Priority Existing Chemical Assessment Report No. 27

Australian Government
Department of Health and Ageing
NICNAS

Tris(2,3-dibromopropyl) phosphate

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National Industrial Chemicals Notification and Assessment Scheme
GPO Box 58, Sydney NSW 2001, Australia www.nicnas.gov.au

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Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are carried out in conjunction with the Australian Government Department of the Environment and Heritage, which carries out the environmental assessment for NICNAS.

NICNAS has two major assessment programs: the assessment of human health and safety and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia, in response to specific concerns about their health/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia. Chemicals selected for assessment are referred to as Priority Existing Chemicals.

This priority existing chemical report has been prepared by the Director of NICNAS, in accordance with the Act. Under the Act, manufacturers and importers of priority existing chemicals are required to apply for assessment. Applicants for assessment are given a draft copy of the report and 28 days to advise the Director of any errors. Following the correction of any errors, the Director provides applicants and other interested parties with a copy of the draft assessment report for consideration. This is a period of public comment lasting for 28 days during which requests for variation of the report may be made. Where variations are requested, the Director's decision concerning each request is made available to each respondent and to other interested parties (for a further period of 28 days). Notices in relation to public comment and decisions made, appear in the *Commonwealth Chemical Gazette*.

In accordance with the Act, publication of this report revokes the declaration of this chemical as a Priority Existing Chemical, therefore, manufacturers and importers wishing to introduce this chemical in the future need not apply for assessment. However, manufacturers and importers need to be aware of their duty to provide any new information to NICNAS, as required under section 64 of the Act.

For the purposes of Section 78(1) of the Act, copies of assessment reports for new and existing chemical assessments are freely available from the web (www.nicnas.gov.au) and may be inspected by the public at the ASCC Library (Office of the Australian Safety and Compensation Council), Department of Employment and Workplace Relations (formerly known as the National Occupational Health and Safety Commission (NOHSC) library). Summary Reports are published in the *Commonwealth Chemical Gazette* (http://www.nicnas.gov.au/Publications/Chemical_Gazette.asp), which are also available to the public at the ASCC library.

Copies of this and other priority existing chemical reports are available on the NICNAS website. Hard copies are available free of charge from NICNAS either by using the prescribed application form, or directly from the following address:

GPO Box 58, Sydney, NSW 2001, AUSTRALIA

Tel: +61 (2) 8577 8800

Fax: +61 (2) 8577 8888

Free call: 1800 638 528

Other information about NICNAS (also available on request and on the NICNAS web site) includes:

- NICNAS Service Charter;
- information sheets on NICNAS Company Registration;
- information sheets on the Priority Existing Chemicals and New Chemical assessment programs;
- safety information sheets on chemicals that have been assessed as Priority Existing Chemicals;
- details for the NICNAS Handbook for Notifiers; and
- details for the *Commonwealth Chemical Gazette*.

More information on NICNAS can be found at the NICNAS web site:

http://www.nicnas.gov.au

Other information on the management of workplace chemicals can be found at the web site of the National Occupational Health and Safety Commission:

http://www.nohsc.gov.au

Overview and Recommendations

Overview

Background

Tris(2,3-dibromopropyl) phosphate (TBPP) CAS No. 126-72-7 was declared a Priority Existing Chemical for a full risk assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989,*(the Act) by notice in the Chemical Gazette of 6 July 2004. The reason for declaration of TBPP was the listing of the chemical in Annex III of the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (Rotterdam Convention). Annex III contains chemicals that have been notified as severely restricted or banned due to health or environmental reasons by two countries participating in the voluntary Prior Informed Consent Procedure. As a party to the Convention, Australia is required to notify the Convention Secretariat if Australia wishes to continue to allow import of this chemical.

Declaration and assessment as a Priority Existing Chemical will assist in formulating Australia's response for purposes of the Convention.

In 2001, a preliminary assessment of TBPP was conducted in conjunction with the assessment of polybrominated flame retardants (PBFRs), as there was concern over the widespread use of flame retardants in household and industrial situations. Although TBPP was considered within this group, minimal occupational and environmental data were provided for this chemical, therefore, a full risk assessment was considered covering all industrial uses of TBPP in Australia.

Uses

TBPP is not manufactured in Australia, and to date, has not been imported into Australia. TBPP is not currently used in Australia, and there is no available information on former uses. However, one chemical company offers the chemical for import into Australia from the U.S.A, packaged as a 1000 mg ampoule. Based on the single package size, it would seem that TBPP is potentially available for use as an analytical standard in research and development.

In the past, TBPP was considered an important commercial flame retardant for children's sleepwear. However, TBPP has since been banned for use in children's clothing in the US, as a fire retardant in textile products in Japan, and in textile articles such as garments and linen in the European Commission (EC). Therefore, clothing and textiles imported from the US, Japan and Europe will not be treated with TBPP.

A review of import data of textiles and ready-to-wear clothing in Australia indicates that textiles and clothing are imported into Australia from countries that do not have any restrictions or ban on the use of TBPP to treat clothing. Imports from these countries have increased from the year 2000 to date.

Health effects

TBPP is readily absorbed in the gastrointestinal tract in rats and at a moderate rate via the skin in rats and rabbits. Rapid distribution of the parent compound and metabolite(s) occurs following absorption. TBPP is also rapidly metabolized and **t**here is evidence that TBPP derived metabolites covalently bind to proteins and DNA in vivo. The main route of excretion in rats and rabbits is via the urine, and very little of the parent compound is excreted. Additionally, there is evidence of enterohepatic circulation mainly of TBPP-derived metabolites.

TBPP has low acute oral and dermal toxicity in animals. It is not an eye or skin irritant in rabbits. Limited evidence in humans indicates a very weak skin sensitization potential. There is no indication of a skin sensitization potential in the available animal studies. No data on respiratory sensitization are available.

Systemic toxicity was observed following repeated exposure to TBPP in oral and dermal animal studies. No human data are available. Animal data indicates that the kidney is the target organ following ingestion of TBPP. Similarly, effects on the kidney were seen in dermal studies.

TBPP is classified as a Category 3 mutagen with positive results being clearly seen in vitro and in somatic cells in animal in vivo studies. In oral carcinogenicity studies the primary focus was the kidney, and TBPP was seen to clearly produce benign and malignant tumours in this organ, in both rats and mice. TBPP was also carcinogenic following dermal application to mice, with benign and malignant tumours seen at distal sites in addition to the site of application. Based on the development of malignant tumours in the kidneys and at distal sites in both rats and mice, TBPP is classified as a Category 2 carcinogen. No human data or animal fertility studies are available for TBPP, and although data are available from repeat dose studies that examined the reproductive organs, no definite conclusion can be drawn from the data regarding the adverse reproductive potential of TBPP. TBPP is not considered to be a developmental toxicant from the available animal studies. TBPP is a genotoxic carcinogen in rodents. This finding is deemed relevant to humans, as no mechanistic data to indicate the contrary are available.

Exposure

Occupational exposure to TBPP can occur in laboratories from drips or spills during use as an analytical standard in research and development procedures.

Public exposure to TBPP could occur through TBPP treated textiles and/or clothing. To date, there is no information to determine whether TBPP-treated garments/textiles have been imported into Australia, however, it is possible that the import of TBPP-treated ready-made garments/textiles may occur from countries that have not banned or restricted the use of TBPP.

TBPP in synthetic textiles/garments can exist both tightly bound within the fibre, and more loosely bound on the surface of the fibre. Dermal absorption occurs when TBPP is more loosely bound on the surface of the fibre. Dermal exposure can occur from new and repeatedly washed TBPP-treated sleepwear. The most reliable available study data indicated that the upper limit following dermal absorption could be as high as 0.18 and 9 μg TBPP/kg bw/day after wearing repeatedly washed and new TBPP-treated sleepwear respectively. Based on available study data and exposure estimates from US Consumer Product Safety

Commission (CPSC) Reports, oral exposure was estimated as 0.0018 and 0.09 μg TBPP/kg bw/day. Total exposure from dermal and oral absorption was therefore 0.18 and 9.09 μg/kg bw/day after wearing repeatedly washed and new TBPP-treated sleepwear respectively. While the reliability of estimates of oral exposure from secondary sources could not be determined, the data suggest that the oral route (i.e. 'sucking and 'mouthing' of TBPP-treated sleepwear) represents a minor route of exposure in comparison with the dermal route. The US CPSC estimated the total exposure following dermal and oral absorption to be 1.1-35.3 μg/kg bw/day.

The US CPSC estimated the risk to the public of developing kidney cancer from TBPP-treated sleepwear based on exposure estimates and modelled data. The lifetime risk of kidney cancer ranged from 60 – 6,000 cases per million male population and in children for 1 year of exposure, the cancer incidence was estimated as 17,000 cases per million children. The use of TBPP in sleepwear therefore constitutes an unacceptable risk (greater than 1 in a million) to the public and supports the elimination of the use of TBPP in textiles and clothing.

Environmental effects

In conducting the environmental assessment, a review of the literature has been undertaken to determine whether any new data are available since the preliminary assessment was conducted in 2001. No additional environmental data are available for TBPP which has a limited database and, therefore, experimental results for a closely related analogue, tris(1,3-dichloropropyl-2) phosphate have been used to fill environmental data gaps for TBPP.

TBPP is not readily biodegradable. While no chronic data are available, modelled results for fish and aquatic invertebrates indicate that some chronic effects could be observed in aquatic systems. Weight of evidence for bioaccumulation indicates that the chemical will not bioaccumulate to a significant extent, as depuration appears to be initially rapid.

Based on the available data, the overall category is Chronic II for environmental effects, and the corresponding hazard statement "Toxic to aquatic life with long lasting effects" is applicable.

The recommendations arising from the assessment of TBPP are based on the chemical's toxicity profile, determined from the available literature including case study reports. Recommendations are directed principally at regulatory bodies and importers of TBPP. The critical issues are summarized in the Preamble.

Preamble to Recommendations

- The toxicity profile of the chemical indicates it is a genotoxic carcinogen, with the target organ for toxicity being the kidney. Findings in animals are deemed relevant to humans, as no mechanistic data to indicate the contrary are available.

- TBPP is not manufactured or imported into Australia except in very small quantities presumably as a reference standard or for research & development (R & D), (1000 mg ampoule). No use beyond R & D were notified to NICNAS.

- The use profile of the chemical in the past was as a flame retardant in children's sleepwear, but this use is now banned in the US, EU, and Japan. Several other countries including Finland, New Zealand and Sweden have also banned or severely restricted the use of TBPP in textiles and clothing. However, there are a number of other countries that have not banned or restricted the use of TBPP in clothing or textiles and data exists that imports from these countries of various goods that may be treated with TBPP have increased over the past 5 years.

- Exposure to TBPP from clothing occurs through the dermal route. In children, in addition to dermal absorption, exposure can also occur orally because of 'mouthing' and 'sucking' of treated clothes. Exposure to children wearing TBPP-treated clothing therefore remains of particular concern.

- As TBPP is not manufactured in, or imported into Australia, it can be assumed that Australian textiles treated with fire retardants do not contain TBPP. Similarly, clothing and textiles imported from the US, Japan and Europe will not be treated with TBPP. However, clothing and textiles are imported into Australia from countries that have not restricted the use of TBPP. Therefore, there is the potential for exposure and risk of adverse effects arising from these imports.

- The Department of Treasury had a regulation from 1977 to 1996 under the Trade Practices Act (TPA), 1974, prohibiting the use of the flame retardant TBPP in clothing and textiles used to make clothing. In 1997, the regulatory controls on TBPP-treated fabrics were repealed. At the same time, the prohibition on the import of TBPP-treated fabrics in the Customs (Prohibited Imports) Regulations was similarly repealed. The rationale for the repeal was that TBPP had not been manufactured internationally for a considerable period of time and the use of TBPP as a fire retardant had been overtaken by more suitable retardants that could be manufactured more cheaply. It was therefore considered that production of TBPP would not recommence once the prohibition was lifted. The previous prohibition under the TPA related to the supply of certain fabrics containing TBPP. The TPA had never controlled the use of TBPP, nor did the Customs (Prohibited Imports) Regulations.

- While outside the jurisdiction of the Act, importation of articles such as textiles or ready-to-wear clothing, especially children's clothing, treated with TBPP, is of concern. Use of these articles therefore constitutes an unacceptable risk (greater than 1 in a million) to the public and supports

the elimination of the use of TBPP in textiles and clothing.

Recommendation 1. AICS annotation

Noting the toxicity profile of TBPP, the use of TBPP beyond research and development purposes is not supported by NICNAS. NICNAS will annotate the Australian Inventory of Chemical Substances (AICS) accordingly. Any other use will be deemed a new use under Section 21 of the Act, 1989, and will require notification to NICNAS prior to import or manufacture of TBPP.

Recommendations to regulatory bodies

NOHSC

Due to the potential for TBPP to be used for research and development purposes the following recommendations are made to NOHSC.

Recommendation 2

TBPP is not currently listed in the NOHSC *List of Designated Hazardous Substances* contained in the Hazardous Substances Information System (HSIS), (NOHSC, 2005).

In accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), TBPP is determined to be hazardous with the following risk phrases:

R45 May cause cancer (Carcinogen Category 2)

R68 Possible risk of irreversible effects (Mutagen Category 3)

The cut-off concentrations are as follows:

Risk Phrase	Concentration Cut-off
R45	≥0.1 % < 1.0 %
R45, R68	≥ 1.0%

The following safety phrases are also recommended for TBPP:

S45 In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)

S53 Avoid exposure – Obtain special instructions before use

S60 This material and its container must be disposed of as a hazardous waste

It is recommended that this classification be included in the NOHSC *List of Designated Hazardous Substances* contained in the Hazardous Substances Information System (HSIS).

Recommendation 3

It is recommended that TBPP be included in Schedule 1 of the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* Part 2- *Scheduled Carcinogenic Substances*. In accordance with the National Model Regulations, a supplier or an employer shall not use TBPP except for the purposes of bona fide research or analysis and only limited to a volume of 1000 mg (ampoule).

Australian Consumer and Competition Commission (ACCC)

Recommendation 4

It is recommended that the Australian Competition and Consumer Commission should give priority consideration to re-introducing appropriate regulations under the Trade Practices Act if evidence becomes available to NICNAS that TBPP - treated clothing or textiles are imported into Australia, to prevent exposure of the public, especially children.

Recommendations to importers of TBPP and State and Territory Authorities

Recommendation 5

Hazard communication - Material Safety Data Sheet

Under the *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994) and the Commonwealth, State and Territory regulations introduced in accordance with these National Model Regulations, employees shall have ready access to Material Safety Data Sheets (MSDS) for hazardous substances at their workplace.

In accordance with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 2003) it is recommended that importers of TBPP review their MSDS for compliance and pay particular attention to the following points:

- risk phrases and hazard information to be updated to reflect the hazard classification provided in Recommendation 2; and
- safety phrases should be included as noted in Recommendation 2.

Recommendation 6

Hazard communication - Label

In accordance with the *National Code of Practice for the Labelling of Workplace Substances* (NOHSC 1994a), it is recommended that importers of TBPP pay particular attention to the following points:

- risk phrases and hazard information to be updated to reflect the hazard classification provided in Recommendation 2; and
- safety phrases should be included as noted in Recommendation 2.

It is recommended that the State and Territory Occupational Health and Safety authorities review compliance with the above information, in the workplace.

Recommendation to textile and clothing retailers and Council of Textile and Fashion Industries of Australia Ltd.

Recommendation 7

Use of TBPP other than for research and development purposes is not supported by NICNAS. Retailers of fire retardant-treated clothing or textiles, under the duty of care should ascertain from their supply sources overseas the type of retardant used in the imported clothing or textiles.

If it becomes known to the Council of Textiles and Fashion Industries of Australia Ltd, and retailers of fire-retardant-treated clothing and textiles, that TBPP-treated clothing or textiles are being imported into Australia, NICNAS should be notified immediately.

Contents

Acronyms & Abbreviations

ACCC	Australian Consumer and Competition Commission
ACS	American Chemical Society
ADG CODE	Australian Code for the Transport of Dangerous Goods by Road and Rail
AICS	Australian Inventory of Chemical Substances
BBBP	Bis(2,3-dibromopropyl) phosphate
BOD	biochemical oxygen demand
bw	body weight
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
COD	chemical oxygen demand
d	days
DBP	2,3-Dibromopropanol
DEH	Australian Department of the Environment and Heritage
DGD	Decision Guidance Document
DOC	dissolved organic carbon
DNA	deoxyribonucleic acid
EC	European Commission
EC_{50}	median effective concentration
EDF	Environmental Defense Fund
EU	European Union
ECL	Korean Existing Chemicals List
ECOSAR	Ecological Structure Activity Relationships
EINECS	European Inventory of Existing Commercial Chemical Substances
ENCS	Japanese Existing and New Chemical Substances
EPI	Electronic Personal Identification
EQC	equilibrium criterion
FM	flame retardant
FORS	Federal Office of Road Safety

g	gram
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GLP	good laboratory practice
h	hour
hPa	hectopascal
HPVC	High Production Volume chemical
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
IUCLID	International Uniform Chemical Information Database
ip	intraperitoneal
iv	intravenous
kg	kilogram
K_{ow}	octanol/water partition coefficient
L	litre
LC50	median lethal concentration
LD50	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LPVC	Low Production Volume Chemical
m^3	cubic metre
mg	milligram
mg/cm^3	milligrams per cubic centimetre
mg/kg bw	milligrams per kilogram body weight
mg/kg bw/d	mg/kg body weight/day
min	minute
MITI	Ministry of International Trade and Industry
mL	millilitre
µg	microgram
MATC	Maximum acceptable toxicant concentration
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
ng	nanogram

NCI	National Cancer Institute
NIHS	National Institute of Health Sciences
NIOSH	National Institute of Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOHSC	National Occupational Health and Safety Commission
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Cooperation and Development
pa	pascals
PBFRs	polybrominated flame retardants
PEC	predicted environmental concentration
PIC	Prior Informed Consent
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
QSAR	Quantitative Structure-Activity Relationship
R and D	research and development
SARS	Structure-Activity Relationships
SCE	sister chromatid exchange
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TBPP	tris(2,3-dibromopropyl) phosphate
TGA	Therapeutic Goods Administration
TPA	Trade Practices Act
TSCA	Toxic Substances Control Act (US EPA)
UDS	unscheduled DNA synthesis
UNEP	United Nations Environment Programme
US CPSC	United States Consumer Product Safety Commission
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

Glossary

NICNAS uses the IPCS Risk Assessment Terminology (IPCS, 2004) glossary which includes Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment and Part 2: IPCS Glossary of Key Exposure Assessment Terminology. The IPCS Risk Assessment Terminology can be accessed at http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf

Adverse effect	Change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.
Assessment	Evaluation of appraisal of an analysis of facts and the inference of possible consequences concerning a particular object or process.
Assessment endpoint	Quantitative/qualitative expression of a specific factor with which a risk may be associated as determined through an appropriate risk assessment.
Chronic exposure	A continuous or intermittent long-term contact between an agent and a target. (Other terms, such as "long-term exposure," are also used.)
Concentration	Amount of a material or agent dissolved or contained in unit quantity in a given medium or system.
Dose	Total amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population.
Dose-effect relationship	Relationship between the total amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population and the magnitude of a continuously-graded effect to that organism, system or (sub)population Related terms: *Effect Assessment, Dose-Response Relationship, Concentration-Effect Relationship*.
Dose rate	Dose per unit time
Dose-related effect	Any effect to an organism, system or (sub) population as a result of the quantity of an agent administered to, taken up or absorbed by that organism, system or (sub) population.
Dose-response	Relationship between the amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population and the change developed in that organism, system or (sub) population in reaction to the agent. Synonymous with Dose-response relationship. Related Term: *Dose-Effect Relationship, Effect Assessment, Concentration-Effect Relationship*.

Dose-response curve	Graphical presentation of a dose-response relationship.
Dose-Response Relationship	Relationship between the amount of an agent administered to, taken up or absorbed by an organism, system or (sub) population and the change developed in that organism, system or (sub) population in reaction to the agent. Related Terms: *Dose-Effect Relationship, Effect Assessment, Concentration-Effect Relationship*.
Effect	Change in the state or dynamics of an organism, system or (sub) population caused by the exposure to an agent.
Exposure	Concentration or amount of a particular agent that reaches a target organism, system or (sub) population in a specific frequency for a defined duration.
Exposure assessment	Evaluation of the exposure of an organism, system or (sub) population to an agent (and its derivatives). Exposure Assessment is the third step in the process of Risk Assessment.
Exposure concentration	The exposure mass divided by the contact volume or the exposure mass divided by the mass of contact volume depending on the medium.
Exposure duration	The length of time over which continuous or intermittent contacts occur between an agent and a target. For example, if an individual is in contact with an agent for 10 minutes a day, for 300 days over a one year time period, the exposure duration is one year.
Exposure period	The time of continuous contact between an agent and a target.
Exposure route	The way an agent enters a target after contact (*e.g.*, by ingestion, inhalation, or dermal absorption).
Exposure scenario	A set of conditions or assumptions about sources, exposure pathways, amount or concentrations of agent(s)involved, and exposed organism, system or (sub) population (i.e. numbers, characteristics, habits) used to aid in the evaluation and quantification of exposure(s) in a given situation.
Fate	Pattern of distribution of an agent, its derivatives or metabolites in an organism, system, compartment or (sub) population of concern as a result of transport, partitioning, transformation or degradation.
Hazard	Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub) population is exposed to that agent.
Hazard assessment	A process designed to determine the possible adverse effects of an agent or situation to which an organism, system or (sub) population could be exposed. The process includes hazard identification and hazard characterization. The process focuses on the hazard in contrast to risk assessment where exposure assessment is a distinct additional step.

Hazard characterization	The qualitative and, wherever possible, quantitative description of the inherent properties of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose-response assessment and its attendant uncertainties. Hazard Characterisation is the second stage in the process of Hazard Assessment, and the second step in Risk Assessment. Related terms: *Dose-Effect Relationship, Effect Assessment, Dose-Response Relationship, Concentration -Effect Relationship.*
Hazard identification	The identification of the type and nature of adverse effects that an agent has inherent capacity to cause in an organism, system or (sub) population. Hazard identification is the first stage in hazard assessment and the first step in process of Risk Assessment
Intake	The process by which an agent crosses an outer exposure surface of a target without passing an absorption barrier, i.e. through ingestion or inhalation.
Margin of exposure	Ratio of the no-observed-adverse-effect level (NOAEL) for the critical effect to the theoretical, predicted or estimated exposure dose or concentration. Related term: *Margin of Safety*
Risk assessment	A process intended to calculate or estimate the risk to a given target organism, system or (sub)population , including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system. The Risk Assessment process includes four steps: hazard identification, hazard characterization (related term: dose-response assessment), exposure assessment, and risk characterization. It is the first component in a risk analysis process.
Risk characterization	The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system or (sub)population, under defined exposure conditions. Risk Characterization is the fourth step in the Risk Assessment process.
Risk management	Decision-making process involving considerations of political, social, economic, and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyse, and compare regulatory and non-regulatory options and to select and implement appropriate regulatory response to that hazard. Risk management comprises three elements: risk evaluation; emission and exposure control; risk monitoring.
Source	The origin of an agent for the purposes of an exposure assessment.
Target	Any biological entity that receives an exposure or a dose (e.g., a human, human population or a human organ).

Threshold	Dose or exposure concentration of an agent below that a stated effect is not observed or expected to occur.
Time-averaged exposure	The time-integrated exposure divided by the exposure duration. An example is the daily average exposure of an individual to carbon monoxide. (Also called time-weighted average exposure.)
Toxicity	Inherent property of an agent to cause an adverse biological effect.
Uptake (absorption)	The process by which an agent crosses an absorption barrier.

1. Introduction

1.1 Declaration

Tris(2,3-dibromopropyl) phosphate (TBPP) CAS No. 126-72-7 was declared a Priority Existing Chemical for a full risk assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989*, (the Act) by notice in the Chemical Gazette of 6 July 2004.

The reason for declaration of TBPP was to determine the extent and types of use of TBPP in Australia. TBPP is listed in Annex III of the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (Rotterdam Convention), and as a party to the Convention, Australia is required to notify the Convention Secretariat if Australia wishes to continue to allow import of these chemicals. Assessment of the chemical as a Priority Existing Chemical will enable formulation of a response. Annex III contains chemicals that have been notified as severely restricted or banned due to health or environmental reasons by countries participating in the voluntary Prior Informed Consent Procedure. The Rotterdam Convention entered into force for Australia on 18 August 2004.

1.2 Objectives

The objectives of this assessment are to:

- identify the extent and uses of TBPP;
- characterize the human health hazards and environmental effects of TBPP;
- assess the potential for environmental, occupational and public exposure to TBPP in Australia;
- determine the risk of adverse effects to the environment, workers, and the general public;
- make recommendations for minimizing environmental, occupational and public health risk, and appropriate hazard communication measures (where applicable); and
- determine if Australia wishes to allow manufacture, import or use of TBPP.

1.3 Sources of information

Literature review

Information for the assessment was obtained solely from literature sources. The major source of information on the toxicology, environmental fate and ecotoxicity of TBPP, was a monograph published by the World Health Organisation under the International Program on Chemical Safety (IPCS, 1995). However, primary sources of data were consulted where necessary. In addition, a comprehensive literature search was carried out for data published since the IPCS report.

Additional environmental data sources included the European Chemical Bureau (ECB) International Uniform Chemical Information Database (IUCLID), the US Environmental Protection Agency (EPA) ECOTOX database, the US EPA High Production Volume (HPV) Challenge robust summary and test plan data. A comprehensive review of internet sources was also undertaken. Robust summaries on a closely related analogue, tris(1,3-dichloropropyl-2) phosphate, prepared under the US EPA HPV challenge program, were used to fill data gaps for environmental fate and ecotoxicity endpoints in this assessment.

No other published national or international risk assessment reports were available for TBPP.

Industry

In accordance with the *Industrial Chemicals (Notification and Assessment) Act 1989*, manufacturers and importers of TBPP, and those wishing to manufacture and import TBPP while the chemical was a Priority Existing Chemical were required to apply for assessment and supply information. One application was received, and the data received from this applicant included an overseas MSDS. No unpublished data on health or environmental effects of TBPP, or data on import volumes or use of TBPP in Australia, were provided by the applicant.

1.4 Peer review

The report has been subjected to internal peer review by NICNAS and the Australian Department of the Environment and Heritage (DEH) during all stages of preparation.

External peer review was not undertaken, because the primary source of the hazard information has already been the subject of peer review via the IPCS process.

2. Background

2.1 International perspective

TBPP is listed in Annex III of the Rotterdam Convention. Annex III contains chemicals that have been notified as severely restricted or banned due to health or environmental concerns by other countries participating in the voluntary Prior Informed Consent procedure (PIC).

A chemical is considered for listing under the Rotterdam Convention when the Secretariat receives at least one notification from each of two Prior Informed Consent regions that the chemical is severely restricted or banned. The information is then forwarded to the Chemical Review Committee, which reviews the information and recommends the chemical be listed in Annex III.

According to information provided in the Decision Guidance Document (DGD) for TBPP, control actions to ban or severely restrict TBPP were taken in at least 5 countries and in the EEC. The main goal of action taken was to protect human health by preventing dermal exposure from textiles containing TBPP.

Use of the chemical in children's clothing was effectively banned in the US in 1977, due to the US Consumer Product Safety Commission adopting an enforcement policy that interpreted TBPP in children's wearing apparel as a banned hazardous substance under the U.S Federal Hazardous Substances Act. This policy was based on evidence of the chemical's carcinogen and mutagenic effects. The policy also covered uncut TBPP-treated fabric intended for sale to consumers for use in such products, and fabric, yarn or fibre containing TBPP intended for use in children's wearing apparel (Consumer Product Safety Commission, 1977).

A Council Directive of the European Communities issued in 1979 directed that Member States ban the chemical from use in textile articles, such as garments, undergarments and linen, intended to come into contact with the skin (EEC, 1979)

In Japan, the chemical is prohibited for use in textile products, pyjamas, beddings, curtains and floor carpets (NIHS, 2004).

The following information on TBPP was obtained from the ECB European Chemical Substances Information System's Data Sheet 2004. Tris(2,3-dibromopropyl) phosphate:

- is not included in a priority list under Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances;
- has not been reported by the EU as a High Production Volume Chemical (HPVC) or Low Production Volume Chemical (LPVC);
- is not classified in Annex 1 of Directive 67/548/EEC; and
- has no information in the ECB IUCLID.

A review of import data indicates that import of clothing and textiles from countries that do not have a restriction or ban on TBPP-treated textiles or clothing have increased from 2000 to date. Since there is currently no information on the regulatory status of TBPP in these countries, it cannot be excluded that clothing treated with TBPP may be included in these imports.

2.2 Australian perspective

TBPP is not manufactured in Australia. Currently there are no restrictions on the manufacture, import and use of this chemical in Australia.

TBPP is not currently listed in the following:

- the NOHSC *List of Designated Hazardous Substances* contained in the Hazardous Substances Information System (HSIS).
- the *Standard for Uniform Scheduling of Drugs and Poisons* (Australian Health Ministers Advisory Council, 2000);
- the Australian Dangerous Goods Code (FORS, 1998); and
- Schedule 1 of the NOHSC National Model Regulations for the Control of Workplace Hazardous Substances Part 2- Scheduled Carcinogenic Substances .

The Department of Treasury had a regulation from 1977 to 1996 under the Trade Practices Act (TPA), 1974, prohibiting the use of the flame retardant TBPP in clothing and textiles used to make clothing. In 1997, the regulatory controls on TBPP-treated fabrics were repealed. At the same time, the prohibition on the import of TBPP-treated fabrics in the Customs (Prohibited Imports) Regulations was similarly repealed. The rationale for the repeal was that TBPP had not been manufactured internationally for a considerable period of time and the use of TBPP as a fire retardant had been overtaken by more suitable retardants that could be manufactured more cheaply. It was therefore considered that production of TBPP would not recommence once the prohibition was lifted. The previous prohibition under the TPA related to the supply of certain fabrics containing TBPP. The TPA had never controlled the use of TBPP, nor did the Customs (Prohibited Imports) Regulations.

2.3 Assessments by other national or international bodies

The International Programme on Chemical Safety (IPCS) published an Environmental Health Criteria (EHC 173) monograph on Tris(2,3-dibromopropyl) phosphate in 1995 (IPCS, 1995).

No other international reviews of the health and/or environmental effects and risk assessments for TBPP have been carried out.

3. Applicant

Following the declaration of TBPP on July 6 2004 as a Priority Existing Chemical, only one company applied for assessment (see below). No data on import volumes or uses of TBPP in Australia were provided, as the chemical has not been used or imported into Australia since 2001. The applicant provided an overseas MSDS. In accordance with the *Industrial Chemicals (Notification and Assessment) Act 1989*, NICNAS provided the applicant with a draft copy of the report for comments during the statutory consultation phase of the assessment.

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4. Chemical Identity and Composition

4.1 Chemical identity

Chemical Name: 2,3-dibromo-1-propanol-phosphate (3:1)

CAS No. 126-72-7

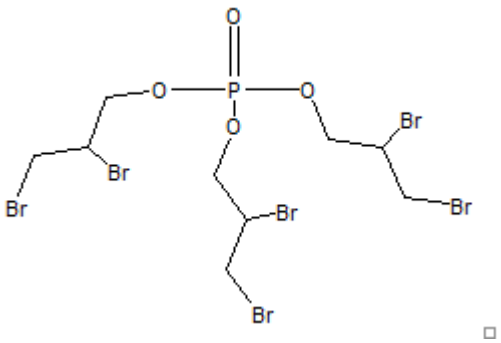
EINECS No. 204-799-9

Synonyms: tris(2,3-dibromopropyl) phosphate; tris(2,3-dibromopropyl) phosphoric acid ester; phosphoric acid, tris(2,3-dibromo-propyl) ester; tris(dibromopropyl) phosphate

Trade names: Anfram 3PB; Apex 462-5; Bromkal P 67-HP; ES 685; Firemaster LV-T-23P; Firemaster T23; Firemaster T23 P; Firemaster T23P-LV; Flammex AP; Flammex LV-T-23P; Flammex T 23P; Fyrol HB32; NSC 3240; Phoscon FR 150; Phoscon PE 60; Phoscon UF-S; T 23P; Tris; tris-BP; USAF DO-41; Zetofex ZN

Molecular Formula: $C_9H_{15}Br_6O_4P$

Structural Formula:



Molecular Weight: 697.7

Commercial TBPP contains up to 0.2% of the following impurities: 2,3-dibromopropanol, 1,2,3-tribromopropane, and 1,2-dibromo-3-chloropropane (cited in IPCS, 1995)

It is reported in IPCS (1995) that two grades of TBPP were available in the USA. However, at the time of writing, TBPP is not being imported to Australia.

5. Physical and Chemical Properties

5.1 Physical properties

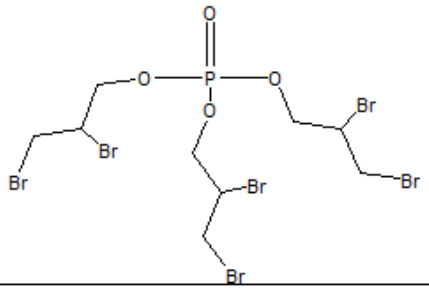
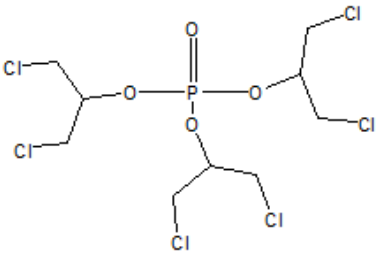
Table 5.1: Physical properties of TBPP

Property	Value	Reference
Physical state	Clear, pale-yellow, viscous liquid	IPCS, 1995
Specific gravity	2.27 g/mL	Kerst, 1974
Boiling point	390°C	IPCS, 1995
Melting point	5.5°C	IPCS, 1995
Viscosity	9200 centipoise	Kerst, 1974
Vapour pressure	1.9 x 10^{-4} mm Hg @ 25°C	Kerst, 1974
Water solubility	8 mg/L	Hollifield, 1979
Partition coefficient (Log Kow)	4.29 3.21 4.98 3.02	Sangster, 1994 Schmidt-Bleek *et al*, 1982 Veith *et al*, 1979 IARC, 1979 (cited in IPCS, 1995)

The value provided from the Electronic Personal Identification (EPI) Suite database for Log Kow of 4.29 is an experimental value obtained from Sangster, 1994. This value is considered in this report. Additionally, Sangster Research Laboratories now provide an on-line database for Log Kow values at http://logkow.cisti.nrc.ca/logkow/index.jsp. The Log Kow values from 2 studies (Schmidt-Bleek *et al*, 1982, and Veith *et al*, 1979) from this database are presented in the above table. Additionally, a Log Kow value of 3.02 is reported in IARC, 1979 (cited in IPCS, 1995).

TBPP is structurally similar to tris(1,3-dichloropropyl-2) phosphate, and for the purpose of the environmental assessment it was considered appropriate to use information on this analogue to fill data gaps that exist for TBPP. A comparison of the molecular weight, and the molecular and structural formulae, of tris(2,3-dibromopropyl) phosphate and the analogue tris(1,3-dichloropropyl-2) phosphate is presented in Table 5.2.

Table 5.2: Comparison of molecular weight, molecular formula and structural formula of Tris(2,3-dibromopropyl) phosphate (TBPP) and the analogue Tris(1,3-dichloropropyl-2) phosphate

Property	Tris(2,3-dibromopropyl) phosphate (CAS number:126-72-7)	Tris(1,3-dichloropropyl-2) phosphate (CAS number:13674-87-8)
Molecular weight	697.62	430.91
Molecular formula	$C_9H_{15}Br_6O_4P$	$C_9H_{15}Cl_6O_4P$
Structurural formula		

5.2 Chemical properties

TBPP is stable in sunlight, virtually insoluble in water and hexane, but is miscible in carbon tetrachloride, acetone, chloroform and other organic solvents (Kerst, 1974, cited in IPCS, 1995).

Major decomposition begins at about 260-300 °C. When heated to decomposition, TBPP emits toxic fumes of bromine and phosphorus (Sax, 1984, cited in IPCS, 1995).

5.3 Conversion factors

1 mg/m^3 = 8.93 ppm @25°C 1ppm = 0.11 mg/m^3 @25°C

6. Manufacture, Importation and Use

6.1 Manufacture and importation

TBPP is not manufactured in Australia. Information provided indicates that TBPP has not been imported into Australia since 2001.

While there is no current import or manufacture of TBPP in Australia, at least one company offers the chemical for import into Australia from the U.S.A. TBPP is offered for import, packaged as an ampoule of 1000 mg (purity 96.9%). According to the applicant, the predicted annual import volume of TBPP is likely to be between 0-4000 mg per year. No definitive data are available.

6.2 Uses

6.2.1 Australian

There is no information available on current, or former use/uses of TBPP in Australia. According to the applicant, based on the single package size, it is likely that TBPP will be used as an analytical standard in research and development. It is not known whether TBPP was previously used as a flame retardant for synthetic textiles and plastics in Australia

6.2.2 Overseas

No current overseas use/uses have been identified for TBPP. The American Chemical Society's Scifinder database lists seven companies that offer TBPP in their catalogues (ACS, 2004). A check of current on-line catalogues of the companies listed, confirmed that at least four of them offer the chemical in small quantities for use as analytical reference standards (Absolute Standards, 2004; AccuStandard Inc, 2004; Chem Service, Inc, 2004; Sigma-Aldrich, 2004).

TBPP was used overseas as a flame retardant additive for synthetic textiles and plastics. A major use of the chemical between 1972-1977 was in the flame-proofing of cellulose and triacetate and polyester fabrics used for children's sleepwear. About 65% of the 4500 tonnes of TBPP produced annually in the USA was applied to fabrics used for children's clothing. TBPP was added to these children's garments to an extent of 5-10% by weight (US EPA, 1976; Kirk-Othmer, 1978-1984, cited in IPCS, 1995).

Apart from its use in textiles, TBPP was reported to have been used in the past as a flame retardant in the following materials (US EPA, 1976; Kirk-Othmer, 1978-1984, cited in IPCS, 1995):

- Rigid polyurethane foams used in insulation, furniture, automobile interior parts and water flotation devices;
- Flexible polyurethane foam, used primarily for cushioning, such as in automotive and aircraft interiors, institutional bedding, cushions and upholstered furniture;

- Acrylic carpets and sheets
- Polyvinyl and phenolic resins
- Polystyrene foam
- Paints
- Laquers
- Paper coatings
- Styrene-butadiene rubber
- Latexes
- Cured unsaturated polyester products

No current use of these applications either overseas or in Australia has been identified.

In 1978, the US Consumer Product Safety Commission listed 22 products that contained TBPP, that were available to USA consumers (IARC, 1979, cited in IPCS, 1995). These included:

- Children's clothing
- Industrial uniforms
- Draperies
- Tent fabric
- Automobile headliners
- Epoxy resins for the electronics industry
- Christmas decorations
- Polyester thread

Other reported uses of TBPP (NTP 2002, cited by HSDB, 2004; IARC, 1979, cited in IPCS, 1995) were its use as a flame retardant in:

- Treatment of packaging
- Toys
- Doll clothing
- Wigs

7. Exposure

7.1 Environmental exposure

7.1.1 Environmental exposure and fate

TBPP can exist both in, and on treated fabric. When it is in the fabric, it is not extractable with solvents. However, when it is on the fibre surface, it can be extracted during laundering, and by acetic acid, other solvents, and saliva. In this case, substantial losses of surface TBPP from fabrics during use and/or laundering of the finished products, will occur, and will contaminate the environment. Furthermore, release of TBPP into the environment has been reported from textile-finishing plants and the ultimate disposal of solid wastes, containing TBPP.

The following discussion on environmental exposure and fate has been prepared following the methodology for preparing assessment reports within the framework of the Organisation for Economic Cooperation and Development (OECD) HPV Chemicals Programme (OECD, 2003). The information on environmental fate and pathways is provided based on the available information on potential sources of release to the environment, use categories and physical-chemical properties as well as specific test or estimation results.

7.1.2 Photodegradation

Direct photolysis is not expected to be a major process, since TBPP should not absorb light of wavelengths found in sunlight (> 290 nm) (Mabey & Mill 1978, cited in IPCS, 1995).

The Level III fugacity model predicts that partitioning to air will not be significant. Therefore, indirect photodegradation, as mediated by attack from hydroxyl radicals ($OH^{\bullet}$) in air will not significantly contribute to the degradation of this chemical. Where partitioning to air does occur, TBPP has the potential to degrade in this compartment.

Potential $OH^{\bullet}$ reaction rate and atmospheric half-life is calculated based on an average $OH^{\bullet}$ radical concentration. The reaction rate and half-life have been calculated using AOPwin (within EPI Suite), and an overall rate constant of 27.7058E-12 cm^3/molecule/sec was derived. This corresponds to a half-life of 0.386 days, and based on a day with 12 hours of sunlight, is the equivalent of 4.633 hours. These values were calculated using an average global $OH^{\bullet}$ concentration of 1.5 E+6 $OH^{\bullet}/cm^3$.

7.1.3 Stability in water

Hydrolysis

TBPP has a measured water solubility of 8 mg/L (Hollifield, 1979). The Level III fugacity model predicts that around 20% of TBPP released to the environment could partition to the aqueous compartment at steady state. In IPCS (1995) it is stated that although hydrolysis of the phosphate ester is not expected to be significant, hydrolysis involving the bromine atoms on the propyl groups may

occur, especially under basic conditions. HYDROWIN (part of EPI Suite) could not estimate an hydrolysis rate constant for the chemical structure of TBPP.

Hydrolysis of the analogue, Tris(1,3-dichloropropyl-2) phosphate has been tested and these results may be used as a substitute (Akzo Nobel, 2001). The test was conducted in 2000 following OECD Guideline 111 and according to GLP.

The rate of hydrolysis was determined in aqueous buffered solutions at pH 4, 7, and 9. The test substance was present at 10.0 mg/L, about half of the estimated water solubility. The test was performed at 50°C for five days. Samples were extracted and analyzed on study days 0, 2, and 4. A validated analytical method (gas chromatography with electron capture detector) was used to measure the concentration in the test samples.

The percent recovery of samples in pH 4 buffer (phthalate buffer) was 93, 101, and 102% on days 0, 2, and 4, respectively, indicating no decline in concentration. Similarly, samples in pH 7 buffer (phosphate buffer) had recoveries of 114, 109, and 109% on days 0, 2, and 4, respectively, showing stability under neutral conditions. At both acid and neutral conditions the hydrolytic half-life is greater than one year. Samples in pH 9 buffer (borate buffer) yielded recoveries of 101, 94, and 84% on days 0, 2, and 4, respectively.

Linear regression analysis of the pH 9 recovery data yielded a hydrolysis rate constant of 0.04727 that corresponds to a half-life of approximately 14.7 days. The chemical demonstrated excellent hydrolytic stability under acid and neutral conditions with some instability shown at pH 9.

Based on these data, TBPP may be expected to be hydrolytically stable under neutral and acidic conditions, with some hydrolysis expected under basic conditions. However, it would be expected to be more stable than the chlorinated analogue, since chlorine is more easily displaced from aliphatic carbon atoms than is bromine (Gould, 1959).

Volatilisation

No data on volatilisation from water are available. A Henry's Law Constant of 2.18E-5 atm m^3/mole has been calculated from the vapour pressure (1.9×10^{-4} mm Hg) and water solubility (8 mg/L). This indicates the chemical will be moderately volatile from water (Mensink et al, 1995).

Using the same solubility and vapour pressure values, the volatilisation half-life from water was estimated. The half-life values for TBPP volatilisation from streams, rivers, and lakes were 3.64, 4.66, and 392 days, respectively, assuming current velocities of 3, 1, and 0.01 m/s, respectively. The river and stream depths were assumed to be 1 m, while the lake was assumed to be 50 m deep (IPCS, 1995).

These modelled results are supported to some extent by estimations from EPI Suite where volatilisation from a river and lake were estimated. The river and lake were assumed to have wind velocities of 5 and 0.5 m/s respectively and current velocities of 1 and 0.05 m/s respectively. Both were assumed to be 1 m deep. The half-life in days was estimated to be 3 and 43 days in the river and lake respectively.

This suggests TBPP has the potential to be more persistent in water bodies where water movement is limited, and the water is deeper.

7.1.4 Transport between environmental compartments

Fugacity based multimedia modelling provides basic information on the relative distribution of a chemical between selected environmental compartments. A widely used fugacity model is the EQC (Equilibrium Criterion) LEVEL III model (Mackay et al., 1996a, 1996b).

For this assessment the Level III fugacity model within the EPI Suite software is considered suitable. Mackay and co-workers developed the methodology and programming approach for this model (Mackay *et al.*, 1996a, 1996b; Mackay, 1991). The model in EPI Suite is a direct adaptation of this methodology and approach. While it uses the same equations as Mackay's EQC Level III fugacity model, it was adapted specifically for use in EPIWIN. It uses exactly the same default values as the Mackay model.

The Level III model in EPI predicts partitioning between air, soil, sediment and water using various user-input parameters and/or inputs estimated by several EPI programs. All fugacity half-life values, emission values, soil Koc and advection values have default values or estimation methods. User intervention is not required to generate model predictions. This is useful for TBPP as no single media half-life values exist in the literature.

The environmental dimensions used by the EQC model are provided in Table 7.1.

Table 7.1: EQC Model Environmental Dimensions (Mackay et al, 1996b)

Parameters for Environment dimensions		
	Area (m^2)	Depth (m)
Volume of air	1E+11 m^2	1000
Volume of water	1E+10	20
Volume of soil	Air-Water	0.2
Volume of sediment	= Water	0.05

The following SMILES string P(=O)(OCC(CBr)Br)(OCC(CBr)Br)OCC(CBr)Br was entered and experimental data from the EPI Suite databank where available were included.

Releases were considered separately to each compartment (air, water and soil), and equally to all three compartments. The partitioning results are presented in Table 7.2

Table 7.2: Level III Fugacity Model Output

Compartment of release	Release	Air (%)	Water (%)	Soil (%)	Sediment (%)
Air	100%	52.4	14.6	27.7	5.4
Water	100%	0.2	72.8	0.09	27
Soil	100%	0.001	0.08	99.9	0.03
All equal	33.3% each	0.453	20.2	71.9	7.46

TBPP tends to partition to the compartment it is released to, with the exception of air, where release to this compartment still results in expected significant amounts found in water and soil. The sediment compartment is only expected to be a significant sink for TBPP where release is to water.

Generally, the most significant environmental compartment for TBPP to partition to, is predicted to be soil except where release is all to water. No data are available for adsorption of this chemical to soil. However, in IPCS (1995) a LogKoc of 3.29 was estimated, while PCKOC (part of EPI Suite) estimate a LogKoc of 3.90. These values suggest strong adsorption to soil.

7.1.5 Biodegradation

The following three biodegradation studies for TBPP are cited in IPCS (1995).

The biodegradability of TBPP was determined following a shake-flask test. TBPP was incubated with a microbial inoculum of raw sewage. Samples of the test solutions were taken at 0, 5, 10, and 15 days for final analysis using neutron activation to determine the bromine content of the liquid. Assuming the increased bromide content of the inoculated samples relative to the blank samples is due to biodegradation, and the solubility of TBPP is 1.6 mg/L, an amount of TBPP equal to 2.4 times the dissolved TBPP was degraded in 5 days (Kerst, 1974).

Activated return sludge (at 21°C), used within 1 hr of collection, diluted with a basal medium, with an added 2 mg 14C-labelled TBPP/kg, showed that 6% of the added radio-activity was evolved as $14CO_2$ after 24 h. A major metabolite bis(2,3-dibromopropyl) phosphate (BBPP) was identified, but neither dibromopropanol (DBP) nor dibromopropionic acid was detected. The half-life of TBPP was 19.7 h (by least squares regression analysis). In a sterilized sludge control study, 93% of the added TBPP was found and metabolites were not identified (Alvarez et al., 1982).

A biodegradation study on TBPP (100 mg/L) was carried out under sewage treatment conditions with sludge (30 mg/L). The degree of biodegradation, as measured by BOD, was 1.8% of TBPP after a 2-week incubation period (Chemicals Inspection & Testing Institute, 1992).

The following study using the analogue Tris(1,3-dichloropropyl-2) phosphate (common name, Fyrol FR-2) was provided by Akzo Nobel (2001) as part of the US HPV Challenge, for review by the US EPA. The study was conducted in 1990 according to OECD Guidelines 301B (Modified Sturm Test) and 301D (Closed Bottle Test) on the inoculum from the effluent of a sewage treatment facility. The

study was GLP compliant, and the duration of the study was 28 days. It was reported as a robust summary that accompanied the Akzo Nobel submission. No specific statistical method was used for analysis. Calculation of theoretical oxygen demand, chemical oxygen demand (COD), biochemical oxygen demand (BOD), and other values utilized the procedures and formulae provided in the OECD guidelines.

Initially the biodegradability of Fyrol FR-2 was determined in a COD test and in a 10-day bacterial inhibition assay conducted under the Closed Bottle Test conditions. The test substance was then evaluated in the Modified Sturm Test. In these tests, the COD was determined by oxidation with an acid dichromate mixture at 50°C, using six replicates per test substance concentration. Fyrol FR-2 nominal concentrations added to the reaction vessels ranged from 250 to 750 mg/L. In the bacterial inhibition assay, Fyrol FR-2 concentrations of 2 and 10 mg/L were used. Groups of 6 bottles per concentration were used to provide sufficient replicates. The dissolved oxygen concentration was measured at the start of the test and after incubation at 20°C in darkness for 5 and 10 days. In the modified Sturm Test, Fyrol FR-2 concentrations of 10 and 20 mg/L were added to vessels containing the inoculum. The vessels were aerated for 28 days after which the amount of carbon dioxide produced by each culture was measured. The amount of dissolved organic carbon (DOC), as an indication of CO_2 production, was the endpoint measured on day 0 and on day 27.

In the COD assay, the mean of six determinations was 0.85 mg O_2/mg, which was 109% of the calculated theoretical oxygen demand of 0.78 mg O_2/mg. This indicates that the Fyrol FR-2 present in the chambers was completely oxidized under the conditions of this test. In the bacterial inhibition assay, the reference material, sodium benzoate, when placed in the sewage effluent inoculum, was readily degraded to 57% of its theoretical oxygen demand. The presence of Fyrol FR-2 had no significant effect on the bacterial action, confirming that the product is not inhibitory to the bacterial inoculum. In the modified Sturm Test, CO_2 was produced in the control group in 28 days confirming the viability of the inoculum and validity of the test. No CO_2 was produced by day 28 in the vessels containing Fyrol FR-2, indicating the test substance was not degradable under the conditions of this test.

Estimated data

BIOWIN (part of EPI Suite) provides several biodegradation probabilities for linear biodegradation, non-linear biodegradation, MITI linear biodegradation and MITI non-linear biodegradation. The linear model, MITI linear model and MITI non-linear model all predict the chemical will not biodegrade rapidly, however, the non-linear model does predict the chemical will rapidly biodegrade..

The ultimate and primary biodegradation timeframes suggested by BIOWIN are months (ultimate) and days-weeks (primary).

Based on the weight of evidence, it is determined that TBPP is not readily biodegradable.

7.1.6 Bioaccumulation

Two bioconcentration studies cited in IPCS (1995) are presented below:

Groups of 30 adult fathead minnow *(Pimephales promelas)* (six months old) were exposed to 47.7 µg TBPP/L for 32 days in a flow-through system. The temperature of the water was 25°C, pH 7.49, dissolved oxygen >5 mg/L, and hardness 45.5 mg/L as $CaCO_3$. The bioconcentration factor determined was 2.7 (Veith *et al.*, 1979).

Bioconcentration of TBPP (0.1 mg/L, 0.03 mg/L) from water to carp was estimated to be between < 0.7 to 1.9, and < 2.2 to 4.3, respectively, after 6 weeks of exposure (Chemicals Inspection & Testing Institute, 1992).

In addition to these results, Sitthichaikasem (1978) describes results of an uptake study in a literature abstract. The original study is not available for review. Uptake of 14C-labelled TBPP by bluegills was rapid with plateau levels achieved within 7 days, and an accumulation factor of 684 calculated (exposure concentrations not reported). It is not known whether this accumulation factor applies to viscera, edible portion or whole organism. When transferred to clean water after 28 days of exposure, the chemical was rapidly eliminated in the first three days and more gradually through the 28-day test. The second-period biological half-life was 49 days, indicating slow overall depuration.

These results indicate TBPP is slightly to moderately concentrating (Mensink et al, 1995), and are supported by modelling data. BCF Program v 2.15 (part of EPI Suite) calculated a Log BCF of 1.823 (BCF = 66.57) using the following formula:

Log BCF = 0.77 Log Kow – 0.70 + correction

For phosphate esters, the correction value is –0.780.

7.1.7 Environmental levels

Use of this chemical has not been identified in Australia. Therefore, no predicted concentrations in the various environmental media can be made.

No monitoring data for TBPP are available in Australia. Monitoring data from international sources cited in IPCS (1995) are presented in this report.

Air

TBPP was identified, but not quantified in Arkansas air particulates.

Water

In 1975, 20 water samples were collected at different places in Japan and analysed for the presence of TBPP. None of the samples contained the compound (limit of determination 1 µg/L).

Soil

In 1975, 20 sediment samples were collected at different places in Japan and analysed for the presence of TBPP. None of the samples contained TBPP (limit of determination 0.4-10 mg/kg). TBPP was identified, but not quantified, in Arkansas soil.

Fish

In 1975, 20 fish samples, collected at different places in Japan, were analysed for the presence of TBPP. None of the samples contained TBPP (limit of determination 1 mg/kg).

7.2 Occupational exposure

No occupational use of TBPP in Australia has been identified to date. The potential for occupational exposure exists as a single company offers the chemical for import into Australia for likely use in research and development as an analytical standard in 1000 mg ampoules. Occupational exposure is possible during transport and handling of the product.

Workers may be potentially exposed through dermal contact. TBPP is a liquid of low volatility, therefore, inhalation is unlikely to be a major route of occupational exposure.

No measured exposure data for TBPP were provided by industry.

There is a potential for dermal and ocular exposure for laboratory workers when used as an analytical standard, when opening the TBPP ampoules, transferring the contents during use and through spills or splashes.

In the past, when used overseas as a fire retardant in synthetic textiles, TBPP was applied to fibre melt prior to spinning by thermal diffusion under pressure dyeing, or padded on to woven or knitted material at 5-10% by weight with heat fixation, or applied to woven or knitted material via emulsion from conventional batch dyeing equipment. Addition of the chemical by dyers and finishers is believed to have been more usual than addition by the textile producers. There are no known data on levels of exposure of workers during these operations (Prival 1975, cited in IPCS, 1995; IARC, 1979).

A National Occupational Hazard Survey conducted by the National Institute of Occupational Safety and Health (NIOSH) from 1972-1974 estimated that 29,000 workers were potentially exposed to TBPP in the United States by dermal contact in the workplace, primarily in the telephone communication industry (NIOSH, 1976, cited in IARC, 1979). No details of this survey, or the levels of exposure in workers in the telecommunication industry are available.

7.3 Public exposure

TBPP is not currently imported into Australia, and there is no known manufacture or use of the chemical in Australia. Overseas, TBPP has been used as a flame retardant in fabrics, particularly in children's sleepwear, but has since been banned in the US, Europe and Japan. In the US, much of the impetus for the use of TBPP in clothing was to meet flammability standards set by the United States Consumer Product Safety Commission (US CPSC) Federal Register, 1977. No information is available as to whether TBPP-treated textiles were ever available to the Australian public, or if Australia had similar flammability standards to those implemented overseas. A review of import data of textiles and ready-to-wear clothing provided by the Textiles Industry indicates that textiles and clothing are imported into Australia from countries that do not have any restrictions or ban on the use of

TBPP to treat clothing. Imports from these countries have increased from the year 2000 to date. Data provided by the Textile Industry are shown in Table 7.3.

Table 7.3 Import of textiles and clothing into Australia from countries with no restrictions

Imports	2000-01	2003-04
Textiles	33%	39%
Ready-to-wear clothing	76%	79%

There is currently no information on the regulatory status of TBPP in these countries and thus, it cannot be excluded that textiles and/or clothing treated with TBPP are included in these imports.

As TBPP is not manufactured in or imported into Australia, it can be assumed that Australian textiles treated with fire retardants do not contain TBPP. Similarly, clothing and textiles from the US, Japan and Europe will not be treated with TBPP.

TBPP in synthetic textiles/garments can exist both tightly bound within the fibre, and more loosely bound on the surface of the fibre. In both cases, TBPP can be removed from the garment by an infant 'sucking' or 'mouthing' on the sleeve or other portion of the garment. When it is loosely bound on the surface, TBPP may also be available for dermal absorption.

7.3.1 Dermal exposure

Two studies are available investigating the dermal absorption of TBPP from TBPP-treated sleepwear, for which conflicting results have been reported. In the most recent study available (Blum et al, 1978), a 7-year old child was exposed to repeatedly-washed sleepwear that may have been treated with TBPP on days 1, 2 and 8-12, and new TBPP-treated sleepwear on days 3-7. Morning urine samples were collected on all days. It was reported that the child did not chew or suck the TBPP-treated sleepwear.

After wearing the repeatedly washed sleepwear on days 1 and 2, the level of dibromopropyl phosphate (DBP), a metabolite of TBPP, in the urine was 0.4 ng/mL on each of the two days. When the child wore new TBPP-treated pyjamas, the DBP level in the urine was 79 ng/mL over 4 d (as the urine sample was lost on day 5). Based on the amount of DBP in the urine the amount of TBPP absorbed after wearing treated sleepwear was calculated. In determining the amount of TBPP absorbed the authors stated that it is likely to be higher than that indicated by DBP in the urine, as it does not take into account the fraction of the chemical or its metabolites excreted in the faeces.

An estimate of the amount of TBPP absorbed relative to the amount of DBP found in the urine was estimated from gavage studies conducted in the rat by the US CPSC. When rats were dosed with 14C-labeled TBPP, 6.5% of the label was found associated with DBP and its conjugates in the urine.

Using this data from animal studies, the amount of TBPP absorbed by the 7-year old child wearing new TBPP-treated pyjamas could be 15 times the amount of DBP found in the urine (i.e. assuming approximately 100 % dermal absorption). The amount of TBPP absorbed by the 7 year old child wearing the new TBPP-treated sleepwear was estimated as follows:

Total amount of DBP excreted in the urine over 4 d	79 ng/mL.
Total amount of DBP excreted in the urine in 1 d (approximately)	20 ng/mL.
Assuming DBP is present at a constant level of 20 ng/mL and 600 mL urine is excreted per day, then amount of DBP excreted daily	12 μg/d
Amount of TBPP absorbed, based on rat data	180 μg/d
Amount of TBPP absorbed by the child based on an average	
Child's weight of 20 kg	9μg/kg bw/d

The above approach was used to determine TBPP absorption in the same child on days 1 and 2, after wearing repeatedly-washed sleepwear that may have been treated with TBPP. DBP level detected in urine was 0.4 ng DBP/mL indicating an absorption of 0.18 μg of TBPP/kg bw/day.

It was noted that urinary DBP levels obtained following wearing of repeatedly washed sleepwear on days 8–12 were significantly greater than on days 1–2. This suggests the wearing of new TBPP-treated sleepwear on days 3–7 influenced urinary DBP levels on days 8–12. Consequently, TBPP absorption was not determined for this period.

Blum et al (1978) also reports urinary excretion of DBP in the range 0.5–5 ng/mL for children wearing treated pyjamas that had been washed for at least five months. The limit of detection of DBP in the urine was 0.1 ng/mL.

In the other available study (St. John et al, 1976), no DBP was detected in the urine of both a child and an adult who wore TBPP-treated pyjamas for seven nights, though the limit of determination was only 0.2 mg/L.

In 1976, the US CPSC (IRPTC, 1987) initiated a testing program based on a petition from the Environmental Defense Fund (EDF) for cautionary labelling of TBPP-treated apparel. Estimates of exposure from TBPP-treated sleepwear were determined from three commissioned reviews: Bureau of Biomedical Science; Environmental Defense Fund; and Hooper and Ames. These commissioned reviews cannot be evaluated, as they are unavailable for this assessment and, thus, limits the significance that can be attached to the data. Brief descriptions of the findings of the review were obtained from the US Federal Register, Volume 42, 1977.

The general assumptions underlying all of the commissioned estimates were:

- a child mouths the garment and ingests available TBPP;
- there is absorption through the skin; and
- the child wears numerous garments containing various amounts of available TBPP over the period.

The estimates provided by the EDF from a report by Harris (1977), was that the total lifetime exposure for a 10-20 kg child ranged between 0.085 – 85 mg/kg, based primarily on dermal absorption following exposure to 1, 10 or 20 pairs of TBPP-treated sleepwear. However, as what constitutes a 'lifetime exposure' cannot be ascertained, the absorption of TBPP in mg/kg bw/day cannot be determined. In contrast, Hooper and Ames (1977) estimated that for a 7 kg child a year's dermal exposure would be 70 mg/kg or 192 μg/kg bw/day.

TBPP has also been shown to penetrate rabbit skin from 14C-TBPP-treated polyester cloth containing 15,000 ppm of surface TBPP (4.3% of the total radioactivity) in 96 h. Soaking the cloth in urine caused the amount of 14C-TBPP absorbed to increase to approximately 17% of the radiolabel over 96 h (Ulsamer et 1980). Considering that some young children at an early age can be prone to bed wetting, it is likely that the dermal value of 9 μg/kg bw/d from the Blum et al (1978) study could be an underestimate in these situations.

7.3.2 Oral exposure

Hooper and Ames (1977) reported that the dose a child received by sucking of TBPP treated-sleepwear would be 1 % of that obtained through dermal exposure. From the dermal data provided in the same report, this would be equivalent to 1.92 μg/kg bw/d. This data suggests that 'sucking' and 'mouthing' represent a minor route of exposure compared to dermal exposure

IPCS (1995) reports that up to 3% of surface TBPP can be extracted from treated fabric by saliva. However, the primary source of the data (Brieger et al, 1968) is unavailable, and therefore reliability of the absorption value cannot be determined.

7.3.3 Dermal and oral exposure

The Bureau of Biomedical Science (1977) estimated that the total dose of TBPP a child receives over a 6-year period from both skin absorption and sucking ranged from 2.5 – 77.4 mg/kg depending upon the body area exposed equating to 1.1 – 35.3 μg/kg bw/day.

7.3.4 Exposure estimates and data

The most reliable data available are exposures of 0.18 and 9 μg/kg bw/day estimated in a child, following dermal absorption, after wearing repeatedly washed sleepwear that may have been treated with TBPP and new TBPP-treated pyjamas respectively (Blum et al, 1978). The values determined represent the upper limit for absorption, as the amount of TBPP absorbed by the skin is considered to be 15 times higher than the amount of DBP that was found in the urine (i.e. assuming approximately 100 % dermal absorption).

Based on the estimates provided by Hooper and Ames for oral exposure and the estimates from dermal exposure in the Blum et al study, exposure estimates for the 7 year old child following oral absorption is 0.0018 and 0.09 μg/kg bw/day for repeatedly-washed and new-treated sleepwear respectively. Therefore, the combined exposure estimate following dermal and oral absorption (using study data for dermal absorption, and extrapolated data for oral exposure) would be 0.18 and 9.09 μg/kg bw/day respectively.

The exposure estimate of 192 μg/kg bw/day reported by Hooper and Ames (1977) via the dermal route was much higher than the estimates of 0.18 and 9 μg/kg bw/day determined from the Blum et al, (1978) study for a child wearing repeatedly-washed and new TBPP-treated sleepwear respectively.

The Bureau of Biomedical Science's (1977) exposure estimates from oral and dermal exposure of 1.1-35.3 μg/kg bw/day exhibited a wide range compared to the combined exposure values of 0.18-9.09 μg/kg bw/day determined from the Blum et al (1978) study. As the primary data from the commissioned reviews are not available for assessment, the significance that can be attached to the dermal and combined exposure is limited.

8. Kinetics and Metabolism

Most of the studies assessed in this section and Section 9 have been primarily summarised from the IPCS (1995) review. However, primary sources of data were consulted where necessary. In addition, a comprehensive literature search was carried out on studies conducted since 1994 to date, for additional material of relevance to the hazard assessment, which was not included in the IPCS (1995) review. References in Sections 8, 9, 10 & 11 that have not been sighted are marked with an asterisk (*).

8.1 Animal and in vitro data

8.1.1 Absorption

Following oral administration of 1.39 mg/kg 14C-TBPP to male Sprague-Dawley rats, 24.0 % of the radiolabel was recovered in the urine over 24 hours (Nomeir & Matthews, 1983).

Following the dermal application of 14C-TBPP to the backs of New Zealand white rabbits 3.5 - 3.8 % of a 0.9 ml/kg dose and 15.2% of a 0.05 ml/kg dose were absorbed over 96 hours. Osborne Mendel rats absorbed approximately 1/6 of each TBPP dose when applied to an equivalent area of skin/kg bw (Ulsamer et al., 1980).

The data indicates that TBPP is readily absorbed by the gastrointestinal tract in rats, and at a moderate rate via the skin in rats and rabbits.

8.1.2 Distribution

Male Sprague Dawley rats were administered 1.39 mg/kg 14C-TBPP by the oral route and radioactivity determined in the blood, muscle, liver, skin, fat, kidneys and lung. The highest initial concentrations of radioactivity (i.e. 15 minutes after dosing) were observed in the lung, liver and kidney. One day after administration, the percentage of the total dose found in the blood, muscle, liver, skin, fat, kidneys and lung was 6.6, 5.5, 3.4, 3.4, 1.3, 0.7 and 0.2% respectively. The half-life of clearance of radioactivity from most of the tissues studied was approximately 2.5 days, though clearance from the liver and kidney was significantly slower with a half-life of approximately 3.8 days (Nomeir & Matthews, 1983).

Following dermal application of polyester fabrics containing 14C-TBPP to New Zealand rabbits, substantially more radioactivity was detected in the kidneys and liver than in other organs (Ulsamer et al., 1980).

Male Sprague-Dawley rats were administered 14C-TBPP by the intravenous (iv) route and radioactivity determined in the blood, fat, muscle, liver, kidney, lung, heart, brain, testes, spleen, stomach, small intestine, large intestine and carcass 5 minutes, 30 minutes, 8 and 24 hours after dosing. Radioactivity was detected in all tissues 5 minutes after dosing but declined rapidly in most tissues. However, in the kidney the concentration of radioactivity was 11 times the average body concentration 5 days after dosing. Analysis of the radioactivity indicated that

TBPP was present in all tissues except the testes after 5 minutes but the parent compound was no longer detectable 8 hours after dosing. The major portion of the radioactive label detected in several tissues was as bis(2,3-dibromopropyl) phosphate (BBPP). The concentration of BBPP in the plasma declined biphasically 1 hour after dosing. The initial plasma half-life was 6-hours, whereas at later times (1 to 5 days) it was approximately 36 h. The half-life of BBPP was relatively long in most tissues (Lynn et al., 1982). Similarly, radioactivity was detected in all the tissues examined of male Sprague-Dawley rats (e.g. muscle, liver, skin, kidneys and lung) 15 minutes after iv administration of 1.39 mg/kg 14C-TBPP (Nomeir & Matthews, 1983).

The data indicates that rapid distribution of the parent compound and metabolite(s) occurs throughout the body in rats and rabbits following absorption.

8.1.3 Metabolism

TBPP was readily metabolised in male Sprague-Dawley rats following oral or iv administration of 1.39 mg/kg 14C-TBPP. Six metabolites were identified in urine and in bile 24- and 3-hours post dosing respectively. These were 2,3-dibromopropanol (DBP) (1.0 and 1.1% of the total radioactivity in urine and bile respectively), bis(2,3-dibromopropyl) phosphate (BBPP) (2.8 and 25.8%), 2-bromo-2-propenyl 2,3-dibromopropyl phosphate (4.8 and 13.8%), bis(2-bromo-2-propenyl) phosphate (10.3 and 5.2%), 2,3-dibromopropyl phosphate (4.1 and 2.6%) and 2-bromo-2-propenyl phosphate (9.5 and 2.4%). Very little TBPP was detected in the urine and bile (0.8 and 2.0% respectively). The majority of the radiolabel excreted in the urine (66.7%) could not be identified and, similarly, nearly half the radiolabel in the bile (47.1%) could not be identified (Nomeir & Matthews, 1983).

Male Sprague-Dawley rats were administered 14C-TBPP by iv injection and the plasma concentrations of the parent compound, BBPP and DBP determined up to 120 hours post dosing. TBPP was the major component in the plasma 2-minutes after dosing, but by 5 min greater than 75% of the radioactivity in the plasma was BBPP. TBPP was not detectable after 1 hour and BBPP concentrations declined after 1 hour. The concentration of DBP declined more rapidly than BBPP and was undetectable beyond 8h (Lynn et al., 1982).

Additionally, Lynn et al (1982) determined concentrations of TBPP and BBPP in a large number of tissues. TBPP was present in all tissues except the testes after 5 minutes but the parent compound was no longer detectable 8 hours after dosing. In contrast, BBPP was detected in nearly all tissues up to 24 h after dosing.

In addition to the TBPP metabolites identified by Nomeir & Matthews (1983) and Lynn et al (1982), 2-bromoacrolein (2-BA), 2-bromoacrylic acid, bis(2,3-dibromopropyl)-3-hydroxypropyl phosphate, *S*-(2,3-dihydroxypropyl) glutathione, *S*-(3-hydroxypropyl) glutathione and *S*-(2-carboxyethyl) glutathione have been detected in vitro and/or in vivo (*Marsden & Casida, 1982; *Nelson et al., 1984), .

The formation of BBPP has been studied and indicates that oxidative metabolism of TBPP to form BBBP is important in vivo. Furthermore, in addition to oxidation at the C3 position of TBPP, BBPP formation may result from oxidation at C2 (*Pearson et al., 1993a; *Dybing et al., 1989).

Although glutathione acts as a detoxifying agent for reactive TBPP metabolites (*Søderlund et al., 1984), it has been suggested that conjugation could also result in the formation of reactive episulfonium ion intermediates (*Pearson et al., 1993a). Other studies noted that there is *S* (2,3-dihydroxypropyl) glutathione in the bile of Sprague-Dawley rats (*Van Beerendonk, 1994). It was suggested that TBPP and or/BBPP are conjugated directly with glutathione by glutathione *S*-transferases, with subsequent formation of episulfonium ions (*Pearson et al., 1993a).

A number of in vitro metabolic studies are also available. It was observed that liver microsomes from mice, guinea pigs, hamsters, and human all metabolised TBPP to reactive intermediates. However, the rate of formation of reactive TBPP metabolites with human liver microsomes was lower than with liver microsomes from rodents (Søderlund et al., 1982). In a study using rat liver microsomes the major metabolite of TBPP was BBPP (Nomeir & Matthews, 1983). In addition to BBPP, 2-bromoacrolein, 2-bromoacrylic acid, and propyl-hydroxylated compounds and metabolites conjugated with glutathione have been found (*Marsden & Casida, 1982; *Nelson et al., 1984).

It has been demonstrated that TBPP is activated to products that bind covalently to proteins and DNA in vitro and in vivo (*Søderlund et al., 1981; 1984; Pearson et al., 1993a*; 1993b).

Nine hours after ip injection of male NMRI mice, male B6C3F1 mice, male Fischer 344 rats and male Duncan-Hartley guinea pigs with 250 mg ^{3}H-TBPP/kg bw, similar levels of covalent binding to proteins were seen in the liver and kidneys of all animals except the rat, which had much higher amounts of radiolabel bound to proteins in the kidney (Søderlund et al., 1982). In contrast, no marked difference was seen in vitro in the rate of 3H-TBPP covalent protein binding with hepatic microsomes from NMRI mice, rats, guinea pigs, hamsters and humans, though covalent binding varied over a 3-fold range using human microsomal preparations from 5 individual human livers (Søderlund et al., 1982).

A comprehensive summary of the available in vitro metabolic and covalent binding data can be found in the IPCS (1995) review.

The in vivo rat data indicates that TBPP is rapidly metabolised. The main metabolite in vitro and in vivo is BBPP, which is present in the urine and bile. BBPP was the major metabolite in several tissues including the kidney. There is evidence that the TBPP derived metabolites covalently bind to proteins and DNA in vivo.

8.1.4 Elimination and excretion

The excretion of TBPP was studied after oral or iv administration of 1.39 mg/kg 14C-TBPP to male Sprague-Dawley rats. Twenty-four hours after oral dosing, 24.0 and 11.5% of the administered radioactivity was excreted in the urine and faeces respectively. The excretion of TBPP derived activity in urine and faeces following iv administration was similar to that seen following oral dosing, though radioactivity expired as CO_2 was also determined after iv administration. Twenty-four hours after dosing, 20% of the total radioactivity was eliminated in expired air.

Analysis of the radioactivity in urine was conducted, and 6 metabolites were identified in addition to the parent compound. The major metabolites identified were bis (2-bromo-2-propenyl) phosphate (10.3% of the total radioactivity) and 2-bromo-2-propenyl phosphate (9.5%). Very little TBPP (0.8%) was detected and the majority (66.7%) of the radiolabel excreted in the urine was unidentified (Nomeir & Matthews, 1983).

Nomeir & Matthews (1983) also undertook an analysis of the radioactivity in bile. As observed with the urine analysis very little TBPP was detected in the bile (2.0%) and a large proportion of the radiolabel was unidentified. Furthermore, all 6 metabolites identified in the urine were also present in the bile, though in contrast the major metabolites were BBPP (25.8%) and 2-bromo-2-propenyl 2,3-dibromopropyl phosphate (13.8%).

It is reported that small amounts of DBP and conjugates were detected in rat urine when the animal was allowed to chew on TBPP treated polyester fabric (St John et al., 1976).

Radiolabel from 14C-TBPP, applied to the skin of rats and rabbits, was excreted primarily in the urine (50 and 70% respectively) with lesser amounts appearing in the faeces and 12 - 18% exhaled as CO_2. TBPP was not detected in the urine, though a number of metabolites including DBP were detected (Ulsamer et al., 1980). Additionally, in a 7-day rat study, DBP and conjugated-DBP were detected in the urine following topical application of 100 mg TBPP (total concentrations were 17.61 and 23.58 mg/L respectively) (St John et al., 1976). In contrast, no DBP was detected in urine after a shaved rat wore a garment made of 100% polyester flannel treated with TBPP for 9 d (St John et al., 1976).

Following iv administration of 14C-TBPP to male Sprague-Dawley rats, urine, faeces and air samples were collected for 5 d, and bile for 1 d in animals with exteriorised bile ducts. In 5 d, approximately 58% of the administered radioactivity was excreted in the urine, 9% in the faeces, 19% expired as $^{14}CO_2$ and 9% remained in the body. The parent compound was not detected in the urine or faeces. In animals with exteriorized bile ducts, 34% of the radiolabel was excreted in the bile over 24 h. Additionally, a comparison of intact rats with bile-exteriorized rats demonstrated that a minimum of 74 % of the radiolabel excreted in bile was reabsorbed (Lynn et al., 1982).

A single study that investigated the potential bioaccumulation of TBPP by measuring bromine levels is available. Male rats received TBPP at concentrations of 0, 100 or 1000 mg/kg in the diet for 28 d and bromine levels determined in the muscle, liver and fat using a neutron activation technique. Compared to controls animals, residue levels of bromine were approximately 6 - 7 and 40 – 50 times greater in animals receiving 100 and 1000 mg/kg TBPP respectively. This study also contained recovery groups, and by the end of a 6-week recovery period residue levels of bromine in the muscle, liver and fat of rats fed up to 1000 mg/kg TBPP were similar to control animals (Kerst, 1974).

The data indicates that the major route of excretion in rats and rabbits is via the urine, and that very little of the parent compound is excreted. There is also evidence of enterohepatic circulation of mainly TBPP-derived metabolites occurring.

8.2 Human data

A 7-year old child was exposed to repeatedly washed sleepwear that may have been treated with TBPP, on days 1, 2 and 8 -12, and new-TBPP-treated sleepwear on days 3 - 7. DBP at a concentration of 0.4 µg/L was present in the urine prior to wearing the new treated pyjamas, and up to 29 µg/L (two days) after wearing the new treated sleepwear. DBP was still excreted at concentrations ranging from 6 – 14 µg/L five days after the child stopped wearing the new TBPP treated sleepwear. Additionally, urine samples were collected from 10 other children and 1 adult. No DBP was detected in the urine from 1 adult and 1 child who had never worn flame-retardant sleepwear. In children wearing well-washed TBPP treated sleepwear, 7 had DBP levels of 0.5 µg/L in the urine and 1 child had a level of 5 µg/L. A quantitative estimation of the amount of TBPP absorbed by children from wearing TBBP treated sleepwear was undertaken, and determined to be approximately 180 µg/day (9 µg/kg body weight), (Blum et al., 1978).

DBP was not detected in the urine of an adult or in the urine of a 5-year old boy after wearing 100% polyester knit pyjamas treated with TBPP for 7 nights. Morning urine samples were collected daily throughout this period and up to 8 days thereafter. The limit of determination in this study was 0.2 mg/L (St John et al., 1976).

9. Effects on Laboratory Mammals and Other Test Systems

9.1 Acute toxicity

9.1.1 Oral

In a well reported study that used 5 male Spartan rats per dose and a total of 5 dose levels, the oral LD50 was determined to be 5240 mg/kg bw. All animals that received 1980 and 3150 mg/kg bw TBPP survived, with deaths observed at 5000 mg/kg bw and above (Kerst, 1974).

LD50 values are reported on 113 chemicals, including TBBP, tested by the order of the Japanese government agencies since 1966. For TBBP, at least 6 dose levels were administered with a combined total of 10 male and female Wistar rats per dose. The LD50 was 810 mg and 1000 mg TBPP/kg bw in males and females respectively, and clinical signs of toxicity observed were sedation and crouching. Hepatic congestion was observed at necropsy (Hasegawa et al., 1989).

IPCS (1995) reports oral LD50 values in the rat of 1880 and 3120 mg/kg bw. However, this data was referenced from a secondary source, Ulsamer at al (1980) that cites the study is by Osterberg et al (1979), and that the manuscript was in preparation. A search of scientific journal databases has not located this study. Consequently, the cited LD50 values of 1880 and 3120 mg/kg bw cannot be considered reliable.

In a study investigating TBPP nephrotoxicity, 56 male Wistar rats received a single oral dose of 286.8 µmol TBPP, and the animals were then killed daily for 10 days. The study also included a control group of 15 animals. The following effects were observed: on day 1, pyknosis of the renal tubular epithelial cells, necrosis on day 2, regeneration from day 3 and large nuclei formation from day 4. It was seen that effects on the kidney were characterised by changes in the renal components and enzyme activities. Increases in the sialic acid content of the kidneys were observed on day 1, suggesting destruction of the epithelial membrane. On day 5, regeneration accompanied by an increase in inositol contents was seen (*Fukuoka et al., 1988).

9.1.2 Dermal

In a well reported study, TBPP was topically applied for 24 h under an occlusive dressing to groups of 2 male and 2 female New Zealand rabbits per dose up to a concentration of 8000 mg/kg bw. No deaths or clinical signs of toxicity were seen at any concentration. The dermal LD50 was >8000 mg/kg bw (Kerst, 1974).

A dose of 2000 mg TBPP was applied to the intact and abraded skin of 10 albino rabbits. No deaths were observed and thus, the dermal LD50 was >2000 mg/kg bw. However, while the study was cited to Moldovan (1972) in IPCS, (1995) no further details of the study, nor the reference was included in the IPCS and a search of scientific journal databases has not located this study. Consequently, the reliability of this data is limited.

9.1.3 Inhalation

No inhalation data are available.

9.2 Skin and eye irritation

9.2.1 Skin irritation

Six albino rabbits received a topical application of 1100 mg TBPP for 24 hours, after which the test site was washed and skin reactions noted immediately and 48 hours later. No signs of irritation were observed in any of the test animals in this study, which employed an extended exposure duration (i.e. greater than 4 hours) and greater dose (i.e. above 500 mg) than recommended in OECD Test Guideline 404 for skin irritation (Kerst, 1974). Additionally, no 'adverse' signs of irritation were reported in an acute dermal study in which TBPP was topically applied to the backs of New Zealand white rabbits at concentrations up to 8000 mg/kg bw for 24 hours (Kerst, 1974).

9.2.2 Eye irritation

Six rabbits received a single instillation of 220 mg TBPP into the eyes, and examined 24, 48 and 72 hours after instillation. No signs of irritation were observed in this study, which used a greater dose (i.e. above 100 mg) than recommended in the OECD Test Guideline 405 for eye irritation (Kerst, 1974).

9.3 Sensitisation

9.3.1 Skin

Studies in animals

Data are available from a single poorly reported study that investigated the skin sensitisation potential of TBPP in guinea pigs in two assays. One was a modified Landsteiner assay and the second used the footpad technique. Both studies used Freund's complete adjuvant and 5 – 10 animals per test group. It is reported that attempts to sensitise guinea pigs were unsuccessful (Morrow et al., 1976).

Studies in humans

Data are available from a study that investigated the skin sensitisation potential of TBPP in a number of assays including three human maximization tests. In the human maximisation assays it is stated that volunteers were challenged with and without pre-treatment to sodium lauryl sulphate. In the first assay, the induction concentration was 100 % TBPP and the challenge concentration was 25% TBPP. In the second assay the induction and challenge concentration were both 20% TBPP. In the third assay the induction concentration was 20% TBPP and the challenge concentration 5%. In the first assay, 8 out of 24 subjects (33%) were sensitised, in the second assay, 2 out of 25 subjects (8%) were sensitised, and in the third assay it is stated that 4 of 20 subjects showed minimal to moderate responses. Therefore, these 4 subjects were rechallenged with patches applied for 48 h and readings taken 24 h after patch removal. Two were considered definitely

sensitised, a third weakly sensitised while no reaction was observed in the fourth (Morrow et al., 1976).

Although skin reactions were seen at challenge in all 3 human maximisation assays the significance attached to these results is limited by the lack of methodological detail. As such, it cannot be reliably determined how long the induction phase was, or the number of patches applied, or how long after the induction phase challenge was undertaken. Furthermore, it appears that test sites were only scored once after challenge. As sensitisation reactions generally persist, and irritation reactions fade, a second evaluation 48 –72 h after challenge can assist in determining the nature of observed skin reactions. The absence of a skin reaction in 1 of the 4 volunteers re-challenged indicates that an irritant skin reaction occurred in at least 1 volunteer in these human maximisation tests.

The 3 volunteers who gave a skin reaction at challenge, along with 3 non-sensitised controls, were also challenged with 8 fabrics treated with TBPP for 72 hours with test sites examined 24 hours after patch removal. Skin reactions were seen for 7 of the 8 fabrics in one or more volunteer. Only 3 fabrics gave a reaction in all 3 test subjects. No reactions were seen in non-sensitised volunteers (Morrow et al., 1976).

The same study also contained information on human patch tests in 200 volunteers. These patch tests were conducted with fabrics containing 4.5% or 8% TBPP. Patches were applied to the arms of males and to the arms or legs of females for 6 days, and the test site examined on day 2 and after removal on day 6. Fifteen days after removal volunteers were challenged with new patches for 48 h, after which the test site was examined. No instance of dermatitis was reported in any of the volunteers (Morrow et al., 1976).

In a repeat insult patch study, a patch containing 1100 mg TBPP was applied to the upper arm of 52 human volunteers for 24-h. After 1 – 3 d this procedure was repeated until 10 patches had been applied over a 24-d period. Subjects were then challenged at the same test site using the same procedure. Fifty persons showed no skin reactions during the study. After the 6^{th} or 7^{th} application two persons had itching and urticaria. The study was stopped for a month in these two subjects and then restarted. No further adverse effects were seen in these individuals (Kerst, 1974; US EPA, 1976). The data from this study does not indicate a skin sensitisation potential for TBPP.

The incidence of sensitisation to TBPP in human subjects from seven European countries patch tested with TBPP was two positives among 1103 patients (*Andersen, 1977).

9.3.2 Respiratory tract

There are no studies available in animals or humans.

9.4 Repeat dose toxicity

9.4.1 Oral

Rat

In some dietary studies, the doses administered were reported in ppm only. Therefore, the following default values have been applied to convert ppm to mg/kg bw. In these calculations, it is assumed that 1000 ppm in the diet represents 1 g TBPP per kg diet. The default values for dose calculations are presented in Table 9.1

Table 9.1: Default values for dose calculations

Species	Sex	Body weight (kg)	Food intake (g/day)
Rat (life-time studies)	M	0.5	20
	F	0.35	17.5
Rat (other studies)	M	0.2	20
	F	0.175	17.5
Mouse	M	0.03	3.6
	F	0.025	3.25

Source: Gold et al (1984).

In groups of 10 female rats gavaged with 100, 150, 500 or 1000 mg TBPP/kg bw for 10 d, mortality rates were 0, 0, 70 and 100% respectively (Seabaugh et al., 1981).

IPCS (1995) reports a study in which rats received daily doses of 250 mg TBPP/kg bw and were sacrificed up to 10 days after dosing. No effects were reported in the liver and testes, but nephrotoxic changes were seen from day 2 with severity increasing with time. However, while the study is cited to be by Osterberg et al (1979), no such reference is provided and a search of scientific journal databases has not located this study. Consequently, this data cannot be considered reliable.

In a 4-week dietary study, groups of 5 male weanling rats received 0, 100 or 1000 ppm TBPP in the diet (equivalent to 0, 10 and 100 mg/kg bw/day respectively). Haematology, clinical chemistry and urine analysis were conducted on day 7 and day 28. In addition to histopathological examination on day 28, bromine levels were determined in the muscle, liver and fat using a neutron activation technique. Compared to controls a significant decrease in body weight gain (16%) and food consumption (12%) was seen in animals at 100 mg/kg bw/day. No treatment-related haematological, urine analysis or biochemical effects were observed. Although, compared to controls, a dose related decrease was seen in relative heart, liver, spleen, kidney and testes weight ($\geq$13% at 100 mg/kg bw/day) no morphological changes were seen in these organs at histopathology. A dose related increase was seen in tissue residues of bromine in the muscle, liver and fat approximately 40-50 times greater than control values at 100 mg/kg bw/day (Kerst,

1974). The no-observed adverse-effect (NOAEL) level for TBPP was determined to be 10 mg/kg bw/day.

The above study (Kerst, 1974) also included recovery groups of 2–5 rats that were sacrificed 2 and 6 weeks after receiving 0, 10 and 100 mg TBPP/kg bw in the diet for 28 days. By 6 weeks, body weight gain, feed consumption and tissue residues of bromine in muscle, liver and fat of TBPP treated animals were comparable to controls.

No adverse responses were observed in rats gavaged with 10, 50 or 100 mg TBPP/kg bw daily for 4weeks and killed at the end of the dosing period or 2-weeks later, however, elevated bromine levels were seen in the blood (*Brieger et al., 1968).

In a 13-week study reported as an abstract only, groups of up to 48 Osborne-Mendel rats received daily gavages of TBPP at 0, 25, 100 or 250 mg/kg bw. Compared to control values, a reduction in body weight gain was seen in TBPP treated males (34-50%) and females (40%) at all doses. Relative liver weights were lower for both sexes in the low dose group, but higher for females in the top dose group, compared to controls. Reductions were also seen in relative kidney weight (18%) in both sexes and relative testes weight in males (25%). At necropsy, effects on the kidney were seen in all TBPP-treated animals: an increased incidence and severity of chronic nephritis with associated regenerative epithelium, hypertrophy, and dysplasia of renal tubular epithelial cell nuclei. Changes were more severe in the top dose group and among males. No treatment related changes were seen in the other tissues examined (Osterberg et al., 1978). A NOAEL for TBPP was not determined from this study.

Groups of 55 male and 55 female rats were fed 50 or 100 ppm TBPP in the diet (equivalent to a daily intake of 2 and 4 mg/kg bw/d in males and 2.5 and 5 mg/kg bw/d in females) for 103 weeks followed by a 1 week observation period prior to sacrifice. A control group of 50 animals per sex were sacrificed after 107 weeks. Only histopathological changes in the kidney were reported. It is not reported if there was a significant difference in survival rates between TBPP-treated and control animals, however, body weight gain between the treated and control group were similar. At histopathology the only significant non-neoplastic finding were small foci of dilated and hyperplastic or dysplastic proximal convoluted tubules. The incidence of dysplasia and hyperplasia were 0/53 in control males, 0/52 in control females, 53/54 in low dose males, 25/54 in low dose females, 39/54 in high dose males, and 46/54 in high dose females (Reznik et al, 1979). As histological changes were seen in the kidneys of both males and females at the lowest dose tested, (2 and 2.5 mg TBPP/kg bw/day respectively), a NOAEL for TBPP was not determined in this study.

A study is reported in the IPCS (1995) review in which rats were fed TBPP-treated fibres in the diet. However, as the dose administered cannot be determined in this briefly reported study, it is not presented here (Ulsamer et al., 1980).

Mice

Groups of 50 male and 50 female mice were fed 500 or 1000 ppm TBPP in the diet (equivalent to 60 and 120 mg/kg bw/day in males, and 65 and 130 mg/kg bw/day in females) for 103 weeks followed by a 1 week observation period prior to sacrifice. Only histopathological changes in the kidney were reported. It is not reported if there was a significant difference in survival rates between TBPP-treated and control animals, however, body weight gain in treated animals was 20 % less than controls throughout the study. At histopathology the only significant non-neoplastic finding were small foci of dilated and hyperplastic or dysplastic proximal convoluted tubules. The incidence of dysplasia and hyperplasia were; 0/54 in control males, 0/55 in control females, 46/50 in low dose males, 20/50 in low dose females, 49/50 in high dose males, and 40/46 in high dose females (Reznik et al, 1979). As histological changes were seen in the kidneys of both males and females at the lowest dose tested (60 and 65 mg TBPP/kg bw/day respectively), a NOAEL for TBPP was not identified in this study.

Dog

Studies are available in which dogs were fed TBPP-treated fibres in the diet for up to 3 weeks. However, as the dose administered cannot be determined in these briefly reported studies, they are not presented here (*Brieger et al., 1968).

In a dietary study, groups of dogs received 50 or 100 mg TBPP/kg bw/day for 4 weeks. A decrease in body weight gain and increase in blood-bromine levels was seen in treated animals. Cholinesterase activity was unaffected. No further details are available (*Brieger et al., 1968).

Overall, a NOAEL could not be determined determined from the available oral data. A LOAEL of 2 and 2.5 mg TBPP/kg bw/day was identified from a 2-year rat study in males and females respectively for histopathological changes to the kidney (Reznik et al, 1979).

9.4.2 Dermal

Rabbit

In a 4-week study, rabbits received daily topical application of 2200, 4400 or 8800 mg TBPP/kg bw/day. All rabbits died within 4 weeks. A dose-related increase in bromine levels was observed in the blood and urine. At necropsy, significant degenerative changes were seen in the kidneys and liver, and slight decreases in cholinesterase activity were noted in the treated groups (*Brieger et al., 1968). In another study in which animals were administered 50 and 250 mg/kg bw/day TBPP no deaths occurred, though bromide levels increased in the blood and urine (Ulsamer et al., 1980). However, in this briefly summarized study a NOAEL of 250 mg TBPP/kg bw/day was determined.

In a 13-week study, groups of 6 New Zealand white rabbits (both male and female animals were available for selection) received a weekly topical application of 0 or 2270 mg TBPP/kg bw/day. A further group of 6 rabbits with abraded skin received 2270 mg TBPP/kg bw using the same dosing regime. The TBPP-treated sites were not occluded, but all treated rabbits were fitted with an Elizabethan collar to prevent ingestion of the test material. There were no treatment related deaths and no significant body weight findings. Skin irritation was not observed during the

study. A statistically significant increase was seen in relative liver weight (approximately 50 – 60%) in the TBPP treated groups (abraded and non-abraded) compared to controls. However, no histopathological changes were seen in the liver at necropsy. In contrast, no effect on relative kidney weight was seen, but severe histopathological changes were seen at necropsy. Chronic interstitial nephritis, as indicated by the appearance of tubular atrophy, interstitial fibrosis or fibrous tissue, was seen in 6/8 TBPP treated males. Additionally, large or bizarre nuclei were seen in the affected areas. Effects were also seen on the testes in TBPP treated animals, which are reported in detail in Section 9.7.1 (Fertility**).** No effect was seen on spleen weight. No histopathological changes were seen in the spleen or any of the other tissues examined. It is stated that female rabbits did not exhibit any adverse effects in this study (Osterberg et al., 1977). A NOAEL could not be determined for both sexes in this study.

A study is reported in the IPCS (1995) review in which TBPP-treated rayon cloth was applied to the skin of rabbits (Ulsamer et al., 1980). However, as the dose administered could not be determined in this briefly reported study, it is not presented in this report (IPCS, 1995).

Mice

IPCS (1995) reports a dermal carcinogenicity study in mice (see sub-section 9.6.2), however, information is only provided on tumour incidence rates (*Van Duuren et al., 1978).

Dog

A study is reported in the IPCS (1995) review in which TBPP-treated rayon cloth was applied to the skin of dogs (*Brieger et al., 1968). However, as the dose administered could not be determined in this briefly reported study, it is not presented in this report.

9.4.3 Inhalation

No inhalation data are available.

9.5 Genotoxicity

In vitro

Studies in bacteria

In an Ames assay using direct plate incorporation, *Salmonella typhimurium* strains TA 1535 and TA 1538 were exposed to TBPP at concentration up to and including 1 µL/plate in the presence and absence of metabolic activation. A positive result was seen with TA 1535 from the lowest dose tested (0.1 µL/plate), and a negative result with TA 1538, with and without metabolic activation. No cytotoxicity was seen in the absence or presence of metabolic activation and positive controls gave results that confirmed the validity of the test (Carr & Rosenkranz, 1978).

Positive results were seen in further Ames tests using direct plate incorporation. In a briefly reported study, *S. typhimurium* strain TA 100 was exposed to TBPP at concentrations up to 11200 μg/plate with and without metabolic activation. A positive result was seen from 112 μg/plate (the lowest dose tested) with metabolic activation and 2240 μg/plate without metabolic activation. No cytotoxicity was seen in the absence or presence of metabolic activation. No further details are available, including whether positive controls were used (Salamone & Katz, 1981). A positive result was also seen with *S. typhimurium* strains TA 100 and TA 1535, and a negative result in strain TA 1537 and TA1538, with and without metabolic activation (*Blum & Ames, 1977; *Brusick et al., 1978; *Prival et al., 1977). Similarly, a positive result was seen with *S. typhimurium* strains TA 100 and TA 1535 in the presence of metabolic activation, and TBPP was reported to be 'weakly' mutagenic in both strains in the absence of metabolic activation (Lynn et al., 1982).

In an Ames test using pre-incubation, TBPP was mutagenic in *S. typhimurium* strains TA 100 and TA 104 in the presence of S9-liver fractions from rats pre-treated with phenobarbital (Van Beerendonk et al., 1998). It is reported that S9-liver fractions from rats pre-treated with phenobarbital increased the mutagenicity of 0.05 mmol TBPP/L in *S. typhimurium* strain TA 100 compared with liver microsomes from untreated rats (*Holme et al., 1983).

Ames tests were conducted in *S. typhimurium* strain TA 1535 on the urine from rats that received up to 500 mg TBPP/kg by the oral route, 5000 mg TBPP/kg by the dermal route or following dermal application of fabrics containing surface TBPP levels of up to 67,000 mg TBPP over 5 days. It is not reported whether metabolic activation was used. A positive response was seen with the urine from animals that received 500 mg/kg by the oral route and 5000 mg/kg by the dermal route. A negative result was seen with the urine from rats treated with the fabric (*Brusick et al., 1978; Ulsamer et al., 1980). A positive result was seen with *S. typhimurium* strain TA 100, and a negative result in strain TA 1535 and TA 1537, with urine collected from CD-1 mice following dermal application of 500 mg TBPP/kg bw (*Brusick et al., 1982).

Further Ames tests are reported in the literature for which positive results have been observed with TBPP (IPCS, 1995).

Overall it is concluded that TBPP is mutagenic in bacteria.

Studies in mammalian cells

In a gene mutation assay with mouse lymphoma L5178Y cells (*tk* locus) a 2- to 3-fold increase in mutations was consistently seen at 5 mg TBPP/L (*Brusick et al., 1978). An increase in the frequency of gene mutations was also seen with 0.02 mmol TBPP/L in V79 Chinese hamster cells in the presence of S9-liver fractions from rats pre-treated with phenobarbital (*Holme et al., 1983; *Søderlund et al., 1985). In contrast, no increase was seen in Chinese hamster V79 cells exposed to TBPP at concentrations up to and including 150 μg/mL with and without metabolic activation. In this study, the positive control gave clear increases in the mutation frequency without metabolic activation, while results with metabolic activation were not presented (Sala et al., 1982).

In chromosome aberration studies conflicting results have been reported. A positive result was seen with TBPP in mouse lymphoma L5178Y cells (*Brusick et al., 1980) and in Chinese hamster lung cells in the presence of metabolic activation (*Ishidate et al., 1981). No significant increase in chromosomal aberrations was seen in Chinese hamster V79 cells (*Furukawa et al., 1978), or the human fibroblastic cell line HE 2144 (from a 10-week old male embryo) following exposure of up to 0.349 mg TBPP/ml in the absence of metabolic activation (*Sasaki et al., 1980).

In contrast, positive results have been reported in sister chromatid exchange (SCE) assays. Significant increases in SCEs were reported in Chinese hamster V79 cells (*Furukawa et al., 1978) and in the same cell line at dose levels of 35 μg/ml and above without metabolic activation and at 50 μg/ml (the top dose level) with metabolic activation in the absence of cytotoxicity (Sala et al., 1982). Positive results were also seen in mouse lymphoma L5178Y cells (*Brusick et al., 1980), and the human fibroblastic cell line HE 2144 with 0.070 mg TBPP/mL in the absence of metabolic activation (*Sasaki et al., 1980).

UDS was detected in rat liver heptocytes, grown as monolayer cultures, exposed to 0.01 – 0.1 mmol TBPP/L for 18–19 hours (*Holme et al., 1983; *Holme & Søderlund, 1984; *Gordon et al., 1985; *Søderlund et al., 1985). Similarly, in monolayer cultures of human (KB) cells TBPP was seen to cause UDS and damage DNA (*Gutter & Rosenkranz, 1977; *Blum & Ames, 1977). DNA damage was also detected in isolated rat hepatocytes exposed to concentrations as low as 5 μmol TBPP/L, while a 10-fold higher concentration was necessary to induce DNA damage in testicular cells (*Søderlund et al., 1992). In contrast, no UDS was detected in a non-standard study using foreskin epithelial cells from a cryopreserved skin pool with 'input' dose ranges of 10 – 99 and 100 – 400 μg TBPP/mL and a 24-hour incubation period (*Lake et al., 1978). Additionally, no DNA damage was seen in Reuber rat hepatoma cells in the absence of metabolic activation (*Gordon et al., 1985).

Conflicting results have been reported in mammalian cell assays. However, TBPP has produced reproducible positive results in vitro and, thus, overall, the available data is considered to indicate a significant mutagenic and clastogenetic activity in mammalian cells.

Studies in Drosophila

In a study to investigate the potential induction of chromosomal rearrangements, male Canton-S *Drosophila* flies were fed a 1% solution of glucose containing 1000 or 10000 mg/ TBPP/L for 48-h and then mated 1:2 with brown ebony females. Females were replaced every 2 days to make a total of 4 broods. Results showed that TBPP caused reciprocal translocations in *Drosophila* (Berkowitz, 1978). In a further study, TBPP induced a significant increase in sex-linked recessive lethal mutations in male germ-cell stages of *Drosophila melanogaster* at a dose of 1000 mg/kg. The spermatids were noted to be most sensitive (*Valencia, 1978). A positive result was also seen in the *Drosophila* (white/white+) (w/w+) eye mosaic assay that detects a broad spectrum of DNA modifications (*Vogel & Nivard, 1993). However, for insect systems such as this, there is too little comparative data with mammalian cells and the relevance of findings to the mammalian in vivo system is uncertain (Aardema et al., 1998).

In vivo

An ip mirocronucleus assay was conducted in female B6C3F1 mice using a single and repeated treatment schedule. For single administration, groups of 3 - 8 mice received 0, 1020 or 1530 mg TBPP/kg and bone marrow was sampled at 25 h. An additional group of 4 animals receiving 1020 mg TBPP/kg were killed at 44 h. Five hundred polychromatic erythrocytes (PCEs) per animal were analysed for the presence of micronuclei. Compared to controls, a statistically significant increase in micronuclei was only seen at 1020 mg/kg 44 h after administration. This result was confirmed in a second independent experiment. It is stated that longer sampling times were not used as increased mortality was seen at the higher dose levels. No further details are available (Salamone & Katz, 1982).

For the repeated schedule, groups of 3–4 mice received 2 ip injections of 0, 204, 408, 612, 816 or 1020 mg TBPP/kg 24-h apart and bone marrow sampled at 48, 72 and 96 h after the initial treatment. Five hundred PCEs per animal were analysed for the presence of micronuclei. Compared to controls, no significant increase was seen in the incidence of micronuclei in TBPP-treated animals (Salamone & Katz, 1982).

In a briefly reported micronucleus assay, groups of two male and female Chinese hamsters received a single ip injection of 0, 200, 400 and 800 mg TBPP/kg bw. Bone marrow was sampled at 24-h. Two thousand PCEs per animal were analysed for the presence of micronuclei. Compared to controls, a statistically significant, and dose-related increase in micronuclei was seen at 400 mg/kg and above. The positive controls gave a clear increase in the frequency of micronuclei. No further details are available (Sala et al., 1982).

The clastogenic effect of TBPP was investigated in bone marrow following iv administration. In this briefly reported study, groups of male C57BL/6J mice (number not reported) received up to 1500 mg TBPP/kg. Bone marrow was assessed for chromosomal aberrations and SCE (sampling time not reported). Results were only presented for the top dose group. Compared to controls a significant increase in the incidence of chromosome aberrations and SCE were seen. It is reported that above 1500 mg TBPP/kg cytotoxicity was observed. Significant increases in chromosomal aberrations and SCE were seen with the positive controls (Nakanishi & Schneider, 1979).

The DNA-damaging potential of TBPP was investigated by an alkaline elution technique. Groups of male Wistar rats (number not reported) received a single ip injection of 0, 36, 72 or 143 µmol/kg of 14C-TBPP and were sacrificed 20, 60 or 180 minutes later. DNA damage was assessed by measurement of the eluciation rate in liver and kidney nuclei (i.e. deuterium substitution). A significant change in the elution rate was observed in a dose-dependent manner in both the kidney and the liver (results presented as graphs). The magnitude of the damage in the kidney was considerably greater than that observed in the liver. Significant DNA damage was apparent in the kidney 20 minutes after the administration of 36 µmol/kg TBPP, whereas a dose of 143 µmol/kg of TBPP was required to cause appreciable DNA damage in the liver. TBPP is considered to give a positive result in this assay for DNA damage (Pearson et al., 1993b). Similarly, DNA damage was detected in male Wistar rats given a single ip injection of 350 µmol/kg TBPP using an automated alkaline elution technique. Extensive DNA damage was found 2 hours after administration in the liver, kidneys and small intestine, substantial damage in

the brain and lungs, and less damage detected in the testes, spleen and large intestine (*Holme et al., 1983; *Søderlund et al., 1992).

Data are available from non-regulatory transgenic rodent mutation assays. In a study using the standardized lambda/*lac1* (Big Blue) transgenic B63F1 mouse, TBPP was administered by gavage to five male mice at a concentration of 150 mg/kg for two days, and to groups of five males at 300 or 600 mg/kg for four days. A control group of six mice received vehicle only for 5 days. Animals were sacrificed on day 20 and the frequency of *lacI* mutations determined in the liver, kidney and stomach. Compared to controls a statistically significant increase in *lac1* mutations was only observed in the kidney at 300 (63 %) and 600 mg/kg (45 %) (Provost et al., 1996). DNA sequence analysis of the recovered mutants from the kidney showed a dose-dependent decrease in G:C to A:T transitions which was accompanied by an increase in the loss of single G:C base-pairs (De-Boer et al., 1996).

A study was undertaken in *lac1* (Big Blue) transgenic F344 rats to study mutation in the kidney at the sub-organ level. Groups of 4-6 male rats received 0, 100 or 2000 ppm TBPP in the feed for 45 days, were then sacrificed and the frequency of *lacl* mutations determined in the cortex, and outer and inner medullas of the kidney. Compared to controls, a dose-related increase in *lacl* mutations was seen in all three tissues that displayed a gradient of induction from the inner medulla to the cortex. Compared to controls, the highest induction seen was a 6.4, 3.7 and 2.2-fold increase in the cortex, outer and inner medulla respectively (De Boer et al., 2000).

Positive results have been observed in two micronucleus assays using a single administration, a briefly reported clastogenicity assay, an assay investigating DNA damage and two transgenic rodent mutation assays. In contrast a single negative result is reported in a micronucleus assay using a repeated dose schedule. Therefore, overall, the data clearly indicate that TBPP is clastogenic in somatic cells in vivo with mutagenic activity also seen in non-regulatory transgenic rodent mutation assays.

9.6 Carcinogenicity

9.6.1 Oral

TBPP was tested in a carcinogenicity bioassay using Fischer-344 rats and B6C3F1 mice (Reznik et al., 1979), as described below.

Groups of 55 male and 55 female rats were fed 50 or 100 ppm TBPP in the diet (equivalent to a daily intake of 2 and 4 mg/kg bw/day in males and 2.5 and 5 mg/kg bw/day in females) for 103 weeks followed by a 1 week observation period prior to sacrifice. A control group of 50 animals per sex were sacrificed after 107 weeks. Only histopathological changes in the kidney were reported. It is stated that 65 to 80% of the treated rats (or mice) survived until the end of the study. No further details available. Body weight gain between the treated and control group were reported to be similar. Tubular-cell adenomas of the kidney were seen in a substantial number of TBPP-treated male and female rats. Additionally, tubular cell carcinomas of the kidney were seen in males at the top dose group. Neither of these tumour types was seen in control males or females, and the authors report that spontaneous tumours of the kidney are rare in F344 rats. These results are

presented in Table 9.2. At histopathology the only significant non-neoplastic finding were small foci of dilated and hyperplastic or dysplastic proximal convoluted tubules that were seen in the same area as tumours. The incidence of dysplasia and hyperplasia in the kidney is presented in Section 9.4.1. ('Repeat dose toxicity') (Reznik et al, 1979).

Groups of 50 male and 50 female mice were fed 500 or 1000 ppm TBPP in the diet (equivalent to a daily intake of 60 and 120 mg/kg bw/day in males, and 65 and 130 mg/kg bw/day in females) for 103 weeks followed by a 1 week observation period prior to sacrifice. Only histopathological changes in the kidney were reported. It is stated that 65 to 80 % of the treated mice (or rats) survived until the end of the study. No further details were available. Body weight gain in treated animals was reported to be 20% less than controls throughout the experiment. Tubular cell adenomas of the kidney were seen in male and female TBPP-treated animals. Additionally, tubular cell carcinomas of the kidney were seen in TBPP-treated males. Neither of these tumours was seen in control animals, and the authors report that spontaneous tumours of the kidney are rare in B6C3F1 mice. These results are presented in Table 9.2**.** At histopathology the only significant non-neoplastic finding were small foci of dilated and hyperplastic or dysplastic proximal convoluted tubules that were seen in the same area as tumours. The incidence of dysplasia and hyperplasia in the kidney is presented in Section 9.4.1 ('Repeat dose toxicity') (Reznik et al, 1979).

The tumour incidence in the kidneys of both rats and mice is presented in Table 9.2.

Table 9.2: Tumour incidence in the kidneys of F344 rats and B6C3F1 mice

	Number of tumour bearing animals/number of animals examined			
Dose (ppm)	**Tubular cell adenoma**		**Tubular cell carcinoma**	
	M	**F**	**M**	**F**
Rats				
0	0/53	0/52	0/53	0/52
50	30/54	4/54	0/54	0/54
100	27/54	13/54	3/54	0/54
Mice				
0	0/54	0/55	0/54	0/55
500	5/50	3/50	1/50	0/50
1000	12/49	3/46	5/49	0/46

Additional data on the incidence of tumours in the fore-stomach, lung and liver in the mouse study is provided in US National Cancer Institute (NCI), 1978 (cited in IPCS, 1995). Details are presented in Table 9.3.

Table 9.3: Tumour incidence in the fore-stomach, lung and liver in B6C3F1 mice fed TBPP

Dose (ppm)	Number of tumour bearing animals/number of animals examined					
	Fore-stomach		Lung		Liver	
	M	F	M	F	M	F
0	0/51	2/53	12/54	4/55	28/54	11/54
500	10/47[a]	14/48[a]	18/44[c]	9/50	31/49	23/50[e]
1000	13/48[b]	22/44[b]	25/50[d]	17/50[d]	23/49	35/49[e]

Fisher analysis of treated group versus control: [a]squamous-cell papillomas; $P < 0.01$; [b]squamous-cell carcinomas and papillomas; $P < 0.01$; [c]alveolar/bronchial adenomas and carcinomas; $P < 0.05$; [d]alveolar/bronchiolar adenomas and carcinomas; $P < 0.01$; [e]hepatocellular adenomas and carcinomas; $P < 0.01$.

Data are also available from a study investigating the effect of TBPP on the histomorphology and ultrastructure of the kidneys. Groups of 2 - 9 male F344 rats were gavaged with 0 or 100 mg TBPP/kg bw/day, 5 days per week for up to 52 weeks. After 52 weeks treatment, 3 of the 5 surviving animals receiving TBPP were found to have polyploid adenomas in the descending colon (Reznik et al., 1981).

There is clear evidence from dietary studies in rats and mice of the development of dose-related increases in TBPP-induced tumours, particularly in the kidney.

The mechanism by which TBPP may induce kidney tumours in rodents is not currently understood. A conceptual framework for considering the mode of action of chemical carcinogenesis of TBPP is presented in Appendix 1 of this report.

9.6.2 Dermal

Groups of 29-30 female ICR/Ha Swiss mice received topical application of 0, 10 or 30 mg TBPP (equivalent to a dose of approximately 0, 400 and 1200 mg TBPP/kg bw/day) 3 times a week for up to approximately 71 weeks. In addition to skin tumours (papillomas and/or carcinomas) a substantial number of tumours were seen at distal sites, such as a statistically significant and dose related increase in squamous cell carcinomas of the tongue and in the gingival area, and papillomas and carcinomas of the fore-stomach (*Van Duuren et al., 1978). Results are presented in Table 9.4.

Table 9.4: Tumour incidence in female ICR/Ha Swiss mice after dermal application of tris (2,3-dibromopropyl) phosphate (TBPP).

Number of animals treated	Dose (mg/animal)	Number of mice with tumours/number necropsied[a]			
		Forestomach	Lung	Skin	Oral cavity
29	0	1/29	7/29	0/29	0/29
29	10	10/29	26/29	2/29	2/29
30	30	20/30	28/30	5/30	4/30

Source: IPCS (1995)

[a]Increase in incidences of tumours of the forestomach, lung, skin and oral cavity in treated animals were statistically significant compared with those in controls ($P < 0.05$).

Data are available from a study that conducted a series of initiation/promotion studies with TBPP in groups of 28 – 34 female Swiss mice. As both oral and dermal bioassays are available for TBPP the results from these non-regulatory tests are briefly reported here. When TBPP was used as an initiator and 12-*O*-tetradecanoyl-phorbol-13-acetate as a promoter, the incidence of skin tumours was significantly increased compared to controls. When dimethylol butanoic acid was used as the initiator and TBPP the promoter a significant increase in TBPP-related lung adenomas was seen compared to controls (Sala et al., 1982).

Therefore, there is clear evidence in mice of the development of TBPP-induced tumours at the site of application and distal sites following topical application.

9.6.3 Other related studies

The cell transformation potential of TBPP was evaluated in a number of studies. As both oral and dermal bioassays are available for TBPP the results from these non-regulatory tests are briefly reported here. TBPP gave a positive result in Syrian hamster embryo (SHE) cells with a high level of transformation being observed at 25 μg/ml (Sala et al., 1982). A positive result was also seen when TBPP was tested in BALB/3T3 cells (*Brusick et al., 1978). In contrast, a very low frequency of transformations were seen in C3H/10T1/2 cells when TBPP was tested at 40 μg/ml and up to 80 μg/ml in the absence and presence of metabolic activation respectively. The authors considered the results to be negative (Sala et al., 1982). Similarly, a negative result was seen with C3H/10T1/2 cells when TBPP was tested up to 20 μg/ml (*Dunkel et al., 1988).

9.7 Reproductive toxicity

9.7.1 Fertility

No fertility studies are available. Information is presented below from repeat dose toxicity studies that examined the reproductive organs.

In a 13-week study, groups of 6 New Zealand white rabbits (both male and female animals were available for selection) received a weekly topical application of 0 or 2270 mg TBPP/kg bw. A further group of 6 rabbits with abraded skin received 2270 mg TBPP/kg bw using the same dosing regime. The TBPP-treated sites were not occluded, but all treated rabbits were fitted with an Elizabethan collar to prevent ingestion of the test material. There were no treatment related deaths and no significant body weight findings. The only non-reproductive organ findings were a statistically significant increase in relative liver weight (approximately 50 – 60%) in TBPP-treated animals (i.e. abraded and non-abraded) compared to controls, and chronic interstitial nephritis in the kidney of 6/8 TBPP-treated males. In the testes, a statistically significant decrease in relative organ weight (approximately 50%) was seen in non-abraded animals compared to controls. Although the decrease in testes weight was not statistically significant in the abraded group (approximately 40%), it is reported that in 2/3 males there was a 50% decrease in testicular weight compared with the control value. At necropsy, moderate to severe testicular atrophy was observed in 7/8 TBPP-treated males with an apparent increase seen in interstitial cells. Spermatogonia were present in the seminiferous tubules, and although progression to secondary spermatocytes was observed at times spermatozoa were rarely seen. Furthermore, the tubule lumina

were usually filled with a fibrin-like mesh and occasionally contained a giant or syncytial cell. There were also sporadic pyknotic cells and other degenerative changes. The testes of the control animals and one animal in the abraded skin test group were normal. In females, ovaries from the control and TBPP-treated groups were normal (Osterberg et al., 1977). Therefore, topical application of 2270 mg TBPP/kg bw/day resulted in severe treatment-related effects on the testes in the presence of other toxic effects: increased relative liver weight and histopathological changes in the kidney.

Effects on the testes and sperm were seen in studies that used the ip route of exposure, though the relevance of the data are uncertain with respect to relevant routes of human exposure.

Groups of 6 male Sprague-Dawley rats received ip injections of 0, 0.4, 0.9, 1.8, 3.5, 7.1, 14.2, 28.4, 56.8 and 113.5 mg TBPP 3 times a week (equivalent to 0, 2.0, 4.5, 9.0, 17.5, 35.5, 71.0, 142.0, 284.0 and 567.5 mg/kg bw.) for a minimum of 72 d. At 14.2 mg and above the test material did not dissolve completely and was injected as an emulsion. Animals were sacrificed at the end of treatment and in addition to examination of the testes, spermatogenesis and sperm motility were assessed and serum testosterone concentrations determined by radioimmunoassay. Two animals died in the top dose group though no clinical signs of toxicity were observed in TBPP-treated animals. Compared to controls, a statistically significant and dose related decrease in body weight gain was observed at 142.0 mg TBPP/kg bw and above (9–25%). At necropsy a statistically significant decrease was seen in prostate (15–24%) and seminal vesicle weight (22 – 43%) at 71.0 mg TBPP/kg bw, epididymal weight at 142.0 mg TBPP/kg and above (19 – 55%) and testes weight at 284.0 mg TBPP/kg bw and above (42 – 58%) that were generally not dose-related. Effects seen on seminiferous tubules at 567.5 mg TBPP/kg bw were the presence of very few germinal cells and macrophages in the interstitium of the affected testes appeared to be phagocytically active. It is not reported whether histopathological changes were seen at lower dose levels. A statistically significant and dose related decrease was seen in sperm content in the epididymis at 142.0 mg TBPP/kg bw and above (41 – 96%) and in sperm production at 284.0 mg TBPP/kg bw and above (40 – 82%). A statistically significant decrease was seen in the % of motile sperm at 567.5 mg TBPP/kg bw (36%). No treatment-related effect was seen on the morphology of sperm heads or serum testosterone concentrations (Cochran & Wiedow, 1986). In conclusion, decreases in relative prostate and seminal vesicle weight were seen in the absence of other toxic effects, while other effects on the testes, including histopathological changes and a reduction in sperm production, were seen in the presence of systemic toxicity (a statistically significant reduction in body weight gain).

The effect of TBPP on sperm was investigated. Groups of 12- 15 male B6C3F1 mice received daily ip injections of up to 817 mg TBPP/kg for 5 days, were killed 35 days after the fifth treatment and 500 sperm heads scored from each epididymis. Compared to controls a significant increase in the incidence of abnormal sperm heads was seen at the top dose. The result was confirmed in a second independent experiment at 817 mg TBPP/kg, with a dose-related increase in the frequency of abnormal sperm heads seen at an additional dose level of 1020 mg TBPP/kg. No further details, such as information on systemic toxicity, are available (Salamone & Katz, 1981).

9.7.2 Developmental

In a dose range-finding study in Sprague-Dawley rats, groups of 10 pregnant dams were gavaged with 0, 250, 1000 mg/kg TBPP on days 6 - 15 of gestation. All animals in the top dose group died between days 9-11 of gestation. One dam died at 250 mg/kg (Seabaugh et al., 1981).

In the main study, groups of at least 30 pregnant Sprague-Dawley rats were gavaged with 0, 5, 25 or 125 mg TBPP/kg bw on days 6 - 15 of gestation. Dams were sacrificed on day 20 of gestation and the foetuses subjected to routine external, visceral and skeletal examination. No deaths, clinical signs of toxicity, or effect on feed consumption were observed in the dams. Compared to controls, a statistically significant reduction in body weight gain (12 %) was seen in dams at 125 mg TBPP/kg bw. At autopsy, no treatment-related effects were seen on the numbers of corpora lutea, implantations, early or late deaths, the percentage of females with resorptions, the number of viable foetuses, the percentage of resorptions, and the percentage of pre-implantation losses. No treatment-related effects were seen in the foetuses (Seabaugh et al., 1981).

In an oral study reported as an abstract only, female Wistar rats received TBPP in olive oil at doses ranging from 25 to 200 mg/kg bw on days 7-15 of gestation. At 200 mg TBPP/kg bw clinical signs of toxicity and death were observed in the dams, along with a marked suppression in maternal body weight gain and food consumption. A significant increase in skeletal variations was seen in foetuses at 200 mg TBPP/kg bw. In offsprings, a significantly lower viability index was seen at 50 and 100 mg TBPP/kg bw only, while it is reported that the lactation and 10-week survival index were comparable to controls. No effects were seen in functional tests. No further details are reported (Kawashima et al., 1983). Although poorly reported, developmental effects were only seen in this study in the presence of severe maternal toxicity (i.e. death).

10. Hazard Classification

This section discusses the classification of the health effects of TBPP according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (NOHSC, 2004) or, in the case of physicochemical hazards, the *Australian Code for the Transport of Dangerous Goods by Road and Rail* (ADG Code) (FORS, 1998). The Approved Criteria are cited in the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994) and provide the mandatory criteria for determining whether a workplace chemical is hazardous or not.

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.

Classification of TBPP in accordance with the OECD *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (OECD 2003) can be found in Appendix 2.

TBPP is currently not listed in the NOHSC *List of Designated Hazardous Substances* contained in the Hazardous Substances Information System (HSIS).

10.1 Physicochemical hazards

TBPP is a clear, pale-yellow viscous liquid with a boiling point of 390ºC, and vapour pressure 2.53 x 10^{-5} kPa @25ºC.

With respect to the ADG Code (FORS 1998), TBPP does not meet the criteria for classification as a dangerous good on the basis of physicochemical hazards.

10.2 Health hazards

10.2.1 Acute toxicity

Only animal data are available. Significantly different oral LD50 values have been reported in the rat. Values of 810 and 1000 mg/kg bw in male and female Wistar rats respectively were reported for TBPP among 113 chemicals tested sometime since 1966. In contrast, a rat oral LD50 value of 5240 mg/kg bw is available in male Spartan rats from a well reported 1974 study. In addition, no deaths were seen in this study at dose levels greater than that reported in the study conducted sometime since 1966; 1980 and 3150 mg/kg bw. Consequently, the LD50 value of 5240 mg/kg bw from the well reported study is considered the most reliable.

Dermal LD50 values of > 2000 and >8000 mg/kg bw are available in the rabbit.

Classification:

TBPP does not meet the Approved Criteria (NOHSC, 2004) for classification for acute oral or dermal toxicity.

10.2.2 Irritation and corrosive effects

Only animal data are available. No signs of irritation were observed in a skin irritation study in rabbits that employed an extended exposure period and used a dose greater than the dose recommended in the OECD test guideline for this endpoint. Additionally, no skin irritation was observed in a rabbit acute dermal study at doses up to 8000 mg/kg bw.

No signs of irritation were observed in an eye irritation study in rabbits that used a dose greater than recommended in the OECD test guideline for this endpoint.

Classification:

TBPP does not meet the Approved Criteria (NOHSC, 2004) for skin or eye irritation.

10.2.3 Sensitising effects

Positive skin reactions to TBPP were observed in 3 human maximisation tests with response rates of up to 33% observed at challenge. However, the methodology employed, and the limited details provided, affects the significance that can be attached to these results, as demonstrated by data (i.e. re-challenge) indicating that an irritant skin reaction occur in at least one volunteer. Furthermore, in the only human maximisation test that employed a re-challenge, only 2 out of 20 volunteers (10%) were reported to be definitely sensitised to TBPP, while a third volunteer reported to be 'weakly' sensitized is considered to have given an equivocal response. When these 3 volunteers were challenged with 8 fabrics treated with TBPP, skin reactions were seen in 7 of the 8 fabrics in 1 volunteer or more, with only 3 fabrics giving a skin reaction in all 3 volunteers. The absence of a second scoring time to assist in determining whether observed skin reactions are irritant, or allergic in nature, is a limitation of all these human maximization tests. Therefore, overall, no reliable conclusion can be drawn on the skin sensitisation potential of TBPP from the data obtained in these human studies.

Data from several European countries indicate that TBPP has a very weak skin sensitisation potential. Only 2 out of 1103 patients patch-tested with TBPP gave a positive response. In contrast, no evidence of a skin sensitisation potential was observed in a human repeat insult patch study where 52 volunteers received patches containing 1100 mg TBPP, or in patch tests conducted with fabrics treated with up to 8% TBPP in 200 volunteers. Similarly, no evidence of a skin sensitisation potential was seen in the only available animal data, a poorly reported modified Landsteiner assay and footpad technique test in guinea pigs.

Classification:

TBPP does not meet the Approved Criteria (NOHSC, 2004) for skin sensitisation.

10.2.4 Effects from repeated or prolonged exposure

Only animal data are available. Overall, the data in rodents indicates that the kidney is the target organ following ingestion of TBPP. Although no effects on the kidney were seen up to, and including, the top dose of 100 mg TBPP/kg bw/d in a 28-day dietary study in rats, small foci of dilated and hyperplastic or dysplastic convoluted tubules of the kidney were seen in animals in the low dose group, and in a 2-year dietary study; from 2 mg/kg bw/d in males and 2.5 mg/kg bw/d in females. Similar effects on the kidney were seen in a 2-year dietary study in the mouse at 60 mg/kg bw/d in males and 65 mg/kg bw/d in females. Effects on the kidney were also seen in a 13-week gavage study in the rat. In the rat gavage study, which was reported as an abstract only, chronic nephritis with associated regenerative epithelium, hypertrophy, and dysplasia of renal tubular epithelial cell nuclei was seen in the low dose group. Similarly, effects on the kidney were seen in dermal rabbit studies at the lowest dose tested i.e. 2200 mg/kg bw/d in a 28 day study and 2270 mg/kg bw/d in a 90-day study. Therefore, a NOAEL could not be established and a LOAEL of 2 mg TBPP/kg bw/d in males and 2.5 mg TBPP/kg bw/day in females was identified from a 2-year dietary study for histopathological changes to the kidney. In a 90 d dietary study, effects on the kidney have been observed in studies from the lowest dose tested i.e. 25 mg/kg/d. However the effects seen in this study are irritant in nature, (hypertrophy and dysplasia of cell nuclei). These irritant and hypertrophic effects are considered adaptive responses. Although the biological significance of an alteration in the size and/or shape of nuclei are unknown, this and the other effects seen are not considered to be severe morphological changes that are clear evidence of marked organ dysfunction.

Classification:

TBPP does not meet the Approved Criteria (NOHSC, 2004) for danger of serious damage to health by prolonged exposure (R48).

10.2.5 Genotoxicity

Only in vitro studies and animal data are available. In vitro, TBPP was clearly positive in the Ames test with (+S9) and without (-S9) metabolic activation. Positive results have also been reported for gene mutation (+S9), chromosome aberration (+S9), sister chromatid exchange (+/-S9), unscheduled DNA synthesis and DNA damage, in mammalian cells. In vivo, a positive result was seen in a bone marrow micronucleus assay in mice and hamsters following single ip administration, though a negative result was seen in mice following repeated administration. Chromosomal aberrations and SCE were also seen in the bone marrow of mice following intravenous administration of TBPP. In rats, DNA damage was detected by alkaline elution in several tissues following ip administration with the greatest damage detected in the kidney. Of the tissues investigated, the least damage was seen in the testes, spleen and large intestine (no further data available). Therefore, the data clearly indicate that TBPP is clastogenic in somatic cells. In addition, mutagenic activity has been detected in the kidney in non-regulatory transgenic rodent mutation assays.

No in vivo studies are available with TBPP in germ cells. Although DNA damage was reported in the testes this data is from a secondary source. Additionally, the extent of the damage was not quantitated but reported to be least in the testes, spleen and intestine following analysis of a number of tissues. Consequently, this single piece of information from a briefly reported study is not considered to be sufficient to justify TBPP being regarded as causing heritable genetic damage.

Classification:

TBPP meets the Approved Criteria (NOHSC, 2004) for classification as a Category 3 mutagen – possible risk of irreversible effects (R68).

10.2.6 Carcinogenicity

Only animal data are available. A 2-year dietary study was conducted in F344 rats and B6C3F1 mice. Rats received 0, 2 - 2.5 or 4 - 5 mg TBPP/kg bw/day and mice received 0, 60 – 65 or 120 – 130 mg TBPP/kg bw/day. The study focus was primarily effects on the kidney. It is stated that 65 to 80% of the treated mice or rats survived until the end of the study (no further details available). While no effect on body weight gain was seen in treated rats, body weight gain was reported to be 20% less than controls throughout the experiment in mice. The totals for tubular cell adenomas and carcinomas of the kidney combined in rats at 0, 2 – 2.5 and 4 – 5 mg/kg were 0/53, 30/54, 30/54 and 0/52, 4/54, 13/54 in males and females respectively. Corresponding totals in male and female mice were 0/54, 7/50, 17/49 and 0/55, 3/50, 3/46 respectively. Compared to controls, incidences were statistically significant in all TBPP treated male rats, female rats at the top dose and male mice at the top dose. Thus, the results in both species provide evidence that TBPP is carcinogenic.

Additional information on tumour incidence in other organs is available for mice in the above study. Compared to controls, a statistically significant increase was seen in alveolar/bronchial adenomas and carcinomas combined in males at 60 mg/kg bw/day and above (12/54, 18/44, 25/50) and in females at 130 mg/kg bw/day (4/55, 9/50, 17/50), and in hepatocellular adenomas and carcinomas combined in females at 65 mg/kg bw/day and above (11/54, 23/50, 35/49). In the fore-stomach, a statistically significant increase in tumours was seen in males at 60 mg/kg bw/day and above (0/51, 10/47, 13/48) and in females at 65 mg/kg bw/day and above (2/53, 14/48, 22/44). Fore-stomach tumour incidences reported at the low dose were for squamous cell papillomas, and squamous cell papillomas and carcinomas combined at the top dose.

A 16-month dermal study was conducted in female Swiss mice. Animals received 0, 400 or 1200 mg TBPP/kg bw/day. No data was reported on survival rates or body weight gain. TBPP was clearly carcinogenic in this study, with tumours observed at distal sites in addition to the site of application. Compared to controls, a statistically significant increase was seen in TBPP-treated animals for papillomas and carcinomas of the skin (0/29, 2/29, 5/30 at 0, 10 and 30 mg/kg bw/day respectively), squamous cell carcinomas of the tongue and in the gingival area (0/29, 2/29, 4/30), papillomas and carcinomas of the fore-stomach (1/29, 10/29, 20/30) and unspecified tumours of the lung (7/29, 26/29, 28/30). Supportive data are available from a series of initiation/promotion studies that showed TBPP had both initiating and promoting activity.

Although TBPP was clearly carcinogenic in the rat and mouse following ingestion, it is unclear whether the test material significantly reduced the rodent life span compared to controls. Additionally in the mouse, a greater than 10% reduction in body weight gain was reported, though it is not reported at which dose level. Similarly, TBPP was also carcinogenic in mice in the only dermal carcinogenicity study available, although information on survival rate and body weight gain was lacking. However, the dermal results are supported by initiation/promotion studies in which TBPP was seen to have both initiating and promoting activity. Consequently, although the absence of clear information on survival rate and body weight retardation questions the significance of the observed tumours, they were still observed in two animal species and at several sites (kidney, lung, liver), and TBPP is genotoxic in somatic cells both in vitro and in vivo. Thus, overall, it is proposed that the data is sufficient for TBPP to be regarded as if it were carcinogenic to man.

Classification:

TBPP meets the Approved Criteria (NOHSC, 2004) for classification as a Category 2 carcinogen - may cause cancer (R45).

10.2.7 Reproductive effects

Fertility

Only animal data are available. Although no fertility studies have been conducted with TBPP, data are available from repeat dose toxicity studies that examined the reproductive organs.

In a dermal study in rabbits, topical application of the only dose tested, 2270 mg TBPP/kg bw/d weekly for 13 weeks, resulted in reduction in relative testes weight, moderate to severe testicular atrophy and degenerative changes in the testes with effects seen on spermatogenesis. No effects were seen in the ovaries of female rabbits. Effects on the testes were seen in the presence of increased relative liver weights in the absence of histopathological changes, and chronic interstitial nephritis in the kidney.

Data are available from ip studies. In a study in which rats were administered TBPP 3 times a week for a minimum of 72 d, a statistically significant decrease in relative prostate (15%) and seminal vesicle weight (22%) were seen at 71.0 mg TBPP/kg bw in the absence of other toxic effects. In addition to these treatment-related effects, a statistically significant increase in relative epididymis weight (19%) and decrease in sperm storage in the epididymis was seen at 142.0 mg TBPP/kg bw in the presence of a statistically significant decrease in body weight gain (9%). Effects on relative testes weight along with histopathological changes and a decrease in sperm production and sperm mobility were seen at dose levels that produced decreases in body weight gain of 15 or 25%. Additionally, administration of TBPP to mice for 5 d resulted in a significant increase in the frequency of abnormal sperm heads, predominantly at 800 mg TBPP/kg bw, on day 35. No information was provided on general toxicity for this study.

Although effects on the testes were seen in these studies that are not considered a secondary non-specific consequence of general systemic toxicity, effects have only been demonstrated in a rabbit dermal study at a very high dose level, while ip injection is an inappropriate route with respect to relevant routes of human exposure. Consequently, no definite conclusion can be drawn from the study regarding the adverse reproductive potential of TBPP. Therefore, based on the available data, TBPP cannot be considered a substance that causes concern for human fertility.

Classification:

TBPP does not meet the Approved Criteria (NOHSC, 2004) for classification of substances that cause concern for human fertility (R62).

Developmental

Only animal data are available. In a well reported rat study, no developmental toxicity was seen in dams receiving up to 125 mg TBPP/kg bw on days 6 – 15 of gestation. This dose level produced marked maternal toxicity: a 12% decrease in body weight gain compared to controls. In a briefly reported rat study, administration of 200 mg/kg bw on days 7 - 15 of gestation resulted in a significant increase in unspecified skeletal variations in fetuses, in the presence of severe maternal toxicity (*i.e.* death). Consequently, the observed skeletal changes in this study are a secondary non-specific consequence of severe maternal toxicity.

Classification

TBPP does not meet the Approved Criteria (NOHSC, 2004) for classification for developmental effects (R63).

11. Effects on Other Organisms in the Laboratory and Field

11.1 Avian toxicity

No data are available.

11.2 Aquatic toxicity

Toxicity data have been obtained where available from the literature. In addition, to build a weight of evidence, the structure of TBPP was modeled through the US EPA ECOSAR v0.99g model. Toxicity predictions have mainly been based on structure activity relationships (SARs) derived from known toxicity of various esters (Ester class). For fish, a SAR has also been developed for phosphate esters (Esters, phosphate class).

The phosphate esters SAR available for fish may be used to estimate the toxicity of phosphate esters with logKow values of less than 5.0 and molecular weights less than 1000. This SAR may be used to estimate toxicity for the following classes of phosphate esters all of which are weak acetylcholinesterase inhibitors:

- Tri-alkyl phosphate esters
- Tri-phenyl phosphate esters
- Halogenated tri-alkyl phosphate esters
- Halogenated tri-phenyl phosphate esters.

By contrast, SARs are available for the broader ester class for all three trophic levels. These SARs may be used to estimate the toxicity of esters with molecular weights less than 1000 and variable LogKow constraints depending on the trophic class for which toxicity is being predicted. Toxicity for the following esters can be predicted:

- Acetates
- Benzoates
- Dicarboxylic aliphatics
- Phthalates derived from aliphatic alcohols and phenol.

11.2.1 Fish

Goldfish *(Carassius auratus)* were exposed to 1 mg TBPP (dissolved in acetone) per litre water. All died within 5 days. The fish appeared to swim in a disoriented manner prior to death. The fish showed necrosis of the kidneys (*Gutenmann & Lisk, 1975). This paper has been reviewed. Being a limit test (only one concentration was tested), no dose-response can be determined. The paper states that six goldfish, around 7.6 cm long, were placed in each of several glass fish tanks containing 20 L of well water through which filtered air was continuously

bubbled. It is not known whether this means fish were placed individually in tanks, or there were several replicates. However, the data presented graphically in the paper suggests there was only one replicate. Fresh water was used to replace that in the tanks when they became cloudy (3-4 days) from the accumulation of metabolic products. A solvent control was included and no goldfish died over the full 30 day test period in this treatment.

TBPP (1 mmol/L) inhibited by 19% the acetylcholinesterase (AChE) activity in the electric organ of the electric ray *(Torpedo ocellata)*. The binding of acetylcholine to its electric organ receptor was not inhibited (*Eldefrawi et al. 1977).

Three results are available from the US EPA ECOTOX database (cited in Sitthichaikasem 1978). This reference has been reviewed and consists of an abstract rather than a full literature report. Consequently, details are lacking. However, all tests were conducted as 96 h acute exposures under static conditions. The fish tested were bluegill sunfish (*Lepomis macrochirus)*, and two tests with rainbow trout (*Salmo gairdneri*), one on sac fry and the other on fingerlings. The fish were exposed to a fire retardant plasticizer formulation (Pydraul 50E), and its components separately, of which TBPP was one.

The results provided were a 96 h LC50 = 1.33 mg/L for bluegill sunfish, and 0.24 mg/L and 1.45 mg/L for rainbow trout sac fry and fingerlings respectively. The range of concentrations tested, and sub-lethal effects observed, are not reported in the abstract. It is not clear whether the results obtained were following exposure to the plasticizer formulation, or to one (TBPP) or other components

The following study using the analogue tris(1,3-dichloropropyl-2) phosphate (common name, Fyrol FR-2) was provided by Akzo Nobel (2001) as part of the US HPV Challenge for review by the US EPA. The study conducted in 1990 according to OECD Guidelines 203, was GLP compliant, and was reported as a robust summary.

Rainbow trout *(Salmo gairdneri)* were exposed to Fyrol FR-2 at different concentrations, for 96 h under static conditions. Initially two range-finding tests were conducted to determine the appropriate doses (water concentrations) for the definitive study. In these preliminary tests, the highest concentration at which no mortality occurred and the lowest dose that caused 100% mortality were 0.1 and 10 mg/L, respectively. In the definitive test, groups consisting of ten trout were exposed to Fyrol FR-2 at nominal concentrations of 0 (negative control), 0.63, 1.25, 2.5, 5 and 10 mg/L for 96 h. Observations were made for signs of toxicity after 2, 4, 24, 48, 72 and 96 h of exposure. Measurements of water parameters were as follows: temperature range, 11.8 to 14.8^{o}C; pH from 7.14 to 7.78; dissolved oxygen concentration ranged from 92 to 100% air saturation value (ASV); water hardness, 218 to 228 mg/L as $CaC0_3$. Other test conditions included a photoperiod of 16 h light, 8 h dark; an unsealed all-glass 15 litre aquaria; aeration was via compressed air.

The median lethal concentration (LC50) was determined using the computer program of Stephan, incorporating the number of fish exposed and the mortality observed at each concentration.

Mortality was dose-related, with a clear dose-response observed. All mortalities occurred within the first 24 hours. One fish died in the lowest dose group (0.63 mg/L) at 24 h. Mortality of 100% occurred in the 5 mg/L and 10 mg/L groups. The median lethal concentration (LC50) of Fyrol FR-2 in rainbow trout was determined to be 1.4 mg/L, with 95% confidence limits of 0.9 and 1.9 mg/L respectively. Since one fish died in the lowest dose group, an NOEC could not be identified, and is therefore determined to be less than 0.63 mg/L.

QSAR Data

As noted at the start of this sub-section, the structure for tris (2,3-dibromopropyl) phosphate has been run through the ECOSAR v0.99g model and toxicity predicted based on the ECOSAR classes of Esters and Esters (phosphate). The results are summarized in Table 11.1**.**

Table 11.1: Predicted toxicities based on the ECOSAR classes of esters and esters (phosphate)

ECOSAR Class	Organism	Duration	Endpoint	Predicted mg/L)
Neutral Organic SAR (Baseline toxicity)	Fish	14 d	LC50	9.485*
Esters	Fish	96 h	LC50	6.287
Esters (phosphate)	Fish	96 h	LC50	3.571
Esters	Fish		ChV (MATC)	0.516

* Chemical may not be soluble enough to measure this predicted effect.

The result for the Esters (phosphate) class is in good agreement with the measured fish toxicity results described above for TBPP except the sensitive rainbow trout result of 0.24 mg/L.

The SMILES string (O=P(OC(CCl)CCl)(OC(CCl)CCl)OC(CCl)CCl) of the analogue, tris(2,3-dichloro-2) phosphate was also modelled using ECOSAR to provide further indication of how close these modelled results may be to measured data. The fish 96 h EC50 for the Esters (phosphate) ECOSAR class was predicted to be 4.731 mg/L which is in good agreement with the measured value of 1.4 mg/L provided above. This compared to a result of 96 h LC50 = 8.543 mg/L when the Esters ECOSAR class was used.

The modelled results for both TBPP and the analogue indicate that the phosphate class is slightly more toxic than the straight Esters class in ECOSAR, by a factor of around 1.8 for TBPP and 1.8 for the analogue. The closeness of the results with the measured analogue data indicates that the ECOSAR model and the analogue data should give a good approximation for ecotoxicity of TBPP using the Esters (phosphate) class.

11.2.2 Aquatic invertebrates

No data are available for TBPP. The following study using the analogue tris(1,3-dichloropropyl-2) phosphate (common name, Fyrol FR-2) was provided by Akzo Nobel (2001) as part of the US HPV Challenge for review by the US EPA. The study conducted in 1999 according to OECD Guidelines 202, EPA Series 8.50 OPPTS Number 850.1010 was GLP compliant, and was reported as a robust

summary. The test type was a 48-Hour Flow-Through Acute Toxicity Test with Cladoceran (*Daphnia magna*). The strain was not applicable.

Two replicate test chambers, (300 mL glass beakers) each containing 10 daphnids, were utilized for each group. Daphnids were exposed in seven groups, which consisted of a negative control, solvent control (0.1 ml dimethylformamide), and Fyrol FR-2 at concentrations of 0.98, 1.6, 2.8, 3.8, and 5.1 mg/L (measured levels). The test substance was added to the chamber 22 h before the daphnids to achieve equilibrium. Water temperature was maintained at 20°C, dissolved oxygen was ≥3.5 mg/L (94% of saturation), hardness was maintained at about 126 mg/L as $CaCO_3$, pH at 8.3 and total organic carbon ranged from less than 1 at study start to 2.6 mg C/L at the end of day 2. Photoperiod was 16 hours of light and 8 hours of darkness. Observations were made at 1, 24 and 48 h for mortality/immobility and clinical signs. Samples were taken from test chambers at the start and end of the test to quantify the concentration of the test substance, using GC with electron capture detection.

The EC50 value was calculated using the EPA program developed by C.E. Stephan. The program calculates the EC50 and the 95% confidence interval by probit analysis, the moving average method, and binomial probability with nonlinear interpolation.

Environmental conditions, including dissolved oxygen, pH, and temperature were within guideline and protocol specifications. Daphnids in the negative and solvent control groups appeared healthy and normal throughout the test. Daphnids in the 0.98 and 1.6 mg/L groups also appeared normal with no mortality or signs of toxicity. After 48 hours of exposure, mortality/immobility in the 2.8, 3.8 and 5.1 mg/L groups was 0, 70, and 80% respectively. Although no mortality occurred at 2.8 mg/L, 15% of the daphnids appeared lethargic at test termination.

The 48 hour EC50 for *Daphnia magna* was 3.8 mg Fyrol FR-2/L, with 95% confidence limits of 3.5 and 4.2 mg/L. The NOEL was 1.6 mg/L.

QSAR Data

The structure for TBPP has been run through the ECOSAR v0.99g model and toxicity predicted based on the ECOSAR class of Esters. The results are summarised in Table 11.2.

Table 11.2: Predicted toxicities based on the ECOSAR classes of esters

ECOSAR Class	Organism	Duration	Endpoint	Predicted mg/L)
Esters	Daphnid	48 h	LC50	4.568

This predicted result is in good agreement with the measured analogue result above. A 48 h LC50 of 10.787 mg/L was predicted using ECOSAR for the analogue that is around 2.8 times less sensitive than the measured value. However, as demonstrated above with the fish QSAR data, the Esters class was slightly less sensitive than the Esters (phosphate) class (not available for invertebrate predictions). Therefore, it is possible that TBPP is slightly more toxic to daphnids than predicted by ECOSAR.

11.2.3 Algae/aquatic plants

Geyer et al, 1985 (cited in the US EPA ECOTOX database) measured the impact of TBPP and 14 other organic chemicals on growth of the green algae, *Scenedesmus abundans* in a 96 hour static test conducted according to the 1983 draft OECD "Guidelines for Testing of Chemicals – Alga Growth Inhibition Test". Prior to use the nutrient medium and washed glassware were sterilized by autoclaving. Experiments and stock cultures were incubated at 22±2°C at constant conditions. For TBPP, acetone was used as a solvent carrier. The doses tested were not reported. However, the dilution series was reported as starting with an 80 mL saturated solution and diluting using a constant dilution ratio of 40 mL preliminary solution plus 40 mL double-distilled water. Five mL of medium and 5 mL of algae suspension were added to each flask of the dilution series. While the number of dilutions in the series was not specified, the solubility of TBPP reported in the paper was 6.3 mg/L. Therefore, the EC50 value would have been calculated based on a nominal dose series of 6.3, 3.43, 1.71, 0.86 mg/L etc. Four controls were used. After 0, 72 and 96 hours, the cell growth of a 10 mm layer of cell suspensions from each test culture and control was measured. Raw data were not provided. The EC50 was determined to be 3.1 mg/L, assumed to be a nominal concentration.

The following study using the analogue tris(1,3-dichloropropyl-2) phosphate (common name, Fyrol FR-2) was provided by Akzo Nobel (2001) as part of the US HPV Challenge, for review by the US EPA. The study conducted in 1992 according to OECD Guidelines 201, was GLP compliant, and was reported as a robust summary.

The Alga Growth Inhibition Test (toxicity to the freshwater alga) was conducted using the species *Selenastrum capricornutum* which was exposed to Fyrol FR-2 for 96 hours in the test chamber.

A dose range-finding test was initially conducted to identify the appropriate concentrations of Fyrol FR-2 for use in the definitive test. The range-finding doses were 0.1, 1, 10 and 100 mg/L. Since growth inhibition was observed in the 10 and 100 mg/L cultures, the definitive test used nominal concentrations of 2, 6, 18, 54 and 162 mg/L. Algal growth was determined by measuring the extinction at 436 nm using a spectrophotometer. The direct relationship between extinction values and cell density has been established. Cell density was also determined microscopically using a counting chamber. The extinction value for each vessel was determined at 0, 24, 48, 72 and 96 h. The algae were maintained under constant light at 21°C. The flasks were constantly shaken at 100 rpm to prevent sedimentation of the algae. The pH ranged from 6.7 at time zero to a high of 7.9 at 96 hours.

The EC20, EC50, and EC80 values were determined using least square method (best fit through the points) obtained from the probit of the percent inhibition and the log of the concentration of Fyrol FR-2. Confidence limits were calculated using Fieller's theorem.

The EC50 value, determined from the area under the curve, and the EC50 value, determined from the specific growth rate, was 12 mg/L (95% confidence limits of 10-l 5 mg/L) and 39 mg/L (95% confidence limits of 3.l-50 mg/L), respectively. The NOEL for Fyrol FR-2 was 6 mg/L.

QSAR Data

The structure for tris(2,3-dibromopropyl) phosphate was run through the ECOSAR v0.99g model and toxicity predicted based on the ECOSAR class of Esters. The results are summarised in Table 11.3.

Table 11.3: Predicted toxicities based on the ECOSAR classes of esters

ECOSAR Class	Organism	Duration	Endpoint	Predicted mg/L)
Esters	Green Algae	96 hour	EC50	0.545
Esters	Green Algae	not provided	ChV (MATC)	0.442

This predicted result is an order of magnitude more sensitive than the measured analogue result above. A 96 h EC50 of 0.723 mg/L was predicted using ECOSAR for the analogue that is around 16 times more sensitive than the measured value.

The modelled results for both TBPP and the analogue are in good agreement. However, because the measured result for the analogue is over an order of magnitude different to the predicted result, there is some concern in relying on the predicted result for TBPP as an indication of its toxicity to algae. There was no Esters (phosphate) class available for algae in ECOSAR, and the Esters class appears to overestimate toxicity for algae based on the analogue test data.

11.2.4 Sediment

No data are available for either TBPP or the analogue chemical.

11.2.5 Micro-organisms

Nitrifying return activated sludge diluted with fresh settled sewage, filtered, aerated and containing Nitromonas and Nitrobacter was used to test nitrification. No inhibition was found with 300 mg TBPP/L and no depression of the BOD was noticed at 170 mg/L (Wood et al., 1981, cited in IPCS, 1995).

The following study using the analogue tris(1,3-dichloropropyl-2) phosphate (common name, Fyrol FR-2) was provided by Akzo Nobel (2001) as part of the US HPV Challenge, for review by the US EPA. This biodegradation study conducted in 1990 according to OECD Guideline 209 Activated Sludge – Respiration Inhibition Test, was Good Laboratory Practice (GLP) compliant, and was reported as a robust summary that accompanied the Akzo Nobel submission. The study was conducted on activated sludge from a sewage treatment facility.

Samples of activated sludge fed with synthetic sludge were exposed to Fyrol FR-2 for 3 hours. Their rates of oxygen consumption were measured using an oxygen electrode and compared with control levels. Two tests were conducted. The first utilized nominal Fyrol FR-2 levels of 1, 10 and 100 mg/L and the second test used 1 and 10 g/L. The positive control respiration inhibitor, 3,5-dichlorophenol, was used in each test at 3.2, 10 and 32 mg/L.

The usual statistical methods were not applicable. Calculations of the respiration rate and inhibition of respiration were done by formulae provided in Guideline 209. The EC50 and the 95% confidence limits were calculated using the computer program of Stephan.

The non-treated sludge maintained normal respiration through the test whereas the 3,5-dichlorophenol inhibited sludge showed EC50s of 7.2 and 7.1 mg/L in the two tests. The respiration rates of the activated sludge in the presence of Fyrol FR-2 were not significantly different than that of the non-treated controls. Fyrol FR-2 did not inhibit the respiration of activated sludge and, thus, an EC50 could not be determined. However it is likely to be greater than 100 mg/L, the highest concentration used in this test.

Therefore, the data indicates that Fyrol FR-2 does not inhibit active sludge respiration.

11.3 Terrestrial toxicity

11.3.1 Micro-organisms

No data are available for TBPP or the analogue chemical.

11.3.2 Plants

Oat seed *(Avena sativa)* was added to loamy sand soil (1.5% organic carbon) and exposed to 1, 10, 100 or 1000 mg TBPP/kg soil for 14 days. The temperature of the soil was 20°C, the pH 6.0 and a 16 h light/8 h dark cycle was used. The study was performed according to a modified OECD terrestrial plant-growth test. The EC_{50} for growth inhibition was at 1000 mg/kg soil (*Pestemer, 1988). In a comparable study, turnip seed *(Brassica rapa sp.)* was tested under the same conditions as the oat seed. With 1000 mg TBPP/kg soil, 100% inhibition of growth was obtained (*Pestemer, 1988)

No analogue data are available.

11.3.3 Earthworms

No data are available for TBPP or the analogue chemical.

11.3.4 Other

A 57% inhibition of southern armyworm *(Spodoptera eridania)* microsomal *p*-chloro- *N*-methylanaline *N*-demethylase was measured at 1 mg TBPP/mL, in an in vitro incubation mixture (*Eldefrawi et al., 1977),.

12. Risk Characterisation and Management

TBPP is not currently used in Australia, therefore, information on control measures in workplaces were not provided for review.

For risk characterization, information on the environmental and health effects of TBPP are integrated with environmental, public and occupational exposure estimates to characterise the potential risks of adverse effects, the chemical may cause to the environment and the Australian public.

12.1 Environmental risk

TBPP is not currently used in Australia. However, from data provided, and the package size (1000 mg ampoule), TBPP is likely to be used as an analytical standard for R & D purposes only. Therefore, no data on the concentrations in environmental media were available to conduct a risk characterization. However, from the data assessed, TBPP is not readily biodegradable and will not bioaccumulate to a significant extent, though it does have the potential to be more persistent in water bodies where water movement is limited, and the water is deeper.

12.2 Occupational risk

TBPP is not presently manufactured nor imported into Australia. Consequently, no occupational exposure data is available. However, the potential exists for importation, as a single company offers the chemical for import into Australia, packaged as an ampoule of 1000 mg (purity 96.9 %). According to the company TBPP is likely to be used as an analytical standard for R & D purposes.

Animal data indicate that TBPP is absorbed orally and through the skin. TBPP is a genotoxic carcinogen with no threshold identified for the genotoxic activity. There is potential for exposure during use of the chemical as an analytical standard, though TBPP may be used in small amounts and for short periods. The risk of adverse effects is low if exposure is kept to a minimum by the use of appropriate control measures.

12.3 Public risk

The risk to the public would mainly occur through consumer use of TBPP-treated clothing.

TBPP is not currently used in textiles or clothing produced in Australia. Current import data indicate that a high percentage of clothing/textiles are imported into Australia from countries that do not appear to have banned or restricted the use of TBPP treatment of clothing. Therefore, there is the potential for TBPP-treated textiles/clothing, particularly children's clothing, to be imported into Australia from such countries. Information from the US indicates that prior to its ban, TBPP was added to fabrics used for children's clothing at approximately 5 – 10 % by

weight. TBPP in synthetic textiles/garments can exist both tightly bound within the fibre, and more loosely bound on the surface of the fibre. Exposure to TBPP via clothing occurs through the dermal route and in children also through the oral route due to 'sucking' or 'mouthing'.

Dermal absorption occurs when TBPP is more loosely bound on the surface of the fibre. Dermal exposure can occur from new and repeatedly washed TBPP-treated sleepwear. The most reliable data available estimated that the upper limit for absorption could be as high as 0.18 and 9 μg TBPP/kg bw/day after wearing repeatedly washed that may have been treated with TBPP and new TBPP-treated sleepwear respectively.

TBPP can also be removed from the garment by the 'sucking' or 'mouthing' by infants. It has been reported in secondary data sources that up to 3% of surface TBPP can be extracted from treated fabric by saliva. Oral exposure is reported to be 1 % of that obtained through dermal exposure. No information was provided on whether TBPP was bound within the fibre or loosely bound on the surface. The primary source of this information could not be accessed and, hence, their reliability cannot be determined. However, the data suggests that, compared to dermal exposure, 'sucking' and 'mouthing' of TBPP-treated garments represents a minor route of exposure.

The hazard assessment of TBPP indicates that it has low acute toxicity. TBPP is a genotoxic carcinogen, with the critical effect being kidney tumours in rodents. The findings in animals are deemed relevant to humans, as no mechanistic data to indicate the contrary are available. Animal data do not indicate a threshold for development of kidney tumours and a 'margin of exposure' approach (i.e. the establishment of a ratio between the experimental NOAEL and the estimate of exposure) is not considered a suitable methodology.

The US CPSC conducted a risk assessment based on the exposures estimated from commissioned reviews (Section 7), and the NCI study's findings in animals. Statistical extrapolations of the NCI study data were based on two mathematical models: the single-hit model (linear no threshold) and the log-probit model (Mantel-Bryan). The use of these mathematical models and the extrapolations from animal to man were based on the following assumptions, that;

- the animal dose can be converted to an 'equivalent' human exposure level;
- mice, rats and humans have equal sensitivities to TBPP;
- infants and children are no more, or less, sensitive to TBPP than are adults; and
- the dose given to an animal during its entire life can be converted to an equivalent daily dose during a specific period of time which is less than a lifetime.

Based on the US CPSC exposure estimates and modelled data from the NCI study, the lifetime risk of cancer ranged from 60 – 6,000 cases per million male population. For females, the projected rate was about 1/5 that of males. In children, for 1 year of exposure the cancer incidence rate was estimated as 17000 cases per million population. An exposure throughout childhood would give a higher risk. The use of TBPP in sleepwear therefore constitutes an unacceptable risk (greater than 1 in a million) to the public.

13. Discussion and Conclusions

TBPP is not manufactured or presently imported into Australia. However, one chemical company offers the chemical for import into Australia from the U.S.A, packaged as a 1000 mg ampoule. The potential importer states that it is likely that TBPP will be used as an analytical standard in R & D.

There is no available information on current or former uses of TBPP in Australia. Overseas, in the past, TBPP was an important flame retardant for cellulose and triacetate and polyester fabrics, especially in children's sleepwear, but has since been banned for these applications in several European countries, the USA (1977) and Japan (1978). However, the potential exists for the import of ready-made garments/textiles treated with TBPP from countries that have not banned/restricted the use of TBPP in clothing.

A summary of the health and environmental hazards, and the potential risk to the public are discussed in the following sections.

13.1 Health hazards

TBPP is readily absorbed by the gastrointestinal tract in rats and at a moderate rate via the skin in rats and rabbits. Rapid distribution of the parent compound and metabolite(s) occurs following absorption. TBPP is also rapidly metabolized, and **t**here is evidence that TBPP derived metabolites covalently bind to proteins and DNA in vivo. The main route of excretion in rats and rabbits is via the urine, and very little of the parent compound is excreted. Additionally, there is evidence of enterohepatic circulation of mainly TBPP-derived metabolites occurring.

TBPP has low acute oral and dermal toxicity in animal studies. It is not an eye or skin irritant in rabbits. Limited evidence in humans indicates a very weak skin sensitization potential. There is no indication of a skin sensitization potential in the available animal studies. No data on respiratory sensitization are available.

Systemic toxicity was observed following repeated exposure to TBPP in animal oral and dermal studies. No human data were available. Animal data indicate that the kidney is the target organ following ingestion of TBPP. Similarly, effects on the kidney were seen in dermal studies.

TBPP is mutagenic, with positive results being clearly seen in vitro, and in somatic cells in animal *in vivo* studies. In oral carcinogenicity studies, the primary focus was the kidney, and TBPP was seen to clearly produce benign and malignant tumours in this organ in both rats and mice. TBPP was also carcinogenic following dermal application to mice, with benign and malignant tumours seen at distal sites in addition to the site of application. No human data or animal fertility studies are available for TBPP, and although data are available from repeat dose studies that examined the reproductive organs, no definitive conclusions can be drawn from the data regarding the adverse reproductive potential of TBPP. TBPP is not considered to be a developmental toxicant from the available animal studies.

13.2 Environmental hazard and risk

Evidence indicates that TBPP is not readily biodegradable. There is also evidence that the chemical has a LogKow >4 http://logkow.cisti.nrc.ca/logkow/index.jsp (LogKow 3.02, IPCS, 1995). While no chronic toxicity data are available, modelled results for fish and aquatic invertebrates were shown to be a reasonable approximation to measured data for acute effects, and the QSAR chronic values for both these trophic levels were <1 mg/L. Therefore, this indicates that some chronic effects could be observed in aquatic systems. While an experimentally derived BCF is available and is <500, a second experimental result shows a BCF >500, although it is not known whether this relates to the whole organism or not as the full study is not obtainable. Weight of evidence for bioaccumulation suggests the chemical will not bioaccumulate to a significant extent, as depuration also appears to be rapid initially.

It may be argued that, even though the chemical is not readily biodegradable, its possible limited bioaccumulation potential means that a chronic categorisation is not necessary. However, the conflicting bioaccumulation results are of concern, and a BCF study following current guidelines should be undertaken.

Acute toxicity data suggest that all trophic levels will result in LC/EC50 values between 1 and 10 mg/L (Acute II toxicity).

13.3 Occupational risk

No occupational use of TBPP has presently been identified in Australia. However, TBPP is available for importation into Australia in ampoules and is likely to be used for research and analysis. Animal data indicate that TBPP is absorbed orally and through the skin. TBPP is a genotoxic carcinogen with no threshold identified for the genotoxic activity.

There is potential for exposure during use of the chemical as an analytical standard, though TBPP may be used in small amounts and for short periods. The risk of adverse effects is low if exposure is kept to a minimum by the use of appropriate control measures.

13.4 Public hazard and risk

TBPP is not currently manufactured or imported into Australia. No information is available as to whether TBPP-treated clothing and/or textiles were ever available to the Australian public.

A review of data on textiles and clothing imported into Australia indicates that import of clothing and textiles from countries that do not have a restriction or ban on the use of TBPP to treat textiles or clothing have increased from 32.6% in 2000/01 to 39.03% in 2003/04 (textiles), and from 75.8% in 2000/01 to 79.4% in 2003/04 (clothing). There is currently no information on the regulatory status of TBPP in these countries, and it is possible that clothing treated with TBPP may be imported into Australia.

TBPP in synthetic textiles/garments can exist both tightly bound within the fibre, and more loosely bound on the surface of the fibre. For children's clothing, exposure can be dermal and oral.

Dermal absorption occurs when TBPP is more loosely bound on the surface of the fibre. Dermal exposure can occur from both new and repeatedly washed TBPP treated sleepwear. The most reliable data available estimated that the upper limit for absorption was 0.18 and 9 μg TBPP/kg bw/day after wearing repeatedly washed sleepwear that may have been treated with TBPP and new TBPP-treated sleepwear respectively. While estimates of oral exposure are reported, the primary data sources could not be obtained, and their reliability could not be ascertained. However, the data suggests that oral exposure (i.e. 'sucking' and 'mouthing' of TBPP-treated sleepwear) represents a minor route of exposure in comparison with dermal.

The risk of acute health effects following exposure to clothes treated with TBPP is low. However, TBPP is a genotoxic carcinogen in rodents, and this finding is deemed relevant to humans as no mechanistic data to indicate the contrary are available.

Based on the US CPSC exposure estimates and modelled data from the NCI Study, estimates of lifetime risk of cancer ranged from 60 – 6,000 cases per million male population, and in children, 17,000 cases per million. Based on these estimates, the use of TBPP in textiles or clothing constitutes an unacceptable risk to the public.

14. Recommendations

Preamble to Recommendations

- The toxicity profile of the chemical indicates it is a genotoxic carcinogen, with the target organ for toxicity being the kidney. Findings in animals are deemed relevant to humans, as no mechanistic data to indicate the contrary are available.

- TBPP is not manufactured or imported into Australia except in very small quantities presumably as a reference standard or for research & development (R & D) (1000 mg ampoule). No use beyond R & D were notified to NICNAS.

- The use profile of the chemical in the past was as a flame retardant in children's sleepwear, but this use is now banned in the US, EU, and Japan. Several other countries including Finland, New Zealand and Sweden have also banned or severely restricted the use of TBPP in textiles and clothing. However, there are a number of other countries that have not banned or restricted the use of TBPP in clothing or textiles and data exists that imports from these countries of various goods that may be treated with TBPP have increased over the past 5 years.

- Exposure to TBPP from clothing occurs through the dermal route. In children, in addition to dermal absorption, exposure can also occur orally because of 'mouthing' and 'sucking' of treated clothes. Exposure to children wearing TBPP-treated clothing therefore remains of particular concern.

- As TBPP is not manufactured in, or imported into Australia, it can be assumed that Australian textiles treated with fire retardants do not contain TBPP. Similarly, clothing and textiles imported from the US, Japan and Europe will not be treated with TBPP. However, clothing and textiles are imported into Australia from countries that have not restricted the use of TBPP. Therefore, there is the potential for exposure and risk of adverse effects arising from these imports.

- The Department of Treasury had a regulation from 1977 to 1996 under the Trade Practices Act (TPA), 1974, prohibiting the use of the flame retardant TBPP in clothing and textiles used to make clothing. In 1997, the regulatory controls on TBPP-treated fabrics were repealed. At the same time, the prohibition on the import of TBPP-treated fabrics in the Customs (Prohibited Imports) Regulations was similarly repealed. The rationale for the repeal was that TBPP had not been manufactured internationally for a considerable period of time and the use of TBPP as a fire retardant had been overtaken by more suitable retardants that could be manufactured more cheaply. It was therefore considered that production of TBPP would not recommence once the prohibition was lifted. The previous prohibition under the TPA related to the supply of certain fabrics containing TBPP. The TPA had never controlled the use of TBPP, nor did the Customs (Prohibited Imports) Regulations.

- While outside the jurisdiction of the Act, importation of articles such as textiles or ready-to-wear clothing, especially children's clothing, treated with TBPP, is of concern. Use of these articles therefore constitutes an unacceptable risk (greater than 1 in a million) to the public and supports the elimination of the use of TBPP in textiles and clothing.

Recommendation 1. AICS annotation

Noting the toxicity profile of TBPP, the use of TBPP beyond research and development purposes is not supported by NICNAS. NICNAS will annotate the Australian Inventory of Chemical Substances (AICS) accordingly. Any other use will be deemed a new use under Section 21 of the ICNA Act, 1989, and will require full notification to NICNAS prior to import or manufacture of TBPP.

Recommendations to regulatory bodies

NOHSC

Due to the potential for TBPP to be used for research and development purposes the following recommendations are made to NOHSC.

Recommendation 2

TBPP is not currently listed in the NOHSC *List of Designated Hazardous Substances* contained in the Hazardous Substances Information System (HSIS), (NOHSC, 2005).

In accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), TBPP is determined to be hazardous with the following risk phrases:

R68 Possible risk of irreversible effects (Mutagen Category 3)

R45 May cause cancer (Carcinogen Category 2)

The cut-off concentrations are as follows:

Risk Phrase	Concentration Cut-off
R45	≥0.1 % < 1.0 %
R45, R68	≥ 1.0%

The following safety phrases are also recommended for TBPP:

S45 In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)

S53 Avoid exposure – Obtain special instructions before use

S60 This material and its container must be disposed of as a hazardous waste

It is recommended that this classification be included in the NOHSC *List of Designated Hazardous Substances* contained in the Hazardous Substances Information System (HSIS).

Recommendation 3

It is recommended that TBPP be included in Schedule 1 of the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* Part 2- *Scheduled Carcinogenic Substances*. In accordance with the National Model Regulations, a supplier or an employer shall not use TBPP except for the purposes of bona fide research or analysis and only limited to a volume of 1000 mg (ampoule).

Australian Consumer and Competition Commission (ACCC)

Recommendation 4

It is recommended that the Australian Competition and Consumer Commission give priority consideration to re-introducing appropriate regulations under the Trade Practices Act, if evidence becomes available to NICNAS that TBPP -treated clothing or textiles are imported into Australia, to prevent exposure of the public, especially children.

Recommendations to importers of TBPP and State and Territory Authorities

Recommendation 5

Hazard communication - Material Safety Data Sheet

Under the *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994) and the Commonwealth, State and Territory regulations introduced in accordance with these National Model Regulations, employees shall have ready access to Material Safety Data Sheets (MSDS) for hazardous substances at their workplace.

In accordance with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 2003) it is recommended that importers of TBPP review their MSDS for compliance and pay particular attention to the following points:

- risk phrases and hazard information to be updated to reflect the hazard classification provided in Recommendation 2; and
- safety phrases should be included as noted in Recommendation 2.

Recommendation 6

Hazard communication - Label

In accordance with the *National Code of Practice for the Labelling of Workplace Substances* (NOHSC 1994a), it is recommended that importers of TBPP pay particular attention to the following points:

- risk phrases and hazard information to be updated to reflect the hazard classification provided in Recommendation 2; and
- safety phrases should be included as noted in Recommendation 2.

It is recommended that the State and Territory Occupational Health and Safety authorities review compliance with the above information, in the workplace.

Recommendation to textile and clothing retailers and Council of Textile and Fashion Industries of Australia Ltd.

Recommendation 7

Use of TBPP other than for research and development purposes is not supported by NICNAS. Retailers of fire retardant-treated clothing or textiles, under the duty of care should ascertain from their supply sources overseas the type of retardant used in the imported clothing or textiles.

If it becomes known to the Council of Textiles and Fashion Industries of Australia Ltd, and retailers of fire-retardant-treated clothing and textiles, that TBPP-treated clothing or textiles are being imported into Australia, NICNAS should be notified immediately.

15. Secondary Notification

Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act 1989*, the secondary notification of a chemical that has been assessed under the Act may be required where change of any circumstances that may warrant a reassessment of its hazards and risks occurs. In the case of TBPP, specific circumstances include:

- additional information has become available to the introducers of TBPP as to adverse health and/or environmental effects of TBPP;
- importation of TBPP treated textiles or clothing occurs into Australia

The Director of NICNAS must be notified within 28 days of the introducer becoming aware of any of the above or other circumstances prescribed under Section 64(2) of the Act. It is an offence under section 64 of the Act if the Director is not notified of the change in circumstances specified above.

16. Appendix 1

Conceptual Framework for Considering Mode-of Action of Chemical Carcinogenesis of Tris(2,3-dibromopropyl) phosphate (TBPP) for kidney tumours

1. Introduction

No epidemiology studies are available investigating the relationship between exposure to TBPP and cancer. An increased incidence of kidney tubular cell tumours was seen in male and female Fischer344 rats, and male and female B6C3F1 mice, when TBPP was administered in the diet. Additionally, an increased incidence of tumours of the fore-stomach, lung and liver were seen in mice. There is evidence indicating that TBPP is carcinogenic by dermal exposure with an increased incidence of tumours at the site of application and distal sites such as the fore-stomach, lung and oral cavity. This framework will focus on kidney tumours as a result of ingestion of TBPP.

2. Postulated mode of action

The mechanism by which TBPP may induce kidney tumours in rodents is presently not understood and a specific mechanism to account for this observation has not been identified. However, given that TBPP was genotoxic in vivo in somatic cells, there is limited evidence to suggest a genotoxic action for TBPP-induced kidney tumours. Additionally, the toxicokinetic profile of TBPP indicates that once absorbed the parent compound is rapidly distributed throughout the body and that the half-life clearance of ^{14}C-TBPP-derived radioactivity was significantly slower in the kidney (and liver) than other organs.

3. Key events

There is presently no experimental data that addresses the mechanism of TBPP-induced kidney tumours. Consequently, the key precursor events associated with the induction of kidney tumours in rodents following ingestion of TBPP have not been defined.

4. Dose-response relationship

No human data are available. In F344 rats, there is evidence of a dose response relationship in females for kidney tubular cell adenomas (0/52, 5/54 and 13/54 at 0, 50 and 100 ppm respectively) and to a lesser extent in males (0/53, 30/54 and 27/54). Tubular cell carcinomas of the kidney were also seen in male rats at the top dose only (3/54). Similarly, in studies conducted in B6C3F1 mice, there is evidence of a dose response relationship for kidney tubular cell adenomas in females (0/55, 3/50 and 3/46 at 0, 50 and 100 ppm respectively) and males (0/54, 5/50 and 12/49) and for tubular cell carcinomas of the kidney in males (0/54, 1/50 and 5/49). Although both studies only used two dose levels with TBPP they provide evidence of a dose response relationship between TBPP exposure and incidence of kidney tumours, which the authors report are rare in untreated F344 rats and B6C3F1 mice. No key events have been identified for TBPP-induced of kidney tumours.

5. Temporal association

No human data are available. No key events have been identified in animal studies for TBPP-induced kidney tumours consequently, an analysis of potential temporal association cannot be undertaken.

6. Strength, consistency and specificity of association of tumour response with key events

No human data are available. The available animal data indicate that exposure to TBPP is associated with the development of kidney tumours that are rare spontaneous tumours in the experimental animals tested (F344 rats and B6C3F1 mice). However, there are no studies investigating TBPP-induced kidney tumours in animals and, hence, no key events have been identified in the formation of such tumours.

7. Biological plausibility and coherence

There are no mechanistic studies investigating the key events in the formation of TBPP-induced kidney tumours in animals and, hence, a postulated mode of action has not been forwarded.

8. Other mode of action

No experimental data that addresses the mechanism of TBPP-induced kidney tumours are available.

9. Assessment of postulated mode of action

Available data indicates that exposure to TBPP causes kidney tumours in rodents. However, no experimental data that addresses the mechanism of TBPP-induced kidney tumours are available and thus no mode of action has been postulated. Though the genotoxic and toxicokinetic profile of TBPP provide limited evidence to suggest a possible genotoxic action in the formation of kidney tumours.

10. Uncertainties, inconsistencies and data gaps

Although no experimental data that address the mechanism of TBPP-induced kidney tumours are available and, hence, uncertainties exist for the mode of action, such tumours were consistently seen in both sexes in two species. No human data are available. Experimental data in animals indicates that following absorption TBPP reaches the kidneys and TBPP is genotoxic in somatic cells in vivo. Consequently, the mode by which genotoxicity may be involved in the production of kidney tumour development needs to be investigated.

11. Relevance to humans

No postulated mode of action has been proposed and no human data are available. However, the observation of kidney tumours in the two species tested, together with the genotoxic and toxicokinetic profile of TBPP satisfy the criteria of consistency and biological plausibility for TBPP-induced kidney tumours. Thus, although the mode of action is unknown, the present understanding of the toxicological profile of TBPP, including its in vivo genotoxic potential, indicates that TBPP-induced kidney tumours should be regarded as being relevant to humans.

17. Appendix 2

Classification under the Globally Harmonized System of Classification and Labelling of Chemicals

In this report, TBPP has been classified against the NOHSC *Approved Criteria for Classifying Hazardous Substances* (Approved Criteria) (NOHSC, 2004) and, in the case of physicochemical hazards, the *Australian Dangerous Goods Code* (ADG Code) (FORS, 1998). However, classifications under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (OECD 2003) will come into force when the GHS is adopted by the Australian Government and promulgated into Commonwealth legislation. GHS documentation is available at

http://www.unece.org/trans/danger/publi/ghs/officialtext.html

The classification of TBPP against the GHS can be found below:

Health and Environmental Hazards	Classification	Hazard Communication
Mutagenicity	**Category 1B**	**Symbol:** Health Hazard **Signal Word:** Warning **Hazard Statement:** May cause genetic effects
Carcinogenicity	**Category 2**	**Symbol:** Health Hazard **Signal Word:** Warning **Hazard Statement:** Suspected of causing cancer
Ecotoxicity	**Chronic: Category 2**	**Symbol:** Fish and tree **Signal Word:** No signal word is used **Hazard Statement:** Toxic to aquatic life with long lasting effects

18. Appendix 3

Sample Material Safety Data Sheet for Tris(2,3-dibromopropyl) phosphate

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Section 1 - Identification of the Material and Supplier

Product name
Tris(2,3-dibromopropyl) phosphate

Other names
Tris(2,3-dibromopropyl) phosphate; tris(2,3-dibromopropyl) phosphoric acid ester; phosphoric acid, tris(2,3-dibromo-propyl) ester; tris(dibromopropyl) phosphate

Recommended use
Research and Development, analytical standard

Company name

Address

State **Postcode**

Telephone number **Emergency telephone number**

Section 2 - Hazard Identification

HAZARDOUS SUBSTANCE. NON-DANGEROUS GOODS
Classified as hazardous according to the criteria of NOHSC

Risk phrases
R45 May cause cancer (Carcinogen Category 2)
R68 Possible risk of irreversible effects (Mutagen Category 3)

Safety phrases
S45 In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)
S53 Avoid exposure-obtain special instruction before use
S60 This material and its container must be disposed of as hazardous waste

Poison Schedule
None allocated

Section 3 - Composition/Information on Ingredients

Chemical entity	Proportion	CAS Number
Tris(2,3-dibromopropyl) phosphate	96.9%	126-72-7

Section 4 - First Aid Measures

General If swallowed, do NOT induce vomiting.. Treat symptomatically. No specific antidote
Eyes If in eyes wash out immediately with water
Skin If skin contact occurs remove contaminated clothing and flush skin with running water

Section 5 - Fire Fighting Measures

Suitable extinguishing media
Determined by cause of fire

Hazard from combustion products
When heated to decomposition (260-300ºC), TBPP emits toxic fumes of bromine and phosphorous

Precautions for fire fighters and special protective equipment
Wear self-contained breathing apparatus when fighting a chemical fire

Section 6 - Accidental Release Measures

Emergency procedures
Avoid eye or skin contact. Wear protective glasses. Use protective gloves to avoid skin contact. Do not hose spills down drains, sewers or waterways. Contact local waste disposal company for disposal

Methods and materials for containment and clean up
Small spills can be wiped up. Large spills should be absorbed by dirt, sand or other suitable absorbents for disposal. Use protective gloves to clean-up spills

Section 7 - Handling and Storage

Precautions for safe handling
Avoid eye or skin contact

Conditions for safe storage, including any incompatibilities
Store in sealed container in cool dry place

Section 8 - Exposure Controls/Personal Protection

National exposure standards
No exposure standard allocated

Engineering controls
Use only with adequate ventilation. Local exhaust ventilation may be necessary for some operations.

Personal protective equipment
Use suitable protective clothing to avoid skin contact. Wear impervious gloves and protective glasses.

Section 9 - Physical Description and Properties

Appearance
Clear pale-yellow viscous liquid

Boiling point
390ºC

Melting point
5.5ºC

Vapour pressure
1.9 x 10^{-4}mmHg @25ºC

Specific gravity
2.27 g/mL

Flash point
Not available

Flammability limits
Not applicable

Solubility in water
8 mg/L

Section 10 - Stability and Reactivity

Chemical stability
Stable in sunlight

Incompatible materials
Strong bases

Hazardous decomposition products
Hydrogen bromide, oxides of phosphorous

Hazardous reactions
Nil

Section 11 - Toxicological Information

Acute effects:
Animal data indicate that TBPP has low acute toxicity by the oral and dermal routes
Eye: Not an eye irritant
Skin: Not a skin irritant
Sensitisation: Not a skin or respiratory sensitiser

Chronic effects:
Animal data indicate that TBPP causes kidney tumours in rodents. Genetic damage has been observed in animals in several tissues including the kidney, liver and bone marrow.

Section 12 - Ecological Information

Ecotoxicity
No data available

Persistence/Degradability
Not readily biodegradable

Mobility
Adsorbs on to soil. Expected to leach slowly into groundwater

Bioaccumulative potential
Possible limited bioaccumulative potential

Section 13 - Disposal Considerations

Disposal methods and containers
Store in closed containers until product can be properly disposed.

Special precautions for landfill or incineration
Contact local waste disposal authority for advice or pass to a licensed waste disposal company for disposal.

Section 14 - Transport Information

UN Number
Not available

UN proper shipping name
Not available

Class and subsidiary risk
Not available

Packing group
Not available

Special precautions for user
Nil

Hazchem code
Not available

Section 15 - Regulatory Information

Australian
NOHSC List of Designated Hazardous Substances

The risk and safety phrases applicable are:
R45 may cause cancer (Carcinogen Category 2)
R68 Possible risk of irreversible effects (Mutagen Category 3)
S45 In case of accident or if you feel unwell seek medical advice immediately (show the label where possible)
S53 Avoid exposure – Obtain special instructions before use
S60 This material and its container must be disposed of as a hazardous waste

International
Priority Informed Consent

TBPP is listed in Annex III of the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (Rotterdam Convention)

Section 16 - Other Information

Date of preparation

Abbreviations/Acronyms
NOHSC - National Occupational Health and Safety Commission

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