**Environmental Health Criteria 218**

FLAME RETARDANTS: TRIS(2-BUTOXYETHYL) PHOSPHATE, TRIS(2-ETHYLHEXYL) PHOSPHATE AND TETRAKIS(HYDROXYMETHYL) PHOSPHONIUM SALTS

Please note that the layout and pagination of this web version are not identical with the printed document

First draft prepared by Dr G.J. van Esch, Bilthoven, the Netherlands

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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**NOTE TO READERS OF THE CRITERIA
MONOGRAPHS**

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (telephone no. + 41 22 – 9799111, fax no. + 41 22 – 7973460, E-mail irptc@unep.ch).

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Environmental Health Criteria

P R E A M B L E

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii) to identify new or potential pollutants;

(iii) to identify gaps in knowledge concerning the health effects of pollutants;

(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In this manner, with the strong support of the new partners, the importance of occupational health and environmental

effects was fully recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are only used when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of risks and are not, in any

sense, recommendations for regulation or standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- Summary — a review of the salient facts and the risk evaluation of the chemical
- Identity — physical and chemical properties, analytical methods
- Sources of exposure
- Environmental transport, distribution and transformation
- Environmental levels and human exposure
- Kinetics and metabolism in laboratory animals and humans
- Effects on laboratory mammals and *in vitro* test systems
- Effects on humans
- Effects on other organisms in the laboratory and field
- Evaluation of human health risks and effects on the environment
- Conclusions and recommendations for protection of human health and the environment
- Further research
- Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in: Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment; international concern, i.e. the substance is of major interest to several countries; adequate data on the hazards are available.

If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

EHC PREPARATION FLOW CHART

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│ necessary    │    └──────────────────────────┘    │ of a few experts     │
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                    │ preparation of Task Group (TG) draft │
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⇒ routine procedure

- - -► optional procedure

The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. While observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking, and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

**WHO TASK GROUP ON ENVIRONMENTAL HEALTH
CRITERIA FOR FLAME RETARDANTS:
TRIS(2-BUTOXYETHYL) PHOSPHATE,
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TETRAKIS(HYDROXYMETHYL) PHOSPHONIUM
SALTS**

Members

Dr R. Benson, US Environmental Protection Agency, Denver,
Colorado, USA

Dr P. Brantom, British Industry Biological Research Association
(BIBRA) International, Carshalton, Surrey, United Kingdom

Dr S. Dobson, Institute of Terrestrial Ecology, Monks Wood,
Huntingdon, Cambridgeshire, United Kingdom (*Chairman*)

Professor J. Liesivuori, Department of Pharmacology and
Toxicology, University of Kuopio, Kuopio, Finland

Mr D. Renshaw, Department of Health, Elephant and Castle,
London, United Kingdom

Dr E. Söderlund, National Institute of Public Health, Department of
Environmental Medicine, Oslo, Norway (*Rapporteur*)

Observers

Dr L. Kotkoskic, FMC Corporation, Princetown, New Jersey, USA

Dr P. Martin, Albright and Wilson UK Limited, European Business
Services – Product Stewardship, Oldbury, West Midlands, United
Kingdom

Secretariat

Dr M. Baril, International Programme on Chemical Safety,
Montreal, Quebec, Canada

ENVIRONMENTAL HEALTH CRITERIA FOR FLAME RETARDANTS: TRIS(2-BUTOXYETHYL) PHOSPHATE, TRIS(2-ETHYLHEXYL) PHOSPHATE AND TETRAKIS(HYDROXYMETHYL) PHOSPHONIUM SALTS

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ABBREVIATIONS

AChE	acetylcholinesterase
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
BCME	bis(chloromethyl) ether
BEHP	bis(2-ethylhexyl) phosphate
BMPA	bishydroxymethyl phosphonic acid
BuCHE	butyrylcholinesterase
CHO	Chinese hamster ovary
DMSO	dimethyl sulfoxide
EC_{50}	median effective concentration
FDA	Food and Drug Administration (USA)
GC	gas chromatography
HPLC	high performance liquid chromatography
IC_{50}	median inhibitory concentration
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
MS	mass spectrometry
nd	not detected
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NPD	nitrogen-phosphorus sensitive detector
NTE	neuropathy target esterase
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
PVC	polyvinyl chloride
SCE	sister-chromatid exchange
TBEP	tris(2-butoxyethyl) phosphate
TEHP	tris(2-ethylhexyl) phosphate
THP	tetrakis(hydroxymethyl) phosphonium
THPC	tetrakis(hydroxymethyl) phosphonium chloride
THPO	trihydroxymethyl phosphine oxide
THPS	tetrakis(hydroxymethyl) phosphonium sulfate
TOCP	tri-*ortho*-cresyl phosphate

PART A

Tris(2-butoxyethyl) phosphate
(TBEP)

A. SUMMARY, EVALUATION AND RECOMMENDATIONS

A1. Tris(2-butoxyethyl) phosphate (TBEP)

A1.1 Summary

Tris(2-butoxyethyl) phosphate (TBEP) is used in floor polishes and as a plasticizer in rubber and plastics. The worldwide production volume is not available but is estimated to be in the range of 5000–6000 tonnes.

TBEP occurs in the environment only as a result of human activity. Its distribution in the environment has been investigated in certain industrialized countries. Concentrations in surface water were found to be below 300 ng/litre, whereas concentrations in sediment were between 100 and 1000 : g/kg. None of 167 analyses detected TBEP in fish. It has been detected in outdoor air in a single study (<200 ng/m^3). Measurement of TBEP in indoor air in offices showed concentrations of 25 ng/m^3 or less. TBEP is associated with particulates and the source is considered to be the application of floor polish. It has been detected at : g/kg levels in human adipose tissue. The reported daily dietary intake from market basket studies, for a range of age groups, was <0.02 : g/kg body weight per day. Drinking-water concentrations of up to 270 : g/litre have been reported, this is considered to arise from migration from rubber gaskets in the plumbing.

TBEP is considered to be readily biodegradable. Sewage treatment plant measurements and semi-continuous sludge laboratory tests have indicated substantial elimination of TBEP (>80%). In river and coastal water TBEP was completely degraded. The half-life in estuarine water was reported to be about 50 days and there was little degradation in unadapted seawater.

The acute systemic mammalian toxicity and irritation potential are low.

Several subchronic studies in laboratory animals have shown that the liver is the target organ for TBEP toxicity. One study in male Sprague-Dawley rats suggested that TBEP might cause focal

myocarditis. Neurotoxic effects in rats after single doses of TBEP are inconsistent. In rats repeatedly given high doses by gavage, TBEP decreased nerve conduction velocity and increased the refractory period. It did not cause delayed neurotoxicity in hens but did inhibit brain and plasma cholinesterases.

Based on an 18-week repeated dose study in rats, the no-observed-effect level (NOEL) for liver effects was reported to be 15 mg/kg body weight per day, while the lowest-observed-effect level (LOEL) was 150 mg/kg body weight per day.

The long-term toxicity and carcinogenicity of TBEP have not been studied.

Bacterial and mammalian cell tests for gene mutation gave negative results, but no tests for chromosomal damage have been reported.

Teratogenicity was not observed in one study in rats. Other aspects of reproductive toxicity have not been reported.

A Repeat Human Insult Patch Test indicated no skin sensitization and minimal skin irritation.

The toxicity of TBEP to aquatic organisms is moderate. The 48-h LC_{50} in *Daphnia magna* is 75 mg/litre and the 96-h LC_{50} values in fish range between 16 and 24 mg/litre.

A1.2 Evaluation

Occupational exposure to TBEP is likely to be by the dermal route during manufacture (accidental exposure) and from the use of floor polishes. The compound is absorbed dermally in experimental animals but no information is available on its kinetics and metabolism. Dermal exposure cannot, therefore, be quantified but is expected to be low. Inhalation exposure in the office environment has been measured to be 25 ng/m^3 or less.

Exposure of the general population is principally via food (from use of TBEP as a plasticizer in packaging plastics) and drinking-water (contaminated by leaching from synthetic rubbers used in plumbing

washers). Exposure from both sources is very low (estimated to be <0.2 ꞉ g/kg body weight per day from the diet and concentrations in drinking-water of <270 ꞉ g/litre).

Given the reported NOEL from animal studies of 15 mg/kg body weight per day from a repeated dose oral study, the risk to the general population is very low. The risk to the occupationally exposed is also considered to be very low, though this cannot be quantified.

In the environment, TBEP is expected (from its low volatility, high adsorption coefficient and moderate water solubility) to partition to sediment. The few measured data confirm this. Degradation in environmental media is expected to be rapid. No information is available on breakdown products; phosphate released during break-down is not expected to contribute significantly to environmental nutrient levels. Fig. 1 plots measured environmental concentrations in surface water against reported acute toxicity values. The margin of safety between highest reported concentrations and lowest reported toxicity values is several orders of magnitude, indicating low risk to organisms in the aquatic environment. No assessment of risk can be made for the terrestrial compartment.
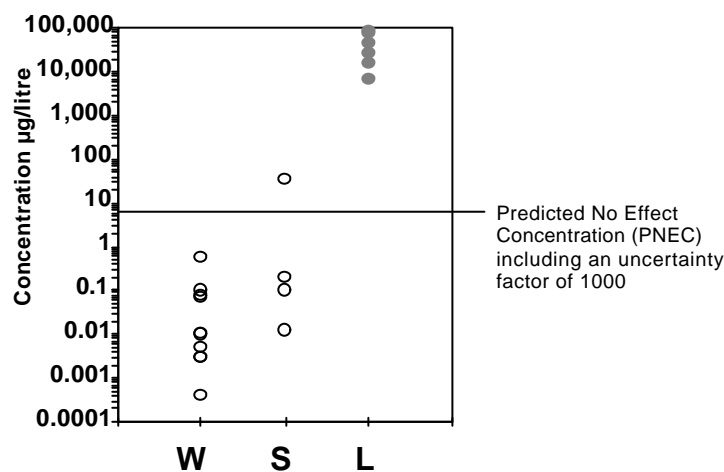
Fig. 1. Plot of measured concentrations in surface waters (W) and sewage effluents (S), and reported acute toxicity values (L) for TBEP (F = measured concentrations in the environment; M = calculated LC_{50})

A1.3 Recommendations

For a full scientific evaluation of the compound, identification and assessment of metabolites in mammals would be required, given the toxicological profile of one of the suggested metabolites, 2-butoxyethanol.

A2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

A2.1 Identity

Molecular structure:

$$CH_3(CH_2)_3OCH_2CH_2O \longrightarrow \underset{\underset{O}{\overset{\overset{\displaystyle OCH_2CH_2O(CH_2)_3CH_3}{|}}{\parallel}}{P} \longrightarrow OCH_2CH_2O(CH_2)_3CH_3$$
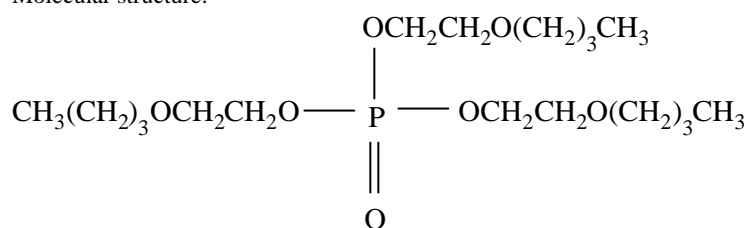
Empirical formula:	$C_{18}H_{39}O_7P$
Relative molecular mass:	398.54
Common name:	tris(2-butoxyethyl) phosphate
Synonyms:	phosphoric acid, tris(2-butoxyethyl) ester; tri(2-butoxyethanol) phosphate; tris(2-n-butoxyethyl) phosphate; tributoxyethyl phosphate; TBOP; TBEP; TBXP (only in Japanese literature); 2-butoxyethanol phosphate (RTCES, 1989); tri(2-butylethylether) phosphate; tris(butylglycol) phosphate; tributyl cello solve phosphate
Trade names:	Kronitex KP-140; KP-140; Phosflex T-BEP; Phosflex 176C; Amgard TBEP
CAS registry number:	78-51-3
CAS name:	Ethanol, 2-butoxy, phosphate (3:1)
EINECS number:	201-122-9

RTECS number: KJ9800000

A2.2 Physical and chemical properties

TBEP is a technical product that may contain as impurities tributyl phosphate (about 3%) and traces of 2-butoxyethanol and phosphoric acid (FMC, 1990; Albright & Wilson (1999) personal communication to IPCS). There is no information on the concentration of mono- or diesters or other impurities in the technical product.

TBEP is a light-coloured, high-boiling, non-flammable viscous liquid with a butyl-like odour under normal conditions. It is more soluble in non-polar than in polar solvents.

Boiling point: 200–230 /C at 5.0–5.3 hPa

Melting point: **!** 70 /C

Density: 1.02 g/ml at 20 /C

Viscosity: 11–15 mPa.s at 20 /C

Vapour pressure:
    at 25 /C 2.8×10^{-7} hPa
    at 150 /C   0.33 hPa (0.03 mmHg)

Refractive index: 1.434 at 25 /C

Solubility: 1.1–1.3 g/litre water at 20 /C; miscible
                              in petroleum at 20 /C

Acidity/alkalinity: neutral
(1 g/litre water at 20 /C)

Flashpoint: 210 /C (approximately);
                            159 ± 2 /C

Ignition point: 251–52 /C

Auto-ignition temperature: 322 ± 5 /C; 261 /C

Log K_{oc}:   4.38 (calculated)

n-Octanol/water partition
coefficient: 4.78 (calculated); 3.65

References: Eldefrawi et al. (1977); Keith & Walters (1985); Laham et al. (1985b); Hoechst (1987); Watts & Moore (1988); Leo (1989); FMC (1990); Hinckley et al. (1990); Lenga (1993); Tremain & Bartlett (1994).

A2.3 Conversion factors

1 ppm = 16.53 mg/m^3 at 20 /C
1 mg/m^3 = 0.0605 ppm at 20 /C

A2.4 Analytical methods

TBEP is usually analysed by gas chromatography (GC) coupled with mass spectrometry (MS), infrared spectroscopy or nuclear magnetic resonance spectrometry. The detection limit is <1 ng/g (adipose tissue) using any of these methods or a nitrogen/phosphorus-selective detector (LeBel et al., 1981; Rivera et al., 1987).

A2.4.1 Air

TBEP has been found associated with particulate matter in the air of offices. Of the methods that can be used to collect the particles, Weschler (1980) used a four-stage impactor with a back-up filter and extracted with a mixture of water and methanol. Later Weschler (1984) and Weschler & Fong (1986) collected particles on Teflon(R) membranes, separating the particles according to whether the aerodynamic diameter was greater or less than 2.5 : m. The samples were analysed by GC/MS after thermal desorption of the collector membranes. Sometimes samples were desorbed or dissolved with toluene.

A2.4.2 Water

TBEP has been extracted either with dichloromethane after acidification to pH 2 or by passage through a column filled with Amberlite XAD-2 resin which is subsequently extracted with acetone

and hexane. After dehydration and concentration, extracts are analysed. The concentrated extracts are determined by GC/MS, or with other detection methods, as described above (LeBel et al., 1981; Watts & Moore, 1988). LeBel et al. (1987) used large-volume resin sampling cartridges to obtain sufficient organic extracts from water for analysis. Recovery at 10 ng TBEP/litre fortification level was 103.4%.

Frimmel et al. (1987) described an analytical method to determine TBEP in water by extracting TBEP with granulated activated carbon and analysing the extract with GC/MS.

Rivera et al. (1987) analysed water samples with different procedures, liquid-liquid extraction, adsorption on granular activated carbon, extraction with dichloromethane, followed by GC/MS/DS (Daughter spectral) detection. Ether-insoluble organic fractions were analysed and fractionated by high-performance liquid chromatography (HPLC) and ultraviolet absorbency detection was carried out with a 2140 diode-array detector, followed by fast atom bombardment (FAB) and FAB-collision-induced dissociation – mass analysis kinetic energy spectroscopy (CID-MIKES) mass spectrometry.

A2.4.3 Sediment

After decanting the supernatant water, the sediment samples are mixed with an equal volume of pre-extracted anhydrous sodium sulfate and transferred to a Soxhlet thimble. Soxhlet extraction is carried out overnight using dichloromethane (300 ml) (Watts & Moore, 1988).

A2.4.4 Soils and foodstuffs

There are no reports of extraction or clean-up methods for soil or food (ECETOC, 1992b).

A2.4.5 Biological media

LeBel & Williams (1983b, 1986) and LeBel et al. (1989) analysed human adipose tissue for TBEP by extraction with a mixture of acetone/hexane in the presence of anhydrous sodium sulfate. The solution was centrifuged and the supernatant filtered and evaporated.

The resulting extract was dissolved in a mixture of 5% dichloromethane in cyclohexane for gel permeation chromatography (GPC) to separate residual lipids from phosphate esters. Using this method the recovery of TBEP from adipose tissue was approximately 90%.

Anderson et al. (1984) measured peaks of TBEP determined by HPLC in spiked samples of serum during the development of an analytical refinement. There was a marked inter-individual variation in peak height, which correlated with serum lipoprotein concentration.

A3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

A3.1 Natural occurrence

TBEP has not been found to occur naturally in the environment (ECETOC, 1992b).

A3.2 Anthropogenic sources

A3.2.1 Production levels and processes

TBEP is produced by reacting phosphorus oxychloride and butoxyethanol (butyl glycol) and stripping hydrochloric acid and excess of butoxyethanol. Another production method uses the sodium salt of the glycol. In this case, the by-product is sodium chloride (ECETOC, 1992b).

The world global production has been estimated to be 5000–6000 tonnes, with less than 1000 tonnes in Europe.

A3.2.2 Uses

TBEP is used mainly as a component in floor polishes, a solvent in some resins, a viscosity modifier in plastisols, an antifoam and also as a plasticizer in synthetic rubber, plastics and lacquers. TBEP is widely used as a plasticizer in rubber stoppers for vacutainer tubes and plastic ware.

A4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

A4.1 Transport and distribution between media

All environmental TBEP derives from human activities but the input rate to the environment cannot be estimated from the available data. The input is expected to be mainly to soil, sediments and surface waters from leachates from plastics on landfills, from spillages and from effluents (ECETOC, 1992b).

The low vapour pressure, the high soil sorption coefficient (K_{oc}) and the water solubility of approximately 1 g/litre suggests that TBEP in the environment will be found mainly in water and sediment. TBEP has been detected in surface water and sediments (ECETOC, 1992b).

A4.2 Biodegradation

No data are available on mechanisms of abiotic or biotic transformation. Analogy with other phosphate esters suggests that enzymatic hydrolysis would be expected to dominate (ECETOC, 1992b).

TBEP was readily biodegradable when tested in the OECD 301B assay, achieving 87% degradation within 28 days (Mead & Handley 1998).

In a test of primary biodegradation using the semi-continuous activated sludge procedure and an addition rate of 3 mg TBEP/litre per test cycle, 88% of TBEP was eliminated. The ultimate biodegradability (using the Monsanto shake-flask procedure) was 51% of the theoretical CO_2 generated after 28 days (Monsanto, 1976).

Hattori et al. (1981) studied the degradation of TBEP in environmental water in 1979–1980. Using the molybdenum blue colorimetric method, the increase of phosphate ions was analysed in Oh and Neya river water and seawater from Osaka Bay to which 1 mg TBEP/litre had been added. The degradation depended on the source of the water (Table 1).

Table 1. Biodegradation of TBEP in water in percentages
(from Hattori et al., 1981)

Test duration (days)	Oh River	Neya River	Osaka Bay	
			Tomagashima seawater	Senboku seawater
7	29.1	0	1.9[a]	0
14	100[b]	100	17.6	100

[a] Test duration 8 days
[b] Test duration 15 days

A sterilized distilled water control did not show any degradation after 15 days. TBEP was rapidly degraded in less than 14 days after an acclimatization period of several days in water containing micro-organisms. Where degradation was rapid, the phosphatase activity increased during the test period.

TBEP was eliminated from estuarine water with a half-life of approximately 50 days (Ernst, 1988).

A4.2.1 Migration

LeBel & Williams (1983a) investigated the difficulties of obtaining representative water samples and the importance of designing suitable sampling protocols. TBEP was detected in tap water at concentrations from 11.0 to 5400 ng/litre. The authors suggested that the TBEP originated from the O-ring and seal in the tap.

A5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

A5.1 Environmental levels

A5.1.1 Air

An indoor aerosol sample was collected in a large building in New Jersey, USA. The abundance of TBEP was greatest both for particles larger than 7.0 : m diameter and for those smaller than 1.1 : m; there was considerably less material present in the intermediate size ranges. This pattern is consistent with its use in floor polish. Buffing operations generate relatively large particles which are likely to contain TBEP. However, this compound may also migrate from the floor polish and be attached to particles. In this case the majority of the adsorbed TBEP would accumulate in the submicron size range (Weschler, 1980). The mean concentrations measured in representative samples of dust from air in 7 offices in the USA was reported to be 15 ng/m^3 (Weschler & Shields, 1986). The significance of floor polish, which may contain 1% TBEP (Nakashima et al., 1993), as a source of these particulates is suggested by the fact that the highest concentration measured (25 ng/m^3) was found immediately following floor polishing work by a night crew.

Airborne concentrations of fine (2.5 : m) and coarse aerosol (2.5–15 : m) particles were simultaneously measured outside and inside two buildings, one in Wichita, Kansas, USA, during the fall and early winter (1981–1982) and the second one in Lubbock, Texas, USA, during late winter and spring 1982. The average indoor concentrations of TBEP in Wichita and Lubbock were 4 and 25 ng/m^3, mainly in fine aerosol particles. TBEP was not found in outdoor aerosol particles (Weschler, 1984).

Yasuda (1980) reported the results of a study of 19 outdoor air samples from 7 locations in 1976. Two samples from Kawauchi Town contained 149.1 and 176.8 ng TBEP/m^3 and one from Ehime University 9.6 ng TBEP/m^3. TBEP was not detected in the other 16 samples.

A5.1.2 Water (drinking-water and surface water)

Levels of TBEP have been determined in rivers, sewage, tap water, lakes and estuaries. The investigations have been carried out in the Great Lakes area of Canada, USA, Japan, Germany and the United Kingdom.

The lower part of the River Weser (over 33 km), Germany, was examined for the presence of TBEP during the period May 1985 to April 1987. TBEP was found at a mean concentration of 125 ng/litre. Systematic measurements of effluent samples from five sewage treatment plants in the Bremen region showed concentrations of TBEP ranging from 800 to 34 900 ng/litre (Bohlen et al., 1989).

Ernst (1988) analysed water of the estuary of the Rivers Elbe and Weser, Germany, for the presence of TBEP during the period 1983–1985. The concentrations that were found ranged from 5 to 70 ng/litre.

One hundred samples of surface water were collected from various locations throughout Japan in 1975 and analysed for the presence of TBEP. TBEP was identified in none of the samples (the limit of determination ranged from 0.02 to 0.5 ：g/litre). In 1978, 114 samples were analysed in Japan and TBEP was not identified (the limit of determination ranged from 0.005 to 1.5 ：g/litre) (Environmental Agency Japan, 1978, 1983, 1987).

In a survey conducted between 1989 and 1990, Fukushima et al. (1992) identified TBEP in Lake Biwa, Yodo River and also in the Yamato Osaka Rivers and Osaka Bay at levels of about 0.2– 2.5 ：g/litre.

Drinking-water was collected in Japan over a 12-month period and analysed. Concentrations ranging up to 0.0585 ng/litre were found (Adachi et al., 1984).

Two samples of drinking-water collected from six Eastern Ontario water treatment plants in the period June–October 1978 contained 0.9–75.4 ng/litre (LeBel et al., 1981). In another study two samples of drinking-water were collected from five Great Lakes water treatment plants of Eastern Ontario and analysed for TBEP. The concentration

found in surface water samples ranged from 9.8 to 54.4 ng/litre as determined by GC/MS. When determined by GC/NPD, concentrations of 0.4 to 73.8 ng/litre were found (LeBel et al., 1987).

Williams et al. (1982) collected samples of drinking-water from 12 Ontario municipal water treatment plants which draw their water from the Great Lakes system in January and August 1980. All samples contained TBEP at concentrations ranging from 1.6 to 271.6 : g/litre. The authors noted that TBEP is a common constituent of rubber gaskets and washers and can be introduced into water from components of the tap used for sampling.

In 1983, LeBel et al. (1983a) found up to 5400 ng/litre in a sample of drinking-water taken after non-use of the tap for 65 h.

In the period August 1976 to March 1977, 16 grab samples of river water were collected from the Delaware River, USA (between river mile 78 and 132). In addition to other compounds, TBEP was identified in all samples. The concentrations ranged from 0.3 to 3.0 : g/litre in the winter and from 0.4 to 2.0 : g/litre in the summer (Sheldon & Hites, 1978).

A5.1.3 Soils and sediment

TBEP was detected in 7 out of 80 samples of sediment collected at different locations in Japan in 1975. The concentrations ranged from 0.22 to 0.54 mg/kg and the limit of determination was 0.002–0.1 mg/kg. In 1978, none of the 114 sediment samples collected at different places in Japan contained TBEP (limit of determination 0.0005–0.12 mg/kg) (Environmental Agency Japan, 1978, 1983).

Watts & Moore (1988) did not detect TBEP in suspended particles or bottom sediments in a river in the United Kingdom, even though TBEP was found in corresponding water columns.

A5.1.4 Aquatic organisms

No TBEP could be detected in 74 samples of fish from numerous locations throughout Japan (limit of determination 0.005–0.1 mg/kg).

Another report from the same agency stated that TBEP was not found in 93 fish samples (limit of determination 0.0005–0.15 mg/kg) (Environmental Agency Japan, 1978).

A5.2 Human tissue levels

LeBel & Williams (1983b) analysed 16 samples of human adipose tissue for TBEP. Four of sixteen samples contained TBEP at concentrations of 4.0–26.8 : g/kg. LeBel & Williams (1986) reported the results of 115 human adipose tissue (omentum) samples for TBEP, obtained at autopsy of humans from the Eastern Ontario cities, Kingston and Ottawa, Canada. TBEP was detectable in 21 out of 68 male adipose tissue samples and in 20 out of 47 female samples. Although the frequency of detection was similar in the two cities, mean concentrations in Ottawa were about 2.5 times those in Kingston. In both cities the concentrations in women were 2–3 times greater than in men. The arithmetic mean concentration of TBEP in the 41 detectable samples was 11.3 : g/kg in extracted fat (in males 6.3 : g/kg and in females 16.6 : g/kg). The mean concentration overall was 4.2 : g/kg in extracted fat. In a different study, LeBel et al. (1989) showed the presence of TBEP in human adipose tissue autopsy samples from 3 out of 6 Ontario (Canada) municipalities (based on a detection limit of 20 ng/g). No statistical difference between sexes was found, the mean concentration being 396 ± 56 ng/g in Toronto and 173 ± 32 ng/g in Cornwall.

A5.3 Food

In a series of articles Gunderson (1988, 1995a,b) reported data on daily intake of TBEP for a range of age groups and for a period between 1982 and 1991 from the USA FDA Total Diet Study (see Table 2).

Similar data were collected in a parallel study on ready-to-eat food from 1982 to 1991. TBEP was found in 5 out of 230 food items (baby food, ketchup, grapefruit juice, strawberries, tomatoes) and in 5 out of 17 050 chemical or pesticide samples, with an average concentration per residue of 0.28 : g/g (Kan-Do Office and Pesticides Team, 1995).

Table 2. Mean daily intake of TBEP per unit body weight (: g/kg body weight per day) according to age and gender

	6–11 months old	2 years old	14–16 years old		25–30 years old		60–65 years old	
			females	males	females	males	females	males
1982–1984	0.0029	0.0144	0.0084	0.0077	0.0129	0.0107	0.0168	0.0137
1984–1986	0.0002	0.0015	0.0007	0.0011	0.0004	0.0008	0.0002	0.0002
1986–1991	0.0052	0.0037	0.0012	0.0011	0.0020	0.0009	0.0034	0.0028

A5.4 Occupational exposure

The only data on occupational exposure to TBEP is from an office environment. Weschler & Shields (1986) measured a mean concentration of 15 ng/m^3 in dust samples from some offices in the USA. NIOSH (USA) has estimated that the number of workers exposed to TBEP is more than 200 000.

A6. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

No data are available on the kinetics or metabolism of TBEP either in animals or humans.

The Task Group considered that 2-butoxyethanol is a metabolite. Information on the toxicity of 2-butoxyethanol is given in IPCS (1998).

A7. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

A7.1 Single exposure

A7.1.1 Oral and dermal

The acute toxicity of TBEP following oral or dermal administration is low (Table 3).

Table 3. Acute toxicity of TBEP

Species	Route	LD_{50} (mg/kg body weight)	Reference
Rat	oral	3000	Eldefrawi et al. (1977)
Rat	oral	4700	Monsanto (1984c)
Rabbit	dermal	>5000	Gabriel (1980c)
Rabbit	dermal	>10 000	Report ICD/T.76.019 by FMC Corporation, Princeton, NJ, USA (1976)

An acute oral toxicity study was conducted according to the "fixed dose" procedure. Two out of three male rats but no females died at 5000 mg/kg body weight; no rats died at 500 mg/kg body weight. Signs of toxicity included chromorhinorrhoea, dyspnoea and decreased locomotion (Freeman, 1991a).

A7.1.2 Inhalation

The median lethal concentration in air has been investigated in a 4-h aerosol inhalation test (Hoechst, 1989). Groups of five male and five female Wistar rats were exposed to measured TBEP concentrations of 3.3, 3.4 or 6.4 mg/litre. No animal died but at all concentrations the animals exhibited depressed and irregular respiration, increased salivation, sneezing, unsteadiness and tremor, but these symptoms had cleared in most animals 9 days later. There were no body weight changes and gross necropsy revealed no abnormality. The 4-h LC_{50} was thus >6.4 mg/litre.

The 4-h LC_{50} in rats was reported to be greater than 4.43 mg/litre determined gravimetrically (particle size 2.46 ± 2.52 ：m) (Mount 1991).

A7.2 Short-term repeated exposure

A7.2.1 *Oral*

In a 14-day oral dosing regime using male and female rats, where the highest dose was 100 mg/kg body weight per day, a comprehensive biochemical, haematological and histopathological evaluation showed no changes (Komsta et al., 1989).

In a 4-week study, diets containing 0, 500, 2000, 7500 or 15 000 mg TBEP/kg were fed to male and female Sprague-Dawley rats. No signs of toxicity were found in male rats of any group whereas there was a slight decrease in body weight and food consumption in females receiving diets containing 7500 or 15 000 mg/kg diet. No compound-related changes were observed at necropsy (Monsanto, 1985a).

In a 14-week oral toxicity study with TBEP, Wistar rats (5 weeks old, male and female, 15 rats/group) were given a diet containing 0, 0.3, 3 or 30 g TBEP/kg. Suppression of body weight gain was observed in both sexes at 30 g/kg. Serum cholinesterase activity was significantly decreased in both sexes at 3 and 30 g/kg, and serum gammaglutamyl transferase activity was significantly increased in both sexes at 30 g/kg. Examination of the liver in both sexes revealed moderate periportal hepatocyte swelling in male rats at 30 g/kg after 14 weeks of exposure but this change was not found in male rats given 3 g/kg or less. The no-observed-effect level (NOEL) of TBEP in the diet was 0.3 g/kg diet (for males 20 mg/kg body weight per day and for females 22 mg/kg body weight per day. The Task Group considered the NOAEL of this study to be 3 g/kg diet (Tsuda et al., 1993; Saitoh et al., 1994).

In a gavage study, groups of 12 male and 12 female Sprague-Dawley rats were administered 0, 0.25 or 0.5 ml/kg body weight undiluted TBEP on 5 days/week for 18 weeks. During the first week, two high-dose females showed muscular weakness and ataxia which had disappeared by the end of the fourth week. After about 7 weeks, nearly all animals exhibited some signs of toxicity, which seemed to be treatment related. All treated animals appeared less active, and one female died during week 13. Breathing difficulties and ataxia were present in several males and females in both treatment groups, though the low-dose group was affected to a lesser extent. Tremors,

piloerection, lacrimation and increased urination were observed in both males and females of the high-dose group. After the last dose, the clinical signs observed in the high-dose group decreased in intensity. High-dose females had significantly elevated level of serum gamma-glutamyltransferase. Red cell acetylcholinesterase (AchE) activity was significantly reduced in males at both doses. There were no haematological changes. Animals were necropsied one week after the last dose. Liver weight was significantly increased (about 20%) in both high- and low-dose groups. Kidney weight was increased by about 20% in both groups and the increase was statistically significant in high-dose groups. Histopathological changes were confined to the heart of male rats of both groups. Three of six high-dose and two of six low-dose animals had multiple foci of mononuclear cell infiltration, haemorrhages and/or myocardial fibre degeneration. Two of six high-dose, three of six low-dose and one of six control rats demonstrated multifocal interstitial fibrosis with or without macrophage containing haemosiderin pigment. The authors concluded that TBEP may have accelerated the development of focal myocarditis, which is a normal feature of older male Sprague-Dawley rats. A NOAEL was not ascertained in this study (Laham et al., 1984a, 1985a).

In an 18-week study, four groups of 20 male and 20 female Sprague-Dawley rats were fed diets containing 0, 300, 3000 or 10 000 mg TBEP/kg. Body weight, food intake and clinical observations were similar in treated and control rats. Haematological and clinical chemistry parameters were normal except for increased platelet counts in the 10 000 mg/kg group, and increased serum gamma-glutamyl-transpeptidase and decreased plasma cholinesterase activity in the 3000 and 10 000 mg/kg groups. Liver weight was increased in the 10 000 mg/kg group. Microscopic examination showed mild periportal hepatocellular hypertrophy and periportal vacuolization in males receiving 3000 and 10 000 mg/kg in the diet. The NOEL was 300 mg/kg diet, equivalent to 15 mg/kg body weight per day (Monsanto, 1987a).

A7.2.2 Dermal

In a 21-day dermal toxicity study on New Zealand White rabbits, groups of 6 male and 6 female animals were treated with TBEP applications of 0, 10, 100 or 1000 mg/kg body weight per day,

5 days/week for 3 weeks. The unabraded dorsal clipped skin was used. The tests sites were occluded for 6 h after each exposure. No animals died and no adverse clinical signs of pharmacological/toxicological effects were observed. There was no indication that dermal exposure to 1000 mg/kg body weight per day resulted in any adverse systemic effect, but local irritation, oedema, atonia and desquamation occurred at all dose levels (Monsanto, 1985b).

A7.3 Skin and eye irritation; sensitization

In three studies TBEP was non-irritating to intact and abraded skin when applied topically to albino rabbits. (Gabriel 1980b; Monsanto, 1984c; Freeman, 1991b).

In the 21-day dermal toxicity study on New Zealand White rabbits, slight to moderate erythema was noted. The skin irritation was dose-related and severity progressed over time. Microscopic observations of the skin (of the 1000 mg/kg group) showed squamous cell hyperplasia, hyperkeratosis, hair follicles distended with keratin and surface accumulation of keratin and cellular debris, erosions ulcers, acute/subacute inflammation and congestion and haemorrhages in various combinations (Monsanto, 1985b) (see also section A7.2.2).

In four studies TBEP was non-irritating to the eyes of albino rabbits (Gabriel 1980a; Monsanto, 1984c; Freeman, 1991c; personal communication from Hoechst AG, Frankfurt, Germany entitled: Eye irritation test on New Zealand rabbit with TBEP, 1988).

No animal data are available on skin sensitization potential.

A7.4 Reproductive toxicity, embryotoxicity and teratogenicity

TBEP was administered by gavage in corn oil to three groups of 25 mated Charles River CD female rats at dose levels of 0 (corn oil), 250, 500 or 1500 mg/kg body weight per day on days 6 to 15 of gestation. The treatment had no effect at any dose level on fetal resorption, fetal viability, post-implantation loss, total implantations or the incidence of fetal malformations. The NOEL was the highest dose level tested, 1500 mg/kg body weight (Monsanto, 1985e). In an earlier range-finding

study maternal weight loss was observed in animals receiving 2000 mg/kg but not 1000 mg/kg body weight per day (Monsanto, 1985d).

A7.5 Mutagenicity and related end-points

A mutagenicity test was carried out with *Salmonella typhimurium* strains TA1535, TA1538, TA1537, TA98 and TA100, with and without metabolic activation. Liver S9 fractions were used from male Sprague-Dawley rats or from male Syrian hamsters induced by Aroclor 1254. TBEP was non-mutagenic (MacKeller, 1978)

TBEP was tested for mutagenic activity with *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, in the presence and absence of rat liver metabolic system, in comparison with positive controls. The concentrations tested were 0, 50, 100, 500, 1000, 5000 and 10 000 : g/plate with and without S9. Toxicity to strain TA100 was observed at 5000 and 10 000 : g/plate in the presence and absence of metabolic activation. The same effect was seen at 10 000 : g/plate with TA1535 and TA98 in the absence of S9 mix. TBEP did not cause any mutagenic response either with or without metabolic activation (Monsanto, 1984d).

A CHO/HGPRT mammalian cell forward gene mutation assay with TBEP was carried out. The tests were conducted at 50, 100, 150, 225 and 300 : g/ml with S9 and at 5, 50, 75, 100 and 130 : g/ml without S9. TBEP was not mutagenic (Monsanto, 1985c).

A7.6 Carcinogenicity

No data on the carcinogenicity of TBEP are available.

A7.7 Special studies

A7.7.1 *Neurotoxicity*

A7.7.1.1 *Acute administration*

An acute delayed neurotoxicity study was carried out using groups of 20 hens. Dermal or oral (in gelatin capsules) TBEP doses of 5000 mg/kg body weight were administered at the start of the study and again 21 days later. Positive control hens were given 750 mg/kg

body weight of tri-*ortho*-cresyl phosphate (TOCP) at the same time intervals. Negative controls were either untreated (dermal study) or given empty capsules (oral study). All hens were treated with 15 mg/kg body weight of atropine sulfate three times a day for 5 days following each dosing. Hens were killed 21 days after being given the final dose, and histological preparations were made from brain, spinal cord and peripheral nerves. No treatment-related lesions were detected in the nerves of TBEP-treated hens. TBEP had no effect on neuropathy target esterase (NTE). Brain and plasma cholinesterases were inhibited in treated hens (Carrington et al., 1990).

In another study, groups of five hens were treated orally with TBEP (5000 mg/kg), with TOCP (750 mg/kg) as positive control group, or with the capsules alone. The animals were killed 24 h after treatment. Brain AChE, brain neuropathy target esterase (NTE) and plasma butyrylcholinesterase (BuChE) activity was measured. No differences were seen between control and TBEP-treated brain NTE activity, although plasma BuChE and brain AChE levels in TBEP-treated hens were depressed to 5% and 13% of the control group, respectively (Monsanto, 1986).

Laham et al. (1985b) reported the results of the administration by gavage to Sprague-Dawley rats of a single dose of TBEP (98.2%). Groups of randomized female and male rats (10 rats of each sex per dose level) were used. The doses were 1.0, 1.5, 1.75, 2.0 and 3.2 g/kg for females and 1.0, 3.2, 6.8, 8.0 and 9.0 g/kg body weight for males. Three weeks after the administration of TBEP, electrophysiological parameters were determined in four or less surviving animals for each group, selected from survivors showing overt clinical signs. Reductions in caudal nerve conduction velocity and increases in refractory period (in males) were observed. Sciatic nerve sections showed degenerative changes in some myelinated and unmyelinated fibres. It should be noticed that the doses were in the region of or greater than the LD_{50}. There was a high mortality. Survivors were ill and had marked weight loss.

The Task Group considered this study of inadequate quality for use in risk evaluation.

A study of similar design as the oral study of Monsanto (1986) but with dermal application of 5000 mg/kg body weight both on day 0

and on day 21 showed no clinical signs of toxicity in chickens (Monsanto, 1986).

A7.7.1.2 *Repeated oral administration*

In a 14-day repeated-dose study on Sprague-Dawley rats dosed at 0.8 to 2.24 ml/kg body weight (08–2.28 g/kg), electro-physiological measurements were made on days 15 and 28. Apart from a significant decrease in the body weight of low-dose females at 7 days, there were no clinical signs or significant differences between dosed groups and controls in the 14-day study. Minor and inconsistent changes in electro-physiological parameters were reported. No morphological changes were found using light or electron microscopy (Laham et al., 1984b).

A second study (Lahman et al., 1984a) involved dosing on 5 days per week for 18 weeks at dose levels of 0 (0.5 ml water), 0.25 and 0.5 ml/kg body weight (0.25–0.51 g/kg) with observations at 6, 12 and 18 weeks. There were no significant body weight differences between exposed groups and their controls at any stage. A few females (2/12) from the high-dose group showed, at the beginning of the experiment, transient muscular weakness and ataxia which disappeared 4 weeks later. In the second half of the study almost all treated animals exhibited tremors, piloerection, lacrimation and increased urination. Males were less affected than females.

Electro-physiological changes were observed at 18 weeks in all test animals (Table 4) and included a statistically significant reduction in nerve conduction velocity and a significant increase of both relative and absolute refractory periods. The increased refractory period and the decreased conduction velocity were dose-related in females, but in males the maximum effect appears to have been reached by the low dose, suggesting that the magnitude of the maximum attainable neurophysiological changes is modest. Three animals of each sex at each dose level were examined for neurohistological abnormalities by light and electron microscopy of the sciatic nerve. Most of the treated animals showed the presence of some degenerative myelin sheaths accompanied by axonal swelling and an advanced stage of degeneration, indicated by the presence of lamellated electron-dense inclusions in unmyelinated nerve fibres (Laham et al., 1984a).

Table 4. Electro-physiological parameters at 18 weeks in rats treated with TBEP (Laham et al., 1984a)[a]

	Control (water)		Low-dose TBEP		High-dose TBEP	
	Males	Females	Males	Females	Males	Females
Number of animals	12	12	12	12	12	12
Dose (ml/kg per day)	–	–	0.25	0.25	0.5	0.5
Nerve conduction velocity (m/s)	36.3	36.3	30.7[b]	32.0[b]	30.1[b]	30.8[b]
Absolute refractory period in caudal nerve (ms)	1.02	0.95	1.24[b]	1.26[b]	1.24[b]	1.34[b]
Relative refractory period in caudal nerve (ms)	2.06	1.93	2.39[b]	2.33[b]	2.32[b]	2.43[b]

[a] results at 6 and 12 weeks were quantitatively similar to those at 18 weeks
[b] $P<0.001$

In the 18-week studies of Monsanto (1987a,b), TBEP was administered to four groups of 20 male and 20 female Sprague-Dawley rats at concentrations of 0, 300, 3000 and 10 000 mg/kg diet for approximately 18 weeks. No clinical signs of neurotoxicity were observed. The only neurophysiological alteration observed was reduced caudal nerve conduction velocity in high-dose females, and there were no treatment-related changes in peripheral nerve or spinal cord histopathology.

A7.7.1.3 *Effects on esterase activity*

Laham et al. (1984b) reported a 5–7% reduction in red cell cholinesterase activity at 18 weeks in male rats dosed by gavage with 0.25 or 0.5 ml TBEP/kg body weight per day but no reductions in female rats.

A study was made of the effect of TBEP on NTE, brain AChE and plasma BuChE in three groups of five hens. Each was administered a single oral dose of 5000 mg TBEP/kg body weight. All animals were killed 24 h after treatment. The NTE activity was unchanged but plasma BuChE and brain AChE levels were depressed to 5% and 13%, respectively, of control levels (Monsanto, 1986).

In an acute delayed neurotoxicity study in hens, two doses of 5000 mg TBEP/kg body weight were given 21 days apart, each followed by antidote treatment with atropine. There was no effect on NTE activity, whereas brain AChE and serum BuChE were inhibited (Carrington et al., 1990).

A8. EFFECTS ON HUMANS

A repeat human insult patch test on a panel of 209 volunteers was undertaken by Monsanto (1984e). In the 3-week induction period, four applications per week of 0.2 ml of the test material were applied for 24 h to occluded skin. During the fourth week, four similar applications were made to previously untreated sites. During induction, minimal irritation was observed in 9 of the individuals. The irritation was only seen once or twice during the 12 applications. There was no dermal reaction to challenge applications. The results indicate minimal skin irritation and do not indicate any sensitizing potential.

A9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

A9.1 Laboratory experiments

A9.1.1 Aquatic organisms

A9.1.1.1 Invertebrates

The 24-h and 48-h LC_{50} values for TBEP in *Daphnia magna* were 84 mg/litre and 75 mg/litre, respectively. The no-observed-effect concentration (NOEC) was 32 mg/litre (Monsanto, 1984a).

A9.1.1.2 Vertebrates

The 96-h LC_{50} in fathead minnow (*Pimephales promelas*) was 16 mg/litre (95% confidence interval 13-22 mg/litre) at 22 /C (Monsanto, 1984b). The 48-h LC_{50} values in killifish (*Oryzias latipes*) at 10, 20 and 30 /C were 44 mg, 27 mg and 6.8 mg/litre, respectively (Tsuji et al., 1986).

In goldfish (*Carassius auratus*) Eldefrawi et al. (1977) reported no death at 5 mg/litre after 168 h (temperature 20 /C).

In rainbow trout (*Oncorhynchus mykiss*), a 96-h LC_{50} of 24 mg/litre and a NOEC of 10 mg/litre were reported in a test conducted under OECD guideline 203 (Wetton & Handley, 1998).

PART B

TRIS(2-ETHYLHEXYL) PHOSPHATE
(TEHP)

B. SUMMARY, EVALUATION AND RECOMMENDATIONS

B1. Tris (2-ethylhexyl) phosphate (TEHP)

B1.1 Summary

Tris(2-ethylhexyl) phosphate (TEHP) is a non-flammable, colourless liquid with low water solubility and very low vapour pressure, which is used as a flame retardant and plasticizer for PVC and cellulose acetate and as a solvent. It is produced from phosphorus oxychloride and 2-ethylhexanol. Figures for current worldwide production are not available. Approximately 1000 tonnes are currently produced in Germany.

TEHP has not been detected in outdoor air; it has been detected in indoor air at concentrations of less than 10 ng/m^3, in river water at concentrations of up to 7500 ng/litre and in sediments at 2–70 ng/g. TEHP was detected in a single sample of drinking-water at 0.3 ng/litre. Reported daily dietary intake from market basket studies, from a range of age groups, was less than 0.05 : g/kg body weight per day.

TEHP is rapidly biodegraded in natural waters, but in laboratory tests with activated sludge the results were equivocal. There is no significant abiotic degradation.

TEHP has a low acute toxicity for mammals, the oral LD_{50} being >10 000 mg/kg body weight for rats.

TEHP is a skin irritant but not an eye irritant. Repeated application of 0.1 ml (93 mg) TEHP to the skin of rabbits produced no signs of systemic intoxication.

Thirteen-week gavage studies in rats and mice revealed no significant toxic effects. The no-observed-adverse-effect level (NOAEL) in rats was 2860 mg/kg body weight per day and in mice was 5710 mg/kg body weight per day, the highest dose tested in each species.

In a 3-month inhalation study at concentrations up to 85.0 mg $TEHP/m^3$, the lungs of dogs showed mild chronic inflammatory

changes, and conditioned avoidance performance deteriorated in relation to the concentration administered.

No studies on reproductive toxicity were available.

TEHP gave negative results in several *in vivo* and *in vitro* tests for mutagenicity.

TEHP was tested for chronic toxicity and carcinogenicity in rats and mice. The NOAEL for chronic toxicity in male rats was 2857 mg/kg body weight per day and in female rats was 1428 mg/kg body weight per day. In male and female mice, the lowest-observed-adverse-effect level (LOAEL) for thyroid follicular cell hyperplasia was 357 mg/kg body weight per day. A NOAEL in mice was not established. The authors concluded there was some evidence of carcinogenicity based on an increased incidence of hepatocellular carcinomas in female mice at the high-dose level and equivocal evidence of carcinogenicity based on the increased incidence of adrenal phaeochromocytomas in male rats in both dose levels. Although there were increases in adrenal phaeochromocytomas in both dose groups of male rats and in hepatocellular carcinomas in female mice in the high-dose group, these results are not considered to indicate that TEHP presents a significant carcinogenic risk to humans. Phaeochromocytomas show a variable background incidence in rats. The incidences of these tumours in two previous National Toxicology Programme (NTP) bioassays were equal to the incidence observed in the TEHP bioassay. The only other significant neoplastic finding was hepatocellular carcinomas in the high-dose group of female mice. Considering the low incidence of this tumour, its occurrence in only one sex of one species, the lack of evidence of genetic toxicity, and the low exposure of humans to TEHP, it is unlikely that TEHP poses a significant carcinogenic risk to humans.

Neurotoxicity studies have been conducted in several species. TEHP causes no alteration in activity of plasma or red blood cell cholinesterase. No studies on delayed neurotoxicity have been reported.

In a study on human volunteers, no skin irritation was reported.

The few data available indicate a low acute aquatic toxicity of TEHP. The IC_{50} for bacteria is greater than 100 mg/litre and the 96-h LC_{50} for zebra fish *(Brachydanio rerio)* is greater than 100 mg/litre, which is the solubility limit of TEHP in water.

B1.2 Evaluation

Occupational exposure to TEHP is likely to be by the dermal route during manufacture (accidental exposure) and from the use of some products. The compound is absorbed dermally in experimental animals but no information is available on its kinetics or metabolism via this route. Dermal exposure cannot, therefore, be quantified but is expected to be low. Inhalation exposure in the office environment has been measured to be 10 ng/m^3 or less.

Exposure of the general population is principally via food and drinking-water. Exposure from both sources is very low (estimated to be <0.05 : g/kg body weight per day from the diet; a single measured concentration in drinking-water was 0.3 ng/litre).

Given the reported LOAEL for thyroid hyperplasia of 357 mg/kg body weight per day in mice, the risk to the general population is very low. The risk to those exposed occupationally is also considered to be very low, although this cannot be quantified.

TEHP is not considered to be carcinogenic in humans.

In the environment, TEHP is expected (from its low volatility, high adsorption coefficient and low water solubility) to partition to sediment. Measured data are too few to confirm this. Degradation in environmental media is expected, although laboratory data on degradation in sewage sludges are equivocal. No information is available on breakdown products; phosphate released during breakdown is not expected to contribute significantly to environmental nutrient levels. Fig. 2 plots measured environmental concentrations in environmental media against reported acute toxicity values (the latter indicating no toxic effects at the limit of water solubility). The margin of safety between highest reported concentrations and lowest reported toxicity values is several orders of magnitude, indicating low risk to organisms in the aquatic environment. No assessment of risk can be made for the terrestrial compartment.
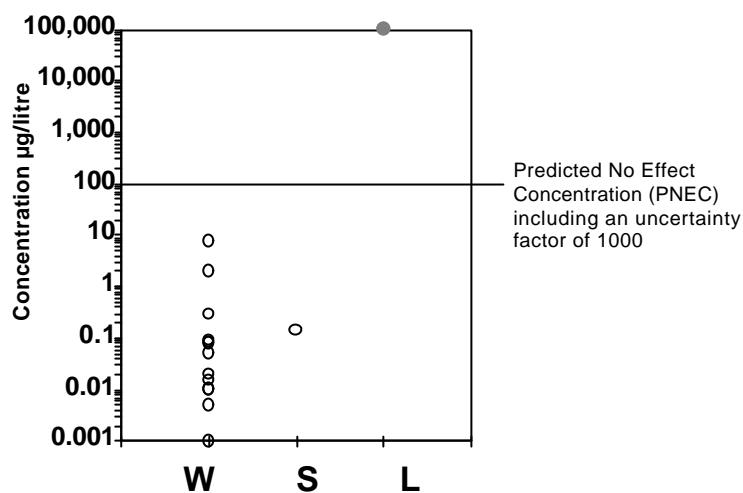
Fig. 2. Plot of measured concentrations in surface waters (W) and sewage
effluents (S), and reported acute toxicity values (L) for TEHP
(F = measured concentrations in the environment; M = calculated LC_{50})

B1.3 Recommendations

For full scientific evaluation of the compound, identification and assessment of metabolites in mammals would be required, given the toxicological profile of one of the suggested metabolites, 2-ethylhexanol.

Reproductive toxicity needs to be investigated, in particular the potential for developmental effects.

B2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

B2.1 Identity

Chemical structure:

$$R - O - \overset{\displaystyle \overset{O}{\parallel}}{\underset{\displaystyle \underset{R}{\overset{\displaystyle O}{\vert}}}{P}} - O - R$$

$$\text{where} \quad R = CH_2 - \underset{\displaystyle \underset{C_2H_5}{\vert}}{CH} - (CH_2)_3 - CH_3$$
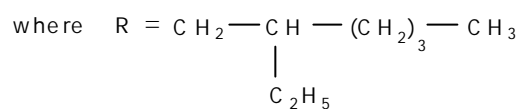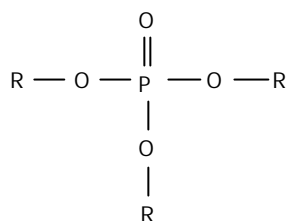
Chemical formula:	$C_{24}H_{51}O_4P$
Relative molecular mass:	434.64
CAS registry number:	78-42-2
EINECS number:	201-116-6
RTECS number:	MP-0770000
CAS name:	phosphoric acid, tris(2-ethylhexyl) ester
Synonyms:[a]	1-hexanol 2-ethyl-phosphate; 2-ethyl-1-hexanol phosphate; triethylhexyl phosphate; tri(2-ethylhexyl) phosphate; tris(isooctyl) phosphate

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[a] The synonym trioctyl phosphate has also been used. However, this chemical has a different chemical abstracts (CAS) registry number (1806-54-8).

Trade names: Disflamoll TOF; Flexol TOF; Reomol TOP; Amgard TOF; Antiblaze TOF

B2.2 Physical and chemical properties

Tris(2-ethylhexyl) phosphate (TEHP) is a colourless to light yellow liquid, non-flammable and nearly odourless (Arias, 1992).

Boiling point: 220 /C at 6.67 hPa; 210 /C at 5 hPa

Melting point: ! 74 /C

Pour point: ! 70 /C

Relative density: 0.926 at 20 /C

Refractive index: 1.4426 at 20 /C

Vapour pressure: <0.1 hPa at 20 /C

Viscosity: 10.2 cP

Stability: stable under normal storage conditions; can react with oxidizers

Flash point: 190–195 /C

Solubility: soluble in acetone, ether and ethanol; in DMSO 1.0 mg/litre at 18 /C; in water less than 0.1 g/litre at 20 /C

n-Octanol/water partition coefficient 4.22

From: MacFarland & Punte (1966); Saeger et al. (1979); Keith & Walters (1987); Hinckley et al. (1990); FMC (1998).

B2.3 Conversion factors

1 ppm	=	17.78 mg/m^3
1 mg/m^3	=	0.056 ppm

B2.4 Analytical methods

The analytical methods for TEHP are based on gas chromatography combined with flame ionization detection (FID), flame photometric detection (FPD), mass spectroscopy (MS) or nitrogen-phosphorus sensitive detection (NPD). The detection limits are in the ng/m^3 (air) and ng/litre (water) range.

Lerche & Morch (1973) determined TEHP using GC combined with FID with a detection limit of 5–30 ng/litre. The separation of various phosphoric acid esters by GC was achieved using columns filled with various liquid silicone phases.

B2.4.1 Air

In a method described by Krzymien (1981), TEHP vapour and aerosol were collected in glass absorber tubes packed with a plug of fine platinum mesh coated with silicone packing material and subsequently thermally desorbed into a GC for analysis. The capacity of the absorber was found to be 2.1 ng pure TEHP when presented with 3 ng TEHP/litre. Concentrations of 20 pg/litre were determined with a precision of better than 10%. The aerosol concentration and its drop-size distribution were determined at the picogram level with around 5% precision using a cascade impactor. Armstrong & Yule (1978) determined TEHP deposited on foliage and twigs by extraction with toluene, drying with anhydrous sodium sulfate and using GC with FPD.

B2.4.2 Water

LeBel et al. (1981) used Amberlite(R) XAD-2 macroreticular resin to collect TEHP from drinking-water. The resin was extracted with an acetone/hexane mixture. TEHP was identified by GC and by GC/MS at ng/litre levels. The recovery by direct fortification was 62%. Determination of TEHP in extracts of activated carbon by means of GC/MS was described by Frimmel et al. (1987). TEHP was extracted from activated charcoal using a mixture of acetone, dichloromethane and toluene.

Kawagoshi & Fukunaga (1994, 1995) showed, by extracting leachate with dichloromethane and analysing the residue by GC-FPD,

that it was possible to detect organophosphoric acid triesters, including TEHP, at a limit of detection of 2 ng/litre.

B2.4.3 Sediment

Sediment samples were extracted with acetone and dried, concentrated and analysed by Ishikawa et al. (1985) in a similar way to that used for water samples. The limit of determination was 10 ng/g.

B3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

B3.1 Natural occurrence

TEHP does not occur naturally in the environment.

B3.2 Anthropogenic sources

B3.2.1 Production levels and processes

In 1992, approximately 1000 tonnes of TEHP were manufactured in Germany (BUA, 1997).

Figures for the world production of TEHP are not available. ECETOC (1992a) estimated the world production to be between 1000 and 5000 tonnes/year.

TEHP is produced by reaction of phosphorus oxychloride and 2-ethylhexanol. The triester is separated by vacuum distillation. Technical grade TEHP is usually 99% pure. The impurities are 2-ethylhexanol, bis(2-ethylhexyl) phosphate (BEHP) and traces of water (ECETOC, 1992a).

B3.2.2 Uses

TEHP is used in PVC plastisols, as a flame retardant in cellulose acetate and as a solvent for certain chemical reactions. It is also used as a flame retardant plasticizer, particularly for PVC, in low temperature application (ECETOC, 1992a).

B4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

B4.1 Biodegradation

Biodegradation of phosphoric acid esters involves stepwise hydrolysis to *ortho*-phosphate and alcohol moieties. The alcohol would then be expected to undergo further degradation (Saeger et al., 1979).

In a ready biodegradability closed bottle test (OECD Guideline 301D), no biodegradation of TEHP was observed after 28 days (Bayer, 1982a).

An activated sludge method, based on a semi-continuous procedure, was used to test primary degradation of TEHP. The addition rate of the compound was 3 mg/litre per 24 h and the biodegradation was 20 ($\pm$ 8)% after 34 weeks (Saeger et al., 1979).

TEHP was rapidly biodegraded (50% in 48 h) by activated sludge (Ishikawa et al., 1985). After a 48-h acclimation period, the biodegradation increased to 60% during a further 48-h test period.

Hattori et al. (1981) studied the fate of TEHP in river water and seawater from the Osaka Bay area, Japan. After addition of TEHP at a level of 1 mg/litre, the biodegradation was followed by analysing the increase in phosphate ion concentration using the molybdenum blue colorimetric method. The percentages of biodegradation are given in Table 5.

Table 5. Biodegradation of TEHP in river water and seawater
(in percentages)

Test duration (days)	Oh River	Neya River	Osaka Bay	
			Tomogashima seawater	Senboku seawater
7	35.9	24.4	1.2[b]	9.9
14	65.2[a]	42.2	32.5	73.2

[a] Test period 15 days
[b] Test period 8 days

In sterilized water TEHP did not show any degradation after 15 days. The authors (Hattori et al., 1981) stated that the degradation rate depended on the microbial content of the water, and this view was supported by the increase of phosphatase activity observed during the test period.

Similar results were reported by Kawai et al. (1985, 1986) for river die-away tests with TEHP in water samples from rivers of the Osaka City area, Japan. Depending on the bacterial content of the water, up to 80% degradation was observed. Usually the TEHP concentration decreased rapidly during the first 10 days. Fukushima & Kawai (1986) found that the removal of TEHP in a wastewater treatment plant (Osaka City) with aquatic bacteria was up to 99%.

B4.2 Bioaccumulation

Saeger et al. (1979) estimated the bioconcentration factor (BCF) of TEHP to be 250, suggesting that some uptake by biota could occur.

B5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

B5.1 Environmental levels

B5.1.1 Air

In New Brunswick, Canada, forest ambient concentrations of TEHP in air were below the limit of determination (20 ng/m^3 with a precision of ± 5%) (Krzymien, 1981).

When samples of particulates in air were collected in a large building in New Jersey, USA, the relative abundance of TEHP in the submicron particle size range was much higher than in any larger size range, suggesting that its presence did not result from abrasion (Weschler, 1980). Airborne concentrations of TEHP were measured in fine (2.5 : m) and coarse (2.5 to 15 : m) particulate fractions collected on filters simultaneously outdoors and indoors in Wichita, Kansas, USA during the autumn and early winter of 1981–1982. The average indoor concentration was 6 ng/m^3, but TEHP was not detected in outdoor air (Weschler, 1984). The mean concentration measured in representative samples of dust of seven office buildings in the USA was reported to be 5 ng/m^3 (Weschler & Shields, 1986).

B5.1.2 Surface water

As a part of the German Monitoring Programme, water from the River Weser was examined for concentrations and loads of various chemicals including plasticizers. Several samples were taken at various points over 35 km of the river. The average concentration of TEHP over 10 sampling points did not exceed 10 ng/litre at any time. On one day in 1987 peak values of 290 ng/litre were measured, indicating direct emissions (Bohlen et al., 1989).

Water samples from estuaries of the German rivers Elbe, Weser and Ems were analysed from 1977 to 1983. TEHP could be identified only in water samples from the estuary of the River Elbe, where concentrations were in the range of 1–5 ng/litre (Weber & Ernst, 1983). In a second series of water samples from the estuaries of the Elbe and Weser (taken in 1983–1985) concentrations of approximately 90 to 7500 ng TEHP/litre were measured (Ernst, 1988).

The concentration of TEHP in Rhine water at Dusseldorf was usually below 20 ng/litre. The maximum concentration found was 50 ng/litre (ARW, 1987).

Ishikawa et al. (1985) could not detect TEHP at 16 river sampling sites or nine seawater sampling sites around Kitakyushu, Japan. The limit of determination was 20 ng/litre.

TEHP was found in water of the Yodo River (Osaka area) at concentrations of 80–2000 ng/litre, with a mean value of 100 ng/litre. The detection limit was 80 ng/litre (Fukushima et al., 1986). In river water of the Osaka City area, Kawai et al. (1985) detected 15–84 ng/litre (determination limit not reported).

No TEHP could be detected in 63 water samples from 21 locations throughout Japan (with a limit of determination of 10 ng/litre) collected during the period 1974–1981 (Environmental Agency Japan, 1983, 1987).

B5.1.3 Drinking-water

In drinking-water samples collected during October 1978 from two Eastern Ontario (Canada) water treatment plants, TEHP was detected at a concentration of 0.3 ng/litre in water from one plant (LeBel et al., 1981).

B5.1.4 Effluents

In a study of organic pollutants from influent and effluent of the Gothenburg regional sewage plant (Sweden) during the period 1989 to 1991, TEHP was not detected (limit of detection unknown) (Paxeus et al., 1992). Effluent from water treatment plants into the River Weser, Germany, contained up to 144 ng TEHP/litre (Bohlen et al., 1989).

In a study of leachate from Osaka North Port (Japan) sea-based solid waste disposal site and surrounding seawater, no TEHP was detected (Kawagoshi & Fukunaga, 1994).

B5.1.5 Sediment

An environmental monitoring programme was carried out during the period 1974–1981. Bottom deposit samples were collected at 21 sites all over Japan. In 43 out of 63 of the samples, levels of 2–7 : g/kg were found. The limit of determination was 1–5 : g/kg (Environmental Agency Japan, 1983).

In one river sediment and five sea sediment samples, Ishikawa et al. (1985) could not detect TEHP. The limit of determination was 10 : g/kg.

B5.1.6 Food

Total-diet studies of the US Food and Drug Administration were reported by Gartrell et al. (1986b). Baskets of 120 food items representing a typical 14-day diet for infants, young children and adults were collected from October 1980 to March 1982 from retail markets throughout the USA. Foods were classified into various groups. TEHP was found in the oil and fat food group of the diet used by young children. The average concentration in this food group was 38.5 : g/kg, and the average daily intake was calculated to be 0.385 : g/day.

In follow-up reports, Gunderson (1988, 1995a,b) presented data for various groups of age (Table 6).

In adult total diet samples, collected during October 1980 to March 1982, TEHP was found only in the meat, fish and poultry food group at an average concentration of 6.7 : g/kg; the average daily intake was calculated to be 1.73 : g/day. All the other food groups, i.e., dairy products, grain and cereals, potatoes, leafy vegetables, legume vegetables, root vegetables, fruits, oils and fats, sugar and adjuncts and beverages (including water), were free of TEHP (Gartrell et al., 1986a).

The daily intakes of TEHP with adult food for 1978, 1979, 1980 and 1981/1982 were nd, nd, nd and 0.025 : g/kg body weight per day, respectively (Gartrell et al., 1986a).

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Table 6. Mean daily intake (: g/kg body weight per day) of TEHP according to age and gender

	6–11 months old	2 years old	14–16 years old		25–30 years old		60–65 years old	
			females	males	females	males	females	males
1982–84	0.0272	0.071	0.0249	0.0317	0.024	0.0282	0.0232	0.0264
1984–86	0.0018	0.015	0.011	0.0101	0.0392	0.0385	0.0444	0.0471
1986–91	0.0015	0.0051	0.0029	0.0033	0.0039	0.0055	0.0033	0.0037

In a similar study on ready-to-eat food sampled during 1982–1991, TEHP was found in 22 out of 230 food items. Raw sweet cherries contained the highest concentration (505 : g/kg) (Kan-Do Office and Pesticide Team, 1995).

B6. KINETICS AND METABOLISM IN LABORATORY ANIMALS

In an inhalation study, nine male rats received a single, head-only exposure of 20 min to an aerosol of [^{32}P]-TEHP. The animals were killed after the following post-exposure intervals: 5 min, 30 min; 1, 4, 17, 18, 24, 48 and 70 h. Exposure concentrations were 0.72 and 0.91 mg/litre. TEHP and/or its metabolites were distributed into the lungs (13% of total radioactivity after 5 min), stomach contents (64% after first hour), brain and liver (9 and 16%, respectively, after 30 min). Spleen, kidney, bone, muscle and fat retained less than 2% of the radioactivity at any time. Faecal excretion was high but urinary excretion was relatively low. Chromatographic analysis of urine and faeces showed TEHP was partly biotransformed but the nature of the metabolites was not mentioned (MacFarland & Punte, 1966).

Kluwe et al. (1985) assumed, although no confirmatory data are available, that TEHP is hydrolysed to 2-ethylhexanol and di(2-ethylhexyl) phosphate. This may be analogous to other compounds containing 2-ethylhexyl ester groups, which could be readily hydrolysed to the corresponding mono- or di-ester and 2-ethylhexanol.

B7. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

B7.1 Single exposure

The LD_{50} values for TEHP are summarized in Table 7.

Table 7. Acute toxicity of TEHP

Route	Species	LD_{50}	Reference
Oral	rat	37.08 g/kg body weight	Smyth & Carpenter (1948)
Oral	rat	>10.0 g/kg body weight	Bayer (1958)
Oral	rat	>36.8 g/kg body weight	MacFarland & Punte (1966)
Oral	rabbit	46.0 g/kg body weight	MacFarland & Punte (1966)

From Table 7, it can be concluded that TEHP has low acute toxicity by the oral and dermal routes.

Acute inhalation toxicity of TEHP has been investigated in Wistar rats and Hartley guinea-pigs. Groups of 10 animals of each species (sex not stated) were used. Rats were exposed to air concentrations of 287 to 460 mg/m^3 for 30 to 210 min without any mortality in any group. Guinea-pigs were exposed to air concentration of 287 to 460 mg/m^3 for 30 to 180 min, with some mortality in each group, varying from 30% (at 450 mg/m^3 for 30 min, 298 mg/m^3 for 60 min, and 460 mg/m^3 for 60 min) to 80% (at 287 mg/m^3 for 120 min). The mass median diameter for the TEHP aerosol was 1.5 ∶ m (MacFarland & Punte, 1966).

B7.2 Repeated exposure

B7.2.1 Oral

Feeding doses of 110–1550 mg TEHP/kg body weight per day to rats in their diet for 30 days revealed a NOEL of 430 mg/kg body weight. At 1550 mg/kg body weight, weight loss was observed (Smyth & Carpenter, 1948).

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In a 2-week dose range-finding study, groups of five male and five female F 344/N rats and five male and five female B6C3F$_1$ mice were administered 0, 375, 750, 1500, 3000 or 6000 mg TEHP/kg body weight in corn oil by gavage for 14 consecutive days. No animals died. There was no effect on body weight gain in mice. The final mean body weights of male rats that received 1500–6000 mg/kg body weight and female rats that received 3000–6000 mg/kg body weight were lower than those of the vehicle controls (US NTP, 1984).

Group s of 10 Fisher-344 rats of each sex received 0, 250, 500, 1000, 2000 or 4000 mg TEHP/kg body weight by gavage in corn oil on 5 days/week for 13 weeks and groups of 10 mice of each sex were administered 0, 500, 1000, 2000, 4000 or 8000 mg/kg body weight. The animals were examined twice daily and body weights were recorded weekly. Postmortem and histopathological examinations were performed on all animals except those excessively autolysed or cannibalized. No deaths, toxic effects or induced histological alteration were attributed to TEHP administration at any of these treatment dosage levels other than a slight to moderate suppression in body weight gain (US NTP, 1984; Kluwe et al., 1985). The suppression of body weight gain at the highest dose in male and female rats was 5%; in male and female mice the suppression of weight gain at the highest dose was 7% and 5%, respectively. The Task Group did not consider these minimal changes biologically significant. Hence, the NOAEL in rats was 2860 mg/kg body weight per day and in mice 5710 mg/kg body weight per day.

Results of a 2-year study on rats and mice are given in section B7.6.

Two cats were administered 1.0 ml (926 mg) TEHP/kg body weight per day by gavage 5 days/week for 4 weeks. During the treatment and the recovery periods there were no signs of intoxication. Measurements of erythrocyte cholinesterase activity during the test period revealed no inhibitory effects (Bayer, 1958).

B7.2.2   Dermal

A daily dose of 0.1 ml (93 mg) undiluted TEHP was applied 5 days a week to the clipped intact skin of six male rabbits (2–3 kg). Four animals received ten applications and the remaining two animals 20

applications. No evidence of systemic intoxication was seen based on gross necropsies and on the fact that animals, with one exception, gained weight throughout the study (MacFarland & Punte, 1966).

B7.2.3 Inhalation

In a 3-month inhalation study, three test groups and a control group, each consisting of equal numbers of males and females and comprising 20 guinea-pigs, two dogs and two rhesus monkeys, were exposed whole body for 6 h/day, 5 days/week for a total of 60 exposures (MacFarland & Punte, 1966). Three concentrations of TEHP aerosol were tested; controls received the same air-flow but without TEHP. The mean concentrations and standard deviations received by the three test groups over the 12-week period were: low-dose, 10.8 ± 6.0 mg/m^3; mid-dose, 24.4 ± 16.8 mg/m^3; high-dose, 85.0 ± 33.3 mg/m^3. The median particle size was 4.4 ∶ m with a geometric standard deviation of 3.0.

No mortality and a normal increase in body weight was observed in dogs and monkeys. There were no treatment-related alterations in a limited range of biochemical and haematological parameters and organs function test. Activities of plasma and erythrocyte cholinesterases were unaffected. While the lungs of monkeys were normal, the lungs of dogs showed mild, chronic parenchymal inflammatory changes. In an evaluation of effects on trained behaviour, no effects were detected in the performance of monkeys in a visual discrimination test; the performance of dogs trained in conditional avoidance deteriorated as the exposure concentration increased. The guinea-pig portion of the study was invalidated due to the high mortality from intercurrent respiratory infections.

The 3-month inhalation study was repeated with guinea-pigs. Two groups of 20 male guinea-pigs were exposed to two concentrations of TEHP. A third group acted as control and inhaled uncontaminated air in the exposure chamber. Tetracycline was administered prophylactically in the drinking-water throughout the study. The mean concentrations and standard deviations for the two test groups were: low dose, 1.6 ± 0.8 mg/m^3; high-dose, $9.6 \pm 1/5$ mg/m^3. Exposures were for 6 h/day, 5 days/week for a total of 60 exposures. The mean particle size was 3.8 ∶ m with a geometric standard deviation of 1.7.

The high-dose guinea-pigs showed a significantly increased body weight in comparison with the controls. Plasma and erythrocyte cholinesterase activities were unaffected in terminal blood samples. Both test groups exhibited a lower kidney-to-body weight ratio than the controls. Histopathological alterations in the lung, liver and kidneys were not related to the treatment. Sections of the spinal cord and sciatic nerve, stained to demonstrate the myelin sheaths, showed no pathological changes (MacFarland & Punte, 1966).

B7.3 Skin and eye irritation; sensitization

No irritation was seen after exposure to TEHP by a saturated cotton swab placed on the inside of the ears of rabbits for 24 h (Kimmerle, 1958).

TEHP was tested in three albino rabbits according to OECD 404 test guideline. Well-defined erythema, slight to moderate oedema, crust formation and desquamation were observed. TEHP produced a primary irritation index of 4.2/8.0 and was classified as a moderate irritant to rabbit skin. No corrosive effects were observed (Guest, 1993b).

A single dose of 250 mg undiluted TEHP applied to the clipped skin of rabbits produced moderate erythema, which persisted for a week (MacFarland & Punte, 1966). Repeated applications of 0.1 ml on 5 days/week (10 or 20 applications) produced moderate erythema after the first application. With further applications a spreading zone of erythema developed with desquamation, leatheriness and some fissuring with haemorrhages. At the end of the observation period, thickening and severe hyperkeratosis of the skin was apparent.

TEHP was non-irritating when tested in the eyes of three albino rabbits according to OECD 405 Test Guideline (Guest, 1993a).

TEHP was instilled into the conjunctival sac of one eye of each of two rabbits at dose levels of 0.01 to 0.5 ml. Doses up to 0.05 ml produced slight conjunctivitis, while doses of 0.1 and 0.5 ml produced moderate conjunctivitis which cleared up in 24 h (MacFarland & Punte, 1966).

B7.4 Reproductive toxicity, embryo toxicity and teratogenicity

No data on the reproductive toxicity of TEHP are available.

B7.5 Mutagenicity

TEHP was shown to be non-genotoxic in a range of mutagenicity assays.

B7.5.1 In vitro *assays*

TEHP was tested for mutagenicity in a *Salmonella*/microsome assay using strains TA1535, TA1537, TA98 and TA100 in the presence and absence of S9 derived from livers of Aroclor 1254-treated Sprague-Dawley rats. Results were negative (Zeiger et al., 1985).

In a mouse lymphoma assay, concentrations of TEHP of up to and exceeding the apparent solubility limit of 62.5 : l/litre produced no gene mutations. The assay was carried out in the presence and absence of S9 from livers of Aroclor 1254-treated male F-344 rats (Myhr & Caspary, 1991).

An *in vitro* cytogenetic assay in Chinese hamster ovary (CHO) cells was carried out using concentrations of TEHP up to 251 : g/ml in the presence and absence of S9 derived from livers of Aroclor 1254-treated Sprague-Dawley rats. There was no evidence of induction of chromosome damage (Ivett et al., 1989).

An *in vitro* sister-chromatid exchange (SCE) assay was carried out in CHO cells in the presence and absence of S9 derived from livers of Aroclor 1254-treated Sprague-Dawley rats. Concentrations of up to 251 : g/ml were used, but at 16.7 : g/ml and above there was severe cell cycle delay, which limited the number of cells available for analysis. TEHP did not increase the number of SCEs (Ivett et al., 1989).

B7.5.2 In vivo *assays*

A mouse bone marrow micronucleus assay was carried out in male B6C3F$_1$ mice, which were given intraperitoneal TEHP injections of 500, 1000 or 2000 mg/kg body weight on three consecutive days. Bone marrow was harvested at 24 h after the last dose, and was examined for micronucleus-containing polychromatic erythrocytes (MN-PCEs). A

statistically significant ($P < 0.001$) dose-related increase in the number of MN-PCEs was detected in the bone marrow from treated mice. The assay was repeated in two further experiments using doses of 1500 and 2000 mg/kg body weight in one and 2000 and 3000 mg/kg body weight in the other. No increase in the number of bone marrow MN-PCEs was detected in either of these experiments. It is concluded that the initial result was an artefact and that TEHP is not mutagenic in this assay (Shelby et al., 1993).

An *in vivo* cytogenetic assay was carried out in male B6C3F$_1$ mice, which were given a single intraperitoneal injection of TEHP (dose not stated). Bone marrow was harvested for analysis at 17 and 36 h post-dosing and metaphase cells were examined for chromosomal aberrations. The number of chromosomal aberrations was not elevated in TEHP-treated mice (Shelby & Witt, 1995).

In an *in vivo* liver unscheduled DNA synthesis (UDS) assay, male B6C3F$_1$ mice were given TEHP doses of 1000 or 2000 mg/kg body weight by gavage. Mice were killed at 24, 39 and 48 h post-dosing and liver preparations were made. There was no evidence of increased UDS in hepatocytes from TEHP-treated mice (Miyagawa et al., 1995).

B7.6 Carcinogenicity

In a US NTP (1984) study, TEHP was administered in corn oil (10 ml/kg body weight) by gavage 5 days/week for 103 weeks to groups of 50 male and 50 female F-344/N rats and B6C3F$_1$ mice. The doses administered were:

| Dose | Fischer-344 rats | | B6C3F$_1$ mice | |
	Male	Female	Male	Female
Control	Vehicle	Vehicle	Vehicle	Vehicle
Low dose	2000 mg/kg	1000 mg/kg	500 mg/kg	500 mg/kg
High dose	4000 mg/kg	2000 mg/kg	1000 mg/kg	1000 mg/kg

The animals were observed twice daily and body weight was measured weekly for the first 13 weeks and once every 4 weeks thereafter. Clinical examinations were performed once every 4 weeks. Necropsies and histopathological examinations were performed on all animals, but organ weight changes were not reported.

No compound-related clinical toxicity was observed in either sex of either species. Decrease in body weight, compared with controls, was limited to male rats at the low dose (11.5%) and the high dose (15.8%). The decreased body weight did not affect survival.

In male rats the incidence of phaeochromocytomas of the adrenal gland increased with dose and two (4%) were malignant in the high-dose group. The incidence of adrenal phaeochromocytomas in male rats was: control 2/50 (4%), low-dose 9/50 (18%) and high-dose 12/50 (24%). In two previous gavage studies in the same laboratory, the incidence of phaeochromocytomas in control male rats was 24 and 26%.

In female mice the incidence of hepatocellular carcinomas was: control 0/48 (0%), low dose 4/50 (8%) and high dose 7/50 (14%). The incidence of hepatocellular carcinomas showed a dose-related increase and the incidence at the high-dose level was statistically significant.

The results of these 2-year gavage studies in rats and mice were interpreted by NTP as showing some evidence of carcinogenicity in female mice based on the increase in hepatocellular carcinomas and equivocal evidence of carcinogenicity in male rats based on the increased incidence of phaeochromocytomas (US NTP, 1984; Kluwe et al., 1985)

In this same study (US NTP, 1984), TEHP caused a dose-related increase in the incidence of follicular cell hyperplasia of the thyroid in male and female B6C3F$_1$ mice. The incidence of hyperplasia was: in males, control 0/49 (0%), low dose 12/48 (25%) and high dose 24/47 (51%); in females, control 1/44 (2%), low dose 13/47 (28%) and high dose 12/46 (26%). There was no dose-related increase in thyroid tumours. The LOAEL for thyroid hyperplasia was 357 mg/kg body weight per day; a NOAEL was not established.

B7.7 Special studies

B7.7.1 *Neurotoxicity*

MacFarland & Punte (1966) tested TEHP for its neurotoxic potential. Four groups of female chickens, each weighing 1.5–2.0 kg, received a single dose of test material into the crops as follows:

Group	Number of chickens	Test material	Dose
1	4	Saline	1.5 ml/kg
2	8	TOCP	500 mg/kg
3	8	TEHP	500 mg/kg
4	8	TEHP	2500 mg/kg

After receiving a single dose of the test material the animals were kept under observation for 4 weeks and then killed. Body weights were recorded weekly and changes in appearance and behaviour noted daily. Gross necropsy was performed on all chickens. Sections of brain, three levels of the spinal cord and the sciatic nerve were examined microscopically.

In the tri-*ortho*-cresyl phosphate (TOCP) group used as positive control, weight loss become apparent by the end of the first week and signs of ataxia and muscular weakness were evident by the 12th day.

These signs increased in intensity, so that the chickens were prostate by the end of the study. The microscopic examination of the nerve tissue sections confirmed that TOCP was producing demyelinization. The chickens in the saline and TEHP groups appeared normal and maintained or gained weight throughout the study. There were no macroscopic signs of neurotoxicity and microscopically no demyelinization was observed.

No evidence of systemic intoxication or, in particular, neurotoxicity was seen in chickens dosed with a single dose of up to 2.500 mg TEHP/kg body weight (MacFarland & Punte, 1966).

Single hens were administered a single dose of 0.25, 0.5 or 1.0 g/kg body weight by gavage. The animals were kept under observation for 2 months and examined for neurotoxicity twice weekly. No abnormalities in behaviour were detected. A single intramuscular injection of 0.25, 0.5 or 1.0 g TEHP/kg body weight to single chicken again induced no signs of intoxication (Kimmerle, 1958).

In 3-month inhalation studies (see section B7.2.3) with guinea-pigs, dogs and rhesus monkeys, determination of plasma and erythrocyte cholinesterase activity and histological examination of sections of tissue including spinal cord and sciatic nerve did not reveal

any abnormalities. In dogs and rhesus monkeys, the cholinesterase were measured after 4, 8 and 12 weeks of exposure to 10.8, 26.4 or 85 mg TEHP/m^3, but in guinea-pigs measurements were made after 12 weeks of exposure to 1.6 or 9.6 mg/m^3 (MacFarland & Punte, 1966).

In two cats receiving 28 doses of 1.0 ml TEHP/kg body weight by gavage (see section 7.2.1) no signs of neurotoxicity and no inhibition in the erythrocyte cholinesterase activity was found (Bayer, 1958).

B8. EFFECTS ON HUMANS

No irritant effects were seen after 24 h of exposure to a TEHP-saturated cotton swab placed on the skin of the forearm of six volunteers. A piece (2 cm^2) of PVC plastic containing 40% TEHP was placed on the arm of 8 volunteers for 72 h. Slight redness but no irritation was observed (Kimmerle, 1958).

No other data are available concerning the effect of TEHP on humans.

B9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

B9.1 Laboratory experiments

B9.1.1 Microorganisms

A bacterial growth inhibition test, carried out according to ISO 8192 indicated an IC_{50} for TEHP greater than 100 mg/litre (Bayer, 1982b).

B9.1.2 Aquatic organisms

B9.1.2.1 Vertebrates

A 96-h exposure of zebra fish (*Brachydanio rerio*) under static conditions to TEHP (100 mg/litre) produced no deaths (Bayer, 1989).

B9.1.3 Terrestrial organisms

No data on the toxicity of TEHP to terrestrial organisms are available.

PART C

TETRAKIS(HYDROXYMETHYL)
PHOSPHONIUM SALTS

C. SUMMARY AND EVALUATION

C1. Tetrakis(hydroxymethyl) phosphonium salts

C1.1 Summary

Tetrakis(hydroxymethyl) phosphonium salts represent the major class of chemicals used as a flame retardant for cotton, cellulose and cellulose-blend fabrics. There is low migration from fabrics treated with tetrakis(hydroxymethyl) phosphonium chloride (THPC)-urea. The sulfate salt (THPS) is mainly used as a biocide. Combined world production is estimated to be >3000 tonnes for THP salts and around 3000 tonnes for the THPC-urea condensate.

Photodegradation and hydrolysis of THP salts are significant abiotic degradation pathways in the environment. THPS binds poorly to environmental particulates and is, therefore, mobile. THPS degrades rapidly under both aerobic and anaerobic conditions. Trihydroxymethyl phosphine oxide (THPO) and bishydroxymethyl phosphonic acid (BMPA) have been identified as breakdown products.

Since no monitoring has been reported, no estimates can be made of exposure to humans or organisms in the environment.

The acute oral toxicity of THPC and THPS is moderate; dermal toxicity is low.

In short-term (up to 28 days) studies in rats and mice, the main toxic effect for both THPC and THPS is decreased body weight. The NOAEL for both chemicals in both species is approximately 8 mg/kg body weight per day. In longer-term studies (13 weeks), the main target organ for toxicity is the liver. The NOAEL for this effect ranged from 3 to 7 mg/kg body weight per day for both salts in both species. Carcinogenicity bioassays on THPC also showed effects on the liver, but a NOAEL was not established. The LOAEL was approximately 3 mg/kg body weight per day for both species. In a carcinogenicity bioassay on THPS in mice, the NOAEL for focal hyperplasia in the adrenal medulla was 3.6 mg/kg body weight per day; in rats the LOAEL for mortality was 3.6 mg/kg body weight per day.

THPS did not cause skin irritation when administered as a single dose to rabbits. However repeated dermal exposure of rats resulted in severe skin reaction. THPC-urea was corrosive. THPS was identified as severe eye irritant in rabbits.

THPS and THPC-urea cause skin sensitization guinea-pigs (Magnusson & Kilman Maximization test).

THPS and THPC-urea did not cause developmental toxicity in orally dosed experimental animals.

THPC and THPS have mutagenic potential *in vitro*, but THPS is not mutagenic *in vivo* (no *in vivo* mutagenicity data are available for THPC). Limited mutagenicity data for THPC-urea suggest that it is not mutagenic *in vivo*. THPO is non-genotoxic. There is no convincing evidence to suggest that fabrics treated with THP salts are mutagenic. Available information indicates that there is no genotoxic hazard to humans.

THPC and THPS were not carcinogenic in rats and mice in 2-year bioassays. Dermal studies have shown that THP salts are promoters of skin cancer but not initiators.

THPS and THPO did not inhibit acetylchlolinesterase activity *in vitro*, suggesting a lack of neurotoxic hazard for humans.

THPC-urea-treated fabric did not cause skin irritation in humans.

For THPS, reported acute toxicity values for algae are less than 1 mg/litre, with one no-observed-effect concentration (NOEC) of 0.06 mg/litre. The acute NOEC for the water flea is 10 mg/litre. Reported acute toxicity values for marine invertebrates range from 1.6 to 340 mg/litre.

Fish 96-h LC_{50} values range from 72 to 119 mg/litre, with NOEC values in the range of 18 to 41 mg/litre. An acute avian LD_{50} of 311 mg/kg body weight and dietary LC_{50} values of 1300 and 2400 mg/kg diet have been reported.

C1.2 Evaluation

No exposure information is available for either humans or organisms in the environment. Therefore no quantitative risk assessment could be made.

C2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

C2.1 Identity

Tetrakis(hydroxymethyl) phosphonium salts (THP salts) have the following general chemical structure :

$$HOH_2C \diagdown \quad \diagup CH_2OH$$
$$P^+ \text{———} R^-$$
$$HOH_2C \diagup \quad \diagdown CH_2OH$$
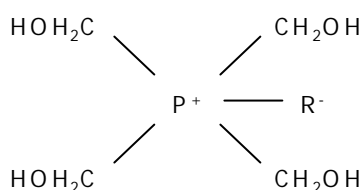
The commercially relevant salts of THP are the sulfate (THPS) and the chloride (THPC). In addition, tetrakis(hydroxymethyl) phosphonium chloride-urea condensate is the major commercially available flame retardant product.

In the past other salts and salt-urea condensates have been used; their names and CAS numbers are listed in IARC (1990).

C2.1.1 Tetrakis(hydroxymethyl) phosphonium chloride (THPC)

Chemical formula: $C_4H_{12}O_4PCl$

Chemical structure:

$$HOH_2C \diagdown \quad \diagup CH_2OH$$
$$P^+ \quad Cl^-$$
$$HOH_2C \diagup \quad \diagdown CH_2OH$$
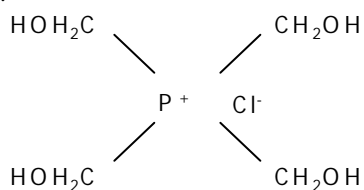
Chemical name: Phosphonium, tetrakis(hydroxymethyl) chloride

Relative molecular mass: 190.56

CAS registry number:	124-64-1
CAS name:	Phosphonium tetrakis(hydroxymethyl) chloride
IUPAC name:	Tetrakis(hydroxymethyl) phosphonium chloride
Trade names:	Tolcide PC800; Tolcide THPC; Retardol C
Synonyms:	Tetrahydroxymethyl phosphonium chloride Tetramethylol phosphonium chloride

C2.1.2 Tetrakis(hydroxymethyl) phosphonium sulfate (THPS)

Chemical formula: $C_8H_{24}O_8P_2O_4S$

Chemical structure:

$$\left[\begin{array}{c} HOH_2C \diagdown \qquad \diagup CH_2OH \\ P^+ \\ HOH_2C \diagup \qquad \diagdown CH_2OH \end{array}\right]_2 SO_4^{2-}$$
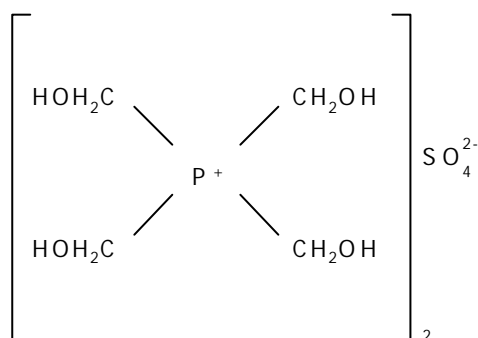
Chemical name:	Phosphonium, tetrakis(hydroxymethyl) sulfate
Relative molecular mass:	406.28
CAS registry number:	55566-30-8

CAS name:	Phosphonium, tetrakis(hydroxymethyl) sulfate (2:1)
IUPAC name:	bis[tetrakis(hydroxymethyl) phosphonium] sulfate (salt)
Trade names:	Tolcide PS75; Tolcide THPS, Retardol S
Synonyms:	Octakis(hydroxymethyl) phosphonium sulfate

C2.1.3 Tetrakis(hydroxymethyl) phosphonium chloride-urea condensate (THPC-urea)

Chemical formula: $[C_4H_{12}O_4P.CH_4N_2O.Cl]_x$

Chemical name:	Tetrakis(hydroxymethyl) phosphonium chloride-urea copolymer

Chemical structure:
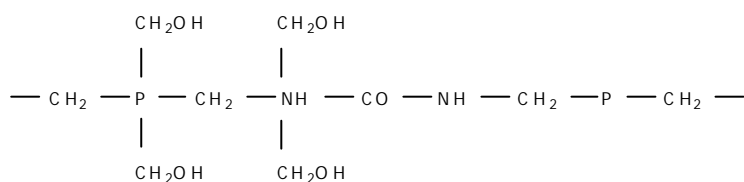
Relative molecular mass:	300 for the repeat unit shown above
CAS registry number:	27104-30-9
CAS name:	Phosphonium, tetrakis(hydroxymethyl)-chloride, polymer with urea
Trade names:	Proban CC; Retardol AC Proban 210 is no longer produced.

C2.2 Physical and chemical properties

Physical and chemical properties are given in Table 8.

C2.2.1 Technical products

THPC and THPS are marketed in concentrated aqueous solutions at approximately 80 and 75% (by weight), respectively (Albright & Wilson, personal communication to IPCS). Typically THPS is marketed with less then 1% of formaldehyde content (Albright & Wilson, personal communication to IPCS). In the past values ranging from 3.79% at pH 0.4 to 14.1% at pH > 5.0 have been reported (Loewengart & Van Duuren, 1977; Ulsamer et al., 1980). Tetrakis(hydroxymethyl) phosphonium acetate/phosphate (THPA/P) was previously available in the USA as a clear, nearly colourless solution with a pH of approximately 5, containing 10% active phosphorus (Hooper et al., 1976).

C2.3 Conversion factors

THPC   1 ppm = 7.76 mg/m^3
                  1 mg/m^3 = 0.128 ppm

THPS   1 ppm = 16.61 mg/m^3
                  1 mg/m^3 = 0.0602 ppm

C2.4 Analytical methods

A standard method for THPS and THPC determination is by iodine titration. However, this not substance specific and is therefore subject to interference by many other chemicals that may be present in the sample to be analysed. The method involves dilution in water containing an aliquot of a saturated solution of disodium hydrogen orthophosphate. A solution of polystyrene sulfonic acid is then added followed by a few drops of a starch indicator. Titration against a previously standardized iodine solution is then carried out (Albright & Wilson, personal communication to IPCS).

The most accurate analytical technique for the quantitative substance-specific determination of THP salts is currently ion chromatography. In this method the sample is chromatographed using an Ionpac CS5 column with a CG5 guard column. The mobile phase

Table 8. Physical and chemical properties of THP salts

Parameter	THPS		THPC	THPC-urea copolymer
	100%	75%	80–85%	
Appearance	Soft waxy solid	Colourless liquid	Clear straw-coloured liquid	Straw-coloured liquid
Odour	Resembles aldehyde	Resembles aldehyde	Pungent	Pungent
Boiling point (/C)		108.5	115	
Melting point (/C)	54.2–81.5			! 21
Flash point			>100	
Vapour pressure	<2.6 x 10^{-4} Pascal at 20 /C	26.7 mmHg at 25 /C		
Viscosity		38 cStp at 25 /C		0.27 Pa.s at 29 /C
pH		3.19 (0.01 M solution)	< 2	5
Stability	21 /C — stable for 14 days	21 /C — stable for 14 days	Stable under normal conditions	Stable under normal conditions
	54 /C — stable for 14 days	54 /C — stable for 14 days		
Decomposition products		Oxides of sulfur, phosphorus and carbon; phosphine	Oxides of phosphorus; chlorine, ammonia	Oxides of phosphorus; chlorine, ammonia
Relative density	1.53	1.39	1.34	1.31
Solubility	Infinitely soluble in water	Completely soluble	Completely soluble	Miscible with water
Log n-octanol/water partition coefficient		! 9.8 (calculated)		

From: Cowlyn (1991a,b); Antony (1993); Barth (1994); Willis (1995)

is hydrochloric acid (0.1 mol/litre) at 1 ml/min. The ion chromatography separates the THP salt from any free formaldehyde, which is largely retained. The THP salt is then detected using a visible wavelength detector at 425 nm following a post-column reaction with an acetylacetone reagent containing acetic acid, ammonium acetate and acetyl acetone. The reagent breaks down the THP salt to form free formaldehyde, which forms a cyclic coloured complex. Free formaldehyde also reacts but two separate and distinct peaks are seen on the chromatogram.

C3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURES

C3.1 Natural occurrence

These compounds are not known to occur as natural products.

C3.2 Anthropogenic sources

C3.2.1 Production levels and processes

THP salts have been produced for commercial use since the 1950s. The first of these, THPC, was introduced in 1953.

THP salts are synthesized in high yields through the reaction of formaldehyde with phosphine and the corresponding acid in an enclosed process (Weil, 1980; Hawley, 1981).

$$PH_3 + HCl + 4CH_2O \div [(HOCH_2)4P]Cl$$
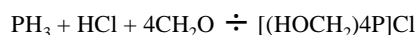
The resulting products exist in an equilibrium with THP^+, which is highly pH dependent. Increasing the pH shifts this equilibrium to the right with the resultant production of formaldehyde, i.e., one of the methylol groups from the THP salt becomes hydrolysed.

Currently there is one major producer of these salts and THPC-urea condensates in the United Kingdom and some production potential in the USA. Combined worldwide production of THP salts is greater than 3000 tonnes; the urea-condensate production is around 3000 tonnes annually of which 40% is consumed in the USA (Albright & Wilson, personal communication to IPCS).

C3.2.2 Uses

THPC-based products represent the major class of chemicals used as flame retardants for cotton, cellulose and cellulose-blend fabrics. Until 1976, THPC was the major THP salt used as a flame retardant. In addition, THPS and some mixed salts were commercially available.

THPC-based flame retardants have been found to be more reactive and efficient as flame retardants when compared with similar THPS-based products (Albright & Wilson, personal communication to IPCS). Nowadays, the THPC-urea condensates dominant the market for flame retardant treatment of cellulose and cellulose-blend fabrics where durability to laundering and dry cleaning is required.

It has been suggested that bis(chloromethyl) ether (BCME) may be formed during the manufacture of THPC and thus may present an occupational hazard (Loewengart & Van Duuren, 1977). However, an extensive airborne monitoring survey coupled with chemical analysis (using mass spectroscopy) conducted at the United Kingdom manufacturing site during 1975 did not detect the presence of BCME at the minimum level of analytical detection of 2.35 $\mu g/m^3$ (0.5 ppb). These results were later independently confirmed in a separate survey carried out by the United Kingdom Factory Inspectorate (personal communication by R. Williams, HM Inspector of Factories, United Kingdom Health and Safety Executive to Albright & Wilson, 1975).

The results of the two occupational hygiene surveys are supported by a study in 1974 in which kinetic measurements in aqueous media (manufacture is via an aqueous route) showed that BCME undergoes rapid hydrolysis with a half-life of approximately 10–40 seconds at ambient temperature (Tou et al.,1974). BCME, if formed, would therefore exist as a transient species in aqueous media containing formaldehyde and hydrochloric acid, or other acid chlorides.

The major application of THPS now is as a biocide in a variety of preservative applications which include leather, textile, paper and photographic films, as well as industrial water treatment and offshore oil production processes.

C4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

C4.1 Transport and distribution between media

A field study was conducted on the use of THPS as a biocide in the water of an industrial cooling tower. THPS was added to produce an initial concentration of approximately 100 mg/litre and lithium chloride was added simultaneously as a marker for determination of dilution volumes in the tower and associated drainage systems. Analysis of THPS was by HPLC. The half-life of lithium (and therefore of THPS by dilution) was calculated to be 3 days. THPS levels were found to decrease more rapidly than simple dilution would have suggested, indicating hydrolysis; actual concentrations in the Rhyne, the drainage channel of the cooling tower, were <0.5 mg/litre (Heaton, 1991).

Adsorption of radiolabelled THPS was studied using agricultural sand, silt loam, sandy loam, pond sediment and marine sediment; the percentage of organic carbon in the tested soil/sediments ranged from 0.17 to 1.1%. Estimated K_{oc} values ranged from 72 to 266 (mean 153 ± 69.2), indicating medium-to-high mobility for the compound (Heim, 1998).

C4.2 Transformation

C4.2.1 Biodegradation

Inherent biodegradability of THPS was assessed using the OECD 302B guideline; >20% degradation occurred within a 28-day period (Douglas & Pell, 1985).

Aquatic aerobic degradation of THPS was assessed in a soil/water system under US EPA Guidelines. The soil was dosed with THPS at 1 : g/g. The compound was metabolized with 60% of applied radioactivity appearing as CO_2 within 7 days. Major metabolites were trihydroxymethyl phosphine oxide (THPO) and bishydroxymethyl phosphonic acid (BMPA), which were both found in the water; neither degradate reached a concentration of 10% of the applied dose (Gorman, 1996). A comparable study at the same initial concentration

of THPS but under anaerobic conditions also showed 60% degradation within 30 days, and the same breakdown products were identified (Gorman, 1997).

Natural seawater was dosed with THPS to an initial concentration of 4.16 mg/litre. Biodegradation (measured as oxygen demand) reached 17.7% after 28 days. A parallel toxicity test showed that the substance was inhibitory to bacteria at the concentration used in the test (McWilliam, 1994).

C4.2.2 Abiotic degradation

Laboratory studies using UV light showed that THPS photodegrades to THPO when at low concentrations in aqueous solution. Conversion to THPO was almost complete at concentrations up to about 20 mg/litre within 2 h. Conversion also took place in synthetic seawater. Photodegradation was pH-dependent, with greater conversion at environmentally relevant pH. Exposure to natural sunlight showed high levels (not stated) of conversion over a 3-month period (Lloyd, 1994).

Hydrolysis of THPS is pH-dependent; half-lives for the compound at 25 /C were 131, 72 and 7 days at pH 5, 7 and 9, respectively (O'Connor, 1992).

C4.3 Migration from textiles

A method is available for the determination of the fixation efficiency of the THPC-urea copolymer in terms of the percentage phosphorus applied and fixed during the flame retardant treatment of various textiles. A fixation efficiency of greater than 90% is common for the PROBAN^R process (Albright & Wilson, personal communication to IPCS). The THPC-urea copolymer is chemically converted to a water-insoluble polymer of high relative molecular mass during the textile processing, first by exposure to ammonia in an enclosed chamber and then by an oxidation process involving hydrogen peroxide. This latter process converts any phosphorus to the inert pentavalent form. At the same time the hydrogen peroxide will convert any unfixed THPC-urea copolymer to tetrakis(hydroxymethyl) phosphine hydroxide (THPOH), which is subsequently removed from the fabric during the final washing-off steps.

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Wetting the treated fabric with water, beverages, liquid foods or urine does not release the flame retardant polymer. The lack of water solubility and the physical entrapment of the polymer inside the fibres (which make up the treated fabric) make the polymer resistant to removal by cleaning materials that a consumer might normally employ to clean these flame-retardant-treated articles.

Industrial work clothing treated with THPC-urea condensate flame retardants have been shown to be flame resistant after 50–100 washings or dry cleanings, demonstrating the durability of the polymer to leaching and washing (Albright & Wilson, personal communication to IPCS).

Appendix A lists flammability standards met regularly by products treated with THPC-urea condensates.

C5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Approximately 20 workers are currently potentially exposed during production of THP salts and THPC-urea condensate in the United Kingdom (Albright & Wilson, personal communication to IPCS). No data on levels of exposure are available.

C6. KINETICS AND METABOLISM IN LABORATORY ANIMALS

A metabolism study on rats has been conducted using ^{14}C-radiolabelled THPS. THPS was not found in rat urine. However, three metabolites were present, identified as trihydroxymethyl phosphine oxide, bishydroxymethylphosphonic acid and possibly a formaldehyde adduct of the trihydroxy compound (Dr P. Martin, Albright & Wilson, personal communication to IPCS).

C7. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

C7.1 Single exposure

C7.1.1 Oral

Acute oral toxicity results are given in Table 9.

Table 9. Oral LD_{50} values for THPC, THPS and THPC-urea condensate in mice and rats (mg/kg body weight)[a]

Species	Sex	THPC[b]	THPS[c]	THPC-urea
Mice	female	280	200 (none died)	400 (all died)
Rats	male	282		
Rats	both sexes	575		962
Rats	male	185	333	
Rats	female	161	248	

[a] From Ulsamer et al. (1980); US NTP (1987); Tuffnell (1991); Guest (1994a)
[b] 75% solution in water
[c] 72% solution in water

In THPC-treated rats that survived, reddish fluids around the nostrils and laboured breathing were observed. All mice were lethargic and had a rough coat. With THPS no signs of intoxication were noted (Ulsamer et al., 1980; US NTP, 1987).

C7.1.2 Dermal

The dermal LD_{50} value in albino rabbits was greater than 4084 mg THPC/kg body weight after a 24-h exposure. Erythema and oedema of the integumentary system were observed (US NTP, 1987).

No deaths occurred when rats were treated dermally with THPS or THPC-urea at 2000 mg/kg body weight (Liggett & Allen, 1989; Snell, 1994).

C7.1.3 Inhalation

The LC_{50} 4-h value for THPS was 5.5 mg/litre in rats exposed to respirable aerosol (nose only) (McDonald & Anderson, 1989).

C7.2 Repeated exposure

C7.2.1 Oral

C7.2.1.1 THPC

Groups of five 6-week-old, F-344/N rats of each sex were administered 0, 9.4, 18.8, 37.5, 75 or 150 mg THPC (as a 75% aqueous solution) per kg body weight in deionized water by gavage for 14 days. At the two highest dose levels an increased mortality was observed. At 75 mg/kg the mortality for males was 20%, and at 150 mg/kg all males and females died. The body weight gain of the male animals administered 18.8 and 37.5 mg/kg was decreased, respectively, by 7 and 11%. This effect was also found in the females administered 75 mg/kg (27%). Rats with 150 mg/kg had yellow to tan or mottled red livers. No histopathology was carried out (US NTP, 1987).

Groups of ten 4-week-old F-344/N rats of each sex were gavaged 5 days/week for 13 weeks with 0, 3.75, 7.5, 15, 30 or 60 mg THPC (as a 75% aqueous solution) per kg. All males and 5/10 females that received 60 mg/kg died. The final mean body weight of males that received 30 mg/kg was 89% of vehicle controls. The final mean body weight of females that received 60 mg/kg was 80% of vehicle controls.

At the highest dose level, clinical signs of toxicity included rough coat, hunched back, diarrhoea, lethargy, paresis and hyperextension of back legs. Periportal hepatocellular necrosis was observed in 9/10 males and 7/10 females that received 15 mg/kg, all males and females that received 30 mg/kg, and 7/10 males and 8/10 females that received 60 mg/kg.

Periportal cytoplasmic vacuolization was observed in 8/10 males that received 7.5 mg/kg, 9/10 males and 8/10 females that received 15 mg/kg, and all rats that received 30 or 60 mg/kg. Degeneration of the axons was found in 2/10 females that received 60 mg/kg. The NOAEL

for this study was 2.7 mg/kg body weight per day; the LOAEL was 5.4 mg/kg body weight per day (US NTP, 1987).

Groups of five 5-week-old B6C3F$_1$ mice of each sex were administered 0, 18.8, 37.5, 75, 150 or 300 mg THPC (as a 75% aqueous solution) per kg body weight by gavage for 14 consecutive days. At the highest dose level all mice died. At 150 mg/kg, body weight was depressed by 18% in males and 20% in females compared to control mice. No clinical sign of toxicity were observed in animals surviving to the end of the study. No compound-related effects were observed at necropsy (US NTP, 1987).

Groups of ten 4-week-old B6C3F$_1$ mice of each sex were administered by gavage 0, 1.5, 4.5, 15, 45 or 135 mg/kg body weight 5 days/week for 13 weeks. Seven of 10 males and 6/20 females that received 135 mg/kg died. The final mean body weight for mice that received 135 mg/kg was 8% lower than that of the controls for males and 19% lower for females. Paresis of the hind legs and loss of coordination were observed in all males and 9/10 females that received 135 mg/kg. Mice in this group also had marked axonal degeneration, characterized by swollen axon sheaths, missing fragmented axons and some proliferation of neurolemmal cells in the sciatic nerve, dorsal roots of the caudal spinal nerves and tracts of the spinal cord particularly in the dorsal column of the lumbar cord. Intracytoplasmic vacuoles were seen in periportal hepatocytes of all mice in the 15, 45 and 135 mg/kg groups. The NOAEL for this study was 3.2 mg/kg body weight per day; the LOAEL was 10.7 mg/kg body weight per day (US NTP, 1987).

C7.2.1.2   THPS

Group of 12 male ICR Swiss mice were administered daily by gavage THPS in saline (2, 10 or 50 mg/kg body weight) for 14 days. In the high-dose group 75% of the animals died (Connor et al., 1980).

Groups of five, 5-week-old, B6C3F$_1$ mice of each sex were administered 0, 12.5, 25, 50, 100 or 200 mg THPS (obtained as a 72% aqueous solution) per kg body weight by gavage for 14 consecutive days. Mice of the two highest dose groups had increased mortality at 100 mg/kg (20% male, 40% female) and at 200 mg/kg (80% male, 100% female). At 25 mg/kg or more there was a decrease in body weight gain.

The animals given 100 or 200 mg/kg had laboured breathing and rough coat and female mice of these groups also showed loss of movement in their hind legs (US NTP, 1987).

Groups of 10, 5- to 6-week-old B6C3F$_1$ mice of each sex were administered 0, 5, 10, 20, 40 or 60 mg THPS (obtained from a 72% aqueous solution) per kg body weight by gavage on 5 days/week for 13 weeks. One of 10 females that received 60 mg/kg and 2/10 males and 1/10 females that received 40 mg/kg died. The final mean body weights of mice that received 20, 40 or 60 mg/kg were 4%, 7% or 11%, respectively, lower than those of the controls for males and 3%, 5% and 11% lower for females. Periportal vacuolar degeneration occurred in all male and female mice that received 60 mg/kg, all males and 9/10 females that received 40 mg/kg, and 8/10 male mice that received 20 mg/kg. The NOAEL for this study was 7.1 mg/kg body weight per day, and the LOAEL was 14.3 mg/kg body weight per day (US NTP, 1987).

Groups of five, 4-week-old, F-344/N rats of each sex were administered 0, 12.5, 25, 50, 100 or 200 mg THPS (obtained as a 72% aqueous solution) per kg body weight by gavage for 14 consecutive days. All rats given 100 or 200 mg/kg died. Animals that received 25 or 50 mg/kg gained less weight than controls by 11% and 21%, respectively, in males and 1% and 7% in females. The animals given the two highest dose levels showed tremors, and one animal had partial loss of movement of the hind legs. At necropsy no abnormalities were seen (US NTP, 1987).

In an oral 28-day study, Charles River derived CD rats (five females and five males/group) were given by gavage 6, 30 or 60 mg THPS (75% obtain as aqueous solution) per kg body weight daily. At the highest dose level, one male rat died on day 20, one female rat on day 21 and the remaining rats on day 22. Post-dose salivation, emaciation, hypoactivity, hunched posture, noisy breathing, urogenital staining and ptosis were seen only in the 60 mg/kg group. There was severe weight loss during week 3 (body weight 52% for male and 74% for female relative to controls at the end of week 3). The NOEL was considered to be 6 mg/kg body weight per day (Hill, 1989).

Groups of ten, 5- to 6-week-old F-344/N rats of each sex were administered 0, 5, 10, 20, 40 or 60 mg THPS (obtained from a 72%

aqueous solution) per kg body weight by gavage 5 days/week for 13 weeks. Three of the male rats that received 60 mg/kg died. Final mean body weights were 5%, 15% and 22% lower than those of the controls for males that received 20, 40 or 60 mg/kg and 9%, 12% and 19% lower for females that received 20, 40 or 60 mg/kg. Vacuolar degeneration of hepatocytes occurred in all males receiving 10 mg/kg or more, in all females receiving 40 or 60 mg/kg, and in 5/10 females receiving 20 mg/kg. Lymphoid depletion in the spleen was seen in three males in the 60 mg/kg group. Bone marrow hypoplasia was diagnosed in 3/10 male and 4/10 female rats in the 60 mg/kg groups. The NOAEL in this study was 3.6 mg/kg body weight per day; the LOAEL was 7.1 mg/kg body weight per day (US NTP, 1987).

Groups of 10 Charles River derived CD rats of each sex received 0, 1, 5 or 10 mg THPS (75% aqueous solution) per kg body weight per day by gavage daily for 13 weeks. One female rat from the 5 mg/kg group died on day 14, one female from the 1 mg/kg group on day 53 and another on day 81. No clinical signs or changes in body weight were attributed to THPS administration at any dose level other than mean plasma ALAT and ASAT levels being twice control values for males of the highest dose group. Histopathology showed moderate to marked cytoplasmic vacuolation of periportal hepatocytes in all male rats and moderate vacuolation in one female rat of the highest dose group. The NOEL for this study was 1 mg/kg body weight per day (Hill & Newman, 1990).

C7.2.2 *Dermal*

Application of 125, 350, 700 or 1000 mg THPS/kg body weight on chemically depilated back skin of groups of 12 male ICR mice daily for up to 14 days caused reduced body weight, paralysed back muscles at 700 mg/kg body weight or more, and some superficial necrosis at all doses (Connor et al., 1980). Similar effects were reported in mice by Afansa'eva & Evseenko (1971).

Both THPC and THPS were toxic when applied dermally for long periods on the skin. Rats and rabbits were dosed daily for 20 days with 15%, 20% or 30% aqueous solutions of THPC. Severe skin lesions occurred and all rats in the highest dose group died after 9 days of application (Aoyama, 1975).

In a study by Wragg et al. (1996), trihydroxymethyl phosphine oxide was administered by dermal application to three groups, each of five male and five female Sprague-Dawley CD rats, for up to 28 consecutive days at dose levels of 0, 300, 650 and 1000 mg/kg body weight per day. There were no deaths or clinical abnormalities attributable to the test material. Body weight gain and food consumption were similar in treated groups and controls. Females treated with 1000 mg/kg showed an increase in plasma total protein and a reduction in albumin/globulin ratio compared to controls. Males treated with 1000 mg/kg and both males and females in the remaining treatment groups showed no toxicologically significant changes in these parameters. Both males and females dosed at 1000 mg/kg showed cortical hypertrophy of the adrenal glands. Adverse dermal reactions (scabs sometimes accompanied by scar tissue) were seen at all dose levels. The incidence of these adverse dermal reactions gradually increased during the second half of the treatment period amongst males (but not females) dosed at 1000 mg/kg, and by day 28 all five males showed dermal abnormalities. A NOAEL for dermal reactions was not established. The NOAEL for systemic toxicity was determined to be 650 mg/kg body weight per day (Wragg et al., 1996).

C7.3 Long-term exposure

C7.3.1 THPC

Groups of 50 F-344/N rats of each sex (7 weeks of age) were administered 0, 3.75 or 7.5 mg THPC (obtained from a 75% aqueous solution) per kg body weight by gavage on 5 days/week for 103 weeks. The mean body weights of different groups were comparable. Clinical signs noted were rough hair coat and diarrhoea. The survival of high-dose female rats was significantly lower than that of controls after week 70 (P = 0.013). A dose-related increase in the incidence of hepatocellular lesions, primarily cytoplasmic vacuolization, was found (males: controls 0%, low-dose 18% and high-dose 47%; females: controls 6%, low-dose 22% and high-dose 50%). The LOAEL for this study was 2.7 mg/kg body weight per day; a NOAEL was not established (US NTP, 1987).

Groups of 50 male B6C3F$_1$ mice (8 weeks of age) were administered 0, 7.5 or 15 mg THPC (obtained from a 75% aqueous solution) per kg body weight, and groups of 50 female B6C3F$_1$ mice received 0, 15 or 30 mg/kg body weight by gavage 5 days/week for 103 weeks. No clear

difference between control and treated groups concerning body weight gain and mortality was observed. Compound-related clinical signs consisted of rough hair coat and diarrhoea. No signs of neurotoxicity were observed. There was a dose-related increase in the incidence of hepatocellular cytoplasmic vacuolization (males: controls 0%, low-dose 80%, and high-dose 88%; females: controls 0%, low-dose 84%, and high-dose 96%). Follicular cell hyperplasia of the thyroid gland was observed in the high-dose females (22% versus 6% in controls). The LOAEL for this study was 5.4 mg/kg body weight per day; a NOAEL was not established (US NTP, 1987).

C7.3.2 THPS

Groups of 49 or 50 F-344/N rats of each sex were administered 0, 5 or 10 mg THPS (obtained from a 72% aqueous solution) per kg body weight by gavage 5 days/week for 104 weeks. Mean body weights of the different groups were comparable. Clinical signs were rough hair coat and diarrhoea. The survival of both the male low-dose (after week 102) and high-dose (after week 67) animals was significantly lower (P = 0.036 and 0.006, respectively). The effect level for mortality in this study was 3.6 mg/kg body weight per day, the lowest dose tested (US NTP, 1987).

Groups of 50 B6C3F$_1$ mice of each sex (7 weeks of age) were administered 0, 5 or 10 mg THPS (obtained from a 72% aqueous solution) per kg body weight by gavage 5 days/week for 104 weeks. Mean body weight and survival of control and treated groups were comparable. Clinical signs were limited to rough hair coat and diarrhoea. Non-neoplastic lesions seen were focal hyperplasia of the adrenal medulla, but the numbers were statistically unrelated to dose (controls 3/49, low-dose 5/48, high-dose 10/49). The NOAEL for this study was 3.6 mg/kg body weight per day; the LOAEL was 7.1 mg/kg body weight per day (US NTP, 1987).

C7.4 Skin and eye irritation; sensitization

C7.4.1 Skin irritation

C7.4.1.1 THPS

When 0.5 ml of THPS (75%) was applied to the skin of six New Zealand white rabbits for a period of 4 h (OECD 404), no dermal irritation was observed (Liggett, 1989a).

In a dermal study, daily doses of 25, 250 or 500 mg THPS (75% aqueous solution) were applied to the shaved neck skin of ten (five females, five males) Charles River derived CD rats. The treatment had to be terminated and animals killed after 6 days due to the nature and severity of the skin reaction observed at the application site (Hill, 1989).

C7.4.1.2   THPC-urea

A single 4-h semi-occluded application of THPC-urea to the intact skin of six rabbits produced corrosive effects at two skin sites and slight-to-well-defined erythema and very slight to slight oedema at the other four treated skin sites (Snell, 1994).

C7.4.2   Eye irritation

In a test for eye irritation (OECD 405), an aliquot of 0.1 ml THPS (75%) was introduced to one eye of a New Zealand rabbit. Opacity was observed 24 h after application and lasted at least for 24 h. Red coloration of the conjunctiva accompanied by considerable swelling was observed. On the basis of these effects, THPS (75%) is considered to be a severe eye irritant (Liggett, 1989b).

C7.4.3   Skin sensitization

C7.4.3.1   THPS

THPS (75%) was assessed for skin sensitization using the Magnusson & Kligman Maximisation test (OECD 406). Fourteen out of 20 animals challenged with the test substance were sensitized (Guest, 1994b). These data clearly demonstrate a sensitization potential for THPS (75%).

C7.4.3.2   THPC-urea

When THPC-urea was tested for skin sensitization potential using the guinea-pig Magnusson & Kligman Maximisation test, 53% of the animals were sensitized (Tufnell, 1992).

C7.5 Reproductive toxicity, embryotoxicity and teratogenicity

C7.5.1 THPS

Three groups of 16 New Zealand white rabbits were administered (OECD 414) by gavage THPS (75%) at 6, 18 and 60 mg/kg body weight per day from day 7 to 19 of gestation. All animals were kill on day 21. At 60 mg/kg mean body weight gain was significantly lower than that of controls, showing maternal toxicity. Treatment at 60 mg/kg resulted in increase incidence (42/120) of fetuses with eye malformation and some with additional hydrocephaly or limb/phalangeal reduction defects. An increase incidence of specific skeleton variation was also observed. No adverse effects were noticed in the two lower-dose group (Barker, 1991a).

Charles River CD rats (24 animals per group) were administered by gavage THPS (75%) at 15, 30 and 60 mg/kg body weight per day from day 6 to 15. All animals were killed on day 21. Treatment at 60 mg/kg reduced significantly body weight gain from day 12 of gestation onwards, indicating maternal toxicity. No treatment-related effects were observed in dams at the low-dose level. At the high-dose level, the incidence of fetuses showing extra thoraco-lumbar ribs was significantly higher than for controls. At 30 mg/kg only minor signs of maternal toxicity were observed (Barker, 1991b).

From these studies a NOAEL of 18 mg/kg body weight per day based on maternal toxicity could be derived. No developmental effects were observed in the absence of maternal toxicity.

C7.5.2 THPC-urea

Dose levels of 10, 30 and 100 mg THPC-urea/kg body weight per day were administered to groups of 16 rabbits from day 7 to 19 of gestation. All animals were killed on day 29. At the high-dose level, an initial mean weight loss was followed by significantly reduced weight gain over the treatment period. Treatment did not affect the incidence of fetuses showing external, visceral or skeletal malformations or variations (Barker, 1992).

C7.6 Mutagenicity and related end-points

C7.6.1 THPC-urea

C7.6.1.1 In vitro *studies*

An *in vitro* cytogenetic assay was performed with THPC-urea using human lymphocytes. Harvest times of 16 and 40 h were used for cells incubated in the presence of S9 from induced rat liver, and times of 20 and 44 h were used when S9 was absent. In one experiment, THPC-urea had no effect on the number of aberrant cells at concentrations up to 40 mg/ml, but, in a repeat experiment, increased numbers of aberrant cells were seen at 20 and 40 mg/ml. The reason for the difference in results between the two experiments is not clear (Durward, 1995; Bailey, 1995).

C7.6.1.2 In vivo *studies*

No mutagenicity of THPC-urea was evident in a mouse micronucleus test in which oral doses of 212.5, 425 and 850 mg/kg body weight were administered (Durward, 1996).

C7.6.2 THPC

Salmonella microsomal assays have shown uniformly negative results for THPC (Table 10).

THPC produced chromosomal aberrations in Chinese hamster ovary (CHO) cells in the absence of metabolic activation, but the results were equivocal when it was tested in the presence of S9 from livers of Sprague-Dawley rats treated with Aroclor 1254 (US NTP, 1987; Loveday et al., 1989). THPC induced chromosomal aberrations in Chinese hamster DON-6 cells in the absence of metabolic activation (Sasaki et al., 1980).

THPC induced sister-chromatid exchange (SCE) in CHO cells when incubated in the absence of metabolic activation (US NTP, 1987; Loveday et al., 1989).

Table 10. Mutagenicity tests with *Salmonella typhimurium*

Strain	Dose (: g/plate)	Metabolic activation	Reference
TA100, TA1535, TA1537, TA98	0.33–33	none, S9 rat liver (male), S9 Syrian hamster liver (male)	US NTP (1987)[a]
TA98, TA100, TA1535, TA1537	10–1000	none, S9 liver (Aroclor 1254, rat)	MacGregor et al. (1980)
TA98, TA100, TA1535, TA1537	10–300	none, S9 liver (Aroclor 1254, rat)	MacGregor et al. (1980)
TA98, TA100, TA1535, TA1537	Up to 10 000	none, S9 liver (Aroclor 1254, rat)	Zeiger et al. (1987)
TA98, TA100	not know	none, S9	Kawachi et al. (1980b)[b]

[a] THPC gave positive results in a mouse lymphoma assay in the absence of metabolic activation (US NTP, 1987).
[b] Kawachi et al. (1980b) found positive results with THPC in the *Bacillus subtilis* rec assay with and without metabolic activation.

C7.6.3 THPS

THPS produced no mutagenicity when tested in the *Salmonella* microsome assay using strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence and absence of S9 from the livers of Aroclor-1254-treated rats (Dillon & Riach, 1990). Leachate from THPS-treated paper also showed no mutagenicity when tested with strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of S9 from Aroclor-1254-treated rats (Ballentyne, 1996b).

When tested in the mouse lymphoma assay, THPS caused mutations both in the presence and absence of S9 from Aroclor-treated rats (Riach, 1996). US NTP (1987) also reported positive results for THPS in the mouse lymphoma assay in the absence of S9.

High levels of structural chromosomal aberrations were detected at metaphase in CHO cells treated with THPS in the presence or absence of S9 from liver of Aroclor-treated rats (Leddy, 1990). Anaphase analysis of THPS-treated CHO cells also showed that chromosomal aberrations were produced along with abnormal spindles (Coutino, 1979).

The results of an *in vitro* assay for unscheduled DNA synthesis in a primary culture of rat hepatocytes were negative (Downey et al., 1990; Riach, 1994).

Bone marrow from THPS-treated mice was analysed for micro-nucleated polychromatic erythrocytes (MN-PCEs) and for metaphase cells showing chromosomal aberrations. There was no effect on the number of MN-PCEs nor on the number of chromosomal aberrations (Connor et al., 1980).

The *in vivo* mutagenicity of dermal doses of THPS was investigated in Swiss (ICR) mice using a similar protocol to that of the previous study. Dermal doses of 125, 350, 700 and 1000 mg/kg body weight per day were used. Urine from treated mice was not mutagenic in the *Salmonella* microsome assay. Analysis of bone marrow from treated mice showed a slight increase in the number of polyploid cells at the highest dose level, but otherwise there was no indication of mutagenicity (Connor et al., 1980).

In a dominant lethal assay in Swiss (ICR) mice, males were dosed with up to 1000 mg/kg body weight. There was no evidence to suggest that THPS produced dominant lethal mutations (personal communication by M. Legator to Hooker Chemicals and Plastics Corp., 1977).

In a dominant lethal study in rats, gavage doses of 5, 10 or 15 mg/kg body weight per day were given to males for 10 weeks. After mating, investigation of the pregnant females indicated no dominant lethal mutations (Clode, 1996).

C7.6.4 THPO

THPO is a metabolite and breakdown product of THP salts. It was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 or in *Escherichia coli* strain WP2 *uvra* when tested in the presence and absence of S9 from livers of Aroclor-1254-treated rats (Ballentyne, 1996a).

THPO was not mutagenic in the mouse lymphoma assay in either the presence or absence of liver S9 from Aroclor-1254-treated rats (Fellows, 1996). It did not produce chromosomal aberrations in CHO cells cultured in either the presence or absence of S9 (Marshall, 1996).

C7.6.5 Treated fabrics

Groups of 12 male ICR mice received 0 (no fabric), 2500 mg untreated fabric per kg diet or 250, 1250 or 2500 mg THPS-treated fabric per kg diet for 5 successive days. Femurs were collected for analyse of bone marrow for MN-PCEs and chromosomal aberrations. All tests were negative (Connor et al., 1980).

C7.7 Carcinogenicity

C7.7.1 Oral studies

C7.7.1.1 Mice

In a 103-week study of THPC (75%) in mice (see section C7.3.1), there was no evidence of carcinogenicity (US NTP, 1987).

In a 104 week study of THPS (72%) in mice(see section C7.3.2), there was no evidence of carcinogenicity (US NTP, 1987).

C7.7.1.2 Rats

In a 103 week study for THPC (75%) in rat (see section C7.3.1), there was no evidence of carcinogenicity (US NTP, 1987).

In a 104 week study for THPS (72%) in rat (see section C7.3.2), there was no evidence of carcinogenicity (US NTP, 1987).

C7.7.2 Dermal studies: Initiation and promotion

A group of 60 female ICR/Ha Swiss mice, 6–8 weeks of age, received skin applications of THPC (2 mg/mouse) in acetone three times a week for 71 weeks. The control group received acetone only. There was no significant increase in tumours (papillary tumours of the lung and papillomas of the forestomach) in the animals treated with THPC (Van Duuren et al., 1978).

Groups of 20 female ICR/Ha Swiss mice, 6–8 weeks of age, received skin applications of THPC (2 mg/mouse) or Pyroset TKP (acetate/phosphate mixture of THP) (7 mg/mouse) in dimethyl sulfoxide three times a week for 57 weeks to examine the initiating, promoting and complete carcinogenic potential in skin carcinogenesis bioassays. Both chemicals were active as tumour promoters using a single application of 7,12-dimethylbenz[*a*]anthracene (DMBA) (20 : g in 0.1 ml acetone) as initiator. Neither chemical was active as a tumour initiator or complete carcinogen (Loewengart & van Duuren, 1977).

C7.8 Special studies

THPS and THPO did not inhibit acetyl cholinesterase when tested *in vitro* using malathion (a known inhibitor of cholinesterase) as a positive control (Thompson, 1997a,b).

C8. EFFECTS ON HUMANS

Fabric treated with THPC-urea condensate was tested on human volunteers in a 48-h skin patch test. The treated fabric was not irritant to exposed human skin (Jackson, 1982).

C9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

C9.1 Laboratory experiments

C9.1.1 Aquatic organisms

THPS showed an EC_{50} for growth inhibition of the marine microalga *Skeletonema costatum* of 0.16 mg/litre over 72 h (Hushagen & McWilliam, 1994). For the freshwater green alga *Selenastrum capricornutum*, EC_{50} values of 0.652 mg/litre (based on growth rate) and 0.204 mg/litre (based on biomass) were determined. The NOEC for both end-points was 0.063 mg/litre. The test was conducted under OECD Guideline 201 (Jenkins, 1991c).

The 48-h LC_{50}, based on immobilization and using nominal concentrations, for THPS in the water flea (*Daphnia magna*) was determined to be 19.4 mg/litre, with a NOEC of 10.4 mg/litre. The test was conducted under US EPA/OECD Guideline 202 (Jenkins, 1989). Concerning estuarine/marine invertebrates, the 96-h LC_{50} for the mysid shrimp (*Mysidopsis bahia)* is 7.3 mg/litre (NOEC 3.5 mg/litre) (Boeri et al., 1995a), the 96-h LC_{50} for the brown shrimp (*Crangon crangon*) is 340 mg/litre (Douglas & Pell, 1986), and the 48-h LC_{50} for the brine shrimp (*Acartia tonsa*) is 0.6 mg/litre (Torp & McWilliam, 1994). The 96-h EC_{50} for shell deposition in juvenile Eastern oysters (*Crassostrea virginica*) was reported to be 1.6 mg/litre, with a NOEC of 0.67 mg/litre for THPS in a test following US EPA guidelines (Boeri et al., 1995c). The 10-day LC_{50} for THPS was determined for the sediment-dwelling amphipod *Corophium volutator* to be 2174 mg/kg dry sediment weight (Roddie, 1994).

The 96-h LC_{50}, based on nominal concentrations of THPS, for the rainbow trout (*Oncorhynchus mykiss*) was determined to be 119 mg/litre with a NOEC of 18.1 mg/litre in a test conducted according to OECD Guideline 203 (Jenkins, 1991a). A test conducted under US EPA/OECD Guideline 203 determined the 96-h LC_{50} for THPS in bluegill sunfish (*Lepomis macrochirus*) to be 93 mg/litre, with a NOEC of 22.7 mg/litre (Jenkins, 1991b). The 96-h LC_{50} for the marine sheepshead minnow (*Cyprinodon variegatus*) was determined to be 72 mg/litre, with a NOEC of 41 mg/litre using US EPA guidelines (Boeri et al.,

1995b). For juvenile plaice (*Pleuronecta platessa*), the 96-h LC_{50} was 86 mg/litre (Douglas & Handley, 1989).

C9.1.2 Terrestrial organisms

The acute oral LD_{50} for young adult mallard ducks (*Anas platyrynchus*) was 311 mg/kg body weight (Roberts & Phillips, 1988a). Dietary LC_{50} values for the mallard duck and bobwhite quail (*Colinus virginianus*) were 1313 and 2414 mg/kg diet, respectively (Roberts & Fairley, 1988; Roberts & Phillips, 1988b).

C10. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The International Agency for Research on Cancer evaluated the carcinogenicity of tetrakis(hydroxymethyl) phosphonium salts in 1989 (IARC, 1990) and concluded:

a) There is *inadequate evidence* for the carcinogenicity of tetrakis(hydroxymethyl) phosphonium salts in experimental animals.

b) No data were available from studies in humans on the carcinogenicity of tetrakis(hydroxymethyl) phosphonium salts.

c) Tetrakis(hydroxymethyl) phosphonium salts *are not classifiable as to their carcinogenicity to humans (Group 3)*.

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Appendix A

Flammability standards met by products treated by THPC-urea condensates[a]

Items	Flammability standards
Protective clothing	ASTM F-1506 ASTM F-955 NFPA 1975 NFPA 1977 EN 533 : 1977 Index 3 after 50 washes at 75 /C EN 531 : 1995 para. 6.2.2 after 50 washes at 75 /C EN 470-1 : 1995 para. 6.1 after 50 washes at 75 /C EN 470-1 : para. 6.2 EN 531 : 1995 para. 6.3 EN 531 : 1995 para. 6.4 EN 531 : 1995 para. 6.6
Sheeting, blankets and counterpanes	BS 7175 Ingnition sources 0, 1 and 5. When tested on top of and below the test fabric, after 200 washes at 74 /C (BS 5651 HLPN). BS 5815 : Part 3 : 1991
Curtains and drapes	NFPA 701 BS 5867 : 1980 Part 2 Type B after 200 washes at 74 /C (BS 5651 HLPN).
Mattress ticking and mattresses	BS 7175 Ignition sources 0, 1 and 5 when tested on top of and below the test fabric, after 3 washes at 74 /C BS 597-1 : 1995 (fabric tested in combination with a non-fire-retardant polyurethane foam block). BS 597-2 : 1995 (fabric tested in combination with a non-fire-retardant polyurethane foam block).
Sleepwear	DOC FF 3-71 BS 5722 : 1984 when testing in accordance with BS 5438 : 1976 Test 2. BS 5722 : 1991 Level 1.
Upholstery	BS 5852 part 1 Ignition sources 0 (smouldering cigarette) and 1 (simulated match) after a 30-min water soak, BS 5651 amended. EN 1021-1 : 1994 (fabric tested in combination with a non-fire-retardant polyurethane foam block). EN 1021-2 : 1994 (fabric tested in combination with a non-fire-retardant polyurethane foam block).

[a] From: Dr P. Martin, Albright & Wilson, personal communication to IPCS

RÉSUMÉ, EVALUATION ET RECOMMANDATIONS

1. Phosphate de tris(2-butoxyéthyle) (TBEP)

1.1 Résumé

Le phosphate de tris(butoxyéthyle) ou TBEP est utilisé pour la confection d'encaustiques destinés à l'entretien des sols ou encore comme plastifiant dans les caoutchoucs et les matières plastiques. On ne connaît pas le volume de la production annuelle mondiale, mais on pense qu'il est de l'ordre de 5000 à 6000 tonnes.

La présence du TBEP dans l'environnement résulte exclusivement de l'activité humaine. Sa répartition dans l'environnement a été étudiée dans certains pays industrialisés. On a trouvé une concentration inférieure à 300 ng/litre dans les eaux de surface et comprise entre 100 et 1000 : g/kg dans les matières particulaires. Aucune des 167 analyses effectuées n'a permis d'en mettre en évidence dans les poissons. Une unique étude en a décelé sa présence dans l'air extérieur (< 200 ng/m^3). Le dosage du TBEP dans l'air de bureaux a donné une concentration de 25 ng/m^3 tout au plus. Le TBEP est associé aux matières particulaires et la source en est dans ce cas les encaustiques que l'on applique sur le sol. On l'a décelé à des concentrations de l'ordre du : g/kg dans les tissus adipeux humains. D'après des études basées sur le panier de la ménagère, la dose journalière ingérée serait de moins de 0,02 : g/kg de poids corporel pour diverses tranches d'âge. On en a également signalé la présence dans l'eau de boisson à des concentrations pouvant atteindre 270 : g/litre. Elle est due, semble-t-il, à la migration du produit contenu dans les joints de caoutchouc de l'installation sanitaire.

On estime que le TBEP est facilement biodégradable. Des mesures effectuées dans des stations d'épuration des eaux d'égout et des dosages pratiqués en semi-continu au laboratoire sur des boues de même provenance montrent que le TBEP s'élimine en grande partie (> 80 %). Dans les cours d'eau et les eaux littorales, le TBEP est totalement décomposé. On a fait état d'une demi-vie d'environ 50 jours dans les eaux estuarielles, la décomposition étant minime dans l'eau de mer non adaptée.

Le composé présente une faible toxicité aiguë pour les mammifères et son pouvoir irritant est également faible.

Plusieurs études subchroniques sur des animaux de laboratoire montrent que la toxicité du TBEP s'exerce au niveau du foie qui en est l'organe cible. Une étude sur des rats Sprague-Dawley incite à penser que le TBEP pourrait provoquer une myocardite focale. Des effets neurologiques ont été observés chez le rat après ingestion d'une seule dose, mais ils n'apparaissent pas systématiquement. Lorsqu'on l'administre répétitivement à forte dose à des rats par gavage, le TBEP réduit la vitesse de conduction nerveuse et augmente la durée de la période réfractaire. Après administration à des poules, on n'a pas constaté de neurotoxicité retardée, mais il y avait par contre inhibition de la cholinestérase cérébrale et plasmatique.

Une étude de 18 semaines au cours desquelles des rats ont reçu des doses répétées de TBEP a permis de fixer à 15 mg.kg^{-1}j^{-1} pc la dose sans effet observable (NOEL) sur le foie, la dose la plus faible produisant un effet observable (LOEL) étant de 150 mg.kg^{-1}.j^{-1} pc.

Ni la toxicité à long terme ni le pouvoir cancérogène de ce composé n'ont été étudiés.

Les tests de mutation génique effectués sur des cellules mammaliennes et sur des bactéries n'ont donné que des résultats négatifs mais il n'existe aucun compte rendu de recherche de lésions chromosomiques.

Une étude effectuée sur des rats n'a révélé aucun effet tératogène. Il n'existe pas de publication faisant état d'autres effets toxiques sur la reproduction.

Les tests de sensibilisation effectués sur des sujets humains par apposition d'un timbre cutané ne font ressortir aucune sensibilisation mais seulement une légère irritation.

Le TBEP est modérément toxique pour les organismes aquatiques. La CL$_{50}$ à 48 h pour *Daphnia magna* est de 75 mg/litre et la CL$_{50}$ à 96 h se situe entre 16 et 24 mg/litre pour les poissons.

1.2 Evaluation

L'exposition sur les lieux de travail se produit vraisemblablement au niveau de la peau pendant la fabrication ou l'utilisation d'encaustiques pour sols (exposition accidentelle). Le composé est absorbé par voie percutanée chez l'animal de laboratoire, mais on ne possède aucune information sur sa cinétique ou son métabolisme. On ne peut donc pas évaluer quantitativement l'exposition par cette voie, mais on peut penser qu'elle doit être faible. Les mesures montrent que l'exposition par la voie respiratoire dans un bureau est au plus égale à 25 ng/m^3.

L'exposition de la population générale s'opère principalement par la voie alimentaire, (du fait que le TBEP est présent comme plastifiant dans les plastiques utilisés pour l'emballage des produits alimentaires) et par la consommation d'eau de boisson contaminée par le TBEP contenu dans les joints de caoutchouc synthétique de la plomberie. Elle est cependant très faible dans les deux cas (estimée à moins de 0,2 : g par kg pc et par jour avec une concentration dans l'eau de boisson inférieure à 270 : g/litre).

Compte tenu de la valeur de la NOEL tirée des études sur l'animal (15 mg.kg^{-1}.j^{-1}, valeur obtenue après administration répétée du composé par voie orale), on peut considérer que le risque est très faible pour la population générale. On estime qu'il est également très faible sur les lieux de travail, encore qu'il ne soit pas possible d'en donner une évaluation chiffrée.

Dans l'environnement, on peut déduire de la faible volatilité, du fort coefficient d'adsorption et de sa solubilité modérée dans l'eau, que le TBEP va se répartir entre les différents types de matières particulaires. Les quelques mesures dont on dispose confirment cette hypothèse. Sa décomposition dans les différents compartiments de l'environnement devrait être rapide. On ne dispose d'aucune donnée sur ces produits de décomposition ; le reste phosphate libéré au cours de ce processus ne devrait pas sensiblement augmenter la concentration globale des nutriments présents dans l'environnement. La Fig. 1 donne la valeur de la concentration relevée dans les eaux de surface en fonction de la toxicité aiguë observée. Il y a plusieurs ordres de grandeur entre la concentration la plus élevée mesurée et la plus faible de la toxicité observée, d'où une marge de sécurité élevée et

donc un faible risque pour les organismes aquatiques. On n'est pas en mesure d'évaluer l'importance du risque pour les organismes terrestres.
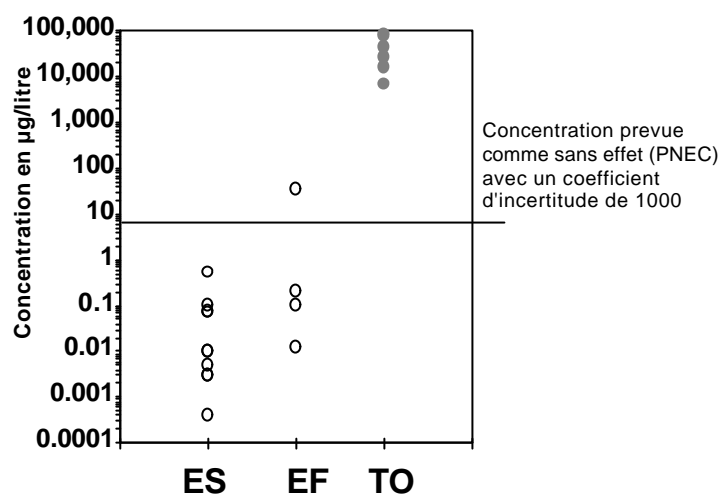
Fig.1. Graphe de la concentration mesurée dans les eaux de surface (ES)
et les effluents (EF) d'égouts en fonction de la toxicité aiguë observée (TO)
($\mathbf{F}$ = concentration mesurée dans l'environnement $\mathbf{M}$; = CL$_{50}$ calculée)

1.3   Recommandations

Pour procéder à une évaluation scientifique complète de ce composé, il faudrait identifier et étudier chacun de ses métabolites chez des mammifères, étant donné le profil toxicologique d'un des métabolites possibles, le 2-butoxyéthanol.

2.   Phosphate de tris (2-éthylhexyle) (TEHP)

2.1   Résumé

Le phosphate de tris (2-éthylhexyle) ou THEP, se présente sous la forme d'un liquide incolore et ininflammable, dont la solubilité dans l'eau et la tension de vapeur sont faibles et qui est utilisé comme retardateur de flammes et comme plastifiant dans le PVC et l'acétate de

cellulose ou encore comme solvant. On le prépare à partir de l'oxychlorure de phosphore et du 2-éthyléthanol. On ne connaît pas les chiffres actuels de production dans le monde. En Allemagne, la production annuelle est actuellement d'environ 1000 tonnes.

On n'a pas décelé la présence de TEHP dans l'air extérieur ; à l'intérieur des bâtiments, sa concentration dans l'air est inférieure à 10 ng/m^3. Dans les cours d'eau, la concentration peut atteindre 7500 ng/litre et dans les matières particulaires, 2 à 70 ng/g. On en a trouvé 0,3 ng/litre dans un seul et unique échantillon d'eau de boisson. D'après des études sur le panier de la ménagère, la dose ingérée journalière pour diverses tranches d'âge serait inférieure à 0,05 : g/kg pc.

Le TEHP est rapidement décomposé dans les eaux naturelles, mais des essais en laboratoire portant sur des boues activées ont donné des résultats équivoques. Il ne subit pas de décomposition abiotique importante.

Le TEHP présente une faible toxicité aiguë pour les mammifères, la DL$_{50}$ par voie orale étant > 10 000 mg/kg pc pour le rat.

Le TEHP irrite la peau mais il n'est pas irritant pour l'oeil. Des applications répétées de TEHP sur la peau de lapins à raison de 0,1 ml (93 mg) n'ont produit aucun signe d'intoxication générale.

Des études au cours desquelles des rats et des souris ont reçu pendant 13 semaines du TEHP par gavage n'ont pas permis d'observer d'effets toxiques importants. Pour les rats, la dose sans effet nocif observable (NOAEL) était égale à 2860 mg/kg pc et pour les souris, à 5710 mg/kg pc, soit les deux plus fortes doses utilisées chez chaque espèce.

Lors d'une étude de 3 mois au cours de laquelle on a fait inhaler du TEHP à des chiens à des doses allant jusqu'à 85,0 mg/m^3, on a observé de légères altérations inflammatoires chroniques au niveau des poumons et constaté que le réflexe conditionné d'évitement s'affaiblissait parallèlement à l'augmentation des doses.

Il n'existe pas d'étude consacrée à la toxicité génésique du TEHP.

Le composé a donné des résultats négatifs dans plusieurs tests de mutagénicité *in vitro* et *in vivo*.

On a étudié la toxicité chronique et le pouvoir cancérogène du TEHP sur des rats et des souris. La NOAEL relative à la toxicité chronique était de 2857 mg.kg^{-1}.j^{-1} pour les rats mâles et de 1428 mg.kg^{-1}.j^{-1} pour les femelles. Chez les souris mâles et femelles, la dose la plus faible produisant un effet nocif observable (LOAEL) était de 357 mg.kg^{-1}.j^{-1}, le critère retenu étant une hyperplasie des cellules folliculaires de la thyroïde. On n'a pas établi de NOAEL pour les souris. Les auteurs de ces études concluent que le composé présente un certain pouvoir cancérogène, compte tenu de l'augmentation des carcinomes hépatocellulaires qui a été observée chez les souris femelles, cette cancérogénicité étant plus équivoque pour les rats mâles chez qui a été relevée une augmentation de l'incidence des phéochromocytomes surrénaliens aux deux doses administrées. Malgré l'augmentation de l'incidence des phéochromocytomes aux deux doses chez les rats mâles et de celle des carcinomes hépatocellulaires chez les souris soumises à la plus forte dose, on estime qu'il n'y a pas lieu de considérer que le TEHP comporte un risque cancérogène important pour l'Homme. En effet, chez le rat l'incidence « naturelle » des phéochromocytomes est variable. Ainsi, dans deux études toxicologiques effectuées antérieurement par le National Toxicology Programme (NTP) on a observé des phéochromocytomes dont l'incidence était égale à celle constatée dans l'étude précédente. Pour ce qui est de l'autre type de tumeur observé, à savoir le carcinome hépatocellulaire chez les souris femelles soumises à la dose la plus forte, le fait que son incidence soit faible, qu'elle ne se soit manifestée que dans un seul sexe et chez une seule espèce, qu'on n'ait pas de preuve d'une quelconque activité génotoxique et que l'Homme ne soit guère exposé au TEHP, rend improbable la possibilité d'un risque cancérogène notable pour l'Homme.

Des études sur la neurotoxicité du TEHP ont été effectuées sur plusieurs espèces. Le composé ne provoque aucune modification dans l'activité de la cholinestérase plasmatique ou érythrocytaire. On n'a pas connaissance d'études sur la neurotoxicité retardée du TEHP.

Une étude sur des volontaires humains n'a pas révélé d'irritation cutanée.

Les quelques données disponibles montrent que le composé présente une faible toxicité aiguë pour les organismes aquatiques. Pour les bactéries, la CI_{50} à 96 h est supérieure à 100 mg/litre et pour un poisson comme le danio (*Brachydanio rerio*), elle dépasse également cette valeur, qui correspond d'ailleurs à la limite de solubilité du TEHP dans l'eau.

2.2 Evaluation

L'exposition au TEHP se produit vraisemblablement par voie cutanée au cours de la préparation du composé (exposition accidentelle) ou par suite de l'utilisation de produits qui en contiennent. Le TEHP est absorbé par voie percutanée chez l'animal de laboratoire mais on dispose d'aucune donnée sur sa cinétique ou son métabolisme après absorption par cette voie. On ne peut donc pas évaluer quantitativement ce type d'exposition, mais on peut penser qu'elle est faible. La mesure de l'exposition par inhalation de l'air des bureaux a donné une valeur au plus égale à 10 ng/m^3.

L'exposition de la population générale se produit principalement par la consommation de nourriture et d'eau de boisson. Quelle que soit la source, cette exposition est très faible (l'exposition par voie alimentaire est estimée à moins de 0,05 : $g.kg^{-1}.j^{-1}$; une seule et unique mesure effectuée sur de l'eau de boisson a donné 0,3 ng/litre).

Si l'on se base sur la LOAEL de 357 $mg.kg^{-1}.j^{-1}$ obtenue chez la souris avec comme critère une hyperplasie de la thyroïde, le risque est très faible à l'échelon de la population générale. On estime que le risque est également très faible sur les lieux de travail, encore qu'il ne soit pas possible d'en donner une évaluation quantitative.

On estime que le TEHP n'est pas cancérogène pour l'Homme.

Dans l'environnement, on peut déduire de la faible volatilité, du fort coefficient d'adsorption et de sa solubilité modérée dans l'eau, que le TEHP va se répartir entre les différents types de matières particulaires. Les mesures dont on dispose sont cependant trop peu nombreuses pour le confirmer. On peut s'attendre à une décomposition dans l'environnement, mais les données de laboratoire relatives à la décomposition du TEHP dans les boues d'égout sont ambiguës. On ne dispose d'aucune donnée sur ses produits de décomposition ; le reste

phosphate libéré au cours de ce processus ne devrait pas sensiblement augmenter la concentration globale des nutriments. La Fig. 2 donne la valeur de la concentration relevée dans divers compartiments du milieu en fonction de la toxicité aiguë relevée (aucun effet toxique observé à la limite de solubilité dans l'eau). Il y a plusieurs ordres de grandeur entre la concentration la plus élevée mesurée et la plus faible valeur de la toxicité observée, d'où une marge de sécurité élevée et donc un faible risque pour les organismes aquatiques. On n'est pas en mesure d'évaluer l'importance du risque pour les organismes terrestres.
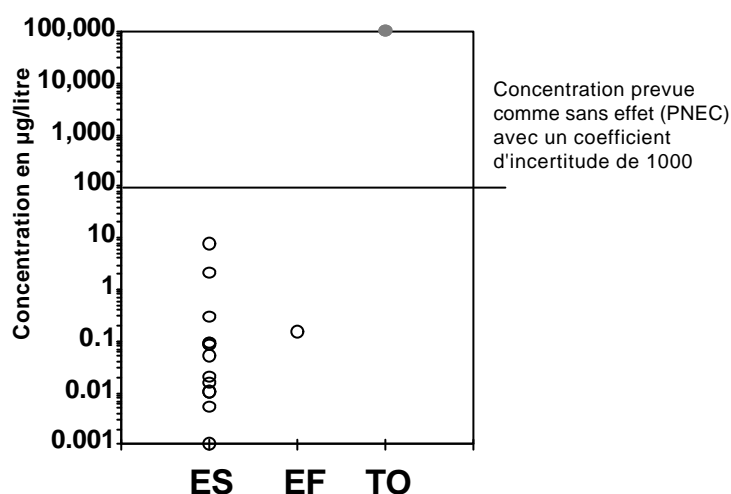
Fig. 2. Graphe de la concentration mesurée dans les eaux de surface (ES) et les effluents (EF) d'égouts en fonction de la toxicité aiguë observée (TO) (F = concentration observée dans l'environnement ; M = CL$_{50}$ calculée)

2.3   Recommandations

Pour procéder à une évaluation scientifique complète de ce composé, il faudrait identifier et étudier chacun de ses métabolites chez des mammifères, étant donné le profil toxicologique d'un des métabolites possibles, le 2-éthylhexanol.

La toxicité génésique doit être étudiée, notamment en ce qui concerne d'éventuels effets sur le développement.

3. Sels de tétrakis(hydroxyméthyl) phosphonium

3.1 Résumé

Les sels de tétrakis(hydroxyméthyl)phosphonium (THP) constituent un groupe important de composés utilisés comme retardateurs de flammes pour le coton, la cellulose et les toiles constituées de mélanges de cellulose. On constate que la migration du chlorure de tétrakis(hydroxyméthyl)phosphonium (THPC) à partir des tissus traités par le condensat de ce composé avec l'urée reste faible. Le sulfate de THP (THPS) est surtout utilisé comme produit biocide. On estime que la production mondiale est de moins de 3000 tonnes par an pour les sels de THP et d'environ 3000 tonnes pour le condensat chlorure de tétrakis (hydroxyméthyl)phosphonium-urée.

La photodécomposition et l'hydrolyse des sels de THP constituent des voies de dégradation abiotiques importantes dans l'environnement. Le sulfate de THP ne se fixe guère sur les matières particulaires et il est donc mobile. Le THPS se décompose rapidement en aérobiose comme en anaérobiose. On a constaté la présence d'oxyde de trihydroxyméthylphosphine (THPO) et d'acide bishydroxy-méthylphosphonique ou BMPA dans les produits de décomposition.

Comme il ne semble pas y avoir de surveillance de ces composés, on ne peut pas évaluer l'exposition de l'Homme ni celle des autres êtres vivants dans leur milieu naturel.

Le THPC et le THPS présentent une toxicité aiguë modérée par voie orale ; au niveau cutané, leur toxicité est faible.

Des études à court terme (jusqu'à 28 jours) effectuées sur des rats et des souris ont montré que le principal effet toxique du THPC et du THPS était une réduction du poids corporel. Chez les deux espèces, la NOAEL est d'environ 8 mg.kg^{-1}.j^{-1}. Des études plus longues (13 semaines) montrent que le principal organe cible est le foie. La NOAEL relative à cet effet varie de 3 à 7 mg.kg^{-1}.j^{-1} pour les deux sels chez les deux espèces. Les tests biologiques de cancérogénicité effectués sur le THPC ont également montré que ces effets se produisaient au niveau du foie, mais on n'a pas établi de NOAEL. Chez les deux espèces, la LOAEL était d'environ 3 mg.kg^{-1}.j^{-1}. Lors d'une étude de

cancérogénicité portant sur le THPS et effectuée sur des souris, on a évalué à 3,6 mg.kg^{-1}.j^{-1} la NOAEL pour une hyperplasie médullo-surrénalienne focale; chez les rats, la LOAEL pour la mortalité avait la même valeur.

Administré en dose unique à des lapins, le THPS n'a pas provoqué d'irritation cutanée. Cependant, l'exposition répétée de rats à ce composé par la voie cutanée a entraîné une sérieuse réaction à ce niveau. Le condensat THPC-urée s'est révélé corrosif. Chez le lapin, le THPS irrite fortement la muqueuse oculaire.

Le THPS et le condensat THPC-urée provoquent une sensibilisation cutanée chez le cobaye (test de sensibilisation maximale de Magnusson & Kilman).

Ni le THPS ni le condensat THPC-urée n'ont eu d'effets toxiques sur le développement lorsqu'ils étaient administrés par voie orale à des animaux de laboratoire.

Le THPC et le THPS manifestent une activité mutagène *in vitro*, mais celle-ci disparaît *in vivo* dans le cas du THPS (on ne dispose pas de données sur l'activité mutagène du THPC *in vivo*). Les résultats limités dont on dispose au sujet du condensat THPC-urée incitent à penser qu'il n'est pas mutagène *in vivo*. Le THPO n'est pas génotoxique. Rien n'indique de façon probante que les tissus traités par des sels de THP puissent avoir des effets mutagènes. Les données disponibles montrent qu'il n'y a pas de risque de génotoxicité pour l'Homme.

Le THPS et le THPC ne sont pas révélés cancérogènes chez le rat ou la souris lors d'études biologiques d'une durée de deux ans. Les tests cutanés montrent que les sels de THP agissent comme promoteurs dans le processus de cancérisation, mais pas comme initiateurs.

Le THPS et le THPO n'inhibent pas l'activité cholinesterasique in vitro, ce qui indique qu'ils ne sont pas neurotoxiques pour l'Homme.

Les tissus traités par le condensat THPC-urée ne provoquent pas d'irritation cutanée chez l'Homme.

Dans le cas du THPS, la valeur de la concentration entraînant des effets toxiques aigus pour les algues est de l'ordre de 1 mg/litre, avec une concentration sans effet observable (NOEC) de 0,06 mg/litre. En ce qui concerne la daphnie, la valeur de la NOEC relative aux effets aigus est de 10 mg/litre. Chez les invertébrés marins, les valeurs correspondant à des effets toxiques aigus oscillent entre 1,6 et 340 mg/litre.

Chez les poissons, la valeur de la CL_{50} à 96 h va de 72 à 119 mg/litre, avec une NOEC comprise entre 18 et 41 mg/litre. Pour les oiseaux, on donne pour la DL_{50} une valeur de 311 mg/litre (effets aigus). Dans le cas de la toxicité par ingestion, on a retenu, pour la CL_{50}, une valeur comprise entre 1300 et 2400 mg/kg de nourriture.

3.2   Evaluation

On ne dispose d'aucune information sur l'exposition de l'Homme ou des autres êtres vivants dans leur milieu naturel. Dans ces conditions, il n'est pas possible de donner une estimation quantitative du risque.

RESUMEN, EVALUACIÓN Y RECOMENDACIONES

1. Tris(2-butoxietil)fosfato (TBEP)

1.1 Resumen

El tris(2-butoxietil)fosfato (TBEP) se utiliza en ceras para el suelo y como plastificante del caucho y del plástico. No se dispone de datos sobre el volumen de producción mundial, pero se calcula que es del orden de 5000 a 6000 toneladas.

El TBEP se encuentra en el medio ambiente sólo como consecuencia de la actividad humana. Se ha investigado en determinados países industrializados su distribución en la naturaleza. Se comprobó que la concentración en las aguas superficiales era inferior a 300 ng/litro, mientras que en los sedimentos oscilaba entre 100 y 1000 ìg/kg. No se detectó TBEP en ninguno de los 167 análisis realizados en peces. Se ha detectado en un estudio único en el aire exterior ($<$200 ng/m^3). La medición del TBEP en el aire de espacios cerrados de oficina puso de manifiesto concentraciones de 25 ng/m^3 o inferiores. El TBEP se asocia a partículas y se considera que la fuente es la aplicación de cera al suelo. Se ha detectado a niveles del orden de ìg/kg en el tejido adiposo humano. La ingesta diaria con los alimentos notificada a partir de estudios de la cesta de la compra, para una gama de grupos de edad, fue $<$0,02 ìg/kg de peso corporal al día. Se han notificado concentraciones en el agua de bebida de hasta 270 ìg/litro, estimándose que procede de la migración desde las juntas de caucho de las tuberías.

Se considera que el TBEP es fácilmente biodegradable. Las mediciones en depuradoras de aguas residuales y las pruebas semicontinuas de laboratorio de los lodos cloacales han indicado una eliminación sustancial de TBEP ($>$80%). En aguas fluviales y costeras, el TBEP se degradó completamente. Se notificó que la semivida en el agua de los estuarios era de unos 50 días y que había poca degradación en el agua marina no adaptada.

La toxicidad aguda sistémica en mamíferos y el potencial de irritación son bajos.

En varios estudios subcrónicos en animales de laboratorio se ha comprobado que el hígado es el órgano destinatario de la toxicidad del TBEP. Los resultados de un estudio en ratas Sprague-Dawley macho parecen indicar que el TBEP podría causar miocarditis focal. Los efectos neurotóxicos en ratas tras dosis únicas de TBEP no son uniformes. La administración repetida de dosis elevadas de TBEP a ratas mediante sonda produjo una disminución de la velocidad de conducción nerviosa y un aumento del período de refracción. No produjo neurotoxicidad retardada en gallinas, pero inhibió las colinesterasas del cerebro y del plasma.

Tomando como base un estudio de dosis repetidas de 18 semanas en ratas, se notificó una concentración sin efectos observados (NOEL) en el hígado de 15 mg/kg de peso corporal al día, mientras que la concentración más baja con efectos observados (LOEL), fue de 150 mg/kg de peso corporal al día.

No se han estudiado la toxicidad y la carcinogenicidad del TBEP a largo plazo.

Las pruebas de mutación genética en bacterias y células de mamíferos dieron resultados negativos, pero no se han notificado pruebas sobre los daños cromosómicos.

En un estudio realizado en ratas no se observó teratogenicidad. No se han notificado otros aspectos de toxicidad reproductiva.

En una prueba epicutánea (con parche) repetida para estudiar los efectos del TBEP en la piel humana se vio que no se producía sensibilización y que la irritación era mínima.

La toxicidad del TBEP para los organismos acuáticos es moderada. La CL_{50} a las 48 horas en *Daphnia magna* es de 75 mg/litro y los valores de la CL_{50} a las 96 horas en peces oscilan entre 16 y 24 mg/litro.

1.2   Evaluación

Es probable que se produzca exposición ocupacional al TBEP por vía cutánea durante la fabricación (exposición occidental) y a partir de las ceras del suelo. El compuesto se absorbe por vía cutánea en

animales de experimentación, pero no se dispone de información sobre su cinética y metabolismo. Por consiguiente, no se puede cuantificar la exposición cutánea, pero es previsible que sea baja. La exposición por inhalación medida en el entorno de oficina ha sido de 25 ng/m^3 o inferior.

La exposición de la población general se produce fundamentalmente a través de los alimentos (debido al uso de TBEP como plastificante en los plásticos de envasado) y del agua de bebida (contaminada por lixiviación del caucho sintético utilizado en las arandelas de las cañerías). La exposición a partir de ambas fuentes es muy baja (estimada en <0,2 ìg/kg de peso corporal al día a partir de los alimentos y concentraciones en el agua de bebida de <270 ìg/litro).

Teniendo en cuenta la NOEL notificada a partir de estudios en animales de 15 mg/kg de peso corporal al día obtenida en un estudio de administración oral con dosis repetidas, el riesgo para la población general es muy bajo. El riesgo para las personas expuestas en el trabajo se considera también muy bajo, aunque no se puede cuantificar.

En el medio ambiente, se supone que el TBEP (dada su baja volatilidad, su elevado coeficiente de adsorción y su solubilidad moderada en agua) se reparte en los sedimentos. Los escasos datos medidos así lo confirman. La degradación en los compartimentos del medio ambiente se supone que es rápida. No se dispone de información sobre los productos de su degradación; no parece que el fosfato liberado durante la degradación contribuya de manera significativa a la concentración de nutrientes del medio ambiente. La Fig. 1 es una representación gráfica de las concentraciones en el medio ambiente medidas en aguas superficiales frente a los valores notificados de toxicidad aguda. El margen de inocuidad entre las concentraciones más altas y los valores de toxicidad más bajos notificados es de varios órdenes de magnitud, lo que indica un riesgo bajo para los organismos del medio ambiente acuático. No se puede hacer una evaluación del riesgo para el compartimento terrestre.

1.3   Recomendaciones

Para una evaluación científica completa del compuesto, sería necesaria la identificación y evaluación de los metabolitos en los

mamíferos, dado el perfil toxicológico de uno de los metabolitos propuestos, el 2-butoxietanol.
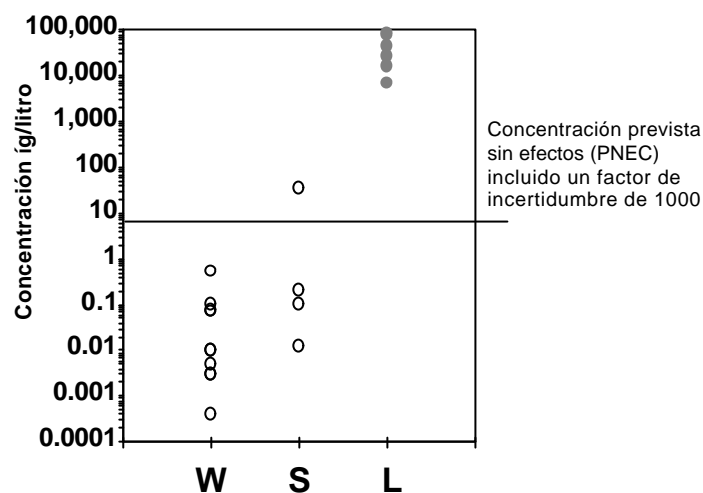
Fig. 1. Representación gráfica de las concentraciones
medidas en aguas superficiales (W) y aguas residuales (S) y de
los valores de la toxicidad aguda (L) notificados para el TBEP
(F = concentración medida en el medio ambiente; M = CL$_{50}$ calculada)

2. Tris(2-etilhexil)fosfato (TEHP)

El tris(2-etilhexil)fosfato (TEHP) es un líquido incoloro no inflamable, poco soluble en agua y de presión de vapor muy baja, que se utiliza como pirorretardante y plastificante para el PVC y el acetato de celulosa, y como disolvente. Se produce a partir del oxicloruro de fósforo y el 2-etilhexanol. No se dispone de cifras para la producción mundial actual. En Alemania se producen actualmente unas 1000 toneladas.

No se ha detectado TEHP en el aire exterior; se ha encontrado en el aire de espacios cerrados en concentraciones de menos de 10 ng/m^3, en aguas fluviales en concentraciones de hasta 7500 ng/litro y en sedimentos de 2–70 ng/g. Se detectó TEHP en una sola muestra de

agua de bebida en una concentración de 0,3 ng/litro. La ingesta diaria notificada en los alimentos a partir de estudios de la cesta de la compra, para una gama de grupos de edad, fue inferior a 0,05 ìg/kg de peso corporal al día.

El TEHP se degrada rápidamente en las aguas naturales, pero las pruebas de laboratorio con lodos activados dieron resultados equívocos. No hay una degradación abiótica significativa.

El TEHP tiene una toxicidad aguda baja para los mamíferos, siendo la DL_{50} por vía oral >10 000 mg/kg de peso corporal en ratas.

El TEHP es irritante cutáneo, pero no ocular. La aplicación repetida de 0,1 ml (93 mg) de TEHP a la piel de conejos no produjo signos de intoxicación sistémica.

En estudios de administración con sonda durante 13 semanas a ratas y ratones no aparecieron efectos tóxicos significativos. La concentración sin efectos adversos observados (NOAEL) en ratas fue de 2860 mg/kg de peso corporal al día y en ratones de 5710 mg/kg de peso corporal al día, la dosis más elevada probada en ambas especies.

En un estudio de inhalación de tres meses con concentraciones de hasta 85 mg de $TEHP/m^3$ se observaron cambios inflamatorios crónicos leves en los pulmones de perros y los resultados de rechazo condicionado empeoraron en relación con la concentración administrada.

No se dispuso de estudios sobre toxicidad reproductiva.

El TEHP dio resultados negativos en varias pruebas de mutagenicidad *in vivo* e *in vitro*.

Se realizaron pruebas de toxicidad crónica y carcinogenicidad del TEHP en ratas y ratones. La NOAEL para la toxicidad crónica en ratas macho fue de 2857 mg/kg de peso corporal al día y en ratas hembras de 1428 mg/kg de peso corporal al día. La concentración más baja con efectos adversos observados (LOAEL) en ratones machos y hembras para la hiperplasia de las células foliculares del tiroides fue de 357 mg/kg de peso corporal al día. No se estableció una NOAEL en ratones. Los autores llegaron a la conclusión de que había algunas

pruebas de carcinogenicidad basadas en una mayor incidencia de carcinomas hepatocelulares en ratones hembra con un nivel de dosificación alto y pruebas equívocas de carcinogenicidad basadas en la mayor incidencia de feocromocitomas suprarrenales en ratas macho en ambos grupos de dosis. Aunque se produjo un aumento de feocromocitomas suprarrenales en ambos grupos de dosis de ratas macho y de carcinomas hepatocelulares en ratones hembra del grupo de dosificación alta, no se considera que estos resultados indiquen que el TEHP presenta un riesgo carcinogénico significativo para el ser humano. Los feocromocitomas muestran una incidencia de base variable en ratas. La incidencia de estos tumores en dos biovaloraciones anteriores del Programa Nacional de Toxicología fue igual a la observada en la biovaloración del TEHP. Solamente hubo otro resultado neoplásico significativo, consistente en carcinomas hepatocelulares, en el grupo de ratones hembra de dosificación alta. Teniendo en cuenta la baja incidencia de este tumor, su presencia en un solo sexo de una especie, la falta de pruebas de toxicidad genética y la baja exposición del ser humano al TEHP, no es probable que este producto cree un riesgo carcinogénico significativo para el ser humano.

Se han realizado estudios de neurotoxicidad en varias especies. El TEHP no produce ninguna alteración de la actividad de la colinesterasa del plasma o los glóbulos rojos. No se han notificado estudios sobre neurotoxicidad retardada.

En un estudio realizado en voluntarios humanos, no se notificó irritación cutánea.

Los escasos datos disponibles indican una toxicidad aguda baja del TEHP en el medio acuático. La CL_{50} para bacterias es superior a 100 mg/litro y la CL_{50} a las 96 horas para el pez *Brachydanio rerio* es superior a 100 mg/litro, que es el límite de la solubilidad del TEHP en agua.

2.2   Evaluación

Es probable que se produzca exposición ocupacional al TEHP por vía cutánea durante la fabricación (exposición occidental) y por el uso de algunos productos. El compuesto se absorbe por vía cutánea en los animales de experimentación, pero no se dispone de información sobre

su cinética o metabolismo en esta vía. Por consiguiente, no se puede cuantificar la exposición cutánea, pero es previsible que sea baja. La exposición por inhalación medida en el entorno de oficina es de 10 ng/m^3 o menor.

La exposición de la población general se produce fundamentalmente a través de los alimentos y el agua de bebida. La exposición a partir de ambas fuentes es muy baja (estimada en <0,05 ìg/kg de peso corporal día a partir de los alimentos; una concentración única medida en el agua de bebida fue de 0,3 ng/litro).

Teniendo cuenta la LOAEL notificada para la hiperplasia tiroidea de 357 mg/kg de peso corporal día en ratones, el riesgo para la población general es muy bajo. El riesgo para las personas expuestas en el trabajo se considera también muy bajo, aunque no se puede cuantificar.

El TEHP no parece ser carcinogénico para el ser humano.

En el medio ambiente, se supone que el TEHP (dada su baja volatilidad, su elevado coeficiente de adsorción y su solubilidad baja en agua) se repartirá en los sedimentos. Los datos medidos son demasiado escasos para confirmarlo. Se prevé su degradación en los compartimentos del medio ambiente, aunque los datos de laboratorio sobre la degradación en lodos cloacales son equívocos. No se dispone de información sobre los productos de la degradación; no parece que el fosfato liberado durante su degradación contribuya de manera significativa a la concentración de nutrientes del medio ambiente. La Fig. 2 es una representación gráfica de las concentraciones en el medio ambiente medidas en sus compartimentos frente a los valores notificados de toxicidad aguda (éstos indican que no tiene efectos tóxicos en el límite de solubilidad en el agua). El margen de inocuidad entre las concentraciones más altas y los valores de toxicidad más bajos notificados es de varios órdenes de magnitud, lo que indica un riesgo bajo para los organismos del medio ambiente acuático. No se puede hacer una evaluación del riesgo para el compartimento terrestre.

2.3 Recomendaciones

Para una evaluación científica completa del compuesto, sería necesaria la identificación y evaluación de los metabolitos en los
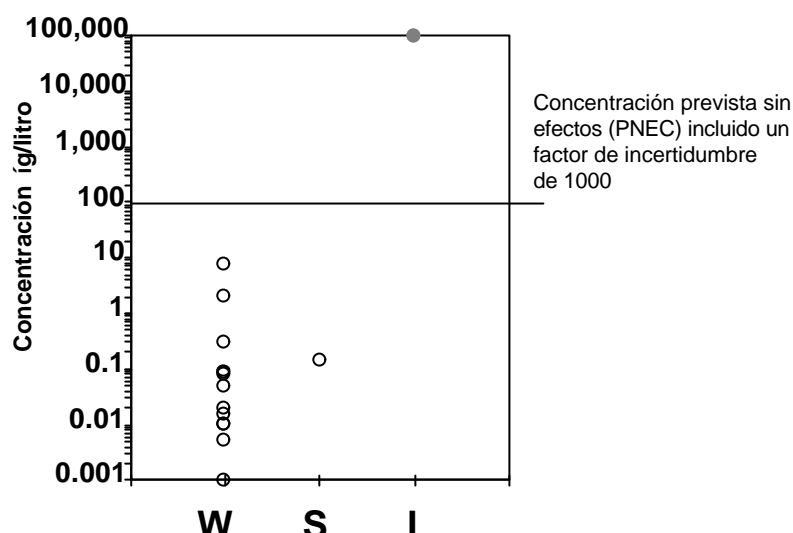
Fig. 2. Representación gráfica de las concentraciones medidas en aguas superficiales (W) y aguas residuales (S) y de los valores de la toxicidad aguda (L) notificados para el TEHP (F = concentración medida en el medio ambiente; M = CL$_{50}$ calculada)

mamíferos, dado el perfil toxicológico de uno de los metabolitos propuestos, el 2-etilhexanol.

Es necesario investigar la toxicidad reproductiva, en particular los posibles efectos en el desarrollo.

3. Sales de tetrakis(hidroximetil)fosfonio

3.1 Resumen

Las sales de tetrakis(hidroximetil)fosfonio representan la clase principal de productos químicos utilizados como pirorretardantes en el algodón, la celulosa y los tejidos con celulosa. Hay una migración baja a partir de los tejidos tratados con cloruro de tetrakis-(hidroximetil)fosfonio (THPC)-urea. La sal sulfatada (THPS) se utiliza fundamentalmente como biocida. La producción mundial combinada se estima que es >3000 toneladas para las sales de THP y de unas 3000 toneladas para el condensado de THPC-urea.

La fotodegradación y la hidrólisis de las sales de THP son vías importantes de degradación abiótica en el medio ambiente. El THPS se une débilmente a las partículas del medio ambiente, por lo que es móvil. Se degrada rápidamente tanto en condiciones aerobias como anaerobias. Se han identificado como productos de su degradación el óxido de trihidroximetilfosfuro (THPO) y el ácido bihidroximetil-fosfónico (BMPA).

Puesto que no se ha notificado ninguna vigilancia, no se pueden hacer estimaciones de la exposición del ser humano o de los organismos en el medio ambiente.

La toxicidad aguda por vía oral del THPC y el THPS es moderada; la toxicidad cutánea es baja.

En estudios breves (hasta 28 días) en ratas y ratones, el principal efecto tóxico tanto del THPC como del THPS es la disminución del peso corporal. La NOAEL para ambos productos químicos en las dos especies es de unos 8 mg/kg de peso corporal al día. En estudios más prolongados (13 semanas), el principal órgano destinatario de la toxicidad es el hígado. La NOAEL para este efecto osciló entre 3 y 7 mg/kg de peso corporal al día para ambas sales en las dos especies. Las biovaloraciones de la carcinogenicidad del THPC también pusieron de manifiesto efectos en el hígado, pero no se estableció una NOAEL. La LOAEL fue de unos 3 mg/kg de peso corporal al día para ambas especies. En una biovaloración de la carcinogenicidad del THPS en ratones, la NOAEL para la hiperplasia focal en la médula suprarrenal fue de 3,6 mg/kg de peso corporal al día; en ratas, la LOAEL para la mortalidad fue de 3,6 mg/kg de peso corporal al día.

El THPS administrado en dosis única a conejos no provocó irritación cutánea. Sin embargo, la exposición cutánea repetida en ratas produjo una reacción grave en la piel. El THPC-urea fue corrosivo. Se comprobó que el THPS ocasionaba una irritación grave de los ojos en conejos.

El THPS y el THPC-urea producen sensibilización cutánea en cobayas (prueba de maximización de Magnusson y Kilman).

En animales de experimentación tratados por vía oral, el THPS y el THPC-urea no produjeron toxicidad en el desarrollo.

El THPC y el THPS tienen potencial mutagénico *in vitro*, pero el THPS no es mutagénico *in vivo* (no hay datos de mutagenicidad *in vivo* para el THPC). Los limitados datos de mutagenicidad para el THPC-urea parecen indicar que no es mutagénico *in vivo*. El THPO no es genotóxico. No hay pruebas convincentes que indiquen que las telas tratadas con sales de THP sean mutagénicas. La información disponible pone de manifiesto que no hay peligro genotóxico para el ser humano.

El THPC y el THPS no fueron carcinogénicos en ratas y ratones en biovaloraciones de dos años. En estudios cutáneos se ha observado que las sales son promotoras de cáncer cutáneo, pero no iniciadoras.

El THPS y el THPO no inhibieron la actividad de la acetilcolinesterasa *in vivo*, lo que parece indicar una ausencia de peligro neurotóxico para el ser humano.

Las telas tratadas con THPC-urea no produjeron irritación cutánea en el ser humano.

Para el THPS, los valores de toxicidad aguda notificados en algas son inferiores a 1 mg/litro, con una concentración sin efectos observados (NOEC) de 0,06 mg/litro. La NOEC para la pulga de agua es de 10 mg/litro. Los valores de toxicidad aguda notificados para los invertebrados marinos oscilan entre 1,6 y 340 mg/litro.

Los valores de la DL_{50} a las 96 horas para los peces van de 72 a 119 mg/litro, con valores de la NOEC entre 18 y 41 mg/litro. Se ha notificado una DL_{50} aguda para las aves de 311 mg/kg de peso corporal y valores de la CL_{50} de 1 300 y 2 400 mg/kg de alimentos.

3.2   Evaluación

No se dispone de información sobre la exposición para el ser humano ni para los organismos del medio ambiente. Por consiguiente, no se pudo realizar una evaluación cuantitativa del riesgo.

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