg bw/day TBBPA was assigned based on no adverse effects seen at the highest dose tested.

A 90-day study was conducted to evaluate the toxicity from repeated exposure to TBBPA in rats and to determine a dose range for a two year study (NTP, 2014). Groups of F344/NTac rats (10/sex/dose) were dosed with TBBPA in corn oil by gavage, 5 days per week, at 0, 10, 50, 100, 500 or 1000 mg/kg bw for 14 weeks. Rats in the control group received 10 mL/kg of vehicle. Body weights were recorded weekly and at the start and end of the study.

No mortality or clinical signs related to treatment were observed during the study. Final body weights between treatment and control groups were also similar. Consistent, progressive, and dose-related decreases in total T_4 concentrations occurred in 500 and 1000 mg/kg males and females, but less so in the 100 mg/kg group. On day 4, T_4 was decreased by approximately 30 % at 1000 mg/kg bw/day; by week 14, it was decreased by approximately 45 %. The decreases in T_4 were not accompanied by decreases in T_3 concentrations or increases in thyroid stimulating hormone (TSH) concentrations.

Haematologic findings indicated a small (<10 %) but significant decrease in erythron parameters (haematocrit, haemoglobin concentrations and erythrocyte counts) on day 23 in

500 mg/kg bw and 1000 mg/kg bw group males. This effect was less pronounced in the females. During week 14, the effect was reduced to ≤5 % decrease in erythron parameters at 500 mg/kg bw/day and 1000 mg/kg bw/day.

Serum concentrations of total bile acids were significantly increased (two fold or more) in the 500 and 1000 mg/kg bw treatment groups on day 4. An increase in this parameter is indicative of hepatic injury and cholestasis; however, as the same effect was not observed on day 23 or in week 14. Another marker of cholestasis, alkaline phosphatase, showed little to no change on day 4. The authors concluded that the transient increases in bile acid concentrations were probably not related to a cholestatic event, but rather a transient effect on hepatic function involving bile acid metabolism.

At week 14, serum alanine aminotransferase and sorbitol dehydrogenase, markers of hepatocellular injury, were decreased in male and female rats at 100 mg/kg bw/day or greater. Decreases in cytochrome P450 enzyme and UDP-glucuronosyl transferase (UDPGT) activities were seen on day 23 and at week 14 in all treated rats; however, no liver enzyme changes were considered to be biologically significant with the exception of 7-pentoxyresorufin-*O*-dealkylase (PROD) activity, which increased 4 to 23 fold over the controls in 500 and 1000 mg/kg bw groups, respectively at week 14. The increased levels indicated some disturbance of liver function, but this was not accompanied by treatment-related liver lesions. Absolute and relative liver weights were significantly increased compared to controls at 500 mg/kg bw (~11 % and ~8 % relative liver weight increases in males and females, respectively) and 1000 mg/kg bw (~14 % and ~15 % relative liver weight increases in males and females, respectively). There were significant decreases in absolute and relative spleen weights in 500 mg/kg bw (~10 % decrease in relative spleen weight) and 1000 mg/kg bw (~8 % decrease in relative spleen weight) males, although no treatment-related histopathological lesions were observed.

In an oral repeat dose study in mice (NTP, 2014), groups of 10 male and 10 female B6C3F1/N mice (7-8 weeks old) were administered TBBPA in corn oil by oral gavage at doses of 0, 10, 50,100, 500 or 1000 mg/kg bw, 5 days per week for 14 weeks. The concurrent control group received 10 mL/kg bw corn oil. Body weights were recorded weekly and at the start and end of the study.

All mice survived until study completion with mean body weights similar to that of control groups. Administration of TBBPA did not result in any observed clinical findings. No clinical findings related to TBBPA administration were observed and no changes in haematology parameters appeared to be attributable to TBBPA administration. At the end of the study, liver acetanilide-4-hydroxylase, 7-ethoxyresorufin-*O*-deethylase (EROD) and PROD activities were significantly lower (30 % to 40 %) in 500 and 1000 mg/kg bw males compared to controls. In females, only PROD activity decreased significantly (30 %) in the 1000 mg/kg bw group. Absolute and relative liver weights were significantly increased in 500 mg/kg males and 1000 mg/kg males and females; absolute and relative spleen weights in 1000 mg/kg males were also significantly increased. Absolute and relative kidney weights were significantly decreased in 1000 mg/kg males.

There were no treatment-related lesions apart from significant increases of renal tubule cytoplasmic alteration (minimal/mild grade) in male mice at 500 and 1000 mg/kg bw. The severity of the lesion in the 1000 mg/kg group was greater than that in the 500 mg/kg group. Renal tubule cytoplasmic alteration was characterised by a decrease or absence of the

normal vacuoles present in the cortical proximal tubules. Based on organ weight changes and enzymatic effects, the NOAEL for this study was determined to be 100 mg/kg bw/day.

In a 13-week oral exposure study (Osimitz et al., 2016), male and female CD rats (10/sex/group) were administered 0, 100, 300, or 1000 mg/kg bw/day TBBPA by gavage, daily for 13 weeks. Recovery groups (6 weeks) for control and 1000 mg/kg bw/day were also included. TBBPA treatment resulted in no marked effect on mortality, clinical signs, body or organ weights, food consumption, histopathology, urinalysis, ophthalmology, neurological outcomes in a functional observation battery, motor activity, serum thyroid stimulating hormone, serum T_3, or other serum chemistry. Although differences were observed for bilirubin and alkaline phosphatase, the observed alterations were within the normal range and were considered neither biologically or toxicologically meaningful. The single thyroid-related parameter affected by TBBPA was a reduction in serum T_4 levels. The NOAEL was at least 1000 mg/kg/day, the highest dose tested.

In a one-generation reproduction study in rats, described in detail in the Reproductive Toxicity Section (Van der Ven et al., 2008), 0, 3, 10, 30, 100, 300, 1000, or 3000 mg/kg bw/day TBBPA was administered in diet to male and female Wistar rats from 70 days and 14 days prior to mating, respectively, and in females continued throughout gestation, lactation, and after weaning of the offspring.

Food intake was temporarily reduced in the parental (P0) animals in the early weeks of exposure to high doses in both sexes. The reduced food intake was associated with reduced body weight of P0 females before mating. In liver tissue of treated animals, there was a dose-dependent increase of TBBPA concentrations, with averages of around 25 ng TBBPA per g wet weight in top dose males and females. The concentrations of TBBPA, TBBPA-sulfate and TBBPA-glucuronide in the plasma also increased with dose in all dose groups. Plasma concentrations of TBBPA and its metabolites were higher in males than in females in all other dose groups. For instance, respective average concentrations of these three analytes in the highest dose group were 94.2, 10.7, and 4.3 nmol/ml in males and 23.9, 4.8, and 4.0 nmol/mL in females. Liver concentrations, were similar in males and females.

In males there was a significant dose-dependent increase in liver weight; although the maximum increase was only 11 %. There were no exposure-related histopathological changes in the liver or any of the assessed organs in the treated animals. There were no TBBPA-related histopathological changes in the thyroid, based on follicle size and cell activation (cell and nuclear hypertrophy and cell vacuolization), although plasma T_4 was decreased in both sexes and plasma T_3 was increased in females. No changes were observed in the histology of the pituitary, and specific immunohistochemistry showed no apparent change in count of immunopositive cells or of immunostaining intensity in thyrotroph cells for TSH between the control and the two highest dose groups tested. A NOAEL was not established in this study.

Repeated dose Dermal Toxicity

In a 3-week dermal repeated-dose study, TBBPA (0, 100, 500 or 2500 mg/kg bw/day as a paste in 0.9 % physiological saline) was applied 6 h per day for 5 days/week to the clipped backs of New Zealand White rabbits (4 males and 4 females/group) (International Research and Development Corporation, 1979). The skin of 2 males and 2 females from each dose group was abraded twice each week. At 100 mg/kg bw/day, one animal with intact skin and

one animal with abraded skin had very slight erythema for 4 and 5 days, respectively, starting from day 3 of the study. At 500 mg/kg bw/day, very slight erythema was seen in all animals. This slight reaction appeared around day 2 and lasted for less than 3 days. At 2500 mg/kg bw/day, very slight erythema was observed in 6 of the 8 rabbits in the group. This effect was persistent for "several days" in 2 animals and for 10 days in 1 animal. Overall, no adverse toxicological effects were seen when TBBPA was applied dermally up to a dose of 2500 mg/kg bw/day. A NOAEL of more than 2500 mg/kg bw/day was established for dermal effects of TBBPA.

Repeated Dose Inhalational Toxicity

In a 14-day inhalation study, four groups of rats (5 males and 5 females per group; strain not reported) were exposed whole body to 0, 2, 6 or 18 mg/L TBBPA for 4 h/day, 5 days/week for 2 weeks (*International Research and Development Corporation, 1975). At the conclusion of the exposure period, blood and urine samples were taken from animals in the 6 and 18 mg/L treatment groups and from the control group. All animals were sacrificed, and tissues from animals in the 6 and 18 mg/L treatment groups and the control group were subjected to histopathological examination.

Salivation, nasal discharge and lacrimation were observed in all animals. These irritation effects are most likely due to mechanical irritation from high dust concentrations used in the study.

There was no animal mortality during the study and no changes in body weight gain, food consumption, biochemical and haematological parameters or urinalysis. A statistically significant decrease in the relative liver weights was observed in the females with relative liver weights being 84 %, 82 % and 83 % of control values in the 2, 6 and 18 mg/L TBBPA treated groups, respectively. However, this effect was not considered to be treatment-related given that it was not dose-dependent. No treatment-related organ weight changes or lesions were observed.

This study indicated that there were no systemic toxic effects in rats following repeated inhalation exposure to concentrations of TBBPA as high as 18 mg/L. Based on the lack of effects at the highest dose tested, a systemic no observed adverse effect concentration (NOAEC) of 18 mg/L was assigned. Given the lack of chemical reactivity of the TBBPA molecule, local irritant effects are considered to be due to mechanical irritation from high dust concentrations used in the study.

12.2.4 Genotoxicity

In vitro studies

Bacterial reverse mutation assays

TBBPA was tested for mutagenicity in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and Escherichia coli WP2 uvrA with and without metabolic activation from liver S9 fraction from phenobarbital and 5,6-benzoflavone-induced rats (Shibuya, 2001). Without metabolic activation, TBBPA was tested up to 156 μg/plate with TA1537, up to 625 μg/plate with TA1535, and over 2500 μg/plate with other strains. With metabolic activation, TBBPA was tested up to 313 μg/plate with TA1537 and up to 5000 μg/plate with other strains.

Cytotoxicity was observed at 156 μg/plate with TA1537, and at 313 μg/plate with TA1535 in experiments without metabolic activation, and at 156 μg/plate with TA1537 with metabolic activation. Vehicle and positive controls were conducted in the absence and presence of metabolic activation and gave expected results. TBBPA did not cause an increase in mutation frequency in any strain with and without metabolic activation.

In another study, TBBPA was tested for mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 in the absence and presence of metabolic activation with Aroclor 1254-induced rat and hamster liver S9 fraction (Mortelmans, 1986). TBBPA was tested up to 10000 μg/plate in dimethyl sulfoxide (DMSO). Cytotoxicity was not evident; however, precipitation occurred at concentrations of 1000 μg/plate and higher. Vehicle and positive controls were conducted in the absence and presence of metabolic activation. TBBPA did not cause an increase in mutation frequency in any strain with and without metabolic activation.

TBBPA (up to1000 μg/plate) was tested for mutagenic activity in *S. typhimurium* strains TA92, TA98, TA100, TA1535, TA1537 and TA1538 both in the presence and absence of metabolic activation (The Dow Chemical Company, 1958b). TBBPA (0.01 % and 0.0075 %) was also tested in the yeast strain *Saccharomyces cerevisiae* D3 with and without metabolic activation. Positive and vehicle controls were also tested. While no increase in the number of revertant colonies per plate was observed with TBBPA in both the bacterial and yeast assays, a decrease in the colonies was observed at the highest concentrations, suggesting cytotoxicity.

A mutagenicity assay was conducted in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation with liver S9 fraction from Aroclor 1254-induced rats (Curren, 1981). TBBPA was tested up to 500 μg/plate in DMSO. Appropriate positive, negative and vehicle controls were undertaken. TBBPA did not cause an increase in mutation frequency in any strain with and without metabolic activation.

TBBPA (1 – 100 μg/plate in DMSO) gave negative results in a briefly reported Ames test in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537, with and without metabolic activation (*Israel Institute for Biological Research, 1978).

A genotoxicity study was undertaken in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and S. cerevisiae strain D4 (Brusick, 1976 cited in EHC, 1995). The assays were conducted out with and without metabolic activation with liver S9 fraction from Aroclor 1254-induced rats. TBBPA was tested up to 50 μg/plate in DMSO. Appropriate control tests were conducted. TBBPA gave negative results.

In another briefly reported study TBBPA (0.25 – 50 μg/plate in DMSO) was negative in an Ames test when tested in *S. typhimurium* strains TA92, TA98, TA100, TA1535, TA1537, TA1538 and S. cerevisiae strains D3 and D4, with and without metabolic activation (Litton Bionetics Inc., 1976).

Two independent tests were conducted to assess the mutagenicity of TBBPA (NTP, 2014). In one test, the protocol was performed as per Mortelmans et al., 1986. TBBPA (up to 10000 μg/plate) was incubated with *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 in either buffer or S9 fraction (from Aroclor 1254-induced rat and hamster liver). In the second test TBBPA up to 6000 μg/plate was incubated with *S. typhimurium* strains TA98 and TA100 and E. coli strain WP2 uvrA/pKM101 in either buffer or S9 fraction (from Aroclor 1254-induced rat and hamster liver). No mutagenic activity was observed in either of the tests.

In vivo clastogenicity

An in vitro chromosomal aberration test (reported in Japanese with an English summary) was conducted according to GLP and OECD TG 473 (Yamakage, 2001). The test was conducted in Chinese hamster lung cells. TBBPA was tested in the absence and presence of metabolic activation with liver S9 fraction from phenobarbital and 5,6-benzoflavone-induced rats. In the short-term exposure experiment, cells were treated for 6 h with TBBPA concentrations of up to 6.5 μg/mL in DMSO and in the continuous exposure experiment cells were treated for 24 h with TBBPA up to 60 μg/mL in DMSO in absence of S9 mix. In the presence of metabolic activation, cells were treated for 6 h with TBBPA (0 - 30 μg/mL in DMSO). Mitomycin C was the positive control in the absence of S9 mix and cyclophosphamide was the positive control in the presence of S9 mix. TBBPA did not cause structural chromosome aberrations or polyploidy in this study.

TBBPA was tested for its clastogenic potential in a GLP compliant mammalian chromosome aberration test in human peripheral lymphocytes (HPL) with and without metabolic activation with liver S9 fraction from Aroclor 1254-induced rats (Gudi, 2001). Duplicate cultures of HPL were exposed to TBBPA concentrations of 0 – 100 μg/mL in DMSO for 4 h in the absence of metabolic activation, and 0 –50 μg/mL TBBPA in DMSO in the presence of metabolic activation. In another assay, cultures of HPL were exposed to TBBPA (0 – 75 μg/mL in DMSO) for a 20 h period in the absence of S9 fraction. In all three assays the cells were harvested at 20 h after the initiation of treatment. Mitomycin C (0.3 – 0.6 μg/mL) was used as the positive control without S9 and cyclophosphamide (20 μg/mL) was used in the study with S9. There was no evidence of TBBPA causing structural or numerical chromosome aberrations in these assays.

Several polybrominated flame retardants, including TBBPA, were investigated for their potential to induce intragenic recombination in the Chinese hamster cell lines Sp5 and SPD8 (Helleday, 1999). The Sp5 and SPD8 clones exhibit a spontaneous duplication of the hprt gene, resulting in a non-functional HG-PRT protein. The duplicated mutants revert spontaneously to a functional hprt gene and some chemicals elevate this reversion. Treatment was performed for 24 h with 0 – 40 μg/mL TBBPA in DMSO in the SPD8 assay and with 0 – 70 μg/mL TBBPA in DMSO in the Sp5 assay. In the Sp5 assay precipitation was observed with 70 μg/mL TBBPA. Camptothecin (100 nM) was the positive control. TBBPA did not cause a significant increase in recombination frequency in either assay.

TBBPA was examined for genotoxic potential using an in vitro screening assay for detection of repairable adducts by growth inhibition (DRAG) in Chinese hamster ovary (CHO) cells lines with (EM9, UV4 and UV5) and without (AA8) defects in DNA repair (Johansson, 2004). Positive controls gave the expected results. Treatment with TBBPA was for a period of 24 h and cells were allowed to grow for another 48 h. Growth inhibition was plotted for each cell line and the dose causing a 50 % decrease in growth (IC_{50}) was calculated. The concentrations of TBBPA used in the assays were not reported. TBBPA was negative in this assay with IC_{50} values calculated for EM9 (65 ± 21 μg/mL), UV4 (54 ± 18 μg/mL) and UV5 (63 ± 24 μg/mL) cells, not being significantly different from the IC_{50} for AA8 cells (60 ± 8 μg/mL).

In vivo studies

The genotoxic potential of TBBPA was assessed in a peripheral blood micronucleus test using blood of B6C3F1/N mice from a 3-month repeat dose toxicity study (NTP, 2014) in accordance with MacGregor et al. (1990). Blood samples were collected at the end of the 3 month study and smears were immediately prepared, fixed in absolute methanol and stained with acridine orange. Slides were prepared from five female and male mice of each dose group (0, 10, 50, 100, 500 and 1000 mg/kg bw/day) and scanned to determine the micronuclei frequency in 2000 normochromatic erythrocytes (NCEs). As a measure of bone marrow toxicity, the percentage of polychromatic erythrocytes (PCEs) in 1000 mature erythrocytes was determined in the peripheral blood was scored for each dose group as a measure of bone marrow toxicity. No significant increases in micronucleated NCEs or percentage of PCEs, compared to controls, were observed in blood smears from any dose group, indicating that TBBPA did not induce bone marrow toxicity or mutagenicity at the doses tested.

Conclusions

TBBPA was not mutagenic in vitro in bacterial and yeast mutagenicity assays with or without the addition of S9 fraction; did not cause structural or numerical chromosome aberrations in chromosome aberration tests in Chinese hamster lung and human peripheral lymphocytes; did not induce other genotoxic effects in Chinese hamster cell lines. In vivo, TBBPA was negative in a peripheral blood micronucleus assay in mice. Altogether, the results from these studies indicate that TBBPA is not genotoxic.

12.2.5 Carcinogenicity

Limited data are available on the carcinogenicity of TBBPA. One high quality 2-year carcinogenicity study using TBBPA by the oral route has been reported (NTP, 2014).

Groups of 50 male and 50 female Wistar Han rats and 50 male and 50 female B6C3F1/N mice were administered 0, 250, 500, or 1000 mg TBBPA/kg body weight (bw)/day (d), in corn oil by gavage, 5 days per week for up to 104 weeks. Vehicle control animals received corn oil only. Dosing volumes were 5 mL/kg bw for rats and 10 mL/kg bw for mice.

Animals were quarantined for 11 or 12 days before the beginning of the study. Rats were 6 to 7 weeks old and mice were 5 to 6 weeks old at the beginning of the study. Rats were housed three (males) or five (females) per cage and mice were housed one (male) or five (females) per cage.

Clinical findings were recorded every 4 weeks beginning week 5 and at the end of the study. Complete necropsies and microscopic examinations were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and complete histopathology was performed on the following tissue: adrenals, bone with marrow, brain, cervix, clitoral gland, oesophagus, eyes, gall bladder (mice only), Harderian gland, heart, large intestine, small intestine, kidney, liver, lung, lymph nodes, mammary gland, nose, ovary, pancreas, parathyroid, pituitary, preputial gland, prostate, salivary gland, skin, spleen, stomach, testes with epididymis and seminal vesicle, thymus, thyroid, trachea, urinary bladder, uterus and vagina.

There were two detailed reviews of the female rat reproductive tissues termed the ''original transverse review'' and the ''residual longitudinal review.'' The original review involved a transverse section through each uterine horn, approximately 0.5-cm cranial to the cervix, and an evaluation of gross cervical and vaginal lesions. The residual longitudinal review involved collection and evaluation of remaining uteri, vaginas, and cervices stored in formalin and sectioned in a longitudinal manner. The weights of uterine tumour masses, when observed at necropsy, were measured.

Observations in rats

Survival of treated groups was not significantly different from the vehicle control group. After study week 25, body weights of male rats in the 500 mg/kg bw/day and 1000 mg/kg bw/day groups were approximately 10 % less than the vehicle control group. Bodyweights of female rats were similar to the vehicle control group at all doses. No treatment-related clinical signs were observed at any dose.

Absolute and relative thymus weights were significantly decreased and relative liver weights were increased of rats at the three month interim evaluation and increased, respectively, compared to the control group. No treatment-related lesions were observed in rats during this evaluation.

Tumour increases were seen in the uterus of female rats and the liver of male mice. Treatment-related neoplastic and non-neoplastic uterine lesions included increased incidences of atypical endometrial hyperplasia, uterine adenocarcinoma, and malignant mixed Müllerian tumour. Chemical induction of uterine tumours in rats was considered by the authors to be an important finding, not present in most of the previous NTP 2-year chemical carcinogenesis studies.

Statistical evaluations were performed for primary uterine tumours identified in the original transverse review, the residual longitudinal review, and the combined original transverse and residual longitudinal reviews. Tumour types were evaluated for statistical significance either individually or combined according to epithelial origin (adenoma, adenocarcinoma, or malignant mixed Müllerian tumour) or mesenchymal origin.

In females, uterine neoplasms were observed in all groups including controls. However, the incidence of uterine epithelial tumours (adenoma, adenocarcinoma and malignant mixed Müllerian tumour (MMMT) combined) increased dose-dependently; with significant increases at 500 mg/kg bw/d and 1000 mg/kg bw/d (6/50 [12 %], 11/50 [22 %], 16/50 [32 %] and 19/50 [38 %]) for control, 250 mg/kg bw/d, 500 mg/kg bw/d and 1000 mg/kg bw/d, respectively). Endometrial atypical hyperplasia (a preneoplastic lesion) was significantly ($P \leq 0.01$) increased in all treatment groups compared to the controls. Adenomas, present on a broad stalk and projected into the uterine lumen, were composed of a collection of endometrial glands that were typical in appearance, with little to no compression of surrounding tissue and no invasion of the adjacent endometrium or myometrium. The glands were lined by a single layer of well-differentiated cuboidal to columnar epithelium without stratification and surrounded by a delicate fibrous stroma.

Adenocarcinomas were often quite large, completely obliterating the normal uterine architecture. Some also invaded distant organs, including the intestines, liver, mesentery, pancreas, adrenals, ovary, lymph node, spleen, thymus, subcutaneous tissue, skeletal muscle,

lung, and kidney. Large areas of necrosis and suppurative inflammation were also associated with larger tumours. Proliferation of fibroblasts and formation of thick stroma were present in many cases. There were also positive trends for the combination of adenoma, adenocarcinoma, or malignant mixed Müllerian tumours (MMMT), and significantly increased incidences were observed in the 500 and 1000 mg/kg bw/d groups in both reviews and when the reviews were combined.

All MMMT were large and infiltrative, with a more solid growth pattern and composed of a mixture of neoplastic epithelial and neoplastic mesenchymal cells. In the areas of glandular formation, these tumours were similar to adenocarcinomas in morphology. Tumours in four animals in the 250 mg/kg bw/d group had extensive metastases to the liver, mesentery, pancreas, stomach, ovary, spleen, subcutaneous tissue, lung, and kidney.

Increased incidence of cystic endometrial hyperplasia was noted in the original transverse review in all dosed groups of females, with statistically significant increase in the 1000 mg/kg bw/d group. To investigate the pathogenesis mechanism of TBBPA induced uterine tumours, mutations in Tp53 (commonly altered tumour suppressor gene) of uterine adenocarcinomas from treated groups and control were compared. The results showed a significant increase in Tp53 mutations in TBBPA-induced uterine adenocarcinomas (10/16 [63 %]) compared with spontaneously arising uterine adenocarcinomas from controls (1/9, 11 %). Based on these findings, the TBBPA-induced uterine adenocarcinomas may be in part due to a Tp53-mediated mechanism.

In males, the incidence of testicular tumour (interstitial cell adenomas) was increased slightly in 500 mg/kg bw/d (1/50 [2 %]) and 1000 mg/kg bw/d (3/50 [6 %]) males, with incidence at 1000 mg/kg bw/d exceeding the historical control incidence [2.7 %] for all administration routes. The adenomas were characterised as a mass of proliferating interstitial cells with prominent cystic spaces that caused compression of adjacent seminiferous tubules. The four animals with adenomas (three unilateral and one bilateral) had tumours that ranged from small (an area of about one sixth of the testes) to large (effacing about 70 % of the testes).

The incidence of testicular germinal epithelium atrophy (characterised by seminiferous tubules devoid of spermatozoa) was increased compared with controls. Though the increase in incidence was not significant or dose-dependent, the severity of lesions was reported to increase with dose. These tumours do not appear to be related to treatment with TBBPA due to the lack of dose response and absence of precursor lesions (NTP, 2014). Affected testes were shrunken with a convoluted tunica albuginea. Interstitial cells appeared prominent.

Based on the statistically significant dose response of the neoplasms and presence of precursor lesions in female Wistar Han rats, the study authors considered the uterine epithelial tumours to be related to TBBPA treatment.

Observations in mice

Survival of male and female mice in the 1000 mg/kg bw/d groups was found to be significantly ($P<0.001$) less than control groups and was considered to be due in part to gastrointestinal toxicity. Mean body weights of 1000 mg/kg bw/day females were 10-25 % less than controls. Body weights of other dose groups were similar to controls.

Due to the low survival in 1000 mg/kg bw/day groups, neoplasm data for these groups were not presented. There was no evidence of carcinogenicity in females.

In males, the incidence of multiple hepatocellular adenomas increased dose-dependently (24 %, 40 % and 56 % in control, 250 mg/kg bw/d and 500 mg/kg bw/d groups, respectively). However, these values were within the historical control values (63 %) and, therefore, not considered to be biologically significant. Hepatocellular adenomas were generally solitary, well-circumscribed lesions occupying an area greater than one liver lobule and causing distinct compression of adjacent parenchyma. The incidence of hepatoblastoma in males was significantly increased in the 250 mg/kg bw/d (22 %) and 500 mg/kg bw/d (16 %) groups. These values exceeded the historical control range for hepatoblastoma (3.6 %) in male B6C3F1/N mice. Hepatoblastomas were irregular-shaped proliferative masses that were often found adjacent to, or arising from, hepatocellular adenomas or carcinomas. However, incidences of hepatoblastoma and hepatocellular carcinoma combined for control (24 %), 250 mg/kg bw/d (48 %) and 500 mg/kg bw/d (40 %) were within the corn oil gavage historical range values for hepatocellular carcinoma and hepatoblastoma (48 %).

The incidences of clear cell foci in 500 mg/kg bw/d (25 %) and eosinophilic foci in 250 mg/kg bw/d (33 %) and 500 mg/kg bw/d (40 %) males, were significantly higher than those of control or the historical range values. Increase in mixed cell foci were considered to be not significant.

The combined incidence of adenoma and carcinoma of the caecum or colon in males exceeded the historical control (0 %) at 500 mg/kg bw/d (3/50, 6 %). However, as there were no supportive precursor lesions observed, these tumours were not considered treatment-related.

Haemangiomas and haemangiosarcomas were observed in males in a variety of organs, including liver, bone marrrow, lymph nodes, skin, spleen, vertebrae and lung serosa. The incidences of haemangiosarcoma and haemangioma and haemangiosarcoma combined occurred in a positive dose-responsive manner in all treatment groups. Though the combined incidences of haemangioma and haemangiosarcoma were within the historical control range for corn oil gavage studies (13 %, range 6 -18 %), the incidences at 500 mg/kg bw/d were at the upper limit of the historical control range (18 %). Based on these factors and the absence of data from the 1000 mg/kg bw/d dose, the occurrence of haemangiomas and haemangiosarcomas may be related to treatment with TBBPA.

Effects in the stomach and forestomach including ulcers, inflammation, epithelial hyperplasia and mononuclear cell infiltration were observed in both males and females. All effects were significantly increased in males at 500 mg/kg bw/d and 1000 mg/kg bw/d and females at 250 mg/kg bw/d, 500 mg/kg bw/d and 1000 mg/kg bw/d. Ulcers were considered by the authors to be the primary lesion, while infiltration, hyperplasia and inflammation were considered secondary.

Summary:

The most significant pathologic findings in this study were treatment-related increases in uterine adenomas and adenocarcinomas in rats. In addition, some animals in the treated groups presented with malignant mixed Mullerian tumours (MMMT). Uterine atypical hyperplasia (considered a pre-neoplastic lesion) was also found in treated rats. The

combined incidence of uterine adenoma, adenocarcinomas or MMMTs was dose-dependent and significantly increased in the highest two dose levels. In combined original and residual tissues reviews, 12 % of control rats had uterine tumours versus 22 %, 32 %, and 38 % in the 250, 500, or 1000 mg/kg bw/day groups, respectively. Uterine tumour metastases were seen throughout the body. In addition, atrophy of the germinal epithelium, decreased spermatozoa and testicular interstitial cell adenomas were observed in treated male rats.

TBBPA is not considered to be genotoxic. Lai et al. (2015) discussed the mode of action (MoA) for the uterine tumours. Available evidence suggests that TBBPA may increase levels of circulating oestrogens by a competitive inhibition of oestrogen conjugation (binding to glucuronosyl-transferases and/or sulfotransferases). Higher oestrogen levels may lead to subsequent promotion of pre-existing Tp53 mutations in the uterus through increased DNA synthesis and cell proliferation, and produce uterine tumours by promoting pre-existing Tp53-mutations due to increased oestrogen levels resulting in increased cell proliferation. However, data on associated events such as DNA synthesis and cell proliferation in the uterus of TBBPA-treated animals are unavailable and there are no data on dose–response and temporal relationship between the serum levels of oestrogen or ratio of progesterone/oestrogen and uterine tumour formation. Based on this mechanism, it is expected that tumour induction would not occur unless TBBPA exposure was sufficient to cause significant changes in oestrogen levels.

In mice, hepatoblastomas were observed in males, with incidences of 4 %, 22 %, and 16 % in the 0, 250, and 500 mg/kg bw/d groups, respectively. The incidences in the 250 and 500 mg/kg/d groups was at least four fold greater than the incidence for this tumour in the concurrent vehicle controls (4 %) and was outside of the range for this tumour in the historical controls for corn oil gavage. Therefore, this was considered to be evidence of a carcinogenic effect by the study authors. The increases in liver foci and multiple hepatocellular adenomas in treated groups of male mice also provided supportive evidence for a liver carcinogenic effect.

Adenomas or carcinomas of the caecum or colon were also found in the treated males, although the incidence was very low. Haemangiosarcoma (all organs) in male mice were only significant at high doses (500 mg/kg/d and above).

Administration of TBBPA resulted in increased incidences of non-neoplastic lesions of the uterus and ovary in female rats, the liver and kidney in male mice, and the forestomach in male and female mice.

12.2.6 Reproductive Toxicity

Toxicity to fertility

A 2-generation reproduction study, conducted according to OECD TG 416, 30 SD rats per sex per group were administered 0, 10, 100 or 1000 mg/kg bw/day TBBPA in corn oil, orally by gavage (Schroeder, 2003*). Parental animals (P_0) were treated for 10 weeks before they were allowed to mate and then during the mating period of 2 weeks. Treatment was continued in females during gestation and lactation. At weaning (Day 21 of lactation), 30 male and 30 female first filial generation (F_1) pups/group were randomly selected for breeding of the next generation. After weaning of second filial generation (F_2) offspring, 10 males and 10 females from each dose group were randomly selected and subjected to clinical tests. At necropsy,

the adrenals, brain, kidney, liver, pituitary, tissue masses, spleen and thymus, ovaries, testes, epididymis, pituitary, prostate, seminal vesicle with coagulating glands, uterus (both horns) with oviducts, cervix and vagina were subjected to histopathological examination. Blood was collected from 10 randomly selected P_0 and F_1 animals/sex several days prior to sacrifice, and analysed for serum T_3, T_4 and TSH levels. F_1 and F_2 offspring not selected for further study were sacrificed and subjected to necropsy. Reproductive tissues were evaluated histopathologically for all P0 and F_1 retained animals in the control and 1000 mg/kg bw/day groups. Sperm evaluations (motility, caudal epididymal sperm counts, homogenisation-resistant testicular sperm head count, and morphology) were conducted in P_0 and F_1 male animals and a count of primordial follicles was conducted in P_0 and F_1 female animals.

No treatment-related mortality occurred in the P_0 or F_1 animals. No treatment-related effects were evident from clinical examinations, reproductive performance evaluations, oestrous cyclicity, food consumption, gestation length, litter data, reproductive organ weights, sperm evaluations, primordial follicle counts or gross or histopathological investigations of reproductive organs. In F_1 males, statistically significant decreases in body weights were observed at several weekly intervals, and significantly decreased weight gains (≈ 7 % decrease compared to the controls) were seen during the entire pre-mating period of 1 – 11 weeks. However, the magnitudes of the decrease in body weights and body weight gains were not likely to be biologically significant.

In F_1 and F_2 pups, no treatment-related effects were seen in clinical findings, sex ratios, survival to weaning, organ weights or other necropsy findings.

A multi-generational reproductive study was conducted to examine the effects of TBBPA at oral doses of 10, 100 or 1000 mg/kg bw/day over the course of two generations on growth as well as behavioural, neurological and neuropathologic functions (Cope et al., 2015). In a concurrent study, the influence of oral TBBPA (0, 100, 300 or 1000 mg/kg bw/d) was examined on embryonic/foetal development from gestation days (GDs) 0–19.

The feeding regime, breeding protocol and clinical and histopathological analyses were similar to those described for the Schroeder study above. P_0 generation females and all F_1 animals were subjected to post mortem evaluations. F_1 and F_2 offspring not selected for further study were sacrificed and also subjected to necropsy. Reproductive tissues were evaluated histopathologically for all P_0 and F_1 retained animals.

The following tissues were collected during necropsies for subsequent histological examination: adrenals, brain, ovaries or testes, epididymis, kidneys, liver, pituitary, prostates, seminal vesicles with coagulating glands, spleen, thymus, uteri (both horns), cervix and vagina. Representative samples of any grossly discernible lesions and any tissue masses were also collected. Specific reproduction parameters examined in the parental (P_0 and F_1 generations) included: number of implantation sites (when present) for all cohabitated females, stage of oestrus cycle, right and left epididymal weights, right cauda epididymis weight, right and left testicular weight. Sperm evaluations (motility, caudal epididymal sperm counts, homogenisation-resistant testicular sperm head count, and morphology) were conducted in P_0 and F_1 male animals and counts of primordial follicles were conducted in P_0 and F_1 female animals. Blood was collected from 10 randomly selected P_0 and F_1 animals/sex several days prior to sacrifice, and analysed for serum T_3, T_4 and TSH levels.

The study indicated that TBBPA treatment did not result in any marked adverse health effects on parental, F_1 or F_2 animals at oral gavage doses of up to and including 1000 mg/kg bw/day, the highest dose tested. There were no significant developmental effects except for thinning of the brain parietal cortex in F_2 generation animals at PND 11 at the maternal dose of 1000 mg/kg bw/day. This effect was not accompanied by any detectable neurodevelopmental, neurofunctional or neurobehavioural deficits. Decreases in serum T_4 were noted in the F_2 generation animals, but with no concurrent changes in serum T_3 and in the absence of increases in serum TSH; there was also a lack of histopathological alterations.

No effects on macro and micro anatomy, fertility, reproduction, development, survival or behaviour were detected in the embryo-foetal development study. No treatment-related effects on developmental neurotoxicity/neuropathology were detected in the developmental study. No other significant treatment-related effects were noted. The NOAEL for maternal and developmental toxicity was 1000 mg/kg bw/d, the highest dose evaluated.

A one-generation reproduction study in rats, conducted under the EU Flame Retardants Integrated Risk Assessment for Endocrine Disruption (FIRE) project has been reported (Van der Ven, 2008). The study was conducted according to OECD TG 415 and using a benchmark design. TBBPA (0, 3, 10, 30, 100, 300, 1000, or 3000 mg/kg bw/day) was administered in diet to male Wistar rats from 70 days prior to mating and to females from 14 days prior to mating, and continued throughout gestation, lactation, and after weaning of the offspring. On the day of birth, the number of live and dead pups, weight, sex, anogenital distance and macroscopic pathology were determined. Early mortality and the time to vaginal opening were recorded during the lactation period. Necropsies were carried out on five animals per sex per dose group at the average age of 14 weeks. During the necropsies, sperm from the cauda epididymis was analysed, and the full range of organs dissected, including sampling of whole blood, bone marrow of one femur, and a defined part of the spleen for analysis of immune cell subpopulations and/or natural killer lymphocyte (NK) activity. Defined parts of the liver, intestine, brain, one of each pair of adrenals, testes and ovaries, and samples of muscle and fat were subjected to biochemical analyses, including analysis for TBBPA. Plasma aliquots were analysed for thyroid and sex hormones (only males). Femurs and tibias were analysed for bone parameters.

Mortality was higher in male pups compared with females in all dose groups, with overall mortality rates in female and male pups of 9 % and 17 %, respectively. During the first 4–7 weeks after weaning, F_1 body weights showed a 10 % decrease. There were no effects on reproduction endpoints including mating success, number of implantation sites, or litter size. There were no changes in sex ratios in F_1 litters. Female pups showed decreased anogenital distance at PND7 and a delayed time to vaginal opening. This was observed only in the highest dose group and when normalised for body weights. There were no effects on female reproductive organs.

In F_1 males, there were dose-dependent increases in testes, liver and pituitary weights. Analysis of testosterone and 17-oestradiol in the plasma of the F_1 males showed no dose-dependent effects. There was no effect on time to preputial separation.

There were no observed histopathological effects in the testes in the adult F_1 males to explain the increased weights of these organs. Specifically, there were no obvious increase of testes tubule diameters, which is a possible cause for increased testes weights (fluid retention). The testes from littermates of these adult F_1 males at PND21 also revealed no

histopathological changes, notably not of Sertoli cell density, lumen formation, tubule diameter, or progression of spermatogenesis, which could have been indicative of a developmental effect as a cause for the increased testes weight. Cauda epididymis sperm counts and morphology were not affected. However, no exposure-related histopathological changes were observed in these organs and cauda epididymis sperm counts and morphology were not affected.

Reproductive organs of male F_1 pups showed increased weight at weaning, but there was no effect in female F_1 gonads at this age. Mortality was higher in male pups, in all dose groups, with overall mortality rates in female and male pups of 9 % and 17 %, respectively, although mortality during lactation showed a dose-dependent decrease. During the first 4–7 weeks after weaning, F_1 body weights showed a decrease around 10 % in the highest dose animals.

There were no changes in the duration of the oestrus cycle as determined on vaginal smears in a 1–2-week period prior to necropsy, nor were there changes in the distribution of stages during the cycle. A NOAEL for reproductive toxicity was not established in this study.

In a study similar to that by Van der Ven et al., a one-generation reproductive study was undertaken to determine the effects of housing conditions on the reproductive toxicity of TBBPA (Verwer, 2007). While in the main study (Van der Ven et al., 2008) females were housed individually and males in groups of 3-4 animals, this study included single-housed males and socially-housed females (2 – 5 animals per cage) for exposure groups 0, 300 and 3000 mg/kg bw/day TBBPA. Five animals/sex/dose were subjected to necropsy which included collection of the following tissues: ovary, uterus, mammary glands, testes, prostate, epididymis, seminal vesicle with coagulation gland, popliteal lymph nodes, spleen, thymus, heart, lung, liver, pancreas, stomach, duodenum, colon, ileum, jejunum, caecum, kidney, urinary bladder, brain, sciatic nerve, pituitary, thyroid, adrenals, skin and bone marrow (from femur).

In general, the single-housed females from the main study were significantly heavier than the socially-housed females, and the socially-housed males had significantly heavier prostates and lighter thymuses than the single-housed males. The uterus weights were significantly heavier in the socially-housed females. These effects were independent of exposure to TBBPA. In the control groups, single-housed females had significantly heavier livers than socially-housed animals.

In TBBPA-treated rats, there were no histopathological changes in either the singled-housed or socially-housed animals, except for the thyroid. It was reported that blind scoring of follicle size, cell vacuolisation and nuclear size by an arbitrary combined score indicated changes in cell activation due to treatment in both males and females. TBBPA treatment caused a change towards cylindrical morphology of the follicle lining cells and enlarged nuclei at 3000 mg/kg bw/day. This effect was more evident in the single-housed animals.

The results of this study showed that differences in parameters between animals under different housing conditions were rarely found. Results of the study also indicated that, in several parameters, significant differences were noted in the un-dosed control group in single versus group-housed animals, meaning that TBBPA can mask or enhance housing effects, or vice versa. In one case, single housing altered the effect of the toxic compound. Depending on the endpoints of the study, the type of housing condition must be taken into consideration as findings like these could have great implications for the interpretation and

validity of results from toxicological assays and the number of animals needed to detect significant effects of toxic compounds.

Developmental Toxicity

In a developmental toxicity study conducted according to OECD TG 414, TBBPA (0, 100, 300 or 1000 mg/kg bw/day in corn oil) was administered by gavage to female CD rats (25 mated female rats/group) (Schroeder, 2001*). Dosing began on GD 0 and continued through to GD 19. Animals were sacrificed on GD 20 and subjected to necropsy. Gravid uterine and liver weights were determined. The number of corpora lutea, uterine implantations, resorptions, viable and nonviable foetuses and weights of foetuses were recorded. Foetuses were examined for skeletal and visceral variations or malformations. No treatment-related effects were seen on gestation parameters or on foetal development at any dose. A NOAEL of 1000 mg/kg bw/day TBBPA is assigned based on no effects at the highest dose tested.

A study was undertaken where pregnant female Wistar rats (22 –24 rats per group) were orally treated with 0, 280, 830 or 2500 mg/kg bw/day TBBPA in olive oil from GD 0 (Noda et al., 1985). The study was reported in Japanese with an English abstract, figures and tables. On GD 20, two thirds of the animals were sacrificed for gross pathological investigation. The remaining dams were allowed to give birth naturally and the pups were then examined for survival and abnormalities. The pups were weaned on PND 21, during which time body weights were measured and growth observed. After weaning, the pups were sacrificed and examined for skeletal abnormalities. The dams were sacrificed on post-partum day 21 and gross pathological examinations conducted. No toxicologically significant effects were observed during the gestation period and no treatment-related adverse effects on development were seen.

In a pilot range finding study to determine teratology, mated Charles River CD female rats (5/group) were administered TBBPA (0, 30, 300, 1000, 3000 or 10000 mg/kg bw/day in corn oil) by gavage on GD 6 – 15 (Goldenthal, 1978). On GD 20, all dams were sacrificed and the number of viable and non-viable foetuses, resorptions, total implantations and corpora lutea were recorded. In the animals treated up to and including 3000 mg/kg bw/day TBBPA, there were no significant changes in appearance, behaviour or body weights compared to controls. In the 10000 mg/kg bw/day TBBPA group, 3 out of 5 animals died by GD 17. Animals in this group had green, soft stools and matted hair in the anogenital area. Although there appeared to be a slight decrease in body weight gains between GD 5 and GD 15 in animals treated with the highest dose, the statistical significance of this decrease was not reported. In terms of the assessed developmental parameters, there were no treatment-related effects up to the highest dose, a dose causing maternal toxicity. A NOAEL of 3000 mg/kg bw/day was assigned for maternal toxicity based on mortality in the 10000 mg/kg bw/day treatment group. The NOAEL for foetal effects was the highest dose tested.

In a study in newborn rats, SD rats (12 animals/sex/group) were administered TBBPA (0, 40, 200 or 600 mg/kg bw/day in 0.5 % carboxymethylcellulose-Na solution with 0.1 % Tween 80) by gavage from days 4 – 21 after birth (Fukuda, 2004). Six animals per sex per treatment group were sacrificed on PND 22 and the rest of the animals were maintained as a recovery group for 9 additional weeks. Diarrhoea occurred sporadically in some animals treated at 200 and 600 mg/kg bw/day TBBPA (no other information was provided). A significant decrease in activated thromboplastin time was seen in males treated at the highest dose, and a significant decrease in haemoglobin was seen in females treated at the highest dose.

In both males and females, the total bilirubin levels were significantly increased at 600 mg/kg bw/day TBBPA. The relative kidney weights were significantly increased in both sexes treated at the highest dose, compared to the controls. Relative liver weights were significantly increased (by 11 %) in males treated at the highest dose. Histopathologically, 2 out of 6 males in the 200 mg/kg bw/day dose group and all animals in the 600 mg/kg bw/day group had polycystic kidney lesions associated with dilation of tubules bilaterally from the cortico-medullary junction to the inner cortex. While the kidney lesions in the 200 mg/kg bw/day group were slight, the lesions in the highest dose group were severe and the tissue samples had a sponge-like appearance. In the liver, slight centrilobular hypertrophy of the hepatocytes was observed in 3 males at 600 mg/kg bw/day TBBPA. On day 7 of recovery, 1 male and 1 female in the highest group died and one male was sacrificed moribund. At the end of the recovery period, absolute kidney weights of the highest dose group animals were 1.3 times higher than controls. In the recovery groups, multiple cysts of the kidney in 1 male and 1 female at 200 mg/kg bw/day group and in all animals at 600 mg/kg bw/day were seen.

In a study not conducted according to OECD Test Guidelines, 24 pregnant ICR mice were allocated to 4 dose groups of 6 animals each (Tada et al., 2006). The animals were treated with 0 %, 0.01 %, 0.1 % or 1 % TBBPA in feed (16 – 42, 140 – 380, or 1640 – 4156 mg/kg bw/day) from GD 0 to weaning at PND 27. Mice were observed for clinical signs, individual food intakes and body weights. At weaning, dams and offspring were sacrificed and blood collected for analysis. At necropsy, histopathological examinations were conducted on the following organs: heart, lung, thymus, spleen, liver, kidney, uterus, ovary, adrenals, brain, pituitary and thyroid glands, salivary gland, pancreas, stomach, intestine, caecum, prostate gland, epididymides and bone marrow.

No mortality or clinical signs of toxicity were seen. There were no treatment-related effects on the average body weights of dams or daily food intake. No treatment-related effects were noted on average litter sizes, litter weights, total number of offspring, or the pup weights. Serum concentrations of aspartate aminotransferase, alanine aminotransferase, glucose, or blood urea nitrogen were not affected by treatment in the dams or offspring. Serum concentrations of total cholesterol were significantly increased in the high dose dams, high dose female pups and the middle and high dose male pups. Serum concentrations of triglyceride were significantly decreased in high dose male and middle and high dose female pups.

In the male offspring, the relative weights of liver and brain were significantly increased (by 7 % and 6 %, respectively) in the high dose group compared to the controls. However, this increase was not considered to be of biological significance. While the relative weight of the spleen was significantly higher in the high dose group female offspring, no corresponding histopathological changes were noted. Major histopathological changes were seen in the kidney and liver. In the kidney, dilation of renal tubules was seen in all treated groups of dams and offspring at low incidence with no dose-response seen. Cysts were seen in the kidneys of some treated dams and offspring, again at low incidence and with no dose-response. Atrophy of renal tubules was reported in some treated dams with no dose-response, and offspring of all groups, including the controls. As 3 out of 12 control female offspring had atrophy of renal tubules, it is difficult to assign as adverse the high incidence (8 out of 12 animals) in the high dose group, occurring in the absence of a clear dose-response effect. In the liver, slight focal necrosis of hepatocytes was seen in all groups, including the controls. Inflammatory cell infiltration of the liver was seen in almost all animals and in all

groups, to some degree. Enlargement of hepatocytes was seen in all groups in the dams and offspring, except male offspring in the control group. While a dose–response effect is apparent in enlargement of hepatocytes in the offspring, no conclusions could be made given the presence of other histopathological changes in the liver of control animals.

In a briefly reported study, Buitenhuis et al. (2004) investigated the effect of exposure to several organohalogens, including TBBPA, at early life-stage. Pregnant Wistar rats were dosed orally with TBBPA (25 mg/kg bw/day) during GD 10 to 16, a critical stage of gonadal development. Offspring were scored for developmental effects, from PND1, such as anogenital distance (androgen disruption marker, PND4), crown-rump length (PND4), age at bilateral eye opening, age at vaginal opening and age at preputial separation. Litter size, gestational period, male to female ratio and body weight (PND4) were also recorded. No significant differences between control and treated groups were observed for these effects. The results indicate that TBBPA at 25 mg/kg bw/day is not associated with developmental effects.

In summary, the only treatment-related adverse developmental effects observed following treatment with TBBPA were cysts and dilation of tubules in kidneys. On a weight of evidence basis, the effects seen in the pituitary of F_1 males in the one-generation reproduction study were considered not related to TBBPA treatment. Histological changes in kidney and liver observed in developmental studies have been argued by some to be due to gavage of large doses of TBBPA to newborn rats as young as PND 4. Glucuronidation is an important process for the clearance of TBBPA and newborn rats are deficient in glucuronidation activity (Kuester, 2007). These effects are severe and more studies are required to determine the significance of these effects.

Neuro-developmental studies

In the two-generation study in SD rats, described in detail in the Reproductive Toxicity Section, F_2 pups (10 animals/sex/group) were subjected to a range of motor activity and memory tests that were conducted on PND 13, 17, 21 and 60 (Schroeder, 2003*). Motor activity was assessed using a Digiscan Activity Monitor. The animals were placed on an activity chamber and tested for a total of 20 min (four 5 min intervals). Horizontal and vertical activity counts and total horizontal distance travelled were recorded using a Digiscan Activity Monitor connected to an electronic analyser-recorder. Behavioural assessment was also made based on defaecation, urination, rearing, grooming and backing. While statistically significant changes were seen during some time intervals (0 – 5 min test period), no dose-dependent effects or meaningful trends were seen in the motor activity test.

Learning and memory were evaluated in F_2 pups (10 animals/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. An animal was placed on the lighted side to acclimatise for 30 s and the barrier was removed for a 3-minute period to allow the animal to cross to the less lighted side. On day 1, animals crossing to the dark side were administered a shock. Animals crossing to the dark side were not shocked on days 2 and 3, but the time was recorded. Each animal was tested once a day for 3 consecutive days. PND 22 males treated with 1000 mg/kg bw/day TBBPA spent significantly less time on the light side compared to the controls on day 2. However, given that a similar behaviour was not seen on day 3, this was not considered to be treatment-related. No treatment-related

effects on learning and memory were evident when tested on PND 60 male and female F_2 animals.

The same animals (10 animals/sex/group) tested in the Step-through Passive Avoidance Test were tested on the Morris water maze on PND 110. To assess short-term memory, each animal was tested 10 times per day for 4 consecutive days. Five days later, the animals were retested to determine long-term memory. Each animal was given 60 s to complete the test. There was no significant difference in the mean number of errors between the treated animals and the controls. There was no significant treatment-related difference in the time taken to complete the maze on each test day. Furthermore, with the time taken to complete the maze on day 4 and day 9 being similar, there was no treatment-related effect on long-term memory.

An auditory startle test was carried out with 10 F_2 animals/sex/group, using the Hamilton Kinder Startle Monitor System. The tests were carried out on PND 22 and PND 60 animals. The animals were tested 50 consecutive times (5 blocks of 10 trials) and the mean response amplitude was calculated for each block of tests. There was no statistical difference in the mean startle response between the controls and the treated animals.

Neuropathological evaluation and morphometric evaluation of the whole brain, including the parietal cortex, hippocampus, cerebellum and thalamus were also evaluated in this study. On PND 60, 10 animals/sex/group were sacrificed and the brain, lumbar spinal cord, sciatic nerves with tibial, fibular and sural extensions were taken. The brain was sectioned to include the cerebrum, cerebellum, pons and medulla. In morphometric studies, a statistically significant decrease in the thickness of the parietal cortex was seen at PND 11 in 1000 mg/kg bw/day dose treated male and female animals compared to the controls. This reduction in thickness was not accompanied with any histological changes. Given that no microscopic alterations of the brain, spinal cord, nerves and ganglia were seen in the highest dose treated PND 60 animals, the authors suggested that the effect observed in PND 11 should be interpreted with caution.

Developmental neurotoxicity of TBBPA was investigated in an unpublished study according to the proposed OECD TG 426 (*Hass et al., 2003). Pregnant rats (Mol: WIST; 20 animals/group) were administered 0, 50 or 250 mg/kg bw/day TBBPA in peanut oil via gavage from GD 7 to PND 17. On PND 21, PND 27 and 12 weeks after birth, animals were subjected to motor activity testing over a 30 min period using activity boxes. There was no treatment-related effect on motor activity. In order to determine habituation, animals were retested in two time periods of 15 min each. The PND 21 female animals from the 250 mg/kg bw/day group showed decreased habituation activity since the motor activity in the second segment was similar to that observed in the first segment and was significantly different to the control. PND 27 females treated with 50 and 250 mg/kg bw/day TBBPA showed decreased habituation activity, but this effect was not dose-dependent. Decreased habituation activity was not seen in male animals at any time point. Histopathological examinations of male PND 15 pups and male/female PND 22 pups found no treatment-related effects in the brain.

Animals were investigated for learning and memory in a Morris water maze at ages 9, 13 and 17 weeks (*Hass et al., 2003). The animals were trained and tested in 4 daily trials for 5 consecutive days to locate a submerged platform from 4 different starting points. The time taken to locate the platform, the path lengths and the swimming speeds were the test

endpoints. Animals were tested again over four trials/day for two consecutive days, 4 weeks after the learning phase to assess memory. On the following day the animals were tested over 4 trials with the platform placed opposite the original location to determine "reversal learning". Similarly, "new learning" was tested by placing the platform in the centre of the pool. During the first day of the learning phase, females from the 250 mg/kg bw/day TBBPA showed a significant decrease in path lengths and the time taken to locate the platform compared to the controls. On day 5 of the learning phase, males treated with the highest dose showed a significant increase in path lengths and the time taken to locate the platform compared to the controls. These differences are not considered to be due to treatment as there was no consistent pattern in the effects. There were no significant differences in swim speed between the treated groups and the control on any of the five days. During the assessment of memory, "new learning" and "reversal learning", no consistent pattern of differences occurred between the control and the treated groups indicating the absence of treatment-related effects.

On PND 31, the animals from each dose group were placed in pairs and the time taken to initiate play behaviour and the number of pinnings were scored. In another test, 5-month-old animals were subjected to a sweet preference test. Animals were provided normal water and sweetened water with 0.25 % saccharin for 3 days and the preference for saccharin intake was determined. In these tests no treatment-related effects were seen.

When the animals were 6 – 7 months old, they were placed in the centre of a standard 8 arm radial maze containing peanut rewards at each of its arms. The animals were tested 5 times/week for 3 weeks and the session was completed when the animals had visited all the arms or 10 minutes have passed. The time taken to visit all the arms was measured and the number of errors made by visiting an arm more than once was also documented. There was no statistically significant difference between the treated rats and the controls in the time taken to visit all the arms during the trails in all three weeks. The mean number of errors per week decreased over the 3 weeks. The 250 mg/kg bw/day males had a slightly higher number of errors in week 1 (mean ± SD: 4.09 for controls and 5.13 for high dose group) and 2 (1.13 for controls and 2.60 for high dose group) compared to the controls. While these effects were statistically significant, similar effects were not seen in males in week 3 or in the females in all three weeks. The high dose group males had a statistically significantly lower frequency of choosing an adjacent arm in week 1 compared to the controls, but not in weeks 2 and 3. Given the absence of a consistent pattern, no firm conclusions can be drawn from this test. While this study showed a decreased habituation effect in PND 21 female animals, a dose–response relationship was not observed at PND 27 or in 12-week old female adult animals. Given the absence of similar effects in males and the lack of a consistent pattern in the females over the differing time periods, it is not possible to consider this isolated observation being due to treatment.

In a developmental neurotoxicity study, neonatal male NMRI mice were orally administered TBBPA (0, 0.75 or 11.5 mg/kg bw/day in a 20 % peanut oil emulsion) by gavage on PND 10. The treatment groups were made up of mice randomly chosen from 3-4 different litters (Eriksson, 2001). At ages 2 and 4 months the spontaneous behaviour of mice was tested in 8 mice/group. The tests consisted of measuring horizontal movement, vertical movement, rearing, and total activity (all vibrations in the cage). In addition, a Morris water maze type test was performed on mice (16-18 animals/group) aged 5 months. The ability of mice to locate the submerged platform was studied over 5 d. No clinical signs of dysfunction or significant changes in bodyweight gain were seen in the treated mice compared to the

controls. There was no significant difference in performance of neurobehavioural tests between the treated and control animals.

The effects of TBBPA exposure on brain development in newborn mice were examined (Viberg & Eriksson, 2011). In this study, a single dose of 11.5 mg/kg bw of TBBPA was given to male NMRI mice (n=6-8) via oral administration (metal gastric tube) at PND 10. Uptake of TBBPA was measured following oral administration of a single dose of 1.5 MBq ^{14}C-TBBPA/kg on PND10. Changes in the levels of protein associated with brain development (cholinergic system), including CaMKII, GAP-43, synaptophysin and tau proteins were measured using slot-blot analysis. Receptor binding assays (3-quinuclidinyl benzilate (QNB)-, AF-DX384-, and cytisine-binding) were conducted to measure effects of TBBPA on all subtypes of muscarinic receptors, M2/M4, and $\alpha 4\beta$nicotinic receptors, respectively. Cholinergic receptors are broadly classified as muscarinic or nicotinic. Based on the results of the uptake and retention experiment, levels of ^{14}C-TBBPA in the brain of pups at 3 and 24 hours and 7 days after oral exposure were 3.7 %, 0.9 %, and 0.3 % of the administered dose, respectively. The results indicated that exposure of mice to TBBPA at 11.5 mg/kg bw dose during the early stages of development did not alter the levels of protein associated with maturation of the brain. Whilst significant increases in levels of CAMKII, GAP-43 and synaptophysin in the hippocampus and cortex of mice treated with the PBDE congener, BDE-99 were reported, these changes were not observed in the brain of the TBBPA-exposed mice. A significant decrease in binding sites of the nicotinic ligand cytisine in frontal cortex was reported in the TBBPA-exposed nice. However, no change in these binding sites was noted in the parietal cortex or hippocampus. Overall, a single dose exposure of mice neonates to TBBPA at 11.5 mg/kg bw dose did not cause neurodevelopmental toxicity. The uptake and retention of TBBPA in the brain were low (Viberg and Eriksson, 2011).

Similar findings were reported in a related study (Saegusa et al., 2009). In this investigation, the authors examined the effects of TBBPA exposure on the rat offspring following maternal exposure (Crj:CD (SD) IGS rats; n=8) to the chemical from mid-gestation through lactation, after dietary administration of 0, 100, 1000 or 10000 ppm of TBBPA (approximately equivalent to 0; 10-23; 87-200; or 819-2130 mg/kg bw/day) from gestation days (GD) 10 to postnatal day (PND) 20 (weaning). Morphometric analyses of brain sections immunostained with NeuN (hippocampal CA1 neurons) and CNPase (cingulate deep cortex oligodendrocytes) did not indicate any TBBPA-induced changes in the developing the rat brain. No changes were reported in the body weight and organ weight of male adult offspring. In females, significant decreases in the relative weights of kidneys and uterus in week 11 were noted in 1000 and 10000 ppm groups ($p<0.05$; 0.66 and 0.14 g/100 g bw, respectively) compared with controls (0.71 g/100 g bw, kidneys; 0.18 g/100 g bw, uterus). There were no significant dose-related changes in the levels of T_3, T_4 and TSH in either newborn or pubertal offspring. The TBBPA treatment did not affect the development of rat offspring.

In a further study (Saegusa et al., 2012), 8 dams per group were treated with soy-free diet containing 0 (control), 100, 1000, or 10000 ppm of TBBPA (0, 10-23; 87-20; or 819-2130 mg/kg bw/day) from GD 10 to PND 20. The highest dose, which has shown to induce changes in the thyroid but does not affect pregnancy, implantation and delivery, was determined in a range-finding study. The treated rats were sacrificed for prepubertal and adult stage necropsy at PND20 or PND77, respectively.

Immunohistochemical staining using antibodies against proteins associated with brain development, including reelin (neuronal migration and positioning), glutamic acid decarboxylase 67 (GAD67; synthesis of neurotransmitter), EphA5 (axon guidance), Tacr3 and neuron-specific nuclear protein (NeuN) was performed on brain sections of rats. Morphometric analyses were performed to quantify the bilateral distribution of reelin (an extracellular matrix glycoprotein), NeuN-, or GAD67-positive cells in the hilus of the dentate gyrus and EphA5- or TAcr3-positive cells in the pyramidal cell layer of the hippocampal CA1 region. Neuronal cell death in the subgranular zone was visualised using cresyl violet staining. The results indicated significant dose-related increases in the number of reelin-positive cells in the dentate hilus of the TBBPA-exposed rats from 100 ppm at PND20. These effects were reversible at PND77 in all of the dose groups. The authors noted that the increase in the reelin-producing cells may be indicative of compensatory regulatory mechanism for neuronal mismigration following disruption in neurogenesis. A dose-related increase in the number of NeuN-positive cells was observed in the hilus from 1000 ppm at PND77. The authors suggested that this could be a sign of TBBPA-induced disruption in the neuronal development and migration. The number of GAD67-positive cells at 10000 ppm was comparable to untreated controls at PND20 and PND77. No changes were reported in the number of EphA5- and Tacr3-positive cells in all TBBPA-dosed groups. The result from the cresyl violet staining showed a significant increase ($p<0.05$) in the number of apoptotic cells at PND77 in the neuroblast-producing subgranular zone at 10000 ppm of TBBPA. However, these results were not validated by immunohistochemical analysis or other assays (Saegusa et al., 2012).

Within the framework of an EU project on risk assessment of brominated flame retardants, TBBPA was studied for neurobehavioural effects in rats. Due to the known implication of thyroid hormones in neurodevelopment, the effect of TBBPA on thyroid-dependent neurobehavioural functions, such as auditory responses and conditioned fear was studied in pups from TBBPA-treated dams. Dose levels were chosen ranging from 0 to 3000 mg/kg bw/day, similar to the one-generation reproduction study by Van der Van et al. (2008). Exposure of parental rats started 2 and 10 weeks before mating in females and males, respectively, and was continued throughout mating, gestation and lactation. No statistically significant effects were found on context or cue conditioned fear.

Auditory brainstem responses (ABR) latencies, that reflect loss of input from the cochlea and changes in brainstem conduction velocity (hearing loss) were examined with brainstem auditory evoked potentials (BAEPs) at approximately 50–110 days of age. The results suggested a predominant cochlear effect of TBBPA in females, while in males neural effects were more apparent. The benchmark doses for effects on the BAEP were similar to values for decreases in circulating thyroid hormones. Considering the treatment-related changes in thyroid hormone levels in offspring (refer Section 12.2.5; Van der Ven et al., 2008), the authors suggested that developmental effects on the auditory system were secondary to thyroid hormone level changes. The comparison of the exposure level at which the most sensitive effect was found with current human exposure levels yielded a margin of exposure of about 5.

In summary, a two-generation reproduction study enhanced to investigate developmental neurotoxicity, and a neurodevelopmental study conducted according to the proposed OECD guidelines found no convincing evidence of developmental neurotoxicity with TBBPA up to 1000 mg/kg bw/day (Hass, 2003; Schroeder, 2003). However, a one-generation reproduction study enhanced for endocrine and neurobehavioural endpoints found neurodevelopmental

effects on the auditory system following treatment with TBBPA (Lilienthal, 2006). An adequate supply of thyroid hormone levels is necessary for normal development of the auditory system within the period GD17 and PND 12. Using an antithyroid hormone drug, methyl mercaptoimidazole, studies have shown that a reduction in thyroid hormone levels after GD17 results in an impaired auditory system with elevated BAEP thresholds (Knipper, 2000). Thereafter, the severity of the impairment increases with each day without a normal supply of thyroid hormone levels. It has also been shown that a reduction in thyroid hormone levels up to PND 8 does not result in prolonged latencies. However, a reduction in thyroid hormone levels up to PND 10 – 14 results in progressively longer latencies. Therefore, it was postulated that the observed developmental effects on the auditory system are a result of treatment-related changes in thyroid hormone levels during the period GD 17 – PND 14.

12.2.7 Neurotoxicity

Neurobehavioural effects in mice following acute exposure to TBBPA were investigated in vivo (Nakajima et al., 2009). In this study, young adult male mice (closed colony ddY) were treated with TBBPA once at doses of 0, 0.1, 5 or 250 mg/kg bw via oral gavage. The distribution and concentration of TBBPA in the brain were assessed using mass spectrometry. The effects on the behaviour of mice were evaluated three hours after the exposure by conducting an open-field activity (anxiety), Y-maze test or training of contextual fear conditioning (learning and memory).

Data obtained from the mass spectrometry analysis indicated a dose-dependent increase of TBBPA concentrations in brain tissues. High amounts of TBBPA in striatum were observed compared with the other brain regions, including hippocampus, cortex, cerebellum, thalamus or medulla oblongata at 0.1 mg/kg bw and 5 mg/kg bw. At 250 mg/kg bw, accumulation of TBBPA in the brain was non-specific. At 0.1 mg/kg bw, significant effects were observed in the contextual fear conditioning paradigm and Y-maze test. At 5 mg/kg bw, TBBPA induced the locomotor stimulating effect in the open field test and memory enhancing effect in the contextual fear conditioning paradigm. By contrast, no change was observed in mice at 250 mg/kg bw.

In summary, the authors concluded that acute oral exposure of mice to TBBPA at doses 0.1 or 5 mg/kg bw caused accumulation of TBBPA in several regions of the brain. These animals also showed TBBPA-induced behavioural and cognitive changes. However, the behavioural effects were not observed in the highest dose of 250 mg/kg bw. The lack of a dose-response relationship was suggested by the authors to be due to a compensatory mechanism, similar to that observed with administration of other neurotoxic compounds.

12.2.8 Endocrine Effects

12.2.8.1 Effect on thyroid system

In Vivo Studies

The distribution of TBBPA and its effects on thyroid hormone levels were studied in pregnant rats (Meerts et al., 1999). Pregnant Wistar WU rats were given 5 mg/kg bw/day TBBPA in corn oil by gavage. There were no significant changes in plasma total thyroxine (T_4) and free T_4 levels in dams or foetuses compared to their respective controls. In dams, T_3 and TSH

were not different between the treated and control groups. The TSH levels were significantly higher in foetuses from treated rats (4.86 ng/mL plasma) as compared to those from untreated mothers (1.64 ng/mL plasma). The authors of the study propose that increased TSH levels found in the foetus should be interpreted with caution given that there has been no investigation of a dose-response relationship, and that the T_4 levels were within normal levels in the foetuses from treated mothers.

The potential of TBBPA to bind to transthyretin (TTR) in vivo and its effect on thyroid hormone homeostasis was examined (Meerts et al., 2000). Pregnant Wistar WU rats were exposed to 5 mg/kg bw/day ^{14}C-TBBPA in corn oil orally from gestation day (GD) 10 to 16 and sacrificed on GD 20. There was a clear lack of TBBPA binding to TTR in vivo. This is in contrast to high affinity binding of TBBPA to TTR in an in vitro study (see below). However, considering the low dose of TBBPA used in this study, the time lag between the last dose and necropsy, and given the short half-life of TBBPA in plasma, this finding is not unexpected. TBBPA did not affect the brain type II deiodinase activity or the hepatic T_4-uridine diphosphate glucuronyl transferase (UDPGT) activity. TBBPA has been reported to competitively bind to TTR in vitro (Meerts et al., 1999).

In the 90-day oral rat study described in Section 12.2.3, thyroid hormone levels were investigated on day 33 and day 90 and again following recovery (Schroeder, 2002*). Both TSH and T_3 levels in treated animals were comparable to control values. In contrast, the mean T_4 levels were significantly lower in males in all treatment groups when compared to the controls on day 33 as well as day 90. However, a clear dose-response relationship was not seen on either day 33 or day 90. In females, statistically significant decreases in T_4 levels were observed on day 33, and this occurred in all treatment groups. Again, a clear dose-dependent effect was not seen. In contrast to day 33, there was no significant difference in T_4 levels on day 90 between treated and control female animals. At the end of the recovery period, the T_4 levels of the highest dose group (1000 mg/kg bw/day TBBPA) were within control levels in both males and females. While a clear dose-response relationship was not seen in this study, based on T_4 levels reported in the one-generation reproduction study (Van der Ven et al., 2008) and the two-generation reproduction study (Schroeder, 2003), decrease in T_4 levels is likely to be treatment-related. However, this effect is reversible and because there are no corresponding changes in organ weights or histopathological changes in the liver, thyroid, parathyroid or pituitary gland in this study, T_4 reduction is not considered an adverse toxicological effect. The author of the study suggested that the reduction in serum T_4 levels could be due to TBBPA displacing T_4 from the thyroxine binding protein, TTR.

A sub-acute toxicity study and a one-generation reproductive toxicity study of TBBPA under the EU FIRE project were conducted (Van der Ven et al., 2008). In the 28-day toxicity study, Wistar rats were dosed with 0, 30, 100 or 300 mg TBBPA/kg bw/day via diet. No major effects were observed in the thyroid hormone system. The only effects observed in the sub-acute toxicity study were decreased circulating T_4 and increased T_3 levels in males. The lower bound benchmark dose at which the change in response is likely to be less than 10% ($BMDL_{10}$) were 48 and 124 mg/kg bw/day, respectively). In females the trends for these parameters were non-significant. In the one-generation reproduction assay, the rats were dosed with 0, 3, 10, 30, 100, 300, 1000 or 3000 mg TBBPA/kg bw/day via diet starting at 70 and 14 days prior to the mating for males and females, respectively. In dams, exposure to TBBPA continued during pregnancy and lactation. Decreased circulating T_4 was observed in both male and female F_1 offspring ($BMDL_{10}$ 31 and 16 mg/kg bw/day, respectively), and

plasma T_3 was increased in F_1 females ($BMDL_{10}$ 2.3 mg/kg bw/day). In F1 males, exposure to TBBPA caused increased weight of testes ($BMDL_5$ of 0.5 mg/kg bw/day) and increased weight of the pituitary ($BMDL_{10}$ of 0.6 mg/kg bw/day). The dose response for the effects on testes and pituitary was however unclear.

Decreased levels of circulating T_4 has been suggested to result from competition of TBBPA at the major thyroid hormone carrier in the adult rat, TTR (Schussler, 2000), making T_4 increasingly available for metabolism, including deiodination. This explanation is supported by the increased T_3, which accompanied the low T_4 to various extents. Decrease in circulating T_4 could induce feedback stimulation, which was suggested by the increased pituitary weight in males. Meerts et al. (2000) have shown that TBBPA binds to TTR in vitro.

In the two-generation reproductive study (Schroeder, 2003*) and described in detail in Section 12.2.5, serum TSH levels were not affected by treatment in either P_0 or F_1 animals. A statistically significant decrease in serum T_3 levels was seen only in the P_0 males at the highest dose. In the P_0 males and females, significant decreases in serum T_4 levels were observed in high dosed groups. In the F_1 animals, T_4 levels were significantly lower in both males and females at the two highest doses. The decrease in T_4 levels followed a clear dose-dependent relationship in the male F_1 animals. Extensive histopathological examination performed in this study did not show any changes in any of the organs. Based on this study, a NOEL of 10 mg/kg bw/day was determined for reduced T_4 levels in both male and female rats.

The effects TBBPA on T_3 mediated transcription of thyrotropin-releasing hormone [Trh] and melanocortin receptor type 4 [Mc4r] genes were investigated (Decherf et al., 2010). The study used in vivo reporter gene expression assays (aromatase-luciferase reporter gene construct (ARO-luc)) to evaluate the changes in hypothalamic gene transcription. Pregnant dams were exposed to 150 mg/kg bw day TBBPA via gavage for 7 days from gestational day 12 (GD12). Additionally, TBBPA was given to newborn pups via subcutaneous injection at 2.1 g/kg bw either once (24 hours prior to T_3 treatment) or twice (24 hours prior to and after T_3 treatment). Treatment with T_3 was conducted to assess its effects on the expression of the reporter gene. TBBPA-induced changes on the transcription of genes [Trh] and [Mc4r], regulated by T_3, were examined 24 hours after gene transfer. TRH and Mc4r are known to be negatively regulated by T_3; being activated in the absence of T_3, and repressed in its presence, (Decherf et al., 2010). In the absence of T_3 treatment, a decrease in Trh and Mc4r transcription (32.4 % and 33.6 %, respectively) was observed following a single injection of TBBPA. Conversely, two injections yielded a significant increase in the Trh and Mc4r transcription (28.7 % and 37.5 %, respectively). The authors concluded that short term exposure of mice to 150 mg/kg bw TBBPA resulted in a decrease in T_3-independent transcription activation of the promoter genes Trh and Mc4r in the hypothalamus of the mice offspring.

TBBPA was administered to pregnant SD rats at dose levels 100, 1000 or 10000 ppm in a soy-free diet from gestation day 10 until the day 20 after delivery (Saegusa et al., 2009) (see Section 12.2.6). Dietary dose levels corresponded to about 9.5-23, 87-202 or 820-2130 mg/kg bw/day, respectively, for maternal exposure. At PND 20, a slight increase in the incidence of diffuse thyroid follicular cell hypertrophy was observed in dams at the mid dose and above. Male offspring of dams exposed to TBBPA showed slight non dose-related decreases in serum T_3 concentration at PND20, while no changes in serum T_4 and TSH concentrations were detected. On PNW11, there were no changes in any of the thyroid

hormone related parameters in any of the dose groups. TBBPA did not affect brain type II deiodinase activity or hepatic T_4 UDPGT activity in the rat.

In vitro studies

A number of in vitro studies have shown that TBBPA binds to TTR and T_3 receptor with low affinity.

A study was conducted to determine the potential of TBBPA binding to human transthyretin (TTR) using a competitive binding assay (Meerts, 2000). ^{125}I-labelled and unlabelled T_4 were incubated with human TTR and increasing concentrations of TBBPA (1.95 – 500 nM). TBBPA displaced ^{125}I-T_4 with a half maximal inhibitory concentration (IC_{50}) of 7.7 nM, while unlabelled T_4 bound TTR with an IC_{50} of 80.7 nM, indicating that TBBPA has a 10-fold higher affinity to the TTR receptor than T_4.

TBBPA and 26 other PBFRs were investigated for the potential to compete with T_4 for binding to human TTR (Hamers, 2006). A mixture of ^{125}I-labelled and unlabelled T_4 (55 nM) was incubated with TTR and increasing concentrations of TBBPA or unlabelled T_4 up to 62.5 μM. TBBPA bound the receptors with an IC_{50} of 0.031 μM while T_4 bound TTR with an IC_{50} of 1.6 μM.

Thyroid hormone-like activity of TBBPA and related compounds was investigated in an assay measuring thyroid hormone-dependent production of growth hormone by GH3 cells (Kitamura, 2005a). The positive control, T_3 (0.001 – 1 nM), caused a concentration-dependent increase in growth hormone production in this assay. At a much higher concentration TBBPA (10 μM), but not bisphenol A (100 μM), caused significant increases in growth hormone production. These results suggest that TBBPA shows thyroid hormone-like activity at high concentrations compared to T_3. TBBPA (10 and 100 μM) had no inhibitory effect on the hormonal activity of T_3 (10 or 100 nM) in this assay.

Thyroid hormone receptor binding of TBBPA and related compounds was investigated using a competitive binding assay containing nuclear fractions of GH3 cells (Kitamura, 2005a). T_3 competitively inhibited the binding of ^{125}I-T_3 (0.1 nM) to thyroid hormone receptors with an IC_{50} of 3.28 nM. TBBPA had 1000-fold less affinity to the receptor compared to T_3 with an IC_{50} of 3.5 μM. Bisphenol A did not bind the receptors up to a concentration of 0.1 mM. Thyroid receptor binding of TBBPA and related compounds were also evaluated using a luciferase reporter assay in CHO-K1 cells transfected with thyroid hormone receptor α1 (TRα1) or β1 (TRβ1). In both TRα1 and TRβ1 assays, T_3 caused an increase in luciferase activity with an EC_{50} of ≈10 nM. TBBPA and bisphenol A had no activity up to a concentration of 0.1 μM. To determine the anti-thyroid hormone activity of TBBPA and related compounds, the substances were incubated with 10 nM T_3. TBBPA inhibited T_3 activity with an IC_{50} of ≈25 μM in both TRα1 and TRβ1 assays. However, cytotoxicity was seen with 50 μM TBBPA. No data were shown for bisphenol A. In contrast to earlier findings using a different cell line (Kitamura, 2005a), these results indicate that TBBPA is a thyroid hormone receptor antagonist.

A study used yeast assay systems to test the thyroid receptor binding activity of TBBPA (Shiizaki et al., 2010). Full length cDNA of the human thyroxine hormone receptor (TR) gene was expressed in yeast. Four chemicals suspected to have thyroid receptor binding activity, including TBBPA (10^{-9} – 10^{-4} M), tetramethylbisphenol A, 2-isopropylphenol, and o-t-

butylphenol were tested. All test chemicals showed agonist activity with both TRs. The activities of these test chemicals were rather weak (only at $>10^{-6}$ M), compared to the endogenous TR ligands. The most potent was TBBPA which significantly ($p < 0.01$) stimulated both TRα and TRβ forms, with a maximum agonistic activity at 2 μM. However, these effects of TBBPA shared the same pattern as other chemicals of this type, and were considered as nonspecific transcriptional regression.

Thyroid receptor activation potential of TBBPA and related compounds was investigated using a thyroid hormone-dependent rat pituitary GH3 cell line (Ghisari and Bonefeld-Jorgensen 2005). Thyroid hormone binds to the thyroid hormone receptor to induce cell proliferation. In this assay, TBBPA caused a significant increase in cell proliferation at 10 μM and 50 μM. When tested in the presence of 0.5 nM T_3, a small but significant additive effect was observed with 10 μM TBBPA. In the presence of fulvestrant, a high affinity thyroid receptor antagonist, the TBBPA response was inhibited to T_3 only levels. Increasing the concentration of TBBPA to 25 μM did not out-compete fulvestrant antagonism. The data indicated that the effect of TBBPA is thyroid hormone-like and is mediated through the thyroid receptor.

The agonist or antagonist activity at the thyroid hormone receptor of TBBPA was investigated using a T_3-dependent cell proliferation rat pituitary cell line assay (GH3) (Hamers, 2006). TBBPA (0.001 nM – 500 nM) was tested in the absence and presence of 0.25 nM T_3. In the absence of T_3, TBBPA had no effect on cell proliferation suggesting no T_3-like agonist activity. In the presence of 0.25 nM T_3, TBBPA (500 nM) potentiated the T_3 response by 23 %. Given that this experiment was only conducted once (n=1) it is not possible to draw any conclusions as to synergistic activity of TBBPA and T_3.

It was hypothesised that due to their structural similarity to thyroid hormones, some halogenated organic contaminants (HOCs) may also inhibit deiodinase (DI) enzymes which regulate thyroid hormone (TH) levels in peripheral tissues by activating/deactivating THs via deiodination (Butt et al., 2011). Therefore, the authors aimed to develop a liquid chromatography tandem mass spectrometry-based (LC-MS/MS) method to investigate the effects of TBBPA and other HOCs on DI activity in human liver tissue. The kinetics of DI activity was assayed by incubating (1 hour at 37ºC) human liver microsomes (diluted to 1 mg protein/mL in 0.1 M phosphate buffer) and various T_4 or rT_3 (isomer of T_3) concentrations (0-120 μM). Reactions were subsequently stopped using ice-cold methanol and "protecting" solution, processed and loaded onto SampliQ SPE cartridges for analysis. The resulting trends observed for T_4->T_3 and rT_3->3,3'-T_2 formation were reported to be consistent with previous studies using human liver microsomes. Further, the addition of iodoacetate (inhibitor of DI) at 10mM, completely inhibited the formation of T_3 and 3,3'-T_2. These results indicate that TBBPA (-3 to 4 log μM) incubated with T_4 inhibited T_3, rT_3 and 3,3'-T_2 formation in a dose-dependent manner with almost complete inhibition at the highest dose tested. Similar results were obtained from other HOCs tested. Based on these results, the authors suggested that inhibition of DI may be a mechanism for TH homeostasis disruption observed in vivo, though it was assumed that the HOCs including TBBPA behaved as competitive inhibitors to DIs.

TBBPA demonstrated both agonist and antagonist activity on thyroid hormone receptor activation in HepG2 cells, activating a transiently transfected thyroid hormone-responsive reporter at or above 10 μM and also inhibiting transactivation of the reporter by T_3 at 1 μM (Hofmann et al., 2009).

TBBPA inhibited luciferase expression induced by T_3 in human embryonic kidney HEK293 cells stably transfected with a construct that would allow the detection of changes in intracellular free T_3 by one or more of several potential pathways. In a follow-up experiment using a murine cerebellar cell line expressing the TRα1 receptor, TBBPA significantly interfered with TRα1-mediated gene expression using a genome-wide RNa-Seq approach (Guyot et al., 2014).

The effect of TBBPA on the normal function of the thyroid hormone receptor in African green monkey kidney cell line CV-1 (transfected with pGal4-L-TRβ) was examined (Sun et al., 2009). A luciferase gene reporter assay was used for the test and Gal4 responsive luciferase reporter and phRL-tk were used as internal control. Cytotoxicity was observed at 100 µM of TBBPA. In the gene reporter assay, TBBPA (up to 50 µM) showed an inhibitory or antagonistic activity to T_3 (10 nM) with an IC_{50} of 5.46 x 10-5 M ($p<0.01$).

Summary and Conclusions

In summary, TBBPA caused a decrease in T_4 levels in both the one-generation and two-generation reproduction studies. Based on the decrease in the T_4 levels observed in F_1 generation (both sexes) exposed to 100 and 1000 mg/kg bw/day in a two-generation reproductive study (Schroeder, 2003*), a NOEL of 10 mg/kg bw/day was determined for reduced T_4 levels in both male and female rats.

In the 28-day study T_3 levels were elevated in the males only, whereas in the 90-day study there was no effect on either sex. In the one-generation reproduction study, T_3 levels were elevated in F_1 females, and in the two-generation study, T_3 levels were decreased in the P_0 males. It was suggested that the variable effects seen on T_3 levels between sexes analysed in the studies might be explained by the different adaptive mechanisms based on gender and exposure duration (Van der Ven et al., 2008). Control T_3 levels are affected by merely changing housing conditions (Verwer et al., 2007). Based on these data, it is difficult to draw any conclusion from the T_3 results reported in vivo.

In general, the rat thyroid system is known to have a greater sensitivity to chemical and physiological perturbations than that of humans given the absence of thyroxine-binding globulin (TBG) in the rat serum (Tanabe, 1969; Capen, 1992 and 1994). While humans have both TBG and transthyretin, the affinity of TBG for T_4 is approximately 1000 times higher than for transthyretin. Therefore, in humans, TBG acts to maintain a stable level of T_4 in the bloodstream. For this reason, it is less likely that levels of T_4 levels will be affected by TBBPA in humans. The effects on other parameters such as the levels of T_3 and TSH as well as effects on the target organs are not consistent throughout different studies.

Differing results were obtained in in vitro studies with respect to the effect of TBBPA on thyroid hormone system. Binding studies indicated TBBPA has 10 to 50-fold higher affinity for TTR receptor than T_4 (Meerts et al., 2000; Hamers et al., 2006 and 2008). However, no such affinity for transthyretin was seen in vivo in rats (Meerts et al., 1999). Several in vitro studies investigated the receptor binding and activation of TBBPA. Two studies reported thyroid hormone-like activity of TBBPA in the rat pituitary tumour GH_3 cell line at high concentrations (Kitamura, 2005a; Ghisari, 2005), whereas in CHO-KI cells transfected with TRα1 and TRβ1, TBBPA caused anti-thyroid hormonal activity at high concentrations, (Kitamura, 2005a). In a recombinant yeast assay system expressing human thyroid receptor TRα or TRβ genes, TBBPA significantly stimulated both TRα and TRβ activity at 2 µM, but at 5

μM and higher concentration it was inhibitory to TRα and TRβ reporter gene activity. TBBPA also antagonised T_3-induced activity (35 nM for TRα or 1.5 nM for TRβ). In contrast, studies utilising the rat pituitary tumour GH_3 cell line found no thyroid receptor binding activity by TBBPA even at high concentrations (Schriks, 2005; Hamers, 2006).

In a human hepatocarcinoma HepG2 cell line, transacted with a thyroid hormone-responsive luciferase reporter gene, TBBPA showed antagonism to TR-mediated transcription at relatively low concentration (~1 μM), while it showed agonism at higher concentrations (10 μM) (Hofmann et al., 2009). TBBPA showed inhibitory effect against T_3–induced activation with an IC_{50} of 5.46 x 10-5 M in an African green monkey kidney cell line (CV-1) (Sun et al., 2009).

TBBPA treatment did not affect expression of phase II enzymes involved in thyroid hormones metabolism (Fini et al., 2012). However, in an in vitro study in human liver microsomes incubated with T_4, TBBPA was found to inhibit T_4-induced T_3, rT_3 and 3,3'-T_2 formation in a dose-dependent manner, with almost complete inhibition at the highest dose tested, suggesting its likely inhibition of deiodinase by TBBPA (Butt et al., 2011).

The observed decrease in serum T_4 levels in many repeated-dose studies with TBBPA reflects a reduction in circulating thyroid hormone functional reserve pool rather than lowering the circulating pool of active hormone (T_3), since T_4 is a pro-hormone and represents a circulating thyroid hormone reserve (Larsen and Zavacki, 2012). This is also evident from the observation that TBBPA did not produce thyroid histopathology alterations or changes in circulating TSH and T_3 levels in rats even at high doses. The circulating ultimate hormone T_3 pool was not depleted to a biologically significant level.

The absence of TBBPA-mediated effects on TSH, T_3 and tissue histopathology suggests that the observed reduction in serum T_4 levels is of low concern regarding potential adverse consequences on thyroid function. Mice treated daily with TBBPA at up to 1000 mg/kg for 90 days displayed no clinical signs, altered serum T_3, T_4 or TSH or histopathology (NTP, 2014), indicating that TBBPA actions on the thyroid may be specific for the rat.

Humans are known to have lower sensitivity to chemical-induced thyroid effects compared with rats. Parkinson et al. (2013) noted that, due to protection of circulating thyroid hormones by the protein chaperone thyroxine binding globulin (TBG) in humans, the plasma half-life of T_3 and T_4 in humans is considerably longer than in the rat. TBG is not present in rats. Accordingly, rats compensate for the more rapid turnover of circulating thyroid hormones by secreting more TSH, resulting in increased T_4 production. In effect, in order to maintain physiological homeostasis, Parkinson et al. (2013) concluded that rats need to have a 10-fold higher rate of T_4 production on a per unit body mass basis than humans.

Thyroid histopathology is a more sensitive indicator of thyroid status as compared to T_3 or T_4 serum concentrations (Jahnke et al., 2004). None of the many available studies with TBBPA reported marked histopathological effects on the liver, thyroid, parathyroid, or pituitary (Colnot et al., 2014). In humans, functionally significant changes in T_4 production during development are known to cause developmental delay, low body mass, brain developmental abnormalities and neurobehavioural developmental disorders (Di Liegro, 2008; Forhead and Fowden, 2014; Koibuchi, 2013; Negro et al., 2011). There were no observable neurological, neurodevelopmental or neuro-performance effects and no evidence of or neurobehavioural developmental disorders in a multigenerational study with TBBPA (Cope et al., 2015). Thus,

while circulating T_4, the functional thyroid reserve pool may have been reduced in the parental and F_1 generations in the multigenerational study, these effects were clearly not considered to be adverse since marked alterations were not noted in other parameters including TSH levels and histopathology. Therefore, minimal effects on thyroid hormone levels induced by high doses of TBBPA are not considered to be of relevance for human health under conditions of chronic exposure.

12.2.8.2 Other endocrine effects

Oestrogenic effect of TBBPA

The oestrogenic potential of TBBPA was studied in vivo in an uterotrophic assay. B6C3F1 female mice were surgically ovariectomised at four weeks of age (Kitamura et al., 2005b). At 8 weeks of age, mice (5 animals/group) were administered TBBPA (20, 100, 300 or 500 mg/kg bw/day) or 17β-oestradiol (50 μg/kg bw/day) once a day via the i.p. route for 3 days. At the conclusion of treatment, mice were sacrificed under anaesthesia and the uterus was removed and weighed. The body weight of mice was not affected by treatment. Administration of 17β-oestradiol (50 μg/kg bw/day) caused a significant increase in the uterus weight with the uterus/bw (mg/kg) increasing to 2157 mg/kg compared to the vehicle control of 435 mg/kg. The uterus/body weights (mg/kg) for 20, 100, 300 and 500 mg/kg bw/day TBBPA were 538, 594, 716 and 538 mg/kg, respectively. Due to the lack of a dose-response relationship and the fact that there was little difference in uterine weights between low and high dose groups, this study is considered inconclusive as to TBBPA's potential to cause oestrogenic activity in mice.

Uterotrophic assays were conducted on 36 chemicals (including TBBPA) suspected to be oestrogen receptor (ER) agonists/antagonists (Ohta et al., 2012). Ovariectomised C57BL/6J mice were assigned to one of 11 treatment groups for oestrogen receptor agonist/antagonist activity. Mice in the positive control were administered 17α-ethinyl oestradiol (EE), an oestrogen derivative. TBBPA (30, 100, 300, 1000 mg/kg bw/day) was administered to groups of mice for 7 consecutive days by oral gavage or subcutaneous injection (s.c.). For detection of antagonistic activity, mice were dosed test compounds in conjunction with a reference dose of EE (0.6 μg/kg bw s.c.). Mice were sacrificed 24 hours after the last dose and uteri were dissected and weighed. Both the wet weight (weight including luminal fluid) and blotted weight (weight after piercing and blotting on filter paper) of the uteri were measured (values not reported). TBBPA was negative for both agonist and antagonistic effects by both routes of exposure up to 1000 mg/kg bw/day. These results indicate that TBBPA does not directly interact with the oestrogen receptor.

The oestrogenic effect of TBBPA was measured in an in vitro cell proliferation assay using oestrogen-dependent human breast cancer cell line MCF-7 (Korner, 1998). The positive control, 17β-oestradiol, induced maximal cell proliferation at a concentration of 0.1 nM. While TBBPA also induced cell proliferation in this assay, it was several orders of magnitude less potent than the positive control, with the maximal cell proliferation induced at 20 μM. An EC_{50} was not obtained for 17β-oestradiol since lower concentrations (<0.01 nM) were not tested. Co-treatment with 5 μM tamoxifen completely antagonised the TBBPA-induced cell proliferation, suggesting that TBBPA binds to the oestrogen receptor.

Another study in the same cell line (MCF-7) was conducted to determine the oestrogenic potential of TBBPA, 3,3',5-tribromobisphenol A (TrBBPA), 3,5-dibromobisphenol A (DBBPA),

3-monobromobisphenol A (MBBPA) and bisphenol A (BPA) (Samuelsen, 2001). All of the test compounds bound to the oestrogen receptor. TBBPA had a binding affinity 25000 times lower than 17β-oestradiol and 12.5 times lower than BPA. Mono-, di-, tri-bromobisphenol A had binding affinities between these values. TBBPA and TrBBPA showed considerably lower affinity to the oestrogen receptor (ER) within the intact cells when incubated with 100 % human male serum compared to incubation with serum-free medium. This suggests that TBBPA and TrBBPA bind to serum proteins preferentially. While all test compounds induced cell proliferation, TBBPA induced only 27 % of maximal cell growth. The authors speculated that this could be due to cytotoxicity. Treated cells were further examined to study the induction of the oestrogen-specific pS2 protein and progesterone receptors. BPA (10 μM) induced the same amount of pS2 protein as 17β-oestradiol (1 nM). TBBPA (30 μM) was the least potent as it only induced half the amount of pS2 protein as 17β-oestradiol (1 nM). Also, TBBPA (30 μM) was the least potent in inducing progesterone receptors. These in vitro experiments indicate that compared to 17β-oestradiol, TBBPA has several orders of magnitude lower oestrogenic potency.

A study determined the oestrogenic activity of 73 phenolic substances including TBBPA (Miller, 2001). Yeast cells were transfected with the human oestrogen receptor α gene and expression plasmids containing oestrogen-responsive elements and *lac*-Z reporter gene encoding the enzyme β-galactosidase. The cells were incubated with the test chemicals in a medium containing chlorophenol red-β-D-galactopyranoside. All chemicals were tested at least twice. The median effective dose (ED_{50}) for 17β-oestradiol was 0.2 nM in this assay, while TBBPA did not induce any oestrogenic activity.

The oestrogenic activity of several polybrominated diphenyl ethers and brominated bisphenol A compounds, including that of TBBPA, was determined using a human T47D breast cancer cell line stably transfected with an oestrogen-responsive luciferase reporter gene construct (Meerts, 2001). The test substances were tested up to 10 μM. In this assay, TBBPA was found to induce less than 1 % of the maximum luciferase activity induced by 17β-oestradiol.

The binding affinities of TBBPA and related compounds to oestrogen receptors were investigated using the human oestrogen receptor α isolated from MCF-7 cells (Olsen, 2003). Oestrogen receptors were incubated with unlabelled 17β-oestradiol or TBBPA or other test substances in the presence of 2 nM radiolabelled 17β-oestradiol. While 17β-oestradiol and bisphenol A had IC_{50} values of 1.66 nM and 1.77 μM respectively, TBBPA showed considerably lower affinity to the oestrogen receptor with an IC_{50} of 25 μM. The potency of TBBPA and related compounds in stimulating the growth of MCF-7 cells was investigated using a cell proliferation assay mediated by the oestrogen receptor-signal pathway. In terms of relative proliferative potential, bisphenol A was ~60000 lower than 17β-oestradiol. Since TBBPA (10 μM) only induced a maximum of 22 % increase in cell growth compared to 17β-oestradiol (1 nM), relative proliferative potential could not be determined. This study also investigated the expression of pS2, PgR and cytosolic oestrogen receptors in the MCF-7 cells in response to TBBPA and related compounds. These proteins are expressed in the presence of oestrogen activity. TBBPA (concentration not indicated), 17β-oestradiol and bisphenol A caused significant increases in pS2 and PgR proteins. However, TBBPA (concentration not indicated) did not cause any significant increase in oestrogen receptors.

A comparative study of the oestrogenic activity of TBBPA and related compounds was undertaken (Kitamura, 2005a). Oestrogenic activity of TBBPA and related compounds was

examined using an oestrogen response element (ERE)-luciferase reporter. ERE-luciferase reporter assay in MCF-7 cells. The anti-oestrogenic activity was also determined using the same assay by investigating the inhibitory effect of TBBPA and related compounds on the oestrogenic activity of 17β-oestradiol (0.01 or 0.1 nM). Although the concentration-response curve was not shown, it was reported that TBBPA caused oestrogenic activity with an EC_{50} of 19 μM. The oestrogenic activity of TBBPA was 30-fold less than that of bisphenol A in this assay. In the assay for anti-oestrogenic activity, 10 μM TBBPA inhibited the oestrogenic activity of 0.01 nM and 0.1 nM 17β-oestradiol by about 50 %.

TBBPA was investigated for agonist or antagonist activity at the oestrogen receptor using T47D human breast cancer cells and the chemically activated luciferase expression (CALUX) assay (Hamers, 2006). The positive control for oestrogenic agonist activity was 17β-oestradiol, and ICI 182,780 was used for antioestrogenic activity. TBBPA was tested at a maximum concentration of 10 μM in the absence or presence of 17β-oestradiol and did not show any agonist or antagonist activity at the receptor.

The oestrogenic effects of TBBPA were investigated in vitro in MCF-7 cells (breast cancer cell line) that express ER-mediated TFF1 gene (Dorosh et al., 2011). MCF-7 cells were exposed to various concentrations of TBBPA (up to 20 μM), and the effects were compared with known oestrogens (oestrone (E1), 17-β-oestradiol (E2) and oestriol (E3)) and an anti-oestrogen, fulvestrant (ICI 182, 780). Cell proliferation was assessed using the MTT assay (cell viability assay). Changes in the expression of TFF1 gene following TBBPA exposure was quantified using quantitative PCR. Compared with controls, cell growth and TFF1 gene expression were not altered by TBBPA exposure at any concentrations tested. Under the conditions of the study, TBBPA did not show any oestrogenic effect up to 20 μM.

Androgenic effects of TBBPA

The androgenic activity of TBBPA was studied in in vitro using NIH3T3 cells transfected with an androgen receptor (AR) responsive luciferase reporter gene (Kitamura et al., 2005b). While dihydrotestosterone caused marked androgenic activity at NIH3T3 cells at low concentrations (at 0.01 nM – 1 nM), TBBPA had no androgenic activity up to 10 μM. Anti-androgenic activity was determined using the same assay by investigating the inhibitory effect of TBBPA and related compounds on the androgenic activity of 0.01 or 0.1 nM dihydrotestosterone. While bisphenol A was found to have anti-androgenic activity, no activity was observed for TBBPA up to 10 μM.

TBBPA was investigated for androgenic and antiandrogenic activity in U-2 OS (human osteoblast) cells and the CALUX assay (Hamers, 2006). The positive control for androgenic activity was dihydrotestosterone and for antiandrogenic activity was flutamide. TBBPA had no androgenic or antiandrogenic activity in this assay up to 10 μM.

Androgenic and anti-androgenic activity of TBBPA *in vitro* were examined using an androgen-sensitive cell line, MDA-kb2, which is a human breast cancer cell line (Christen et al., 2010). TBBPA was toxic to MDA-kb2 cell at concentration higher than 50 μM. While TBBPA did not show androgenic activity, weak but dose-dependent anti-androgenic activity was observed in the concentration ranges 10 to 50 μM.

In an in vitro study (Roy et al., 2004), the Chinese hamster ovarian cell line (CHO) was modified by cotransfecting with plasmids encoding mouse mammary tumour virus-

neomycin-luciferase and human androgen receptor (hAR), referred to as the CHO-AR-Luc cell line. The cell line was functionally characterised by known androgen-like agonists and antagonists, and confirmed for its luciferase activity, and then used as a cell-based androgen reporter assay for screening of some anti-androgenic endocrine disruptors. Large groups of about 60 chemicals including TBBPA were screened by incubation for 24 hours with the CHO-AR-Luc cell line for their ability to stimulate luciferase activity or to inhibit response that evoked by 0.1 nM R1181 (a potent steroid agonist). TBBPA showed neither androgenic agonist-like nor antagonist-like effects on luciferase activity in the CHO-AR-Luc cell system.

Effect on aromatase activity

The effects of TBBPA and polybrominated diphenyl ethers on steroidogenesis were studied using the human adrenocarcinoma H295R cell line, which is known to express all the key enzymes of steroidogenesis (Song et al., 2008). Following exposure to 0, 0.025, 0.05 and 0.5 μM TBBPA for 48 hours, the cells were assessed for viability by a sulforhodamine B (SRB) assay. Changes in the expression of genes associated with steroidogenesis were quantified using real-time quantitative polymerase chain reaction (PCR). An aromatase enzyme-linked immunosorbent assay (ELISA) was used to measure the activities of CYP19 and hormones, testosterone and 17β-oestradiol (E2). Aromatase is a key steroidogenic enzyme that catalyses the conversion of androgens to oestrogens. CYP21 forms part of the aromatase enzyme complex. Based on the results, TBBPA did not affect the expression of the majority of the genes tested, except for the 1.4-fold upregulation of CYP21 gene at an effective concentration of 0.5 μM. Aromatase activity was not affected by TBBPA exposure.

Studies were undertaken to determine the effects of TBBPA on aromatase (CYP19) activity in H295R human adrenocortical carcinoma cells (Canton et al.,2004 and 2005). Aromatase mediates the conversion of androgens to oestrogens, and induction of this enzyme will increase oestrogen production. In this assay, TBBPA (0.5-7.5 μM) did not induce aromatase activity, and in inhibition studies TBBPA (2.5-7.5 μM) had no significant effect. These studies suggest that TBBPA does not affect hormone levels via this pathway.

The inhibitory and inductive effects of TBBPA and related compounds on CYP17 activity were reported in a conference proceedings (Canton et al.,, 2004). CYP17 enzyme is responsible for the biosynthesis of dehydroepiandrosterone (DHEA) in the adrenals. The catalytic activity of CYP17 enzyme was determined in the presence of test substance and precursor (0.1 μM pregnenolone) using a human adrenocortical carcinoma cell line (H295R). The production of DHEA was measured using a radioimmunoassay kit. TBBPA (0.01-10 μM) induced a concentration-dependent increase in CYP17 activity. While there was no indication whether the effect was statistically significant, the CYP17 activity was 2-fold higher compared to the control in the presence of 10 μM TBBPA. This study suggests a new possible pathway for endocrine activity of TBBPA.

Progesteronic activity

TBBPA was investigated for progestagenic and antiprogestagenic activity using the U-2 OS (human osteoblast) cells and the CALUX assay (Hamers, 2006). The positive controls for progestagenic activity were medroxyprogesterone and for antiprogestagenic activity was RU-486. TBBPA had no progestagenic or antiprogestagenic in this assay up to 10 μM.

Other receptor binding sites

The potential effects of TBBPA and other halogenated analogues of BPA on oestrogen receptors (ERs) and peroxisome proliferator-activated receptors (PPARs) were investigated, using a luciferase reporter cell line derived from HeLa cells (HGELN cell line) which was stably transfected with plasmids containing human ER and PPAR (Riu et al., 2011). TBBPA (10^{-4} M-10^{-13} M) was found to have little effect on ERα, ERβ, PPARα and PPARδ, while it appeared to partially activate PPARγ in a clear dose-dependent pattern, and the potency was ~100-fold lower than rosiglitazone. A competitive binding using the HGELN- PPARγ cell line and [^{3}H]-rosiglitazone gave an IC_{50} of 0.7 µM for TBBPA, compared to 12.0 nM for rosiglitazone (control). TBBPA (10 µM) alone induced adipogenesis (a function regulated by PPARγ activation) in NIH3T3L1 preadipocytes, and the effect did not occur when a combination of TBBPA and CD5477 (a PPARγ antagonist) was used, suggesting an agonist effect of TBBPA on adipogenesis. Using real time PCR assay, TBBPA induced similar levels of PPARγ expression, whereas AP2 expression was lower, compared with rosiglitazone, reflecting the partial agonism of TBBPA to PPARγ. Crystallography analysis was performed on the PPARγ-TBBPA complex to investigate the binding mechanism. The resolved PPARγ-TBBPA complex showed that TBBPA occupied a smaller region of the PPARγ ligand-binding pocket due to its small size compared to rosiglitazone which occupies a region spanning to C-terminal helix H12. Further, TBBPA was found to engage only two hydrogen bonds with PPARγ compared with five for rosiglitazone. These results are consistent with reports that partial agonists of PPARγ activate PPARγ independent of H12 (Bruning et al., 2007). Altogether, these observations support that TBBPA acts as partial agonist of PPARγ. However, results from in vivo studies are required to determine whether the extent of partial agonism in this study translates to an observable biological effect.

Effect on aryl hydrocarbon receptors

TBBPA was investigated for its potential to activate of the aryl hydrocarbon receptor (AhR) and AhR-signal transduction pathway (Brown, 2004). AhR binding and activation was studied using a gel retardation assay (GRA) and induction of AhR-dependent genes was detected using the CALUX assay. The GRA measured the ability of TBBPA to transform the AhR into its DNA binding form, and the experiment was performed using guinea pig hepatic cytosol and ^{32}P-labelled dioxin responsive element (DRE)-containing oligonucleotide. The ligand:AhR:^{32}P-DRE complex was resolved by gel retardation chromatography and expressed as a percentage of the positive control (20 nM 2,3,7,8-tetrachlorodibenzo-*p*-dioxin) response. TBBPA (20 µM) induced a weak response that was only 12 % of the positive control response. In the CALUX assay utilising recombinant mouse hepatoma (Hepa1c1c7) cells the positive control, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) caused a concentration-dependent increase in luciferase activity with an EC_{50} of 0.03 nM. TBBPA showed no activity in this assay up to a concentration of 10 µM. This study indicates that TBBPA has weak or no activity at the AhR.

TBBPA and 26 other PBFRs were investigated for dioxin-like activity mediated via the AhR receptor using the CALUX assay (Hamers, 2006). TCDD was the positive control. For studies conducted to determine anti-dioxin like activity, PCB-128 was the positive control. In this assay, TBBPA had no dioxin-like or anti-dioxin like activity up to 10 µM.

Several classes of test substances, including TBBPA, were tested for potency of AhR activity. Congener-specific relative potencies (REPs) and efficacies (% of TCDDmax) were also

evaluated, and concentration response curves for each test compound were produced. The data were analysed according to WHO criteria for dioxin-like compounds. When ranked by REP values, TBBPA was one of the most potent compounds tested, with an EC_{50} 2.6 x 10^{-6} pM and an efficacy of 46 %.

Summary

There is so far no clear in vivo evidence for TBBPA showing any oestrogenic activity. Three in vitro studies (Korner, 1998; Samuelsen, 2001 and Olsen, 2003) have shown that TBBPA binds to the oestrogen receptor and mimics oestrogen in the oestrogen-dependent human breast cancer MCF-7 cell line assay. However, TBBPA was at least 10000-fold less potent than 17β-oestradiol and 10 to 30-fold less potent than BPA in terms of oestrogenic activity. One study (Kitamura, 2005a) reported that TBBPA demonstrated both oestrogenic and anti-oestrogenic activity at high concentrations in the MCF-7 cell line assay. Given the full concentration-response curve was not shown, it is not possible to determine whether TBBPA was a partial agonist for the oestrogen receptor investigated. In contrast to studies undertaken with the MCF-7 cell line assays, TBBPA had no significant oestrogenic activity in studies using the yeast cells and human T47D breast cancer cell line assays containing the oestrogen receptor (Meerts, 2001; Miller, 2001 and Hamers, 2006). Overall, TBBPA displays weak oestrogenic activity, depending on the in vitro assay utilised. One study showed that TBBPA could inhibit oestradiol sulfotransferase enzymes (Hamers, 2006).

In androgen-sensitive MDA-kb2 cell line, TBBPA (10 - 50 µM) did not show androgenic activity, whereas weak but dose-dependent anti-androgenic activity was observed in a luciferase assay (Christen, et al., 2010). In another in vitro study with CHO-AR-Luc cell line (Roy et al., 2004), TBBPA showed neither agonist-like nor antagonist-like effects on AR-mediated luciferase activity.

In several other studies, TBBPA had no androgenic or anti-androgenic activity and no progestogenic or antiprogestogenic activity (Roy, 2004; Kitamura, 2005a; Hamers, 2006; Hamers et al., 2008 and Riu et al., 2011).

TBBPA had no activity at the AhR receptor in many cell lines (Brown, 2004; Hamers, 2006), consistent with its non-planar structure, except in one study ((Behnisch et al., 2003) where TBBPA was a relatively potent agonist in AhR based cell bioassays in two different rat liver cell lines. While TBBPA did not affect aromatase (CYP19) activity (Song et al., 2008), it induced CYP17 enzyme activity in some cell lines (Canton et al., 2004 and 2005), but not all (Canton et al., 2006). In the human adrenocarcinoma H295R cell line, TBBPA did not affect the expression of the majority of genes for steroidogenesis, except for CYP21 gene where 0.5 µM TBBPA induced 1.4-fold up-regulation of the gene expression (Song et al., 2008).

TBBPA was shown to act as partial agonist of PPARγ. Some interactions of TBBPA with hormone-mediated pathways were noted in vitro; however, when studied in vivo, TBBPA did not produce adverse effects that might be considered to be related to disturbances in the endocrine system. Therefore, in accordance with internationally accepted definitions, TBBPA is not considered an "endocrine disruptor."

12.2.9 Immunotoxicity

The immunotoxic potential of TBBPA was investigated in in vitro assays by determining the induction of cytochrome P450 1A1 (CYP 1A1) in C57BL/6 mice hepatocytes and inhibition of interleukin-2 receptor α chain (CD25) in splenocytes (Pullen, 2003). TBBPA (2 µM) caused no significant induction of CYP1A1, suggesting that it is not likely to cause immunotoxicity via the aryl hydrocarbon receptor (AhR) gene complex. However, when splenocytes were incubated with concanavalin A and TBBPA (3 µM) for 48 h, significant attenuation of CD25 expression was observed compared to the control. The authors reported that this is indicative of a possible immunosuppressive effect. Given that multiple concentrations of TBBPA were not investigated, it is not possible to determine whether this effect is concentration–dependent.

TBBPA was not found to be cytotoxic to splenocytes of bone marrow from NC/Nga mice in an in vitro study investigating the immunological effects of TBBPA. Treatment with TBBPA was found to increase the expression of major histocompatibility complex II (MHC II) molecules, CD86 (co-stimulatory protein for T-cell activation), T-cell receptors, DEC205 (mature dendritic cell marker) and interleukin-4 (IL-4) (Koike et al., 2013).

Using a respiratory syncytial virus mouse model, the effects of TBBPA on host immunity were investigated in female BALB/c mice (Watanabe et al., 2010). TBBPA (1 % in diet) and TBBPA was found to significantly increase levels of inflammatory cytokines and decrease levels of anti-inflammatory cytokines. Histopathological analysis also showed higher levels of inflammation in the lungs of TBBPA-treated mice. Apart from an increase in the population of CD4+/CD8+ T-lymphocyte cells, no other differences in immune cell populations were found. Though the authors concluded that these cells represented a population of immature T-cells, mature populations of CD4+/CD8+ T-cells have also been reported in the literature (Overgaard et al., 2015).

A one-generation reproduction study described earlier (Section 12.2.5), was enhanced for immunological endpoints (Van der Ven et al., 2008). Whole blood, bone marrow, from one femur, and the spleen were sampled for analysis of immune cell subpopulations and/or splenocyte natural killer activity. TBBPA treatment had no effect on any of the immunological endpoints measured, including blood and bone marrow immune cell subpopulations and splenocyte natural killer activity.

Overall, the immunotoxicity of TBBPA is unclear. While TBBPA appears to exacerbate the immune response in the in vivo mouse study (Watanabe et al., 2010), no effects on the immune system were detected in rats. However, as the in vivo mouse study was not guideline-compliant, study results could not be validated. Despite evidence that TBBPA may suppress the immune system from the in vitro splenocyte assay, there is no conclusive evidence of TBBPA supressing the immune system in vivo.

12.3 Other in vitro studies

A study was undertaken to investigate the effects of nine commercially available BFRs on the uptake of dopamine, glutamate and γ-amino-*n*-butyric acid (GABA) into male rat (Wistar) brain synaptosomes and to determine the effect of TBBPA, HBCD and pentaBDE on vesicular uptake of dopamine (Mariussen, 2003). TBBPA inhibited neurotransmitter uptake in a concentration-dependent manner. The IC_{50} values for the inhibition of dopamine, glutamate and GABA uptake into synaptosomes were 9, 6 and 16 µM, respectively. TBBPA also inhibited vesicular dopamine uptake with an IC_{50} of 3 µM. While this study shows that TBBPA affects

the uptake of neurotransmitters by brain synaptosomes and vesicles in vitro, in the absence of supporting in vivo studies it is difficult to extrapolate these findings to the in vivo situation and draw conclusions on the neurological consequences.

In vitro toxicity (calcium imbalance, oxidative stress and mitochondrial dysfunction) of TBBPA to neurons (cerebellar granule cells; CGCs) was studied (Zieminska et al., 2012)). In this study, CGCs from 7-day old rats were exposed to TBBPA, at concentrations 10 – 50 μM for 30 min. TBBPA showed a tendency to reduce the number of live cells at 10 μM, and was significantly toxic at 25 and 50 μM. TBBPA (25 μM) showed moderate but significant enhancement of ^{45}Ca uptake.

In an in vitro study, TBBPA interfered with cellular functions that led to cell death in CGCs from 7-day old rats (Reistad et al., 2007). Treatment with TBBPA (2-20 μM) for 24 hours caused death of CGCs in a dose-dependent manner, with statistical significance at 10 and 20 μM (85-100 % cell deaths,) and an estimated median lethal concentration (LC_{50}) of 7 μM. The cell deaths caused by 10 μM TBBPA were significantly reduced by the N-methyl D-aspartate (NMDA) receptor antagonist, MK-801, at 3 μM (by 86 %) and the antioxidant vitamin E at 50 μM (by 60 %). TBBPA-induced cell death was reduced by 68 % in the presence of rat liver S9 fraction, indicating that TBBPA is the ultimate toxicant responsible for cell death.

TBBPA was found to be cytotoxic to SH-SY5Y human neuroblastoma cells (Al-Mousa and Michelangeli, 2012). In this study, TBBPA caused dose-dependent reduction of cell viability, with a LC_{50} of 15μM. TBBPA also caused dose–dependent and significant increase in caspase activity (a protease enzyme important in apoptosis) over the concentration ranges tested (at 1, 5 and 30 μM). The caspase inhibitor, Z-IETD-FMK, afforded significant protection from cell death, indicating that cell death is at least partially by apoptosis through activation of caspases. Additionally, the following effects were also reported in TBBPA-exposed neuronal cells: rapid polarization of the mitochondria; increased intracellular calcium levels; release of cytochrome C and formation of reactive-oxygen-species. Elevated intracellular calcium levels appear to occur through a mechanism involving microsomal Ca^{2+}-ATPase inhibition which may be responsible for Ca^{2+}-induced mitochondrial dysfunction.

A study investigating the in vitro toxicity of TBBPA to cultured rat embryos was described in a briefly reported abstract (Akita, 2004). At day 11.5 of gestation, rat embryos were removed and cultured in a medium containing TBBPA (1 or 1000 ppm) for 48 h. Embryo, placenta and the yolk sac were fixed in Bouin's solution and subjected to histological examination. At the doses tested, no significant changes were observed in the eyeball, nasal cavity, epithelial cells or other organs of the embryos and no significant changes were observed in the placenta or yolk.

The in vitro cytotoxic effects of TBBPA and its interaction with the mitogen-activated protein (MAP) kinase pathway were reported briefly in conference proceedings (Strack, 2004). TBBPA caused cell death in the normal rat kidney (NRK) epithelial cell assay with a calculated LC_{50} of 52 μM. TBBPA was less toxic to the human epithelial alveolar type II-like lung cells (A549) and human thyroid anaplastic carcinoma cells (Cal-62) with a LC_{50} of 168 μM and 200 μM, respectively. Incubation with TBBPA caused decreased growth rate of NRK cells at 25 μM, and the growth rates of the other two cell lines were reduced at >75 μM. The interaction with the MAP kinase pathway was determined by the activation or deactivation of extracellular signal-regulated protein kinases (ERK 1 and 2). In Cal-62 cells, ERK activation

peaked at 100 μM TBBPA, and in NRK and A549 cells, ERK activation decreased 25 μM TBBPA.

In conclusion, although TBBPA is cytotoxic to cells (including neurons) in vitro, this was only observed at high concentrations. Suggested mechanisms of action underlying the in vitro toxicity of TBBPA include pathways associated with apoptosis, reactive oxygen species and disruption of cellular homeostasis and neurotransmitter uptake.

12.4 Effects in Humans

12.4.1 Toxicokinetics

Three male and two female healthy volunteers were given a single oral dose of TBBPA (0.1 mg/kg bw) in a gel capsule (Schauer, 2006). Urine samples were collected at predetermined intervals (0, 3, 6, 9, 12, 15, 23, 27, 32, 36, 39, 47, 53, 58, 63, 71, 77, 82, 87, 95, 101, 124 and 178 h). Blood samples were also taken at predetermined intervals (0, 1, 2, 4, 6, 8, 12, 24, 32, 36, 48, 60, 72, 84, 96, 124 and 178 h). Blood and urine were spiked with the internal standards D_{16}-bisphenol A and D_{14}-bisphenol A glucuronide and analysed for TBBPA and its metabolites (TBBPA-glucuronide and TBBPA-sulfate) by liquid chromatography/mass spectrometry-mass spectrometry (LC/MS-MS).

In plasma, the parent TBBPA molecule was not seen at any time point. However, the metabolite TBBPA-glucuronide was detected in the blood of all volunteers for up to 72 h after administration of TBBPA (Schauer, 2006). Between 2 and 6 h after TBBPA administration, TBBPA-glucuronide in the blood reached a peak concentration of 16 nM, and then slowly decreased over time. The half-life of TBBPA-glucuronide in the blood was estimated to be 26 h. TBBPA-sulfate was detected in the blood of only 2 volunteers. In these subjects, concentrations peaked to 20 nM, between 4 and 6 h after the oral administration of TBBPA. At 8 h post-dosing, the levels of TBBPA-sulfate had declined to the limit of detection (value not reported). TBBPA-glucuronide was detected in all urine samples and peaked to a concentration of 4 nM at 63 h. The urinary concentration of the metabolite reached the limit of detection at 96 h post administration. Less than 0.1 % of administered TBBPA was recovered as TBBPA-glucuronide in urine. TBBPA-sulfate was below the limit of detection in all urine samples. These results suggest that TBBPA undergoes absorption in the gastrointestinal tract and metabolism to TBBPA-glucuronide and TBBPA-sulfate but minimal urinary excretion. The systemic bioavailability of TBBPA after oral administration is low due to efficient hepatic metabolism and biliary excretion.

The half-life of TBBPA in the blood of four workers at an electronics dismantling plant in Sweden was investigated (Hagmar, 2000). TBBPA was present in all serum samples collected from the four workers just prior to the vacation, with a range of 2.1 – 7.4 pmol/g lipid. During the vacation, the concentration of TBBPA in the blood decreased to levels under the limit of quantification (<2 pmol/g lipid). The half-life of TBBPA in the blood was estimated to be 2.2 days (95 % CI 1.4-2.9 days).

12.4.2 Skin Sensitisation

TBBPA was investigated for its skin sensitisation potential in a modified Draize multiple insult patch test (*International Research and Development Corporation, 1978c). A 50-70 % concentration of TBBPA (≈3 to 5 mg in water) made to a thick paste was applied occlusively to the upper arm of 54 human volunteers. The induction patches were applied for a 48-72 h period every other day or every third day for a total of 10 induction exposures. The same site was used for all induction exposures and the site was examined for reactions after removal of each patch. At 10 to 14 d after the last induction exposure, the subjects were challenged with the same concentration of TBBPA as in the induction exposure but at a site (location not specified) distinct from the induction site. The challenge exposure was for a period of 48 h, and the site was examined at 48 and 72 h post application.

One subject had either a low-grade erythema or a "questionable" reaction during the induction exposures, and 3 other subjects had questionable reactions. A questionable reaction was considered to be a reaction that was not a true irritant reaction or when the presence of the reaction was uncertain. With the challenge exposure, 1 out of 54 subjects had a low-grade erythema. The authors of the study considered this reaction to be an irritant reaction that was aggravated by the tape of the occlusive patch. Overall, the study indicates that TBBPA is not a skin sensitiser in humans. Therefore, TBBPA is not considered to be a skin sensitiser.

12.4.3 Epidemiological Studies

The association between exposure to brominated flame retardants (BFRs), including TBBPA, and neurobehavioural functions in Flemish adolescents was investigated (Kicinski et al., 2012). The association between BFRs and thyroid function was also investigated as a mechanism of neurotoxicity for these chemicals.

Participants (13.6-17 years old) were recruited from two industrial areas (Genk and Menen) and from the general population in Flanders, Belgium, between 2008 and 2011. Participants were recruited by letters or home visits. Although the response to the call for participation was low (22.1 % for general population, 34.3 % in Genk and 22.5 % in Menen), a separate analysis of non-responders conducted by the authors from a group of 106 did not show differences in socio-economic status.

Prior to study commencement, participants received questionnaires including information on smoking, alcohol use, diet and socioeconomic status. The neurobehavioural tests administered during the study session included Continuous Performance (attention), Digit-Symbol (visual scanning and information processing), Digit-span (working memory) and Finger-tapping (motor function) tests. Blood samples, height and weight measurements were also taken during the study session. Data from 515 out of 606 participants were used in multiple regression models, accounting for potential confounders to analyse the association between BFRs, cognitive performance and thyroid hormone levels. Serum levels of TBBPA were not found to be significantly associated with performance in neurobehavioural tests or thyroid hormone levels. From the results of the study, there was no evidence that exposure to TBBPA is associated with neurobehavioural function or thyroid hormone levels in blood.

13 Human Health Hazard Characterisation

13.1 Physicochemical hazards

TBBPA is a white free flowing crystalline powder. While a boiling point of ≈250 °C was measured, this is considered to be the decomposition temperature rather than the actual boiling point temperature (DSBG, 2003). TBPPA has no flash point and does not undergo autoignition. It is not expected to have explosive properties based on its physical properties and chemical structure.

According to the ADG Code (FORS, 1998), TBBPA does not meet the criteria for classification as a dangerous good on the basis of its physicochemical hazards.

13.2 Health Hazards

13.2.1 Acute toxicity

In a toxicokinetics study, 3 male and 2 female human volunteers were given a single oral dose of TBBPA (0.1 mg/kg bw) in a gel capsule (Schauer, 2006). No signs of toxicity were reported. There are no other studies providing information on acute toxicity in human subjects.

Several acute oral studies have been undertaken in both rats and mice (refer Table 23). These studies showed that TBBPA has very low acute oral toxicity with no LD_{50} reported under 5000 mg/kg bw. In one briefly reported range-finding study, no mortality was observed but slight liver damage and questionable kidney damage were seen in rats orally exposed to 1000 mg/kg bw TBBPA (The Dow Chemical Company, 1958a). The study also reported moderate liver and kidney damage with TBBPA doses of 2000 and 4000 mg/kg bw. These pathological findings were not reported in other studies. With no signs of toxicity and deaths in a limit test study conducted under GLP and to current regulatory standards, an acute oral LD_{50} of >5000 mg/kg bw was established in rats (Malloroy et al., 1981e). In mice, the studies indicate a very low acute oral toxicity with a LD_{50} of >10000 mg/kg bw.

Two acute inhalation studies are available. In one study, rats, mice and guinea pigs were exposed (whole body) together (5 animals/sex/species) in a stainless steel inhalation chamber for 8 h to an aerosol of 0.5 mg/L TBBPA. No mortality, toxic effects or pathological lesions were observed. The LC_{50} was determined to be >0.5 mg/L TBBPA. Another study indicated a LC_{50} of >1.3 mg/L for 1 h in male Dublin strain rats. These two studies show that TBBPA has no toxic effects via the inhalation route at the concentrations tested.

Based on a well-conducted limit test study, carried out according to GLP, in New Zealand White rabbits (5 males and 5 females), a dermal LD_{50} of >2000 mg/kg bw TBBPA was determined (Malloroy et al., 1981a). No mortality occurred in this study and no toxic effects were seen, other than slight erythema and oedema in one male on day 1. No gross lesions were evident at autopsy. In a reportedly less well-conducted study in albino rabbits, a dermal LD_{50} of >10000 mg/kg bw TBBPA was determined (Hill Top Research Inc., 1966, Num: 263). Two other reportedly poor studies observed no deaths when rabbits were dermally treated with 200 or 3160 mg/kg bw TBBPA (Leberco Laboratories, 1958b; EHC, 1995).

13.2.2 Irritation and Corrosive Effects

Three skin irritation studies have been conducted in rabbits. In one study, where TBBPA (500 mg) was applied occlusively to 3 intact and 3 abraded skin animals for 24 h, a mean oedema score of 1 and 0 was seen in animals with abraded skin at 24 h and 72 h, respectively. In the same animals, the mean score for erythema was 0 and 0.3 at 24 h and 72 h, respectively. No irritation was observed in animals with intact skin. Two other studies, including one conducted under GLP, found no irritation when TBBPA (500 mg) was applied for a 24 h exposure period. These studies suggest that TBBPA is not an irritant to skin.

There are no human data indicating that TBBPA is irritating to skin, eye or the respiratory system. A repeated-dose inhalation study in rats (5 males and 5 females/ group) exposed whole body to 0, 2, 6 or 18 mg/L TBBPA particulate aerosol for 4 h/day and 5 days/week for 2 weeks reported excessive salivation, nasal discharge and excessive lacrimation in a dose-dependent manner following treatment (*International Research and Development Corporation, 1975). No other toxicological effects or histopathological changes were evident. Given the lack of chemical reactivity of the TBBPA molecule, and in the absence of similar findings in the acute inhalation studie,s the observed effects are considered to be due to the mechanical irritation from high dust concentrations used in the study. Therefore, TBBPA is not considered to be an irritant to the respiratory system.

13.2.3 Sensitising Effects

There are no human or animal data indicating that TBBPA causes sensitisation by inhalation.

In the only available human study, a 50-70 % concentration of TBBPA (~3-5 mg in water) paste was tested in 54 volunteers using a modified Draize multiple insult test (International Research and Development Corporation, 1978c). With the challenge exposure, 1 out of 54 subjects had a low-grade erythema. However, this reaction was considered to be an irritant reaction, aggravated by the tape of the occlusive patch. Overall, the study indicated that TBBPA was not a skin sensitiser in humans.

Two guinea pig studies (neither conducted according to OECD guidelines) investigating the sensitisation potential of TBBPA have been reported (EURAR, 2006; Malloroy et al., 1981e). In the slightly modified Buelhler test, application of 500 mg TBBPA occlusively to shaved skin (induction) was followed by a challenge with the same concentration 14 days later. While positive responses were observed with the positive control (2,4-dinitrochlorobenzene). In the other guinea pig study, 0.1 % TBBPA was injected intradermally into the shaved skin (induction), and again, 14 days later, challenged with the same concentration, intradermally. No treated animal showed a skin reaction at the challenge site. Overall, these studies suggest that TBBPA is not a skin sensitiser.

13.2.4 Effects from Repeated or Prolonged Exposure

Seven repeated dose dietary studies in rats and two in mice have been conducted using TBBPA. Table 24 provides the results of these studies. No serious adverse effects were noted in experimental animals with TBBPA up to 1000 mg/kg bw/d. Increases in absolute and relative liver and spleen weights were consistently noted in these studies. In some studies,

induction of liver enzymes was also demonstrated, leading to the suggestion that increase in liver weight is due to enzyme induction. The same study reported dose-related effects on the thyroid axis, i.e. decreased total thyroxin (TT4), increased pituitary and thyroid weight and thyroid follicle cell activation. The postulated mechanism for these changes is that the hepatic enzymes involved in the metabolism of T_4/ T_3 are induced by TBBPA, leading to increased excretion of T_4 and consequently, by feedback mechanism, to induction of TSH and T_4 production with thyroid weight increase.

In two 90-d oral toxicity studies in rats, the clinical chemistry changes, although significant, were not considered of sufficient magnitude to be adverse, as they also occurred in otherwise clinically-normal animals and tended to be within or close to historical or control values.

Table 24 – Summary of repeat-dose studies

Study	Dose mg/kg bw/day	Effects	NOAEL	References
ICR mice, 14-d, gavage	350, 700, 1400	Increased incidence of hepatocyte focal necrosis and hepatocyte enlargement in all treatment groups. Inflammatory cell infiltration of liver increased significantly.	Not established	Tada et al., 2007
Wistar rats 28-d, dietary	30, 100, 300	Liver concentrations of TBBPA increased in a dose-dependent way. Plasma T_4 was decreased significantly and plasma T_3 was increased in both sexes of treated rats.	Not established	Van der Ven et al., 2008
28-d dietary	10, 30, 100, 300, 1000	Kidney and liver weight changes at higher doses, but not dose-dependent. No gross or histopathological changes	1000 mg/kg bw/day	Sato, 1996
28-d dietary	10, 50, 250	No dose related or toxicologically significant effects were noted.	250 mg/kg bw/day	Frydrych and Szymanska, 2001
90-d dietary in CD rats	100, 300, 1000	Transient decrease in platelet count and absolute spleen weights in the male rats at 1000 mg/kg bw/day. Bilirubin values were significantly elevated but not dose dependent.	1000 mg/kg bw/day	Schroeder, 2002*
90-d dietary in SD rats	0.3, 3, 30, 100	Overall, no adverse toxicological effects were found up to the highest dose tested.	100 mg/kg bw/day	Quast, 1975
90-d dietary in F344 rats	10, 50, 100, 500, 1000	Dose-related decreases in total T_4 concentrations and serum ALT. Increased PROD activity (PXR–activator) indicating disturbance of liver function, but this was not accompanied by treatment-related liver lesions.	Not established	NTP, 2014
90-d dietary study in mice	10, 50,100, 500, 1000	Significant increase in liver and spleen weights and decrease in kidney weights at 500 mg/kg bw/day and above. Renal tubule cytoplasmic alteration also occurred at these doses.	100 mg/kg bw/day	NTP, 2014

13.2.5 Genotoxicity

In vivo and in vitro genotoxic studies did not show mutagenic potential for TBBPA. TBBPA is not considered to be genotoxic.

13.2.6 Carcinogenicity

A detailed 2-year carcinogenicity study was conducted in rodents (NTP, 2014). The main findings were treatment-related uterine tumours in rats at 500 and 1000 mg/kg bw/day groups (Dunnick et al., 2015). Additional sites for TBBPA tumour induction included testes (rat), liver and large intestines (male mice).

The most significant pathologic findings were treatment related increases in uterine tumours in rats, but not in mice. Incidences of adenoma and adenocarcinoma of the uterus in the high dose groups, female rats were higher than those in the vehicle control group. TBBPA uterine lesions in the rat included increases in adenomas, adenocarcinomas, malignant mixed Müllerian tumour (MMMT), and atypical endometrial hyperplasia. When the incidences of adenoma, adenocarcinoma, or MMMT of the uterus were combined, they were significantly increased in the 500 and 1000 mg/kg bw/day groups. The uterine adenocarcinomas and MMMTs showed evidence of invasion into the myometrium and in some cases metastasis to other tissues.

Atypical endometrial hyperplasia was significantly increased in the treated groups of female rats. Atypical endometrial hyperplasia is considered a preneoplastic lesion in women (Bartels et al., 2012; van der Zee et al., 2013). It is diagnosed as simple (which is rare) or complex (which is more common), depending on the architectural changes in the lesion. In this rat study, the atypical hyperplasia was morphologically consistent with the complex type (Dunnick et al., 2015). Additional sites for TBBPA tumour induction included testes (rat) and liver, large intestine and vascular system (male mice).

In the male mice, the incidence of multiple hepatocellular adenoma was significantly increased in 500 mg/kg bw/day group. The incidences of hepatoblastoma and hepatocellular carcinoma or hepatoblastoma (combined) in 250 mg/kg bw/day males were significantly greater than those in the vehicle controls. The incidences of adenoma or carcinoma (combined) of the large intestine (caecum or colon) and the incidences of haemangiosarcoma (all organs) occurred with significant positive trends. No evidence of carcinogenicity was found in female mice.

Table 25 – Summary of non-neoplastic and neoplastic effects following TBBPA treatment in rats/mice

Effect	Rats	Mice
Survival after 2 years	Comparable to controls	Reduced in males and females at 1000 mg/kg bw/day.
Gastro-intestinal non-neoplastic lesions	Not observed	Male and female mice had ulcers, cellular infiltration, inflammation and epithelial hyperplasia. Severity did not increase with dose.
Uterine tumours: • **atypical endometrium hyperplasia** • **uterine adenocarcinoma** • **malignant mixed Müllerian tumour.**	Study considers them to be clear evidence for carcinogenic activity because the incidences of malignant uterine epithelial tumours were significantly increased in the 500 and 1000 mg/kg bw/day groups by pair-wise comparison and by the trend test.	Not observed
Liver tumours: • **Hepatoblastoma** • **multiple hepatocellular adenomas**	Not observed	Male mice Study does not consider them to be clear evidence, because they were significant only in the 250 mg/kg bw/day group and the trend test was not significant.
Testicular tumours	Occurred with a positive trend, incidence at high dose exceeded historical control incidence, however it was only slightly greater than that in some historical studies. Thus, these tumours were considered to be equivocal evidence for carcinogenic activity.	Not observed

Effect	Rats	Mice
Intestinal tumours (adenoma or carcinoma)	Not observed	Male mice Study does not consider them carcinogenic evidence. Increased incidence of tumours at 500 mg/kg bw/day was low (not significant by the pairwise Poly-3 statistic) and there was no supportive evidence of a carcinogenic effect in female mice.
Haemangiosarcoma (all organs)	Not observed	Male mice Study does not consider them carcinogenic; haemangiosarcoma at 500 mg/kg bw/day (16 %) was within historical control ranges.

The NTP concluded that under the conditions of these 2-year gavage studies, there was equivocal evidence of carcinogenic activity of TBBPA in male Wistar Han rats based on the slight increased incidence of testicular adenoma. There was clear evidence of carcinogenic activity of TBBPA in female Wistar Han rats based on increased incidence of uterine epithelial tumours (predominantly uterine adenocarcinoma). There was some evidence of carcinogenic activity of TBBPA in male B6C3F1/N mice based on the slight increased incidence of hepatoblastoma. The large intestine neoplasms and haemangiosarcoma (all organs) observed were considered equivocal findings. There was no evidence of carcinogenic activity of TBBPA in female B6C3F1/N mice.

The US EPA Cancer Assessment Review Committee (CARC) evaluated the carcinogenic potential of TBBPA (CARC, 2014). The CARC determined that the uterine epithelial tumours (combined adenoma, adenocarcinoma, malignant mixed Müllerian) observed in female rats at the high dose were treatment-related based on the increased incidences at all dose levels (12 % at 250 mg/kg bw/day, 32 % at 500 mg/kg bw/day and 38 % at 1000 mg/kg bw/day) when compared to controls (12 %), a statistically significant dose trend and the presence of supportive precursor lesions. Haemangiomas/ haemangiosarcomas observed in male mice were determined to be treatment-related due to the presence of a dose trend and mortality-adjusted incidence in the high dose group at the upper limit of the historical control range (18 %).

The testicular tumours were not considered to be treatment-related by CARC since there was no dose trend nor pair-wise statistical significance compared to high dose group, and the

total all-group incidence (4/200) in the study was within the historical control range (0-4 %). In addition, there were no supportive precursor lesions in the testes.

The liver adenomas in male mice at the high dose were within the historical control range and there were no supportive precursor lesions. There was lack of statistical significance on pairwise (high dose) or dose trend for the adenoma or carcinoma observed in the large intestine (caecum or colon) of male mice and no supportive precursor lesions in the intestines. The CARC determined these tumours to be not treatment-related.

In the first transverse review of the rat uterine tissue, cystic endometrial hyperplasia appeared to be a treatment-related lesion; however, after a longitudinal review, additional lesions were identified in all groups, and the differences were no longer statistically significant.

The mode(s) of action (MoA) related to the uterine tumour induction by TBBPA is unclear. A possible mode of action for uterine tumours has been discussed by (Lai et al., 2015) as follows:

Available data appear to support interference of high dose TBBPA with oestrogen disposition as the most likely MoA for the induction of uterine tumours in rats. Studies in Sprague Dawley rats have shown that considerable amounts of TBBPA can be absorbed by the gastrointestinal tract and about 30 % can undergo phase II metabolism/conjugation via glucuronidation and/or sulfation (by glucuronyl transferases and/or sulfotransferases, respectively) and be excreted (Hakk et al., 2000). These are the only pathways for biotransformation and excretion of TBBPA in rats. These pathways are also shared by oestrogen and its catechol metabolite (Raftogianis et al., 2000).

Competition for glucuronyl transferases and/or sulfotransferases by TBBPA could result in decreased oestrogen elimination and higher serum levels of oestrogen when high concentrations of TBBPA are present (NTP, 2014). Increased oestrogen levels may trigger mutations in the tumour suppressor gene (Tp53) (Konduri et al., 2010). The Tp53 gene is responsible for cell cycle check point maintenance and genomic stability, and loss of cell cycle checkpoint control due to inactivation of this gene by mutations can result in various types of tumours in rodents and humans (Muller and Vousden, 2013). A significant increase in the incidence of mutations of the Tp53 tumour suppression gene was noted in uterine adenocarcinomas of rats treated with TBBPA compared to spontaneous tumours from control rats (NTP, 2014). Lai et al., have also proposed that reactive oxygen radicals produced from metabolism of oestrogen may produce increased incidence of mutations in Tp53. High doses of TBBPA may thus produce uterine tumours in the rats by promoting pre-existing Tp53 mutations in the uterus resulting from increased levels of circulating oestrogens that turn on oestrogen responsive genes and promote DNA synthesis and cell proliferation. Although this is the most likely MoA for the induction of uterine tumours by TBBPA in rats, data on associated events such as DNA synthesis and cell proliferation in the uterus of TBBPA-treated animals are unavailable and there are no data on dose–response and temporal relationship with the serum levels of oestrogen.

The proposed mechanism would require very high levels of TBBPA in the body to lead to depletion of the activity of phase II enzymes.

Other modes of actions known for chemical-induced uterine tumours, such as genotoxicity, direct oestrogen receptor binding; induction of cytochrome P450 1A enzymes are not supported by the available data for TBBPA.

Human relevance of uterine tumours observed in the NTP studies.

The mode of action for uterine tumours in rats suggested by Lai et al., 2015) may be **qualitatively** applicable to humans. However, it is unlikely that this MoA is **quantitatively** plausible for humans, especially taking into account the absorption, distribution, metabolism, and elimination of TBBPA. In the two year NTP bioassays, TBBPA was administered in corn oil at high doses by gavage to maximise gastrointestinal tract absorption, whereas in humans, the major route of exposure to TBBPA articles/powders is inhalation – little will be absorbed by the lungs or reach the gastrointestinal tract (through the respiratory tract) for absorption. In addition, Wistar Han strain rats are known to have elevated levels of oestrogens (Kacew et al., 1995), and uterine tumours detected in aged Wistar Han rats treated with high doses of TBBPA may be a strain-related effect.

Another mode of action, as suggested by Choi et al. (2011), is via DNA damage by free radicals produced by TBBPA. Repeated exposure of young rats to TBBPA resulted in dose-dependent increase in the expression of antioxidant enzyme, superoxide dismutase (SOD2) in rat liver, indicating that TBBPA may generate reactive oxygen species (ROS) or other stresses in the cell. Levels of cytochrome P450 enzymes, CYP2B1 and CYP2B2 were also higher in rats treated with TBBPA.

Choi et al. (2011) suggested that active oxygen or hydroxyl radicals produced by CYP2B1/B2-induced oxidative stress may contribute to oxidative DNA damage and cause tumours observed in the uterus and kidneys. This is supported by the observation that levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a critical biomarker of oxidative stress and resultant carcinogenesis (Valavanidis et al., 2009) were significantly higher in the kidney and testes in 500 mg/kg bw/day TBBPA-treated group (Choi et al., 2011). This mode of action may not be relevant to humans as CYP2B1 and CYP2B2 are not present in humans.

Due to the absence of a genotoxic MoA for uterine tumour induction by TBBPA, and low levels of exposure to TBBPA in humans, a carcinogenic risk in humans after environmental exposures to TBBPA is expected to be very low.

13.2.7 Reproductive Effects

Effects on Fertility

In a two-generation reproduction study in rats, no treatment-related effects were evident from clinical examinations, reproductive performance evaluations, oestrous cyclicity, gestation length, litter data, organ weights, sperm evaluations, primordial follicle counts, gross and histopathological investigations of reproductive organs in the P_0 and F_1 animals up to a dose of 1000 mg/kg bw/day TBBPA (Schroeder, 2003*).

In a one-generation reproduction rat study there were no treatment-related effects on mating success, number of implantation sites or litter size up to a dose of 3000 mg/kg bw/day TBBPA. In addition, there were no treatment-related effects on sperm characteristics

such as sperm counts, coiled tail, broken tail, separate heads and head defects. No other reproductive organs were affected by treatment (Van der Ven, 2008).

Overall, no adverse effects on fertility were evident up to 1000 mg/kg bw/day in a two-generation reproduction study and up to 3000 mg/kg bw/day in a one-generation reproduction study.

Effect on Development

No treatment-related effects were seen on gestation parameters or on foetal development at doses up to 1000 mg/kg bw/day TBBPA in well-conducted developmental or teratology studies in rats.

In a two-generation reproduction rat study, F_1 and F_2 pups showed no treatment-related effects on body weights, clinical findings, sex ratios, survival to weaning, organ weights or other necropsy findings up to a dose of 1000 mg/kg bw/day TBBPA (Schroeder et. al., 2003*).

In the one-generation reproduction study (Van der Ven et al., 2008), there was no change in sex ratios in F_1 litters. Female pups showed decreased anogenital distance at PND7 and delayed time to vaginal opening. This was observed only in the highest dose group and when normalised for body weights. There was no effect on weight of female reproductive organs. Reproductive organs of male F_1 pups showed increased weight at weaning, but there was no effect in female F_1 gonads at this age. In F_1 males, there were significant dose-dependent increases in the weights of liver, pituitary and testes. However, no exposure related histopathological changes were observed in these organs and cauda epididymis sperm counts and morphology were not affected. There was no effect on time to preputial separation. Analysis of testosterone and 17-oestradiol in the plasma of the F1 males showed no dose-dependent effects.

In the study of newborn rats, sporadic diarrhoea, biochemical and haematological changes, significantly increased kidney and liver weights, and severe histopathological changes in the kidney were observed when newborn rats (PND 4 – 21) were gavaged with 600 mg/kg bw/day TBBPA (Fukuda et al., 2004). The effects observed in the neonatal animals were attributed to the immature metabolic capability and/or immature kidneys. As similar adverse effects were not seen in other one- and two-generation reproductive studies at doses up to 3000 mg/kg bw/day, these effects were not considered sufficient for classification of TBBPA as a developmental toxicant.

In terms of developmental neurotoxicity (Eriksson et al., 2001), no treatment-related effects were seen on motor activity, auditory startle response or learning and memory in F_2 pups in an enhanced two-generation reproduction rat study. In a developmental neurotoxicity study, TBBPA caused no treatment-related effects on motor activity, habituation, learning and memory, play behaviour or sweet preference up to a dose of up to 250 mg/kg bw/day. When neonatal male mice were gavaged with up to 11.5 mg/kg bw/day TBBPA, on PND 10, there were no significant differences in the performance in neurobehavioural tests between the treated and control animals

A one-generation reproduction study enhanced for endocrine and neurobehavioural endpoints found no treatment-related effects on the conditioned fear test or sweet preference behaviour (Lilienthal et al., 2006). However, the study found neurodevelopmental

effects on the auditory system following treatment with TBBPA at doses that are not maternally toxic. Given an adequate supply of thyroid hormone levels is necessary for normal development of the auditory system, it has been argued that the observed developmental effects on the auditory system were a result of treatment-related changes in thyroid hormone levels, particularly during the period GD 17 – PND 14.

This study provides some evidence that TBBPA causes developmental toxicity in rats. However, the rat thyroid system is known to have a greater sensitivity to chemical and physiological perturbations than that of humans given the absence of TBG in the rat serum. Therefore it is concluded that there is insufficient evidence to classify TBBPA as a developmental toxin.

TBBPA is not considered to be bioaccumulative and there is no evidence to suggest that it is found in potentially toxic levels in breast milk. Therefore, there is no cause for concern for developmental effects via lactation.

13.3 Hazard Classification

This section discusses the classification of the health effects of TBBPA according to Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE, 2013) and, in the case of physicochemical hazards, the Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG Code) (FORS, 1998).

Where adequate human data were unavailable, the classification for health hazards has been based on experimental studies (animal and in vitro tests). In extrapolating results from experimental studies to humans, consideration was given to relevant issues such as quality of data, weight of evidence, metabolic and mode of action/mechanistic profiles, inter- and intra-species variability and relevance of exposure levels.

Acute toxicity: TBBPA does not meet the GHS (UNECE, 2013) for classification as it is not a hazardous substance with respect to acute oral, inhalation or dermal toxicity.

Skin and eye irritation: TBBPA does not meet the GHS criteria (UNECE, 2013) for classification as it is not a hazardous substance with respect to being a skin, eye or respiratory irritant. TBBPA does not meet the criteria for classification as a corrosive substance.

Skin sensitisation: TBBPA does not meet the GHS criteria (UNECE, 2013) for classification as it is not a hazardous substance with respect to sensitisation by skin contact.

Repeat dose toxicity: TBBPA does not meet the GHS criteria (UNECE, 2013) for classification as a hazardous substance with respect to danger of serious damage to health by repeated and prolonged exposure.

Genotoxicity: TBBPA does not meet the GHS criteria for classification as it is not a hazardous substance with respect to mutagenic potential.

Carcinogenicity: In the only reliable carcinogenicity study available with TBBPA, there was clear evidence of carcinogenic activity of TBBPA in female rats at high doses, based on

increased incidences of uterine epithelial tumours (predominantly uterine adenomas). In addition, there was equivocal evidence of carcinogenic activity of TBBPA in male Wistar Hans rats based on the slight increase in incidence of testicular adenoma.

Based on these observations, TBBPA meets the GHS criteria (UNECE, 2013) warranting classification as a Category 2 carcinogen, with the Health Hazard statement – "Suspected of causing cancer - H351".

Reproductive toxicity: TBBPA does not meet the GHS criteria (UNECE, 2013) for classification as it is not a hazardous substance with respect to substances that cause concern for human fertility or development.

Developmental toxicity: TBBPA does not meet the GHS criteria for classification as it is not a hazardous substance with respect to developmental effects.

The classification of TBBPA under the Globally Harmonized System of Classification and Labelling of Chemicals is provided in Appendix I.

14 Environmental effects

Some of the following discussion on the toxicity of TBBPA has been paraphrased from EC (Health/Env Canada, 2013). References are marked with an asterisk (*) have not been independently reviewed for this assessment.

The bioavailability of TBBPA in an aqueous system is expected to decrease as the pH approaches and exceeds its dissociation constant (pKa) (7.5 – 8.5 (WHO (1995)) due to increasing ionisation; that is, above pH 7.5, TBBPA becomes deprotonated (charged - monobasic) and is expected to be less likely to cross cell membranes into the tissue of an organism. Above pH 8.5, TBBPA becomes doubly deprotonated (doubly charged - dibasic) which further reduces its bioavailability. However, relationships between the charge of an ionisable organic substance and its bioavailability are complex and this is an area of uncertainty and ongoing research (Health/Env Canada, 2013). Accordingly, EC used the conservative assumption that the neutral, monobasic and dibasic forms of TBBPA are equally toxic. This assumption is adopted in the following assessment.

14.1 Aquatic Toxicity

14.1.1 Fish

Numerous studies have investigated the aquatic toxicity of TBBPA to fish. Lethal and sub lethal effects are observed in both acute and chronic studies with higher sensitivity observed for early life stages.

A 48-hour LC50 of 30 mg/L was measured for Oryzias latipes (CITI, 1992*), and a 30-day LOEC (acute) of 1.63 mg/L was determined for zebrafish (Danio rerio) (Kuiper et al., 2007a*) indicating that TBBPA is harmful to fish. A 35-day study on fathead minnow (Pimephales promelas) embryos and larvae showed reproductive toxicity (35-day LOEC (embryo survival) = 0.31 mg/L; Brominated Flame Retardants Industry Panel, 1989f), and a reproductive study on zebrafish showed effects on egg production, hatching and development at low concentrations (30-day LOEC (egg production) = 0.047 mg/L; 47-day LOEC (hatching) = 0.013 mg/L; 3-day LOEC (development) = 1.63 mg/L for *Danio rerio;* Kuiper *et al*., 2007a).

Several studies indicate that TBBPA may also influence enzyme function and oxidative capacity in fish (Ronisz et al., 2001*, Christiansen et al., 2000*, Jurgella et al., 2006*). Concentrations of TBBPA >0.75 mg/L have been shown to cause lethality or malformation (Hu et al., 2009*), and TBBPA can cause oxidative stress and overexpression in a dose-dependent manner (Hu et al., 2009*). Maternal transfer of TBBPA from female zebrafish to eggs has also been observed by Nyholm et al., (2008).

Lethal and sub-lethal effects were observed in a six day flow-through acute toxicity test with fathead minnow (Pimephales promelas) (Surprenant, 1988*). Fish were exposed to five nominal concentrations of 0.18, 0.27, 0.42, 0.65 and 1.0 mg TBBPA/L. At 144 hours, all fish in the control groups and the 0.19 mg/L exposure group were normal. One fish in the 0.26 mg/L group was noted as having darkened pigmentation. In the 0.32 mg/L group, all fish had a partial loss of equilibrium while several fish were swimming at the surface or had darkened pigmentation. In the 0.45 mg/L group, a complete loss of equilibrium was shown by all fish and all had darkened pigmentation. All fish were dead by 96 hours in the highest exposure group. A 96-hour LC50 could not be determined from this test, but the 144-hour NOEC was determined to be 0.26 mg TBBPA/L.

This endpoint is close to the one used by EC (Health/Env Canada, 2013) to derive their predicted no effect concentration (PNEC), in which the 35-day LOEC (embryo survival) was 0.31 mg/L for Pimephales promelas.

Two further results are described in limited detail in the Environmental Health Criteria 172 Tetrabromobisphenol A and Derivatives (WHO, 1995). The 96-hour LC50 of TBBPA for bluegill sunfish (Lepomis macrochirus) was 0.51 mg/L (nominal concentration) in a static system. With dose levels above 0.32 mg/L, the fish became irritated and exhibited abnormal behaviour. The NOEC was 0.10 mg/L (Calmbacher, 1978a*). The 96-hour LC50 of TBBPA for rainbow trout (Salmo gairdneri) was 0.40 mg/L (nominal concentration) in a static system. The NOEC was 0.18 mg/L. At higher levels, the fish became irritated and exhibited twitching, erratic swimming, dark discolouration and laboured respiration (Calmbacher, 1978b*).

Acute toxicity for a range of brominated flame retardants to zebrafish embryos has been investigated by Godfrey et al. (2017). Embryos were collected at 4.5 hours post-fertilisation and exposed to test solutions for 96 hours. Each test used at least two replicates per treatment and was repeated at least three times. Concentrations were not measured during the study as the test solutions were renewed daily and TBBPA was stable over the exposure period. Embryos exposed to TBBPA at concentrations ranging from 0.625 to 5 mg/L. The 96-hour LC50 was 1.3 mg TBBPA/L with a 95 % CI of 1.1-1.6 mg TBBPA/L.

An evaluation of neurodevelopmental toxicity of TBBPA was undertaken in zebrafish (Zhu et al., 2018). Fish were exposed to 50, 100, 200 and 400 µg TBBPA/L (nominal). These concentrations are higher than those commonly found in environmental samples. There was a significant impact on survival at the highest concentration. Malformations (including axial spinal curvature, pericardial oedema or yolk sac oedema) occurred at 200 and 400 µg TBBPA/L. Embryos were exposed to TBBPA two hours after fertilisation and continued until 144 hours post fertilisation (*i.e.* approximately six days) when the fish had reached the free swimming larval stage. Test solutions were renewed daily (50 %). The embryos were also exposed to TBBPA in combination with T_3 (triiodothyronine) to determine if the observed effects were due to disruption of thyroid hormones. Exposure to TBBPA affected the levels of thyroid hormones as expected. The study reported that the exposed fish had decreased locomotive activity and average swimming speed. These effects were potentially due to impacts of TBBPA exposure on (acetylcholine) esterase activity. Changes in gene expression relevant to these effects and effects on swimming speed were observed even at 100 µg TBBPA/L.

Effects on reproduction and development were investigated in Oryzias melastigma – a marine fish (Huang et al., 2017). Exposure to TBBPA resulted in increased embryonic heartbeat, delayed hatching and decreased rate of hatching (increased embryo mortality). The study exposed embryos (two days post fertilisation) to 50, 200, 800 and 1600 µg TBBPA/L and exposure was continued for four months. Embryo heartbeat was tested at six days post fertilisation using 12 embryos for each treatment. Hatching rate was determined at eight days post fertilisation. The hatching rate decreased with increasing concentration. Hatching rate was 74 % at 50 µg/L, 75 % at 200 µg/L, 66 % at 800 µg/L and 3 % at 1600 µg/L. Heartbeat increases were observed in the two highest concentrations. After exposure for four months, there were no significant effects on body weight or histological changes in reproductive organs. Gene expression was also assessed in this study and effects were observed at the two highest concentrations.

The endocrine activity of TBBPA in zebra fish (Danio rerio) has been investigated (Kuiper et al., 2007a*). Adult fish were exposed to TBBPA for 30 days at nominal concentrations of 0-

0.82 mg/L. This was followed by exposure of the offspring to the same concentrations. Egg production decreased in fish exposed to TBBPA concentrations ≥0.026 mg/L. Hatching of larvae in TBBPA-exposed groups was decreased and at the highest exposure concentration (0.82 mg/L), mortality was high (81 %) in larvae and the surviving juveniles showed a significant predominance of females. These results indicate decreased reproductive success in zebrafish at environmentally relevant TBBPA concentrations.

Another study examined the long term effects of exposure of European flounder (Platichthys flesus) to TBBPA (Kuiper et al., 2007b*). Fish were exposed to TBBPA at seven measured concentrations in the range 0 – 193 µg/L for 105 days. Exposure at these levels did not affect general health and toxicity parameters (behaviour, survival, growth rate, relative liver and gonad weight). Aromatase activity in male gonads showed a small increase with rising TBBPA levels. Levels of the thyroid hormone thyroxine (T_4) increased with internal concentrations of TBBPA, possibly indicating competition of TBBPA for plasma protein binding. T_3 levels were not affected and histology showed no signs of altered thyroid activity. Other organs (liver, gills, kidney, skin and gonads) showed no histological changes related to TBBPA exposure. Overall, the results indicated limited endocrine effects of TBBPA up to 193 µg/L and at internal muscle concentrations of 4300 µg TBBPA/kg ww.

A study of the effects of TBBPA on zebrafish has recently been reported (Liu et al., 2018). Embryos were exposed to 85, 160, 330, 650, 1300 and 2600 µg TBBPA/L for 122 hours post-fertilisation. The study found that exposure to 160 µg TBBPA/L down-regulated expression of genes related to the thyroid system, exposure to 330 µg/L down-regulated gene expression related to the androgen receptor and exposure to 650 µg/L down-regulated gene expression related to the oestrogen receptor. An 74-hour LD50 of 18000 µg TBBPA/kg bw was determined for embryos based on internal dose. The external dose LD50 was 27000 µg TBBPA/kg bw at 74 hours post fertilisation based on delays in development and 22000 µg TBBPA/kg bw based on deformities. Delayed hatching of larvae occurred upon exposure to ≥ 650 µg TBBPA/L due to inhibition of cellular differentiation leading to developmental effects.

The developmental toxicity of TBBPA in zebrafish embryos and larvae has been studied (Song et al., 2014). Embryos were collected and exposed to 500, 1000 and 1500 µg TBBPA/L. 100 % mortality was observed after 144 hours after fertilisation at a test concentration of 1500 µg TBBPA/L. A 144-hour LC50 of 1240 µg TBBPA/L was determined. The lowest-observed-effect loading rate (LOELR) was 500 µg TBBPA/L. Effects including haemorrhage, yolk sac oedema and pericardial oedema were observed in embryos exposed to TBBPA at the two higher test concentrations. Exposure of embryos to these test concentrations was repeated at least three times.

14.1.1.1 Reviews

The US EPA (2015) chemical review for TBBPA surveyed measured acute toxicity results for various species of fish. The LC50 values range from 0.4-1.1 mg/L. The EU chemical review for TBBPA also lists acute toxicity results for several species of fish (EURAR 2008). The LC50 results for freshwater fish for studies of appropriate quality range from 0.4-8.2 mg/L.

Three key, short term studies on the toxicity of TBBPA to fish have been identified by ECHA (2015). The endpoints from each study were: i) 144-hour NOEC = 0.26 mg/L (Pimephales promelas; Surprenant, 1988*), ii) 96-hour LC50 = 1.1 mg/L (Oncorhynchus mykiss; Blankinship et al., 2003*), and iii) 96-hour LC50 = 0.71 mg/L (Cyprinus carpio). ECHA selected the 96-hour LC50 of 1.1 mg/L for PNEC derivation.

The US EPA chemical review only lists one longer term study (35 days' exposure) with a NOEC of 0.16 mg/L (USEPA, 2015). The EC review lists several long term studies with NOEC values ranging from 0.013 to 0.8 mg/L (Health/Env Canada, 2013). The EU chemical review documents two studies on long term toxicity in freshwater fish with results similar to the US EPA review (EURAR, 2008). Key endpoints for aquatic toxicity are collected in Table A.3.4 (Appendix 3) of this report.

14.1.2 Amphibians

Two studies suggest that TBBPA may affect thyroid hormone function in developing amphibians after a brief exposure to environmentally relevant concentrations of the chemical.

Kitamura and co-workers (2005a*) report that TBBPA may act as a thyroid hormone agonist in developing amphibians at environmentally relevant concentrations (approximately 0.005 mg/L to 0.5 mg/L).

The effects of environmentally-relevant concentrations of TBBPA on the thyroid hormone-mediated process of metamorphosis has been investigated in Pacific tree frogs (Pseudacris regilla; Veldhoen et al., 2006*). The study revealed that normal thyroid hormone-mediated gene expression was significantly altered at concentrations as low as 0.005 mg/L. Moreover, these changes in gene expression were shown to occur within 48 hours of exposure to low concentrations of TBBPA and developmental effects were evident within 96 hours.

EC conclude that TBBPA may disrupt thyroid hormone function in developing amphibians. Several key reports and their findings are cited in support of this conclusion; these are briefly summarised as follows. Tail shortening was observed in Rania rugose tadpoles exposed to concentrations of 0.005 – 0.5 mg/L TBBPA (Kitamura et al., 2005a*). Morphological development was effected in tadpoles of Xenopus laevis exposed to ≥ 0.5 mg/L TBBPA for 21 days while thyroid hormone-regulated biomarkers were only slightly affected (Jagnytsch et al., 2006*). TBBPA exhibited T_3 agonist and antagonist activities at a concentration of 0.5 mg/L (Kudo et al., 2006). Thyroid hormone activity was observed in Xenopus laevis embryos exposed to 1 µM TBBPA (Fini et al., 2007*).

14.1.3 Aquatic invertebrates

A number of studies have examined the acute and chronic toxicity of TBBPA to aquatic invertebrates.

14.1.3.1 Acute toxicity

TBBPA is moderately acutely toxicity to Daphnia magna (48-hour NOEC = 1.8 mg/L; Wildlife international, 2003*) and Acartia tonsa (48-hour LC50 = 0.40 mg/L).

The acute toxicity of a range of brominated flame retardants in Daphnia magna was investigated following the OECD TG 202 protocol (Waaijers et al., 2013). Fourteen chemicals were tested. Negligible or no effects were observed for many of the more recently developed flame retardants up to their water solubility limits. By contrast, TBBPA was found to be highly toxic to Daphnia magna with an EC50 of 0.6 mg/L (95 % CI 0.24 – 0.97 mg/L). These results are based on nominal concentrations only.

Two further results are described in Environmental Health Criteria No. 172 - Tetrabromobisphenol A and Derivatives (WHO, 1995). The 48-hour, acute LC50 for Daphnia

magna (less than 20 hours old) was 0.96 mg TBBPA/L (Morrissey, 1978*). Mysid shrimp (Mysidopsis bahia), aged <1, 5, and 10 days old, were exposed to TBBPA in a flow-through system for 96 hours (Goodman et al., 1988*). The 96-hour LC50 values for the three life stages were 860 (670-1200), 1100, and 1200 µg TBBPA/L, respectively.

The US EPA chemical review lists acute toxicity studies for a range of aquatic invertebrates with EC50 values ranging from 0.098-0.96 mg/L (US EPA, 2015a). The EU chemical review documents acute toxicity studies for a range of aquatic invertebrates with EC50 values ranging from 0.098-1.8 mg/L (EURAR, 2008).

14.1.3.2 Chronic toxicity

TBBPA has chronic reproductive and developmental toxicity to aquatic invertebrates at low levels. A 21-day study of chronic toxicity in Daphnia magna gave a LOEC and NOEC of 0.98 mg/L and 0.30 mg/L respectively (Brominated Flame Retardants Industry Panel, 1989d*).

A two generation toxicity test was undertaken in a copepod species Pseudodiaptomus inopinus (Gong et al., 2017). The test concentrations were 0.18, 1.8 and 18 µg TBBPA/L. These concentrations were chosen based on the maximum concentrations measured in Chinese coastal waters (1.8 µg TBBPA/L). Exposure to TBBPA significantly delayed the maturation of nauplii into copepodids and also delayed maturation of copepodids into adults at 1.8 and 18 µg TBBPA/L. The overall cohort generation time (nauplii through to adult females with eggs) was also significantly longer at the highest test concentration. Hatching rate was affected at the highest test concentration. Mortality of nauplii was increased in the highest test concentration for both generations. Effects on development times and rates were higher in the second generation for the low and middle test concentrations than in the first generation. The study indicated that effects on these organisms could be expected at the maximum concentration being reporting in coastal areas in China.

The US EPA chemical review lists a number of longer term studies with NOEC values ranging from 0.017 to 0.3 mg/L (US EPA, 2015a). The EU chemical review reports similar studies on long term toxicity to aquatic invertebrates with NOEC values ranging from 0.017 – 0.98 mg/L (EURAR 2008). Chronic effects have been observed with a range of aquatic invertebrate species and these have been summarised by EC (Health/Env Canada, 2013); the key endpoints are collected in Table A.3.4 (Appendix 3) of this report.

14.1.3.3 TBBPA-sorbed sediment

The sensitivity of aquatic invertebrates to sediment-sorbed TBBPA has also been studied. A 28-day NOEC (survival) of 250 mg TBBPA/kg sediment dw was determined for *Hyalella azteca* in sediment containing 5.7 % organic carbon (OC); the 28-day NOEC (growth) was ≥ 1000 mg/kg sediment dw (Wildlife international, 2006). Reproductive effects were reported for *Lumbriculus variegatus* in TBBPA-sorbed sediments containing different concentrations of organic carbon (ACCBFRIP, 2002a,b). A 28-day LOEC (survival and reproduction) of 151 mg TBBPA/kg sediment dw was reported in sediment containing 2.5 % OC and a 28-day LOEC (survival and reproduction) of 426 mg TBBPA/kg sediment dw was reported in sediment containing 5.9 % OC.

14.1.4 Algae/Aquatic plants

TBBPA has been demonstrated to be acutely toxic to algae. One study in marine algae has reported a 72-hour EC50 of 0.09-0.89 mg/L for Skeletonema costatum and a 72-hour EC50 = 0.13-1.0 mg/L for Thalassiosira pseudonana (Walsh et al., 1987*), while a second study demonstrated significant effects on cell viability size and growth at 5 mg/L for two freshwater microalgae (Pseudokirchneriella subcapitata and Nizschia palea). It is noted that 5 mg/L is rather high when compared with the water solubility of TBBPA.

The effects of TBBPA have been screened in a range of freshwater algal species (Peng et al., 2014). Tested algal species included Pseudokirchneriella subcapitata, Scenedesmus acuminatus, Scenedesmus quadricauda, Coelastrum sphaericum, Scenedesmus obliquus and Chlorella pyrenoidosa. Growth inhibition was evaluated at 0.4 mg/L for a period of 10 days. None of the species demonstrated inhibited growth at this concentration. The last two species listed were further evaluated over a range of TBBPA concentrations (0.2-5 mg/L), with algal cell density measured at 24 and 72 hours and photosynthetic pigment content measured at 120 hours. Algal cell density was only affected at 5 mg/L – the highest concentration. Photosynthetic pigments were inhibited at 2 mg/L and above.

The same study investigated the ability of algae to transform TBBPA in growth medium and in natural waters (pH 7.7). Algae were exposed to 0.4 mg TBBPA/L for 10 days. TBBPA and potential transformation products were measured in the test solutions at 0, 72, 120 and 168 hours. Different species showed different types of transformation. S. quadricauda and C. sphaericum achieved 100 % removal of the parent compound by the end of the exposure period while the other four species achieved 60-90 % removal in growth medium. Degradation of TBBPA was slower in natural waters. The degradation products included TBBPA-sulfate, TBBPA-glucosyl, TBBPA-sulfate-glucosyl, O-methylated TBBPA and tribromobisphenol A. The algal species P. *subcapitata, S. quadricauda and C. sphaericum* transformed TBBPA into the sulfate- and glucosyl-products. This was also the case for S. *obliquus* and *C. pyrenoidosa*. S. cuminatus was the only species for which the O-methylated product was reported. Trace amounts of tribromobisphenol A were reported for all species.

The US EPA chemical review lists studies on the effects of TBBPA on aquatic plants with EC50 values ranging from 0.09-5.6 mg/L (US EPA, 2015a). The Health Canada review lists studies on the effects of TBBPA on aquatic plants with EC50 results ranging from 0.09-1.0 mg/L (Health/Env Canada, 2013). The EU chemical review studies on the effects of TBBPA on aquatic plants (algae) with EC50 results ranging from 0.13-5.6 mg/L (EURAR, 2008).

14.2 Terrestrial Toxicity

Some of the following discussion on the terrestrial toxicity of TBBPA has been paraphrased from EC (Health/Env Canada, 2013). References are marked with an asterisk (*)have not been independently reviewed for this assessment.

Acute toxicity and reproductive toxicity have been investigated in earthworms (Eisenia fetida). A 2003 study (ACCBFRIP*) reported a 28-day LOEC (survival) of greater than 4840 mg/kg soil dw and a 56-day LOEC (reproduction) of 4.50 mg/kg soil dw. The 56 day NOEC for reproduction was 2.11 mg/kg soil dw and the 56 day EC10 and EC50 endpoints for reproduction were 0.12 and 0.17 mg/kg soil dw, respectively. The organic carbon content of the soil in this study was relatively high (4.5 %) and, as discussed earlier, TBBPA is likely to be more bioavailable in soils with a lower carbon content. This study shows that earthworms are

not very susceptible to TBBPA in terms of mortality (very slightly toxic). However, under the study conditions, TBBPA is toxic to earthworm reproduction. The second study (ACCBFRIP 2005a*) reports a 28-day NOEC (survival) of greater than or equal to 20 mg/kg soil dw and a 56-day LOEC (reproduction) of 0.63 mg/kg soil dw. The EC10 and EC50 values were <0.31 and 0.91 mg/kg soil dw, respectively. These values are consistent with the 2003 study and support the conclusion that TBBPA is toxic to earthworm reproduction.

A 21-day LOEC (survival) of greater than 1000 mg/kg soil dw and a 21-day LOEC (reproduction) of 10 mg/kg soil dw for Enchytraeus crypticusi has been reported (Sverdrup et al., 2006). This indicates that TBBPA is very slightly acutely toxic to Enchytraeus crypticus, but has moderate reproductive toxicity in this species of earthworm.

Studies have investigated the effects of TBBPA on terrestrial plants. A study exposed 6 plant species to doses up to 5000 mg/kg soil dw. Seedling emergence was unaffected at all concentrations tested. The species and 21-day LOECs for growth were:

- corn (Zea mays) was 1250 mg/kg soil dw
- onion (Allium cepa) was 1250 mg/kg soil dw
- ryegrass (Lolium perenne) was 313 mg/kg soil dw
- cucumber (Cucumis sativa) was 78 mg/kg soil dw
- soybean (Glycine max) was >5000 mg/kg soil dw
- tomato (Lycopersicon esculentum) was 1250 mg/kg soil dw (ACCBFRIP 2002c).

Other studies showed that TBBPA significantly altered physiological processes in wheat (Triticum aestivum). Decreased chlorophyll content and altered activity of antioxidant enzymes confirmed this (Li et al., 2008). TBBPA can be absorbed from soil by plants. A study measured TBBPA up to 18 and 5 µg/kg tissue dry weight when wheat was grown in soil initially containing TBBPA at 1000 µg/kg dry weight (Li et al., 2011). A further study in red clover (Trifoluim pretense) showed no statistically significant, treatment-related effects on seedling emergence or growth at 1000 mg/kg soil dw.

There were 2 studies on soil microorganisms that showed that TBBPA is very slightly toxic to:

- soil nitrifying bacteria (28-day LOEC (nitrification) = 1000 mg/kg soil dw; Sverdrup et al., 2006)
- soil microorganisms (28-day EC10 >1000 mg/kg dw; ACCBFRIP, 2005b).

A number of studies on toxicity of TBBPA in rodents are summarised in the Human Health section of this report. EC (Health/Env Canada, 2013) reported that Japanese quail (Coturnix japonica) and domestic chicken (Gallus domesticus) eggs showed significant embryo mortality at 45 mg TBBPA/kg egg dose in both species, and that mortality was not significantly different from the control at 15 mg/kg egg dose.

14.3 PNEC and PBT properties

14.3.1 Aquatic PNEC

EC selected the 31-day LOEC for embryo survival of fathead minnow (0.31 mg/L) as the critical endpoint for determining an aquatic PNEC. To account for interspecies and intraspecies variability and extrapolation from laboratory to field conditions, they applied an assessment factor of 100, giving a PNEC of 0.0031 mg/L. This was considered to be an appropriate assessment factor because TBBPA effects were observed at lower concentrations in marine oysters (96-hour LOEC (shell deposition) = 0.018 mg/L). EC also identified a study

that reported a 70 day LOEC (shell length) of 0.032 mg/L and a 70 day LOEC (wet tissue weight) of 0.126 mg/L for the common mussel (Mytilus edulis), both of which are below the 31-day LOEC for Pimephales promelas, but above the PNEC determined from this value. Additional studies not considered in the EC (Health/Env Canada, 2013) report, but identified here for this Priority Existing Chemical assessment, provide further evidence that an aquatic PNEC of 0.0031 mg/L is appropriate. This endpoint will be used for quantitative risk assessment calculations for the aquatic compartment.

14.3.2 Sediment PNEC

The US EPA chemical review concludes that TBBPA effects sediment dwelling organisms at concentrations greater than 100 mg/L (US EPA, 2015a).

The EC review concludes that for sediment dwelling organisms the critical toxicity value is 151 mg/kg dw (based on an oligochaete) giving a PNEC of 60 mg/kg dw (Health/Env Canada, 2013).

The EU chemical review concludes that a PNEC of 2.7 mg/kg ww is appropriate for sediment dwelling organisms (EURAR 2008). This is based on a 28-day NOEC of 125 mg/kg dw, determined for Chironomus (ACCBFRIP, 2005d). The EU review also concludes that the study with Lumbriculus is appropriate for use in setting a PNEC. The review converts the reported NOEC (90 mg/kg dw) into a 'wet-weight' NOEC (20 mg/kg ww) using default sediment water content and an organic carbon content of 2.5 %. This new NOEC is used to derive an alternative PNEC of 2 mg/kg ww. For marine sediment dwelling species, the review indicates that a PNEC of 0.54 mg/kg ww is appropriate.

For the purposes of this assessment, the aforementioned study with Lumbriculus is used to calculate the sediment PNEC because this study reports the most sensitive endpoint (a 28-day NOEC of 90 mg/kg sediment dw). An assessment factor of 50 is applied to this end-point to determine a $PNEC_{sediment}$ of 1.8 mg TBBPA/kg dw sediment which is similar to the PNEC calculated by the EU. The number of available results, and different sediment characteristics tested, support the notion that 90 mg/kg sediment dw is an accurate representation of the more sensitive end of sediment toxicity and, therefore, an assessment factor of 50 is justified.

14.3.3 Terrestrial PNEC

Several studies indicate that TBBPA is toxic to earthworm reproduction and the endpoints for earthworm reproduction are amongst the most sensitive terrestrial toxicity values available. Earthworms may be exposed to TBBPA through application of sewage sludge containing residues of the chemical to agricultural soils. Therefore, the 56-day EC10 of 0.12 mg/kg soil dw for earthworm reproduction was selected to derive a terrestrial PNEC. To account for interspecies and intraspecies variability and extrapolation from laboratory to field conditions, an assessment factor of 100 is appropriate. The endpoint was derived from studies in soil with an organic carbon content of 4.5 %. This is much higher than the median Australian organic carbon content of 0.98 % (Viscara et al., 2014). The chemical is likely to be more bioavailable in soils with low carbon content. As the release of TBBPA to the environment is expected to be highest in the more densely populated regions of Australia, it is considered appropriate to use the average organic carbon content of Victorian soils (approximately 2 %; Viscara et al., 2014) to normalise the endpoint for organic carbon content. This results in a PNEC of 0.0005 mg/kg for earthworm reproduction. The same endpoint was derived by EC (Health/Env Canada, 2013).

Table 26 – Predicted No Effect Concentration (PNEC)

Environmental compartment	PNEC
Aquatic	3.1 µg/L
Sediment	1.8 mg/kg dw
Terrestrial	0.5 µg/kg dw

14.4 PBT Assessment

Organic chemicals that are persistent (P) have the potential to become widely dispersed environmental contaminants. Once in the environment, persistent chemicals that bioaccumulate (B) pose an increased risk of accumulating in exposed organisms and of causing adverse toxic (T) effects. They may also biomagnify through the food-chain resulting in high concentrations in body tissues and lipids, especially in top predators. Importantly, it is difficult or impossible to mitigate the risk of adverse effects of PBT chemicals once they have been released. As a result, these chemicals are a high priority for managing and reducing the risks of chemical contamination of the environment.

PBT Criteria

The persistence (P), bioaccumulative (B) and toxic (T) characteristics of organic chemicals are determined according to Australia's environmental PBT criteria.

14.4.1 Persistence

Laboratory studies indicate that TBBPA is very persistent in sediment under abiotic conditions and is persistent in some (biotic) aerobic soils (half-life >6 months). Modelling indicates that TBBPA is persistent in air (half-life >2 days) and the chemical is not expected to be degraded by hydrolysis. The photolytic degradation half-life in water exceeded two months under simulated winter sunlight. TBBPA is routinely detected in soils, sediments and water in urban and industrial areas. It has been found in sediments accumulated over several decades. Accordingly, the substance is categorised as persistent (P).

14.4.2 Bioaccumulation

Laboratory and modelling studies on the bioaccumulation of TBBPA, and analyses of the chemical in biota, indicate that TBBPA has low bioaccumulation potential. Laboratory studies show that the chemical can be significantly metabolised and excreted by all the organisms tested. Measured and modelled data for BCF and BAF are well below the lower limit for a chemical to be considered 'bioaccumulative (BCF/BAF > 2000 L/kg). Analyses of TBBPA and

its metabolites in biota show that concentrations are highly variable. The available evidence does not demonstrate a correlation between concentration and trophic level, indicating that the chemical does not biomagnify in the food chain. Therefore TBBPA is considered to be 'not bioaccumulative' (not B).

14.4.3 Toxicity

In general, TBBPA has low acute toxicity to most organisms. However, laboratory studies show that TBBPA can cause adverse chronic reproductive and developmental effects in various fish species and some amphibians at NOEC and EC_x concentrations below the toxicity criteria (≤ 0.1 mg/L). TBBPA has adverse effects on reproduction of some earthworm species at low soil concentrations. Accordingly, TBBPA is classified as toxic (T).

PBT Summary.

TBBPA is categorised as:

- P
- Not B
- T

15 Human Health Risk Characterisation

A margin of exposure (deterministic) method is used frequently in international assessments to characterise risks to human health (ECB, 2003). Where an appropriate point of departure (POD) such as a NOAEL is available, the risk characterisation is conducted by comparing quantitative information on exposure to the POD and deriving a Margin of Exposure (MOE) as follows:

1. Identification of the critical effect(s);
2. Identification of the most appropriate/reliable POD (if available) for the critical effect(s);
3. Where appropriate, comparison of the estimated (or measured) human dose (EHD) or exposure to provide a Margin of Exposure:
4. MOE = POD/EHD;
5. Characterisation of risk, by evaluating whether the Margin of Exposure indicates a concern for the human population under consideration.

The MOE provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. In deciding whether the MOE is of sufficient magnitude to allow safe use of a chemical, expert judgement is required. Such judgements are usually made on a case-by-case basis, and take into account uncertainties arising in the risk assessment process such as the completeness and quality of the database, the nature and severity of effect(s) and intra/inter species variability.

Default uncertainty factors for intra- and inter-species variability are usually 10-fold each and so a MOE of more than 100 is usually considered acceptable.

15.1 Critical health effects

The acute toxicity of TBBPA is low via the oral, inhalation and dermal routes. TBBPA is not a skin, eye or respiratory irritant. It is not a skin sensitiser.

No human data are available for repeat dose toxicity to identify a robust NOAEL or profile the systemic toxicity of TBBPA.

In the repeat-dose toxicity studies in adult animals, no TBBPA treatment-related findings regarding body weight gain, organ weights, haematology, clinical chemistry, bone, testicular function or sexual development were detected. No histopathological changes were observed in any of the large number of tissues examined, including the thyroid. Treatment-related changes were limited to decreased circulating thyroxine (T_4) and increased triiodothyronine (T_3) levels in male animals, only at high doses of TBBPA. The observed transient changes in circulating T_4 levels without a histopathological correlate and/or without concurrent changes in T_3 or TSH are not considered to constitute an adverse effect as defined by IPCS/WHO (2007). Neurobehavioural effects, as a result of the treatment with TBBPA were not observed in the functional observational battery tests and motor activity evaluations. The NOAEL for TBBPA in adult animals after oral administration was 1000 mg/kg bw/day.

Toxicity data generated in newborn animals indicated a higher sensitivity during early life stages (Fukuda et al., 2004). In a study of newborn rats, directly treated (gavage) with TBBPA,

relative kidney weights were significantly increased in both sexes treated with TBBPA when compared to the controls. Histopathological examination showed that rats in higher dose groups had renal polycystic lesions associated with dilation of tubules occurring bilaterally from the cortico-medullary junction to the inner cortex. The NOAEL from this study was 40 mg/kg bw/day based on the effects seen at the next higher dose (200 mg/kg bw/day).

TBBPA was not shown to cause genotoxicity. In the only carcinogenicity study available, treatment-related increases in uterine adenomas and adenocarcinomas were observed in rats. Some animals in the treated groups presented with malignant mixed Mullerian tumours (MMMT). The combined incidence of uterine adenoma, adenocarcinomas, or MMMTs, was dose-dependent and significantly increased in the top two dose levels. However, based on the most plausible mode of action, these tumours are not expected to be relevant to humans. There were no significant tumourogenic effects in male rats or male and female mice.

Repeated dermal and inhalation exposure to TBBPA elicited no serious effects, except for slight erythema in dermal exposure and salivation, nasal discharge and lacrimation during repeat inhalation exposure.

Table 27 – Critical studies for determination of NOAEL for risk characterisation

Toxicity observed; Reference	Species and dose	POD	Effect at LOAEL
28-day oral; Van der Ven et al. (2008)	Wistar rats (diet)0, 30, 100, 300 mg/kg bw/day	BMDLs: 48 and 124 mg/kg bw/day	Decreased circulating T_4, increased T_3 levels in males, no histopathological findings.
One-generation developmental study with neurobehavioural evaluation of F_1 animals Lilienthal et al. (2008), Van der Ven et al. (2008)	Wistar rats (diet) 0, 3, 10, 30, 100, 300, 1000, 3000 mg/kg bw/day Maternal: 2 weeks prior to mating; Paternal: 10 weeks prior to mating; Offspring: from postnatal day 21	BMDL10 for thyroid hormone changes: 31 and 16 mg/kg bw/day BMDL for neuro-developmental changes: 8 mg/ kg bw/day	Decreased circulating T_4 in male and female F_1 animals, increased T_3 in male F_1 animals, decreased testes and increased pituitary weights in F_1 males. No effects on cue conditioned fear and sweet preference. BAEPs evaluated at 50–110 days of age show cochlear effects in females, and neural effects in males.
90-day oral Repeat dose (Schroeder, 2002*)	SD Rats 100, 300 or 1000 mg/kg bw/day (gavage)	NOAEL: 1000 mg/kg bw/day	No effects on clinical chemistry, no remarkable changes in histopa-thology, no effects on behaviour or neuropathology.
2-generation reproductive and developmental toxicity study (Schroeder, 2003*),	SD rats 0, 10, 100 or 1000 mg/kg bw/day (gavage)	NOAEL: 1000 mg/kg bw/day	No effects on clinical chemistry, no changes in histopathology, organ weights, sexual maturation, or sex ratio, no effect on behaviour, auditory startle habituation, learning, memory, locomotor behaviour.
Developmental study Tada et al. (2006)	ICR mice (diet) Gestation: 16, 141, 1640 mg kg/bw/day	NOAEL: 42 mg/kg bw/day	Slight increases in incidence of focal hepatocyte necrosis and atrophy of renal tubules in female offspring at 0.1 and 1 % TBBPA.

Toxicity observed; Reference	Species and dose	POD	Effect at LOAEL
	Lactation: 42, 380, 4156 mg/kg bw/day	LOAEL: 141 mg/kg bw/day	
Developmental study Fukuda et al. (2004)	Newborn Wistar rats (gavage) PND 4–21; 0, 40, 200, 600 mg /kg bw/day	NOAEL: 40 mg/kg bw/day	Polycystic kidneys with tubular dilatation.

15.1.1 Selection of NOAEL for risk characterisation

Based on the potential for long-term exposure of the general population to TBBPA, a NOAEL from a long-term exposure study would be most appropriate for characterising risk to the general population. However, no significant adverse effects were observed with TBBPA in long term studies in rats.

In the 13-week study conducted by the NTP, a dose-dependent decrease in total serum T_4 was observed in male and female Fischer 344 (F344) rats, with no significant changes in serum T_3, TSH, thyroid weight or thyroid histopathology. Also, no changes were observed in the thyroid after administration of TBBPA to either Wistar–Han rats or B6C3F1 mice for 2 years (NTP, 2014). Based on the lack of consistent and concordant changes in T_4, T_3 and TSH serum levels, as well as lack of adverse effects associated with this decreased T_4 reported, the toxicological significance of this endpoint is uncertain. Therefore, this endpoint was not considered to be adverse, and was not further considered as a critical effect for risk assessment.

Histopathological changes in young animals treated with TBBPA were observed in two studies considered relevant for hazard assessment. In one developmental study, polycystic kidneys with tubular dilatation were observed in newborn rats directly administered high doses of TBBPA during postnatal days 4-21 (Fukuda et al., 2004), while in the other study mice were exposed during gestation and lactation. Target organs for TBBPA toxicity were the liver and kidneys (Tada et al., 2006). The renal effect in newborn rats could be due to a combination of limited capacity for conjugative biotransformation of TBBPA and the immature kidney function (EURAR, 2006). However, due to the severity of these effects, and the increased vulnerability of young children to higher exposure to the chemical, the NOAEL of 42 mg/kg bw/day from the postnatal developmental study (Tada et al., 2006) is used for the risk assessment. This point of departure is also considered protective of any potential transient effects on neurogenesis (increase in reelin-expressing interneurons in the dentate hilus in newborn rats).

It can be argued that selecting a NOAEL for risk characterisation from developmental studies would accurately estimate risk only for a small section of the population (infants and females

of child-bearing age) and thus a NOAEL based on adverse effects observed in both male and female animals would be more appropriate for estimating risk to the general population.

The other pronounced effect of TBBPA was a significant increase of renal tubule cytoplasmic alteration (minimal/mild grade) in male mice at 500 and 1000 mg/kg bw/day. The severity of the lesion in the 1000 mg/kg bw/day group was greater than that in the 500 mg/kg bw/day group. Renal tubule cytoplasmic alteration was characterised by a decrease or absence of the normal vacuoles present in the cortical proximal tubules. Based on organ weight changes and enzymatic effects, the NOAEL for this study was determined to be 100 mg/kg bw/day, which is more than twice the NOAEL for developmental effects. Therefore, the more conservative NOAEL of 42 mg/kg bw/day was used for all risk assessments.

Studies on the mode of action for uterine tumour incidence indicated that high concentrations of TBBPA seem to compete for glucuronosyltransferases and/or sulfotransferases. Therefore, TBPPA indirectly results in higher serum levels of oestrogen. This leads to subsequent promotion of pre-existing Tp53 mutations in the the uterus through increased DNA synthesis and cell proliferation, which leads to uterine tumours and is consistent with the findings of the study. The worker exposure data indicate that workers are not likely to be exposed to high concentrations of TBBPA by inhalation or dermal routes. Workers in this sector of industry are predominantly males and, moreover, they do not use or handle powdered TBBPA throughout the year, but intermittently during the year for shorter periods of time. The risk of carcinogenicity to workers is, therefore, very low.

15.1.2 MOE calculations

The MOE for each exposure scenario was determined using measured exposure data and exposure values derived from EASE model and the NOAEL of 42 mg/kg bw/day established in a developmental toxicity study in mice.

For determining risk from dermal exposure, modelled dermal exposure data were converted to internal dose using estimated dermal absorption values for powder, granules and liquid formulations.

A NOAEL for inhalation effect is not available. The inhalation exposures estimated for the general public and workers handling powdered TBBPA are very low (0.025 µg/kg bw/day and 3.75 µg/kg bw/day, respectively). In a repeat dose inhalation exposure study, no systemic effects were observed in male or female rats exposed to as high as 18 mg/L TBBPA for four hours daily for two weeks. Therefore, exposure to TBBPA via the inhalation route is not expected to pose any risk to the public or the workers. No further risk assessment was conducted for this route of exposure.

Total exposure was determined to be the sum of the internal dose determined from dermal exposure values and dermal absorption rate and inhalation exposure, assuming 100 % absorption from respiratory tract.

15.2 Public health risk estimates

Consumers using articles comprised of plastics treated with TBBPA may be directly exposed to TBBPA that is released from the articles. The potential risk of adverse effects following

exposure to TBBPA has been considered separately for adults and children since the routes of exposure may differ for each group.

TBBPA has a low vapour pressure and significant emission from treated articles is not expected. Dermal exposure is possible through contact with dust containing TBBPA or plastics treated with TBBPA. However, an estimation of dermal exposure from dust indicated very low dermal exposures for adults as well as for young children.

The highest calculated exposure to TBBPA is via food, particularly for infants and toddlers. However, the calculation of exposure via food used a method that was believed to greatly overestimate exposure, because the highest TBBPA concentration found in any food was then attributed to all foods (EHC, 2009). In spite of this conservative method, all MOEs were found to be above 3000, indicating a low risk from exposure through food.

Exposure to TBBPA through inhalation and ingestion of indoor dust was generally the next highest contributor to exposure. Properties of the indoor environment have a large influence on intake via this route, with nearly a 20-fold difference between the reasonable worst-case estimate of exposure of the general public and the estimate for a maximally exposed individual living in a house with one of the highest measured TBBPA concentrations in dust.

Table 28 provides a summary of the exposure data and MOEs when the overall daily exposure is compared with the NOAEL of 42 mg/kg bw/day. As shown in the table, the MOEs for all population groups are greater than 100, even without further refinement of the food intake method. This indicates very low risk.

Recently Wikoff et al. (2015) calculated MOE for different age groups using average daily dose (ADD) calculated from TBBPA concentrations in drinking water, soil and dust and diet and their average daily intake. A NOAEL of 72.8 mg/kg bw/day was calculated using benchmark dose modelling from the uterine effects in female rats in the NTP 2-year carcinogenicity study (NTP, 2014). Very high MOEs were obtained for all age groups of population.

Table 28 – Calculated margin of exposure (MOE) from combined indoor and outdoor exposure to TBBPA

Groups	TBBPA Exposure (ng/kg bw/day)								MOE[1]
	Indoor exposure			Outdoor exposure		Food	Breast milk	Total	
	Oral	Inhalation	Dermal	Oral	Inhalation				
Infants	Negl.[3]	0.011	Negl.	Negl.	Negl.	-	31.8	31.81	>1000
Toddlers	9.04	0.023	Negl.	0.107	0.00007	7.0	-	16.17	
Children	1.24	0.025	Negl.	0.015	0.00008	3.7	-	4.98	
Adults	0.42	0.025	Negl.	0.005	0.00008	1.6	-	2.05	

[1]MOE = NOAEL/total exposure. MOEs calculated based on a NOAEL of 42 mg/kg bw/d from a developmental toxicity study.

[2]Estimate of outdoor exposure from inhalation of dust and ingestion of soil and dust.

[3]Negl. = negligible

All estimates are for reasonable worst-case scenarios.

15.3 Occupational Health Risk Estimates

As TBBPA is not manufactured in Australia there is no risk to workers during its manufacture. However, TBBPA is imported for use as a reactive or additive flame retardant. The occupational exposure assessment identified 4 scenarios where workers would be exposed to TBBPA based on the information provided by Australian industry. These are:

- exposure from handling TBBPA powder
- exposure from handling semi-finished products containing TBBPA
- exposure from the use of final products containing TBBPA
- exposure from recycling components containing TBBPA.

Since no sampling data are available from the Australian industry, exposure was estimated using a combination of modelled data (EASE) and overseas measured data. When using overseas measured data, the median and the 90th percentile values were selected for a typical and worst-case situation, respectively. The occupational exposure was assessed without taking the use of personal protective equipment (PPE) into account. The use of PPE is expected to reduce the exposure depending on the efficiency and correct use of the equipment.

The possible routes of exposure to TBBPA in workers include inhalation, dermal and oral. Workers handling powdered TBBPA may be exposed to TBBPA via the inhalation route. However, inhalation exposures estimated for workers handling powdered TBBPA are very low (3.75 µg/kg bw/day). In a repeat dose inhalation exposure study, no systemic effects were observed in male or female rats inhalationally exposed to TBBPA as high as 18 mg/L for four hours daily for two weeks. Exposure to TBBPA via the inhalation route is not expected to pose an unacceptable risk to workers.

In general, occupational exposure directly via the oral route is not expected unless poor hygiene practices are observed. However, as described in Section 10.1.2, a fraction of the inhalable TBBPA dust will be deposited in the upper respiratory tract and will be available for oral ingestion. In the occupational exposure assessment the inhalable dust fraction available for absorption by the gastrointestinal tract was taken as 70 %.

15.3.1 Risk from physicochemical hazards

TBBPA is a non-flammable solid (powder or granules) that does not undergo autoignition and has no evidence of explosive properties. It has a melting point of 182 °C and decomposition occurs at >316 °C.

TBBPA is stable under normal storage conditions. Based on the properties of TBBPA, the risk from physicochemical hazards during storage and handling of TBBPA is considered to be very low.

15.3.2 Acute risks due to occupational exposure

TBBPA has low acute oral, dermal and inhalation toxicity. The LD_{50} is greater than 10 g/kg for both dermal and oral routes of administration, and LC_{50} greater than 18 mg/L by the inhalation route. The toxicological profile of TBBPA indicates that it is not a skin or eye irritant, nor a skin sensitiser. The risk of acute effects such as inhalation toxicity, skin, eye and

respiratory irritation when handling technical TBBPA or products containing TBBPA is considered to be low.

15.3.3 Chronic risks due to occupational exposure

15.3.3.1 Model for exposure estimates

Measured and modelled data were used to estimate oral, inhalation and dermal exposure for workers engaged in repackaging, mixing and compounding tasks. Overseas monitoring data were used to determine risk to workers during the weighing and adding TBBPA to polymers and for additional tasks. Short-term and full shift measurements were available for tasks involving adding TBBPA to polymers, and full shift measurement for the weighing task. The 50th and 90th percentiles were used as the typical and worst-case scenarios to estimate the risk during these tasks.

The dermal exposure for workers conducting these tasks was determined using the EASE model. The internal dose was estimated using the EASE results, dermal absorption (6 %) and concentration of TBBPA in the formulations.

Oral, inhalation, dermal and total exposure and MOE for workers conducting the various tasks in typical and worst-case scenarios are presented in Table 29. MOEs for all scenarios are above 100, indicating low risk to workers handling TBBPA for various tasks.

Table 29 – Internal exposure via oral, inhalation and dermal routes, total internal exposure and MOE for workers conducting various tasks

Tasks	Exposure	oral route (µg/kg bw/d)	Inhalation route (µg/kg bw/d)	Dermal route (µg/kg bw/d)	Total internal exposure (µg/kg bw/d)	MOE[1]
Handling powder	Typical	57.3	3.28	32.1-321	92.7-382	109-453
	Worst-case	62.4	3.57		98.1-387	108-428
Handling semi-finished products	Typical	0.06	0.003	Very low	0.063	>1000
	Worst-case	0.48	0.027		0.507	
Recycling (dismantling)	Australian data not available; worker exposure during dismantling circuit boards is expected to be very low as TBBPA is bound within the resin and dermal absorption for TBBPA is very low. Shredding of circuit boards does not occur in Australia.					

[1]MOE = NOAEL/Total Internal Exposure. MOEs calculated based on a NOAEL of 42 mg/kg bw/d from a developmental toxicity study.

Risk of carcinogenicity to workers is considered very low. The most significant carcinogenic effect of TBBPA is the incidence of uterine tumours in female rats at high TBBPA doses and following prolonged exposure. The proposed mechanism suggests that there is an exposure level below which no effect occurs (Section 12.2.5 Summary). Worker exposure to powdered TBBPA is only intermittent – a few days every month. In addition, worker inhalation and dermal exposure to TBBPA is estimated to be very low at these workplaces and dermal absorption of TBBPA is also very low (6 %).

15.4 Risk estimates for specific occupations

15.4.1 Risk from Importation and transport

The risk of harmful effects by oral, inhalation or dermal exposure to workers handling the powder form of TBBPA during importation and transport is likely to be negligible except in the case of breached packaging or accidental spillage. Based on the exposure estimates determined from measured data for oral and inhalation and modelled data for dermal contact, the risk to workers handling packaged TBBPA in both typical and realistic worst-case scenarios was found to be acceptable.

15.4.2 Risk from handling TBBPA powder

In Australia the major use of imported pure TBBPA is in the manufacture of flame retarded vinyl ester resins. While the process is semi-enclosed, manual handling of TBBPA powder occurs during the charging of the reactor.

Manufacture of the phenolic resin is conducted in a closed reactor, with manual handling of the TBBPA powder occurring only when it is added to the reactor via an open floveyor system.

The compounding process of TBBPA-containing polystyrene is also semi-enclosed, and manual handling of TBBPA occurs when the powder is weighed out and loaded into the ribbon blender.

At sites where TBBPA powder is used, manual handling of TBBPA during weighing and charging of the reactors leads to the highest dermal exposure. MOEs during weighing of TBBPA powder and adding to the reactor (compounding) were determined using:

- overseas measured data for oral and inhalation exposure
- modelled data for dermal contact.

Based on the exposure data and Australian industry information, oral and inhalation exposure during these tasks were within safe limits. The MOEs were higher than 100 for the typical and worst case scenarios, indicating low risk to workers. Dermal exposure, estimated using EASE, was high for the worst case scenario resulting in unacceptable risk to workers handling TBBPA powder.

15.4.3 Handling semi-finished products containing TBBPA

TBBPA is used as a reactive flame retardant in FR4 type laminates used in the production of printed circuit boards. While there is potential for worker exposure during the assembly of

printed circuit boards, the amount of unreacted TBBPA is low. Thus, the potential inhalation and dermal exposure is also low.

Phenolic resin containing TBBPA is used in the production of decorative laminates. However, the manufacturing process used to produce laminates is generally an enclosed process so the inhalation exposure will be minimal. Dermal exposure may occur during handling of phenolic resin. However, due to the low concentration of TBBPA in the phenolic resin (0.1 - 0.4 %) this exposure is likely to be minimal. ABS copolymer masterbatch pellets containing TBBPA are used for injection moulding applications. The injection moulding process is generally conducted in a closed or semi-closed system so the inhalation exposure is minimised. While handling of masterbatch pellets may occur, dermal exposure to TBBPA is minimal given that TBBPA is encapsulated in the polymer matrix. Based on the overseas measured data it is estimated that Australian workers are typically exposed to 0.063 μg/kg bw/day TBBPA when handling semi-finished products containing TBBPA as a reactive flame retardant, and the worst-case exposure is 0.507 μg/kg bw/day.

15.4.4 End-use products

The risk to workers handling end-use products containing TBBPA is expected to be low, as these products contain TBBPA at low concentrations, encapsulated or reacted into polymer matrices. TBBPA plasma levels of three different occupational groups (electronics dismantlers, circuit board producers and laboratory personnel) in Norway were compared (Thomsen et al., 2001a). The laboratory personnel were considered a non-occupationally exposed group. Although some computer work was involved in their daily routines, it was expected to be no greater than for the general population. The highest levels were found amongst the electronics dismantlers (Table 18).

In order to calculate the risk to these workers, the authors first converted the ng/g lipid weight to ng/kg body weight (the average lipid weight in human blood is about 5 g/L and a total blood volume of 5.2 L is assumed for an adult (Grimvall et al., 1997). When this value was compared with the NOAEL of 42 mg/kg bw/day, the MOEs were greater than 1000, indicating very low risk to these workers.

15.4.5 Recycling of TBBPA-containing products

The recycling of printed circuit boards is carried out at one site in Australia. Inhalation and dermal exposure to TBBPA is expected to be low as TBBPA is chemically bound within the resin of printed circuit boards. Furthermore, as the printed circuit boards are not shredded at this site, exposure to TBBPA should be lower than exposures reported overseas. Based on the overseas measured data, it is estimated that Australian workers are potentially exposed to 2 – 70 ng/kg bw/day TBBPA during recycling of printed circuit boards. Therefore, risk to workers under this scenario is considered to be low.

16 Environmental Risk Characterisation

Where possible, the risk characterisation involves calculation of a risk quotient (RQ). This is a comparison of exposure versus effects. The RQ is calculated by dividing the predicted environmental concentrations (PEC) by the predicted no effect concentration (PNEC). In other words, it is the PEC/PNEC ratio. If the predicted environmental concentration (PEC) is greater than the predicted no-effect concentration (PNEC) in a particular compartment, then the risk quotient (RQ) will be greater than 1. In that case, there is considered to potentially be a risk to organisms in that compartment. Conversely, if the RQ is less than 1, organisms in that compartment are not considered to be at risk.

Risk quotients have been calculated, where possible, for the environmental compartments that are exposed to TBBPA. The PECs below (Table 30) were determined in Section 11.5 and the PNECs in Section 14.3.

16.1 Air

An environmental RQ has not been calculated for air, since this is not expected to be a significant direct exposure pathway for TBBPA and no data are available on the effects to biota from airborne TBBPA. Atmospheric concentrations of TBBPA are typically very low, except in the immediate vicinity of facilities that handle and process TBBPA or near e-waste and metal recycling facilities. The risk to the environment from atmospheric emissions of TBBPA is expected to be very low, except in the immediate vicinity of such facilities. The available evidence indicates that most TBBPA released to air near such facilities is bound to particulates and rapidly partitions to soil. A PEC in soils surrounding these facilities has not been determined, but concentrations in the mg/kg range have been reported near such facilities overseas, and other flame retardants have been detected at similarly high concentrations near Australian facilities (McGrath et al., 2016).

16.2 Water

16.2.1 Marine

Industrial use of TBBPA in Australia mostly occurs in Melbourne. Industrial waste water from Melbourne's main industrial area is treated by the Western Treatment Plant, which releases effluent to the ocean. An RQ was calculated for the marine environment exposed to TBBPA in effluent from the Western Treatment Plant. The PEC for effluent from the Western Treatment Plant was determined using the SIMPLETREAT model (Struijs, 1996) in Section 11.4 as 112 ng/L.

To calculate a marine RQ, it is assumed that the effluent from a treatment plant will be diluted by a factor of 10 (EPHC, 2009). Thus, the estimated PEC of TBBPA in the vicinity of the outflow of the Plant is 11.2 ng/L. The aquatic PNEC was determined to be 3.1 µg/L (see Section 14.3), leading to an RQ of 0.0036. This value is far below one and therefore marine organisms are not expected to be at risk from adverse effects from residual TBBPA in the effluent from the Melbourne Western Treatment Plant.

16.2.2 Rivers

Effluent from sewage treatment plants (STPs) may be discharged to rivers. However, most industrial use of TBBPA in Australia occurs in Melbourne and the Melbourne Western Treatment Plant treats waste from industrial use of TBBPA. This plant releases effluent to the ocean. Therefore, emissions of TBBPA to rivers from other STPs will occur via dispersed release of TBBPA from its use in articles (such as from contaminated dust or laundry water that has been discharged to the sewage system). Release of TBBPA from articles is expected to be limited, since most of the TBBPA used worldwide is incorporated into articles as a reactive flame retardant, and will remain bound within the plastic articles into which it is incorporated.

Releases from articles are only expected when TBBPA is used as an additive flame retardant. No monitoring data are available on the concentration of TBBPA in Australian STP effluents, and international data on effluents from STPs that do not process industrial waste are also limited. The available information is insufficient to calculate an RQ for rivers. However, this (limited) information suggests that residual TBBPA in effluents from STPs that do not process industrial waste is unlikely to pose a risk to the environment.

16.3 Sediment

Available monitoring data for TBBPA in Australian sediments indicates concentrations are generally low or below the limit of detection. However, no data are available for sediments near the outfall of the Western Treatment Plant in Melbourne, where significant levels might be expected. In the absence of measured data, it is assumed that the concentration in sediment near the Western Treatment Plant outfall is up to 500 µg/kg dw, based on values found in sediment overseas. This is a very conservative assumption and, even so, results in an RQ below one. Therefore, it is expected that, in Australia, sedimentary organisms are not at risk of adverse effects from TBBPA.

16.4 Soil

In Australia, sewage sludge is applied to soils on farms and cultivated forests, primarily to replace plant nutrients and to improve soil properties (Pritchard et al., 2010). The concentration of TBBPA in sewage sludge from the Western Treatment Plant was estimated to be 1.25 mg/kg (see Section 11.5). Concentrations in soil amended with biosolids from the Western Treatment Plant were estimated using the model in EPHC (2009). For a single application of biosolids to land, the resulting concentration in soil is 8.3 µg/kg. Using the PNEC derived for earthworm reproduction (0.5 µg/kg dw) the estimated RQ is 16.6. This value is > 1 and suggests that there may be risks to earthworm reproduction from exposure to TBBPA in soils that have been amended with sewage sludge.

The risk quotients for each of the relevant environmental compartments are summarised in Table 30. The calculations predict that there is a risk to organisms in soil that has been amended with one application of biosolids. Marine organisms in the aquatic and sediment compartments near the outfall of the Western Treatment Plant in Melbourne are not predicted to be at risk. It is expected that concentrations of TBBPA in the water and sediment in the vicinity of the outfall of the Western Treatment Plant will be amongst the highest concentrations in Australia. Consequently, organisms in the aquatic and sedimentary

compartments in other parts of Australia where TBBPA is not used industrially are not likely to be at risk of adverse effects from exposure to TBBPA.

Table 30 – Risk quotients for different exposure scenarios

Exposure scenario	PEC	PNEC	RQ
Ocean	11.2 ng/L	3.1 µg/L	0.0036
Sediment	0.5 mg/kg dw	1.8 mg/kg dw	0.28
Soil	8.3 µg/kg dw	0.5 µg/kg dw	16.6

As discussed above, there may be a risk to soil-dwelling organisms in soils amended by a single application of biosolids from the Western Treatment Plant. The half-life of TBBPA in soil is difficult to determine from the available data, but TBBPA is resistant to mineralisation in soil and becomes reversibly bound to the humin fraction. Consequently, significant concentrations of TBBPA may build up in soil following multiple applications of biosolids, resulting in risk quotients much greater than 1.

International data reveal that concentrations of TBBPA in the mg/kg range have been measured in soil near facilities where TBBPA is used industrially, as well as near auto-dismantlers and e-waste recycling facilities. No data are available on the presence of TBBPA in soils near similar Australian facilities, but studies have detected other flame retardants at high concentrations near Australian facilities (McGrath et al., 2016). The international data suggest that earthworm reproduction is likely to be adversely affected in soils in the immediate vicinity of these industrial facilities.

17 Discussion and Conclusions

17.1 Identification and Uses

TBBPA is not produced in Australia, but it is produced in the USA, China, Israel and Japan. Health/Env Canada (2013) estimated global production volume in 2004 to be between 120000 and 170000 tonnes per year. TBBPA is imported into Australia as a raw chemical and as an ingredient of intermediate products and articles. The main industrial use of TBBPA in Australia (and globally) is as a reactive flame retardant in epoxy resins for printed circuit boards in computers and telecommunications equipment. TBBPA used in this way becomes chemically bound to the resin and is no longer available for release to the environment. TBBPA is also used as an additive flame retardant in plastic housings for electrical and electronic equipmentin the manufacture of acrylonitrile-butadiene-styrene (ABS) resins and phenolic resins where it remains chemically unchanged. This may result in TBBPA being released to the environment through use or disposal of the product or article containing the chemical.

There is a lack of data on the use of consumer products containing TBBPA in Australia and the release of TBBPA from these products. Measured data on exposure of the Australian public to TBBPA present in articles are also lacking. This does not permit a realistic exposure assessment. Consequently, exposure models have been used to determine the exposure that represents the greatest risk to consumers. Such models are not as reliable as measured data as they generally use conservative assumptions.

Overall, the available information indicates widespread low level public exposure. The risk characterisation indicates that, under normal conditions of consumer use, the risk of adults and children being exposed to levels of TBBPA leading to health effects noted in repeat-dose animal studies is very low.

Under occupational conditions, the risk to workers of acute adverse health effects such as inhalation toxicity, skin, eye and respiratory irritation and skin sensitisation is low.

In animal studies, repeated exposure to TBBPA did not result in severe effects. Risk characterisation indicated that, for all tasks, the risk of adverse effects to workers was very low as evidenced by high MOEs (>100). In addition, the risk to workers handling semi-finished products or during recycling procedures was also low.

17.2 Uncertainties in occupational risk assessment

Uncertainties in any risk characterisation process arise from:

- data limitations
- inadequate exposure information
- assumptions made during the process
- variability in experimental conditions.

The uncertainties inherent in characterising the risks from TBBPA arise mainly from inadequate data and include:

- absence of representative atmospheric monitoring in Australia
- lack of data on TBBPA in Australian food products
- absence of dermal exposure data
- lack of exposure methods to characterise the contribution of exposure from dust particles and particulate matter in indoor air
- lack of data on the health effects of TBBPA in humans following repeated exposures
- use of a default oral NOAEL for determination of MOE estimates, as no reliable evidence of systemic toxicity was seen in dermal studies in a suitable animal model.

We used the maximum concentration of TBBPA based on a study that measured indoor dust in homes in the UK, because the data:

- were consistent with levels found in office buildings
- are expected to be similar to those in households and/or in cars.

There is uncertainty regarding the potential of TBBPA to affect the endocrine system, including the thyroid and the immune system. In addition, the assumptions used in EASE modelling add uncertainties to the risk characterisation.

17.3 Pathways to the Environment

TBBPA is imported into Australia in three main forms: as a raw chemical, as an ingredient of an article/good in a reacted form, or as an ingredient of an article/good in an additive form.

Release to the environment will mostly be through wastes generated during reformulation into resins or during the use of the articles/goods and from leachates from landfills where some of the wastes containing TBBPA are disposed. Release from articles containing TBBPA as a reacted flame retardant is not expected to be significant.

A significant proportion of waste that contains TBBPA will be released via the sewage system or to industrial water treatment plants. Concentrations of TBBPA in effluents from sewage and waste water treatment plants are expected to vary according to the influent load and the efficiency of the treatment plant. Monitoring data from the UK indicate that TBBPA in the particulate phase of influent to treatment plants is in the range 2.6 - 85 ng/kg dw. International data indicate that TBBPA in the particulate phase of effluents from treatment plants is in the range n.d. – 63 µg/kg dw.

Local emissions of TBBPA are highest in the vicinity of facilities that process and handle TBBPA in the manufacture of articles and near e-waste recycling facilities, car wrecking yards and metal recycling facilities. Emissions to the air will partition to the soil in the vicinity of these facilities.

When TBBPA is released to the environment, it predominantly partitions to sediment and soil. In STPs, TBBPA predominantly partitions to biosolids, and will be released to the environment when biosolids are applied to agricultural soil as soil improver.

17.4 Persistence

According to Australia's PBT criteria, TBBPA is classified as a persistent (P) chemical. Laboratory studies indicate that TBBPA is not readily biodegradable and is very persistent in

sediment under abiotic conditions and is persistent in some (biotic) aerobic soils (half-life >6 months). Mineralisation (ultimate degradation) was generally limited over the course of laboratory studies.

Modelling indicates that TBBPA is persistent in air (half-life >2 days) and the chemical is expected to be resistant to degradation by hydrolysis. The photolytic degradation half-life in water exceeds 2 months under simulated winter sunlight. TBBPA is routinely detected in soils, sediments and water in urban and industrial areas. It has been found in sediments accumulated over several decades. Some of the degradants of TBBPA are persistent, including BPA and the bis-methyl ether derivative. These degradants are more likely to be formed under anaerobic conditions than aerobic conditions.

17.5 Bioaccumulation

According to Australia's PBT criteria, TBBPA is classified as not bioaccumulative (Not B). Laboratory and modelling studies on bioaccumulation of TBBPA, and analyses of the chemical in biota indicate that TBBPA has low bioaccumulation potential. Laboratory studies show that the chemical can be significantly metabolised and excreted by all the organisms tested. Measured and modelled data for bioconcentration factor (BCF) and bioaccumulation factor (BAF) are well below the bioaccumulation criteria (BAF > 2000 L/kg). Analyses of TBBPA and its metabolites in biota show that concentrations are highly variable. The available evidence does not show a correlation between concentration and trophic level, which indicates that the chemical does not biomagnify in the food chain.

17.6 Toxicity

According to Australia's PBT criteria, TBBPA is classified as a toxic (T) chemical. In general, TBBPA has low acute toxicity to most organisms. However, laboratory studies show that TBBPA can cause adverse chronic reproductive and developmental effects in various fish species and some amphibians at low concentrations (≤ 0.1 mg/L). Laboratory studies provide evidence that TBBPA may affect the thyroid system in some amphibians, fish and marine bivalves at environmentally relevant concentrations. TBBPA has adverse effects on reproduction of some earthworm species at low soil concentrations (56 day EC10 = 0.12 mg/kg soil dw).

Based on these observations, TBBPA meets the GHS criteria (UNECE, 2013) for classification as:

- H400 Acute Toxicity Category 1
- H410 Chronic Toxicity Category 1

17.7 Levels of TBBPA in the Environment

17.7.1 Australia

Studies have detected TBBPA in sediments from the Parramatta River at a concentration of 0.13 µg/kg dw. This river is in a mixed industrial and urban area. No other Australian data are available to demonstrate TBBPA in other sites.

17.7.2 International data

17.7.2.1 Air

Studies have detected TBBPA in air and precipitation from industrial, urban and remote locations. In general, measured air concentrations are very low with typical concentrations for rural and urban air in the range 0.5 – 25 pg/m^3. The available evidence indicates that adsorption to particulates is the major mode for the presence of TBBPA in air.

Studies have detected TBBPA in the air of remote locations in the Arctic at concentrations in the range 0.05 pg/m^3 – 70 pg/m^3. This provides some (limited) evidence that TBBPA may undergo long range transport. The concentrations of TBBPA in the air near TBBPA manufacturing facilities may be much greater than in air at remote locations (for example, 1.8 µg/m^3 near a US facility and 95 ng/m^3 at a Chinese e-waste facility).

17.7.2.2 Water

Numerous studies have been published in the scientific literature on the presence of TBBPA in the aqueous compartment. These studies provide compelling evidence that the highest concentrations of TBBPA in water are associated with wastewater treatment plants in heavily populated regions and in water the studies sampled at (or near) heavily industrialised areas. Analysis of TBBPA in remote lakes and rivers indicates very low levels (the studies often could not detect them). However, in lakes and streams near urban areas concentrations in the range 1 – 5 ng/L are typical. Waterways near industrialised areas carry higher concentrations of TBBPA (typical concentrations range from about 1 ng/L to about 100 ng/L). Studies have detected TBBPA in effluents from sewage and wastewater treatment plants at concentrations up to 63 ng/L, indicating that these effluents are a significant pathway for TBBPA to enter the environment. Concentrations of TBBPA in leachates from landfills vary from levels a study could not detect up to about 1 µg/L.

17.7.2.3 Household and indoor dust

Studies have detected TBBPA and many other flame retardant chemicals in household and indoor dust. This dust contributes to emissions of the chemical to the environment, especially through the sewage system when clothing and household fabrics are washed and the waste-water is discharged to the sewer. The concentrations of TBBPA in hundreds of dust samples from 14 countries ranged from <1 to 3600 ng/g. However, typical concentrations for household dust were in the range 20 – 60 ng/g.

17.7.2.4 Sediments

International data for sediment concentrations show high levels of TBBPA in sediments near factories producing brominated flame retardants with concentrations up to 9753 µg/kg dw.

Generally, in other industrial or urban areas, levels are the range n.d. – 500 µg/kg dw. In more remote locations, sediment levels are typically below 1 µg/kg dw.

17.7.2.5 Soils

International data on the presence of TBBPA in soils in most locations were generally in the range n.d. – 10 µg/kg dw. Soils at sites where TBBPA is manufactured or used, or where e-waste or metal recycling occurs, contain much higher concentrations, up to 7700 µg/kg dw.

17.7.2.6 Sewage Sludge

Studies detected TBBPA in most samples of sewage sludge and sludge from waste water treatment plants in Europe, Canada and the USA. The studies reported concentration ranges from not detected up to 1329 µg/kg dw. However, typical mean concentrations are in the range 10 – 100 µg/kg dw.

17.8 Predicted Australian Environmental Concentrations of TBBPA

The Western Treatment Plant in Melbourne processes the industrial waste from most of the Australian facilities that handle and process TBBPA. Consequently, it is expected that emissions of TBBPA to the environment from this treatment plant are likely to be amongst the highest in Australia. Therefore, the predicted environmental concentrations are focused on emissions from this facility.

Based on the OECD method (OECD, 2009), the concentration of TBBPA in the ocean in the vicinity of the effluent outflow of the Western Treatment Plant is predicted to be 11.2 ng/L. However, comparison with international data suggests that this estimate is conservative by a factor of at least nine.

Suitable models are not available to estimate the concentration of TBBPA in sediments near the effluent outflow of the Western Treatment Plant and monitoring data are not available. Based on international data, the concentration of TBBPA in marine sediments in the vicinity of the effluent outflow of this plant was assumed to be 0.5 mg/kg dw.

The concentration of TBBPA in soils amended with one application of sewage sludge from the Melbourne Western Treatment Plant was predicted to be 2.8 µg/kg dw. The concentration of TBBPA in Melbourne air is predicted to be 13 pg/m^3.

17.9 Risk to the Australian Environment

A risk quotient has not been calculated for air because this is not expected to be a significant direct exposure pathway for TBBPA and information on the toxicity of TBBPA to organisms via this exposure route is not available. International data indicate that atmospheric concentrations of TBBPA are generally very low. Any TBBPA released to air is expected to rapidly partition to soil.

Releases of TBBPA to sewer from articles are expected to be limited because the majority of TBBPA used worldwide is as a reactive flame retardant which will remain bound in the plastics in which it is incorporated. The risk to the Australian environment from wide-dispersed release of TBBPA from articles is expected to be low.

Industrial use of TBBPA in Australia mostly occurs in Melbourne. Industrial waste water from Melbourne's main industrial area is treated by the Western Treatment Plant, which releases effluent to the ocean. Therefore, concentrations of TBBPA in the Australian environment are expected to be highest in ocean water and marine sediments in the immediate vicinity of the outflow of effluents from this treatment plant. Quantitative estimates indicate that aquatic and sedimentary organisms are not at risk from exposure to TBBPA emitted in effluents from the Western Treatment Plant and, therefore, are not at risk from any other sites in Australia.

Quantitative estimates indicate a risk to soil-dwelling organisms (earthworms) in soils amended by a single application of biosolids from the Western Treatment Plant. The half-life of TBBPA in soil is difficult to determine from the available data, but it is known that TBBPA is resistant to mineralisation in soil, and becomes reversibly bound to the humin fraction. Consequently, significant concentrations of TBBPA may accumulate in soil following multiple applications of biosolids produced by this plant, resulting in a significant risk to soil dwelling organisms in the affected soil. The results of quantitative risk estimates (RQs) are summarised in Table 31.

Table 31 – Risk quotients for different exposure scenarios

Exposure scenario	PEC	PNEC	RQ
Ocean	11.2 ng/L	3.1 µg/L	0.0036
Sediment	0.5 mg/kg dw	1.8 mg/kg dw	0.28
Soil	8.3 µg/kg dw	0.5 µg/kg dw	16.6

In summary, based on the evidence presented in this assessment, there is a low risk to organisms in the Australian environment and to the Australian environment as a whole from TBBPA introduced into Australia as a raw, unprocessed chemical.

The most significant route of exposure to the environment is expected to occur via release to the sewage system from industrial facilities in Melbourne involved in the compounding and handling of TBBPA. This release to sewer is not predicted to result in a risk to the environment in the vicinity of the effluent outfall of the Wetern Treatment Plant where environmental emissions are expected to be highest.

The only identified risk is to soil dwelling organisms amended with sewage sludge from the Melbourne Western Treatment Plant. This risk is identified only for the soils directly affected by this process and not to the broader Australian environment.

When TBBPA is incorporated into articles as an additive flame retardant, emissions are expected to be widely dispersed and result in low environmental concentrations that do not pose a risk to the environment.

Release of TBBPA to the air in the vicinity of industrial facilities involved in compounding and handling the chemical and e-waste and car wrecking facilities may result in localised contamination of soil at levels that have adverse effects on soil dwelling organisms. Such effects will be limited to the immediate vicinity of these facilities.

18 Current Risk Management

This Section discusses measures currently employed in the management of human risks from exposure to TBBPA.

18.1 Occupational Health and Safety

According to the Safe Work Australia National Model Regulations for the Control of Workplace Hazardous Substances (Safework Australia, 2019), exposure to hazardous substances should be prevented or, when this is not practicable, adequately controlled, so as to minimise risks to health and safety.

The National Code of Practice for the Control of Workplace Hazardous Substances (Safework Australia, 2017) provides further guidance in the form of a hierarchy of control strategies:

- elimination
- substitution
- isolation
- engineering controls
- safe work practices
- personal protective equipment (PPE).

These measures are not mutually exclusive and effective control usually requires a combination of these strategies.

Although TBBPA is determined not to be a hazardous substance, the following should be implemented to eliminate or minimise exposure to TBBPA in the workplace.

18.2 Elimination and Substitution

Elimination is the removal of a chemical from a process and should be the first option considered when minimising risks to health. In situations where it is not feasible or practical to eliminate the use of a chemical, substitution should be considered. Substitution includes replacing with a less hazardous substance or the same substance in a less hazardous form.

None of the applicants have indicated that they are looking to eliminate or substitute TBBPA with another flame retardant. An applicant stated that there are no commercially viable alternatives to TBBPA in the manufacture of printed epoxy resin circuit boards. They may not have considered elimination or substitution of TBBPA as they considered it to be less hazardous to human health than some other popular brominated flame retardants.

18.3 Isolation

Isolation is a control measure that aims to separate employees as far as practicable from the chemical hazard. This can be achieved by the use of barriers or enclosures. In the case of TBBPA, an applicant stated that TBBPA is weighed and prepared for use in the Pigment Room area and that only 1 operator works in the Pigment Room in any given 8 h shift. No other applicant provided any information to indicate that isolation as a control measure is actively being pursued.

18.4 Engineering controls

Engineering controls are used in plants or processes to:

- minimise the generation of hazardous substances
- contain hazardous substances or
- limit the area of contamination in the event of spills or leaks.

These controls include:

- enclosure or partial enclosure
- local exhaust ventilation
- automation of processes.

Manufacture of TBBPA-flame retarded vinyl ester resin is undertaken at a site in Australia. This process is semi-enclosed, with manual handling occurring during charging of the reactor via the charge chute. While the site did not contain an extraction hood associated with the chute, the reactor is under vacuum and, therefore, acts as an extraction system. The packing process at the site is semi-automated, but the operators are required to take samples manually for quality control. The compounding of the phenolic resin is carried out in a closed reactor. At this site, TBBPA is added to an enclosed extracting unit for charging to the reactor. This device is also fitted with an exhaust extraction unit.

In another site, the compounding process of TBBPA-containing polystyrene is semi-enclosed. Manual handling of TBBPA occurs when the powder is weighed out and when the powder is loaded into the ribbon blender. However, an extraction system is in operation at each weigh station and a dust extraction system is in place at the ribbon blender. ABS copolymer masterbatch pellets containing TBBPA are used for injection moulding applications. TBBPA is not expected to be available from masterbatch pellets and the injection moulding process is generally conducted in a closed or semi-closed system. While high temperatures are involved in the process, the heating process is carried out in a closed vessel.

18.5 Safe work practices

Safe work practices are administrative practices that enable people to work in a safe environment. These include:

- avoiding prolonged skin contact
- minimising inhalation of dust
- removal of contaminated clothing.

The use of PPE during repackaging, formulation and application of the product and compliance with label and MSDS information contribute to a safe working environment. Some of the current safe work practices are:

- Workers have access to the MSDS via the process instruction sheet.
- Material Handling Codes are indicated on formulation paperwork.
- Training in handling chemicals is provided as part of training process operators.
- Containers of TBBPA are kept upright and tightly closed when not in use.
- Prompt cleanup of spills.

- Limiting the number of workers manually handling TBBPA, such as during weighing.
- Disposal of product is handled by registered waste disposal contractors.

18.6 Personal protective Equipment

Personal protective equipment (PPE) is used to minimise exposure to or contact with chemicals. PPE should be used when other control measures are not practicable or in conjunction with other controls measures to increase protection to workers. PPE should not be used as a replacement for other control measures.

Information from industry submissions indicates that PPE is used to protect workers from exposure where manual handling of TBBPA is involved. During charging of the reactor for the manufacture of TBBPA-flame retarded vinyl ester resin, the operators wear protective clothing, safety glasses and leather or chemical gloves. Although the use of respiratory protection is not compulsory at this site, dust masks as well as half-face and full-face respirators are available. At this site PPE is used in addition to engineering controls.

In the TBBPA-flamed retarded phenolic resin manufacture site, in addition to engineering controls at the reactor, the workers are supplied with gloves, masks and overalls for personal protection.

At the site where compounding of TBBPA-containing polystyrene occurs, the workers weighing the TBBPA or charging the ribbon blender are required to wear a cartridge-type full respirator, disposable gloves and disposable overalls. The PPE used at this site is in addition to the weigh station and the blender having engineering controls.

19 Appendices

19.1 Appendix 1 – Classification under the Globally Harmonized System of Classification and Labelling of Chemicals

Health and environmental hazards	Classification	Hazard communication
Health Hazard		
Carcinogenicity	Category 2 H351	 **Signal word**: Danger **Hazard statement**: Suspected of causing cancer.
Environmental hazard		
Acute toxicity	Category 1 H400	 **Signal word**: Warning **Hazard statement**: Very toxic to aquatic life.
Chronic toxicity	Category 1 H410	 **Signal word**: Warning **Hazard statement**: Very toxic to aquatic life with long-lasting effects.

19.2 Appendix 2 – Exposure Calculations

19.2.1 Occupational exposure

19.2.1.1 Calculations of internal dose following inhalation exposure

The internal dose arising from inhalation (D_i) is calculated using the following formula:

$$D_i = \frac{C \times R \times F \times E \times B}{BW}$$

Where:

D_i = inhalation exposure (µg/kg bw/day)

C = concentration of a substance in air (µg/m^3)

R = inhalation rate (1.3 m^3/hour)

F = fraction of respirable particles in air (4 %)

E = exposure duration (hour/day)

B = bioavailability (100 %)

BW = average body weight of workers (70 kg)

Scenario	Data source	C (µg/m^3)	E	D_i (µg/kg bw/day)
TBBPA powder	measured	1470	3 h/d	3.28
	measured	6400	3 h/d	14.26
	modelled	2000	3 h/d	4.46
	modelled	5000	3 h/d	11.14
TBBPA semi-finished products	measured	0.6	8 h/d	0.003
	measured	4.6	8 h/d	0.027
Recycling	measured	0.03	8 h/d	0.0002
	measured	0.97	8 h/d	0.0058

19.2.1.2 Calculations of internal dose following oral exposure

The internal dose arising from oral ingestion after inhalation of TBBPA particles (D_i) is calculated using the following formula:

$$D_o = \frac{C \times R \times F \times E \times B}{BW}$$

Where:

D_o = oral exposure (μg/kg bw/day)

C = concentration of a substance in air (μg/m^3)

R = inhalation rate (1.3 m^3/hour)

F = fraction of particles in air available for oral ingestion after inhalation (70 %)

E = exposure duration (hour/day)

B = bioavailability (100 %)

BW = average body weight of workers (70 kg)

Scenario	Data source	C (μg/m^3)	E	D_o (μg/kg/day)
TBBPA powder	measured	1470	3 h/d	57.3
	measured	1600	3 h/d	62.4
	modelled	2000	3 h/d	78.0
	modelled	5000	3 h/d	195.0
	modelled	50000	3 h/d	1950
TBBPA semi-finished products	measured	0.6	8 h/d	0.06
	measured	4.6	8 h/d	0.48
Recycling	measured	0.03	8 h/d	0.003
	measured	0.97	8 h/d	0.100

19.2.1.3 Calculations of internal dose following dermal exposure

The internal dose from dermal exposure (D_d) is calculated using the following formula:

$$D_d = \frac{C \times A \times Ex\ Abs}{BW}$$

Where:

D_d = Internal dermal exposure dose (μg/kg bw/day)

C = EASE estimated exposure (mg/cm^2/day) for 8-hour shift

A = Skin surface area exposed (1000 cm^2)

E = Exposure duration (3 hrs)

Abs = Dermal Absorption (6 %)

BW = average body weight of workers (70 kg)

Scenario	Data source	C (μg/cm^2/day)	E (hours/day)	D_d (μg/kg/day)
TBBPA powder	modelled	100	3	32.1
	modelled	1000	3	321

19.2.2 Public exposure

19.2.2.1 Calculations of internal dose following Inhalation exposure from indoor dust and outdoor air

The exposure arising from the inhalation of indoor or outdoor air can be derived by using the following equation:

$$U_{inh} = \sum \frac{C_{air} \times V_{inh} \times 0.75 \times t}{BW \times 24}$$

The parameters used and the values derived from the equation are summarised in the following table:

Parameter	Description	Units	Infants (9 months)	Toddlers (2 years)	Children (12 years)	Adults
BW	Bodyweight	kg	5.8	12.9	46.9	70
V_{inh}	Ventilation rate	m^3/day	0.8	3.8	15	22
Exposure to TBBPA in indoor air						
C_{indoor}	Concentration of TBBPA in indoor air (dust)	ng/m^3	0.126	0.126	0.126	0.126
t_{indoor}	Duration of exposure (indoors)	h/d	20	20	20	20
U_{indoor}	Inhalation uptake from indoor air	ng/kg bw/d	0.011	0.023	0.025	0.025
Exposure to TBBPA in outdoor air						
$C_{outdoor}$	Concentration of TBBPA in outdoor air	ng/m^3	0.013	0.013	0.013	0.013
$t_{outdoor}$	Duration of exposure (outdoors)	h/d	4	4	4	4
$U_{outdoor}$	Inhalation uptake via outdoor air	ng/kg bw/d	0.0002	0.00048	0.00052	0.0005

19.2.2.2 Calculations of internal dose following Oral exposure from ingestion of indoor and outdoor dust particles and soil

The oral exposure arising from the ingestion of soil and dust particles can be derived by using the following equation:

$$U_{oral} = \sum \frac{C \times R_{ing} \times t}{BW \times 24} \times B_{oral}$$

The parameters used and the values derived from the equation are summarised in the following table:

Parameter	Description	Units	Infants (9 months)	Toddlers (2 years)	Children (12 years)	Adults
B_{oral}	Bioavailability	%	100	100	100	100
BW	Bodyweight	kg	9.4	12.9	46.9	70
R_{ing}	Ingestion rate for dust	mg/d	Negligible	100	50	25
Exposure to TBBPA in indoor soil and dust						
C_{dust}	Concentration in dust	µg/g	1.40	1.40	1.40	1.40
t_{indoor}	Duration of exposure	h/d	20	20	20	20
U_{dust}	Uptake from oral exposure via dust	ng/kg/d	Negligible	9.04	1.244	0.486
Exposure to TBBPA in outdoor soil and dust						
C_{soil}	Concentration in soil	µg/g	0.028	0.028	0.028	0.028
$t_{outdoor}$	Duration of exposure	h/d	4	4	4	4
U_{soil}	Uptake from oral exposure via soil	ng/kg/d	Negligible	0.036	0.005	0.0017

19.2.2.3 Calculations of internal dose following oral exposure from the consumption of breast milk

The oral exposures arising from the consumption of breast milk are derived by the following equation:

$$U_{milk} = \frac{C_{milk} \times \mathrm{FC} \times \mathrm{R}_{\mathrm{milk}} \times F \times t}{\mathrm{t}_{\mathrm{ave}}} \times B_{oral}$$

The parameters used and the values derived from the equation are summarised in the following table:

Parameter	Description	Units
U_{milk}	Uptake from ingestion of contaminated breast milk	ng/kg bw/day
C_{milk}	Concentration of TBBPA in breast milk	ng/g lipid wt
FC	Fat content or lipid content in breast milk	4 %
R_{milk}	Ingestion rate of breast milk for infants who are fully breast fed (= BW adjusted intake x 1.03*)	g milk/kg bw/day
F	Exposure frequency	day/month
t	Exposure duration	Month (mth)
t_{ave}	Averaging time	day
B_{oral}	Bioavailability of the ingested TBBPA	100 %

***density of human breast milk**

Group	Bodyweight (kg)			Typical case		Reasonable worst-case	
	Girl	Boy	Mean	Milk intake (mL/day)	BW adjusted intake (mL/kg/d)	Milk intake (mL/day)	BW adjusted intake (mL/kg/d)
1 month	3.98	4.29	4.14	702	169.6	1007	243.2
3 months	5.40	5.98	5.69	759	133.4	1025	180.1
6 months	7.21	7.85	7.53	765	101.6	1059	140.6
				Average:	134.9	**Average:**	188.0

From the table above, the bodyweight (BW)-adjusted average intakes for the typical case and the reasonable worst-case are 135 and 188 mL/kg bw/day, respectively. When combining the BW-adjusted intake rates with a human milk density factor of 1.03 g/mL, the intake rate of breast milk for infants who are fully breastfed (R_{milk}) is calculated to be 139 g/kg bw/day and 194 g/kg bw/day for the typical and the worst-case, respectively.

Case	C_{milk}	FC	R_{milk}	F	t	t_{ave}	B_{oral}	U_{milk}
Typical case	4.1	4 %	139	30	6	180	100 %	22.8
Reasonable worst-case	4.1	4 %	194	30	6	180	100 %	31.8

19.2.3 The EASE model

The EASE (Estimation and Assessment of Substance Exposure) model used for the assessment of workplace exposure to TBBPA is the Windows Version 2 from the Health & Safety Executive, UK. Definitions from the EASE model that have been used in the report are listed below.

- Dry manipulation – This category includes any manipulation of the dry material, including brushing.
- Readily aggregating solids – Substances which are waxy in texture or are in some other way sticky so particles of the solid readily aggregate will give rise to less dust than those solid particles of which do not readily aggregate.
- Non-dispersive use – Non-dispersive use refers to processes in which substances are used in such a way that only certain groups of workers, with the knowledge of the

processes, come into contact with these chemicals. Procedures are normally worked out to achieve adequate control of exposure commensurate with the risk. The EASE model intends this category to cover most occupational use not specifically assignable to other categories.

- Intermittent – The EASE model assumes intermittent exposure to be 2 to 10 events per day involving exposure as part of a process. For example, material transfer by a device which involved judgement such as at a weighing plant.

19.3 Appendix 3 – Bioaccumulation, ecotoxicity and environmental monitoring data.

Table A.3.1: Bioaccumulation

Species	BCF (L/kg)	Reference
Fathead minnow (*Pimephales promelas*)	1200[1]	Brominated Flame Retardants Industry Panel, 1989c
	160	EU, 2008 review of above study
Bluegill sunfish (*Lepomis macrochirus)*	20 (edible tissue)	Velsicol Chemical Corporation, 1978
	170 (visceral tissue)	
Carp (*Cyprinus carpio*)	30 – 485	CITI, 1992
Eastern oysters (*Crassostrea virginica)*	720, 780[2]	Brominated Flame Retardants Industry Panel, 1989b
Freshwater midges (*Chironomus tentans*)	240 – 510[3]	Brominated Flame Retardants Industry Panel, 1989e
	490 – 1100[4]	
	650 – 3200[5]	
Earthworms (*Eisenia fetida*)	No bioaccumulation	Aufderheide et al., 2003
Zebrafish embryos (*Danio rerio*)	160 – 180	Liu et al., 2018
Orange-red killifish (*Orizias latipes*), and Japanese carp (*Cyprinus carpio*)	30 – 485	Hardy, 2004

[1]BCF value included metabolites; revised by EU (2008) to be 160; [2]estimated based on uptake and depuration rates; [3]High organic carbon content (OC) sediment, [4]medium OC sediment, [5]low OC sediment.

Table A.3.2: **Monitoring Data – biota**

Location	Organism	Concentration	References
North Sea	Cod	< 0.1 – 0.8 µg/kg ww	de Boer et al., 2002
	Whiting	< 97 – 245 µg/kg lw	
	Hermit crab	< 1 – 35 µg/kg lw	
	Sea star	< 1 – 10 µg/kg lw	
	Whelk	5 – 96 µg/kg lw	
	Harbour porpoise	0.05 – 376 µg/kg ww	
	Whelk	5.0 – 96 µg/kg lw	Morris et al., 2004
	Hermit crab	< 1 – 35 µg/kg lw	
	Whiting	< 97– 245 µg/kg lw	
	Cod	< 0.3 – 1.8 µg/kg lw	
	Harbour porpoise	< 11 µg/kg lw	
	Harbour seal	< 14 µg/kg lw	
Norway	Predatory bird's eggs	< 0.004 – 0.013 µg/kg ww	Herzke et al., 2005
	Blue mussel	0.01 – 0.03 µg/kg ww	SFT, 2002
	Cod	0.08 – 0.16 µg/kg ww	
	Moss	0.019 – 0.89 µg/kg ww	
	Freshwater fish	0.01– 0.18 µg/kg ww	Fjeld et al., 2004
	Marine fish	0.35 – 1.73 µg/kg ww	
Japan	Mussels	ND	Watanabe et al., 1983

Location	Organism	Concentration	References
	Sea bass	3.4 – 23 µg/kg lw	Ohta et al., 2004
	Fish (various species)	< 0.03 – 0.15 µg/kg ww	USEPA, 2015
Germany	Eel	0.045 – 0.10 µg/kg ww	Asplund et al., 1999
	Perch	0.033 µg/kg ww	
	Pike	0.021 µg/kg ww	
	Shrimp	< 7.7 – 0.9 µg/kg lw	Verslycke et al., 2005
UK	Freshwater fish	< 0.29 – 1.7 µg/kg lw	Harrad et al., 2009
	Porpoise (Rivers)	0.1 – 418 µg/kg lw	USEPA, 2015
	Porpoise (Coastal)	< 4 – 35 µg/kg lw	
	Porpoise (North Sea)	ND	
	Cormorants	2.5 – 14 µg/kg lw	USEPA, 2015
USA	Dolphins	0.056 – 8.48 µg/kg lw	Johnson-Restrepo et al., 2008
	Bull sharks	0.035 – 35.6 µg/kg lw	
	Sharp nose sharks	0.495 – 1.43 µg/kg lw	
China	Birds (various species)*	0.23 – 1482 µg/kg lw	Malkoske et al., 2016
	Fish (various species)	29 – 39 µg/kg dw	USEPA, 2015

ND – not detected. * Collected near e-waste recycling facilities.

Table A.3.3: **Monitoring Data – Ambient environment and sewage sludge**

Medium	Location	Concentration	Reference
Air	Arctic (northeast Atlantic)	< 4.0×10^{-8} – 1.7×10^{-7} µg/m^3	Xie et al., 2007
	Wadden Sea	2.1×10^{-7}, 5.0×10^{-7} µg/m^3 (vapour)	Xie et al., 2007
		1.0×10^{-7}, 1.9×10^{-7} µg/m^3 (particle)	
	Germany	< 4.0×10^{-8} – 2.5×10^{-7} µg/m^3 (vapour)	Xie et al., 2007
		1.6×10^{-7} – 8.5×10^{-7} µg/m^3 (particle)	
	United States	< 0.01–1.8 µg/m^3	Zweidinger et al., 1979
		0.0297 µg/m^3	Bergman et al., 1999
	Russian Arctic	0.070 µg/m^3	de Wit et al., 2006
Rainwater	Netherlands, Belgium, Germany	0.0005 – 0.0026 µg/L	Peters, 2003
Sediment	Australia	0.13 µg/kg dw	Toms et al., 2006
	USA/Canada	0.6 – 1.84 µg/kg dw	Quade, 2003
	Sweden	34 – 270 µg/L dw	Sellström and Jansson, 1995
	Germany	0.02 – 18.68 µg/kg ww	Kemmlein, 2000
	Ireland	< 2.4 – 3.7 µg/kg dw	Morris et al., 2004
	UK	< LOD – 9753** µg/kg dw	Morris et al., 2004
		0.33 – 3.8 µg/kg dw	Harrad et al., 2009
	France	0.065 – 0.28 µg/kg dw	Labadie et al., 2010
	Netherlands	< 0.1 – 6.9 µg/kg dw	Morris et al., 2004
	Finland	0.4 – 21 µg/kg dw	Peltola, 2002
	Norway	0.06 – 6.2 µg/kg dw	Fjeld et al., 2004

Medium	Location	Concentration	Reference
	Japan	2 – 150 µg/kg dw	Environment Agency Japan, 1996
		0.7 – 12 µg/kg dw	Ohta et al., 2002
		0.08 – 5 µg/kg dw	Ohta et al., 2004
	China	0.06 – 304 µg/kg dw	Feng et al., 2012
		4 – 230 µg/kg dw	Zhang, X-L et al., 2009
		0.056 – 2.15 µg/kg dw	Xu, J et al., 2013
	Korea	0.05 – 150 µg/kg dw	Lee et al., 2015
		ND – 0.62 µg/kg dw	Gu, S-Y et al., 2017
Soil**/***	USA	220 000 µg/kg (dw or ww not specified)	Pellizzari, 1978
	Israel	450 000 µg/kg	Arnon, 1999
		0.2 µg/kg dw	Leisewitz, 2001
	China	0.8, 5.6 µg/kg dw	Xu et al., 2012
		≤ 7.76 µg/kg dw	Liu et al., 2016
		1 – 7700 µg/kg dw	Malkoske et al., 2016
	Vietnam	< 0.5 – 2900 µg/kg dw	Malkoske et al., 2016
Water	Germany	< 0.0002 – 0.0204 µg/L (river water)	Kuch et al., 2001
	UK	0.00014 – 0.0032 µg/L (lake water)	Harrad et al., 2009
	China	ND – 0.000112 µg/L (lake water)	Xu et al., 2013
		0.85 – 4.87 µg/L (lake water)	Liu et al., 2016
		ND – 1.8 µg/L (coastal water)	Gong et al., 2017
	Sweden	≤ 0.062 µg/L (river water)	Gustavsson et al., 2018
	Korea	ND – 0.00279 µg/L (sea water)	Gu, S-Y et al., 2017
Leachate	Finland	0.90 µg/L	Peltola, 2002
	Netherlands	< 0.3 – 320 µg/kg dw	Morris et al., 2004

Medium	Location	Concentration	Reference
	Japan	0.009 – 0.62 µg/L	Osako et al., 2004
Sewage	UK	0.0026 – 0.085 µg/L (dissolved, influent)	Morris et al., 2004
		< 0.015 µg/L (dissolved, effluent)	
		< 3.9 – 21.7 µg/kg dw (sorbed, influent)	
		< 3.9 µg/kg dw (sorbed, effluent)	
	Netherlands	3.1 – 63 µg/kg dw (sorbed, effluent)	Morris et al., 2004
	South Africa	6.6 – 6.8 µg/L (dissolved, influent)	Chokwe et al., 2012
		3.3 µg/L (dissolved, effluent)	
Sewage Sludge	Sweden	5, 10 and 45 µg/kg dw	Sellström et al., 1999
		< 0.3 µg/kg – 220 µg/kg ww	Öberg et al., 2002
	Spain	≤ 472 µg/kg dw	Gorga et al., 2013
	Germany	0.6 – 62 µg/kg dw	Metzger and Kuch, 2003
	Ireland	< 2.4 – 192 µg/kg dw	Morris et al., 2004
	UK	15.9 – 112 µg/kg dw	Morris et al., 2004
	Netherlands	2 – 600 µg/kg dw	Morris et al., 2004
	Canada	2.9 – 46.2 µg/kg dw	Lee and Peart, 2002
		9.04 – 43.1 µg/kg dw	Quade et al., 2003
		2.09 – 28.3, µg/kg dw	Chu et al., 2005
	USA	2.98 – 196 µg/kg dw	Quade et al., 2003
	Korea	4 – 618 µg/kg dw	Hwang et al., 2012
	Various	< 0.4 – 732 µg/kg dw	Malkoske et al., 2016
	Various	n.d. – 1329 µg/kg dw	Gorga et al., 2013

ND – not detected; * Collected near e-waste recycling facilities; ** Collected near brominated chemical manufacturing facilities.

Table A.3.4: Ecotoxicity

Organism	Species	Endpoint	Value	Reference
Fish	Japanese rice fish (*Oryzias latipes*)	48-hour LC50	30 mg/L	CITI, 1992
	Zebrafish (*Danio rerio*)	30-day LOEC (egg production)	0.047 mg/L	Kuiper et al. 2007
		47-day LOEC (hatching)	0.013 mg/L	
		3-day LOEC (development)	1.63 mg/L	
		96-hour LC50 (embryo)	1.3 mg/L	Godfrey et al., 2017
	Fathead minnow (*Pimephales promelas*)	35-day LOEC (embryo survival)***	0.31 mg/L	Brominated Flame Retardants Industry Panel, 1989f
		144-hour NOEC	0.26 mg/L	Surprenant, 1988
		144-hour NOEC	0.26 mg/L	Surprenant, 1988
	Bluegill (*Lepomis macrochirus*)	96-hour LC50	0.51 mg/L	Calmbacher, 1978a
		96-hour NOEC	0.10 mg/L	
	Rainbow trout (*Salmo gairdneri*)	96-hour LC50	0.40 mg/L	Calmbacher, 1978b
		96-hour NOEC	0.18 mg/L	
	Various*	LC50	0.4 – 1.1 mg/L	USEPA, 2015
	Various freshwater*	LC50	0.4 – 8.2 mg/L	EU, 2008

Organism	Species	Endpoint	Value	Reference
	Rainbow trout (*Oncorhynchus mykiss*)	96h LC50**	1.1 mg/L	Blankinship et al., 2003
	Common carp (*Cyprinus carpio*)	96-hour LC50	0.71 mg/L	Bogers, 1998
Aquatic Invertebrate	Water flea (*Daphnia magna*)	48-hour NOEC	1.8 mg/L	Wildlife international, 2003
		21-day LOEC	0.98 mg/L	Brominated Flame Retardants Industry Panel, 1989d
		21-day NOEC	0.30 mg/L	
		72-hour EC50	0.6 mg/L	Waaijers et al., 2013
		48-hour LC50	0.96 mg/L	Morrissey, 1978
	Mysid shrimp (*Mysidopsis bahia*)	96-hour LC50	0.860 – 1.100 mg/L	Goodman et al., 1988
	Common mussel (*Mytilus edulis*)	70-day LOEC (shell length)	0.032 mg/L	ACCBFRIP, 2005c
		70-day LOEC (wet tissue weight)	0.126 mg/L	
	Eastern oyster (*Crassostrea Virginica*)	95-hour EC50	0.02 – 0.210 mg/L	Brominated Flame Retardants Industry Panel, 1989a
	Copepod (*Acartia tonsa*)	2-day LC50	0.40 mg/L	Wollenberger et al., 2005

Organism	Species	Endpoint	Value	Reference
	Midge (*Chironomus tentans*)	14-day LOEC (survival)	0.2 mg/L	Brominated Flame Retardants Industry Panel, 1989e
		14-day LC50	0.13 mg/L	
	Various	Acute EC50	0.098 – 0.96 mg/L	USEPA, 2015a
	Various	Acute EC50	0.098 – 1.8 mg/L	EU, 2008
	Hyalella Azteca	28-day NOEC (survival)	250 mg TBBPA/kg sediment dw (5.7% OC)	Wildlife international, 2006
		28-day NOEC (growth)	≥ 1000 mg/kg sediment dw (5.7% OC)	
	Oligochaete (*Lumbriculus variegatus*)	28-day LOEC (survival and reproduction)	151 mg TBBPA/kg sediment dw (2.5% OC)	ACCBFRIP, 2002a,b
		28-day NOEC (survival and reproduction)	90 mg TBBPA/kg sediment dw (2.5% OC)	
		28-day LOEC (survival and reproduction)	426 mg TBBPA/kg sediment dw (5.9% OC)	
	Midge (*Chironomus riparius*)	28-day LOEC (emergence ratio, development rate, development time)	250 mg/kg dw	ACCBFRIP 2005d

Organism	Species	Endpoint	Value	Reference
		28-day NOEC (sediment ratio, development rate, development time)	125 mg TBBPA/kg sediment dw	
Algae	*Skeletonema costatum*	72-hour EC50	0.09 – 0.89 mg/L	Walsh et al., 1987
	Thalassiosira pseudonana	72-hour EC50	0.13 – 1.0 mg/L	
	Pseudokirchneriella subcapitata	10-day EC50	> 0.4 mg/L	Peng et al., 2014
	Scenedesmus acuminatus	10-day EC50	> 0.4 mg/L	
	Scenedesmus quadricauda	10-day EC50	> 0.4 mg/L	
	Coelastrum sphaericum	10-day EC50	> 0.4 mg/L	
	Scenedesmus obliquus	10-day EC50	> 0.4 mg/L	
	Chlorella pyrenoidosa	10-day EC50	> 0.4 mg/L	
Earthworm	*Eisenia fetida*	28-day LOEC (survival)	> 4840 mg/kg soil dw	ACCBFRIP, 2003
		56-day LOEC (reproduction)	4.50 mg/kg soil dw	
		56-day EC10 (reproduction)	0.12 mg/kg soil dw	
		56 day EC50 (reproduction)	0.17 mg/kg soil dw	

Organism	Species	Endpoint	Value	Reference
		28-day NOEC (survival)	≥ 20 mg/kg soil dw	ACCBRIP, 2005a
		56-day LOEC (reproduction)	0.63 mg/kg soil dw	
	Enchytraeus crypticusi	21-day LOEC (survival)	> 1000 mg/kg soil dw	Sverdrup et al., 2006
		21-day LOEC (reproduction)	10 mg/kg soil dw	

* A review of acute toxicity.

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