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143. Phosphate triesters with flame retardant properties

Bengt Sjögren, Anders Iregren and Jill Järnberg

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Preface

The main task of the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) is to produce criteria documents to be used by the regulatory authorities as the scientific basis for setting occupational exposure limits for chemical substances. For each document, NEG appoints one or several authors. An evaluation is made of all relevant published, peer-reviewed original literature found. The document aims at establishing dose-response/dose-effect relationships and defining a critical effect. No numerical values for occupational exposure limits are proposed. Whereas NEG adopts the document by consensus procedures, thereby granting the quality and conclusions, the authors are responsible for the factual content of the document.

The evaluation of the literature and the drafting of this document on *Phosphate triesters with flame retardant properties* were done by Dr. Bengt Sjögren, Karolinska Institutet, Sweden, Dr. Anders Iregren and Dr. Jill Järnberg, Swedish Work Environment Authority, Sweden. The draft versions were discussed within NEG and the final version was accepted by the present NEG experts on September 28, 2009. Editorial work and technical editing were performed by the NEG secretariat. The following present and former experts participated in the elaboration of the document:

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All criteria documents produced by the Nordic Expert Group may be downloaded from *www.nordicexpertgroup.org*.

Gunnar Johanson, Chairman of NEG

Contents

Abbreviations and acronyms

Phosphate triesters

TBEP	tris(2-butoxyethyl) phosphate
TBP	tri-*n*-butyl phosphate
TCEP	tris(2-chloroethyl) phosphate
TCP	tricresyl phosphate
TDCPP	tris(1,3-dichloro-2-propyl) phosphate
TEHP	tris(2-ethylhexyl) phosphate
TEP	triethyl phosphate
TIPP	isopropylated triphenyl phosphate including triisopropylated phenyl phosphate
TMCP	tri-*meta*-cresyl phosphate, tri-*m*-cresyl phosphate
TMCPP	tris(monochloropropyl) phosphate, all isomers
TOCP	tri-*ortho*-cresyl phosphate, tri-*o*-cresyl phosphate
TPCP	tri-*para*-cresyl phosphate, tri-*p*-cresyl phosphate
TPP	triphenyl phosphate

Other

ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
BDCPP	bis(1,3-dichloro-2-propyl) phosphate
bw	body weight
CAR	constitutively active receptor
CAS	Chemical Abstracts Service
ChE	cholinesterase
CHO	Chinese hamster ovary
CNS	central nervous system
CYP	cytochrome P450
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ED_{50}	effective dose for 50 % of the population exposed
EPA	Environmental Protection Agency
EU	European Union
GC	gas chromatography
HPRT	hypoxanthine-guanine phosphoribosyl transferase
IPCS	International Programme on Chemical Safety
LC_{50}	lethal concentration for 50 % of the exposed animals at single administration
LD_{50}	lethal dose for 50 % of the exposed animals at single administration
LOAEL	lowest observed adverse effect level
MAK	Maximale Arbeitsplatzkonzentration (maximum concentration at the workplace)
MN-PCE	micronucleus containing polychromatic erythrocyte
NADPH	nicotinamide adenine dinucleotide phosphate

NOAEL	no observed adverse effect level
NTE	neurotoxic or neuropathy target esterase
NTP	National Toxicology Program (United States)
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OPIDN	organophosphorus-induced delayed neuropathy
PNS	peripheral nervous system
PVC	polyvinyl chloride
RACB	reproductive assessment by continuous breeding protocol
SCE	sister chromatid exchange
SP(M)E	solid-phase (micro)extraction
TLV	threshold limit value
TWA	time-weighted average
US	United States

1. Introduction

Phosphate esters are frequently utilised as flame retardants and plasticisers but also as stabilisers and additives in products such as floor polishes, lubricants and hydraulic fluids. Both phosphorous and chlorine provide the flame retardant properties. The organic parts of the molecule make it possible for the substance to be incorporated in organic materials. These parts can also interpose themselves between the polymer chains in a plastic and in that way plasticise it. The global consumption of organophosphorus compounds used as flame retardants was estimated to about 207 000 tonnes in 2004 and the consumption is expected to increase (52).

In Western Europe, the consumption, evenly distributed between chlorinated phosphate and non-chlorinated organophosphorus flame retardants, increased from 58 000 to 83 000 tons between the years 1998 and 2001 (145). In 2006, the estimated annual consumption of chlorinated phosphate and non-chlorinated organophosphorus flame retardants within the European Union (EU) was 51 000 and 40 000 tons, respectively (52).

This document reviews some phosphate triesters with flame retardant properties, as particularly requested by the Swedish Work Environment Authority. The phosphorylated mono- and diesters are thus excluded. The following phosphate triesters are included:

Tricresyl phosphate (TCP)
Tris(2-butoxyethyl) phosphate (TBEP)
Tri-*n*-butyl phosphate (TBP)
Tris(2-chloroethyl) phosphate (TCEP)
Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)
Tris(2-ethylhexyl) phosphate (TEHP)
Triethyl phosphate (TEP)
Triisopropylated phenyl phosphate (TIPP) [1]
Tris(monochloropropyl) phosphate (TMCPP)
Triphenyl phosphate (TPP)

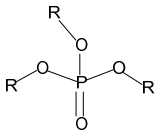
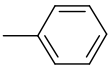
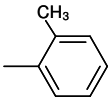
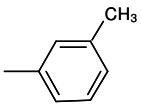
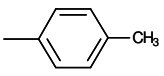
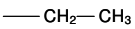
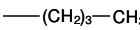
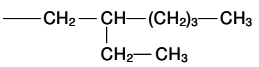
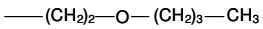
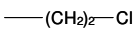
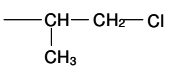
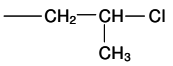
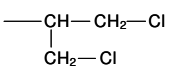
Thus, emphasis is on compounds having three identical esters although mixed phosphate esters are briefly mentioned as they occur in commercial mixtures. This document does not include organophosphate pesticides, a highly diverse group of chemicals characterised by their strong ability to inhibit the enzyme acetylcholinesterase, which deactivates the neurotransmitter acetylcholine (213).

2. Substance identification

Substance identification data for the phosphate triesters covered in this document are presented in Tables 1-2. In Table 1, the substances are ordered according to chemical structure beginning with triaryl followed by trialkyl, and chlorosubstituted compounds. Figure 1 reveals the complete structural formulas. From Table 2 and onwards, substances are listed in alphabetical order with regard to the abbreviations used in this document, except for tricresyl phosphate, which is covered first due to the early toxicological interest for this particular compound.

[1] More specifically, the abbreviation TIPP in this document covers isopropylated triphenyl phosphates with an unspecified number of isopropyl groups.

Table 1. Substance identification data for the phosphate triesters.

Common name	Abbreviation	Molecular formula	Molecular weight	Structural formula/ Side chain R
General phosphate triesters		R_3O_4P	–	
Triaryl phosphate esters				
Triphenyl phosphate	TPP	$C_{18}H_{15}O_4P$	326.3	
Tri-*o*-cresyl phosphate	TOCP	$C_{21}H_{21}O_4P$	368.4	
Tri-*m*-cresyl phosphate	TMCP	$C_{21}H_{21}O_4P$	368.4	
Tri-*p*-cresyl phosphate	TPCP	$C_{21}H_{21}O_4P$	368.4	
Triisopropylated phenyl phosphate/isopropylated triphenyl phosphate	TIPP	Unspecific	–	Unspecified structure
Trialkyl phosphate esters				
Triethyl phosphate	TEP	$C_6H_{15}O_4P$	182.2	
Tri-*n*-butyl phosphate	TBP	$C_{12}H_{27}O_4P$	266.3	
Tris(2-ethylhexyl) phosphate	TEHP	$C_{24}H_{51}O_4P$	434.6	
Tris(2-butoxyethyl) phosphate	TBEP	$C_{18}H_{39}O_7P$	398.5	
Tris(chloroalkyl) phosphate esters				
Tris(2-chloroethyl) phosphate	TCEP	$C_6H_{12}Cl_3O_4P$	285.5	
Tris(1-chloro-2-propyl) phosphate	TMCPP	$C_9H_{18}Cl_3O_4P$	327.6	
Tris(2-chloropropyl) phosphate	TMCPP	$C_9H_{18}Cl_3O_4P$	327.6	
Tris(3-chloropropyl) phosphate	TMCPP	$C_9H_{18}Cl_3O_4P$	327.6	
Tris(1,3-dichloro-2-propyl) phosphate	TDCPP	$C_9H_{15}Cl_6O_4P$	430.9	

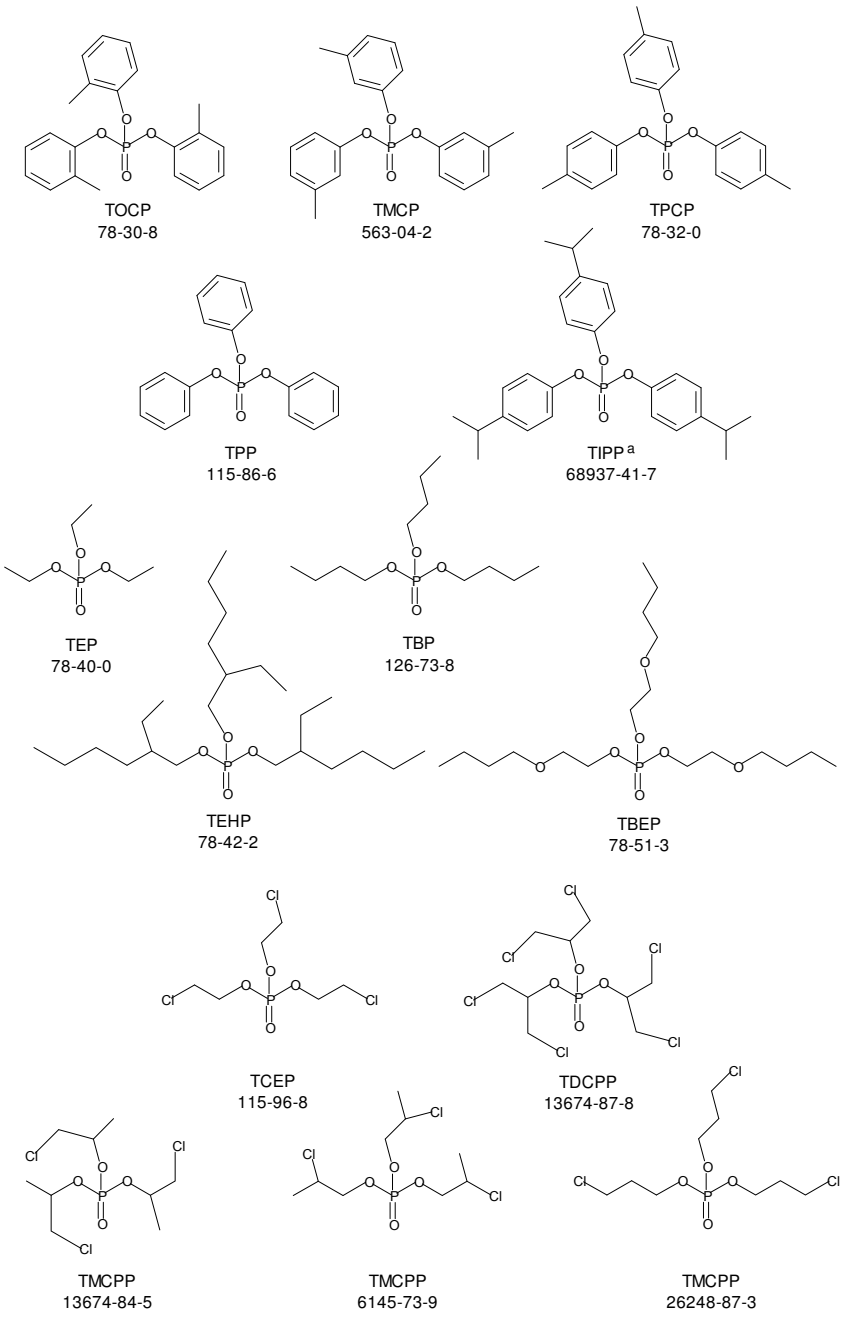


Figure 1. Structural formulas of the phosphate triesters.

[a] One example of isopropylated triphenyl phosphate.

Table 2. Substance identification data of the phosphate triesters (alphabetically ordered, except for TCP) (39, 59, 89, 99, 101, 185, 190, 243).

Common name	Abbrev.	CAS No.	Synonyms (*IUPAC name*)	Selected trade names
Tricresyl phosphate [a]	TCP	1330-78-5 [b]	Phosphoric acid, tris(methylphenyl) ester; tritolyl phosphate; tris(methylphenyl) phosphate; *unspecific*	Kronitex TCP; Lindol; Durad; Disflamoll TKP; Celluflex 179C; Phosflex 179A; Fyrquel 150; Caswell No. 884
Tri-*o*-cresyl phosphate	TOCP	78-30-8	Phosphoric acid, tris(2-methylphenyl) ester; tri-*o*-tolyl phosphate; *tris(2-methylphenyl) phosphate*	-
Tri-*m*-cresyl-phosphate	TMCP	563-04-2	Phosphoric acid, tris(3-methylphenyl) ester; tri-*m*-tolyl phosphate; *tris(3-methylphenyl) phosphate*	-
Tri-*p*-cresyl phosphate	TPCP	78-32-0	Phosphoric acid, tris(4-methylphenyl) ester; tri-*p*-tolyl phosphate; *tris(4-methylphenyl) phosphate*	-
Tris(2-butoxyethyl) phosphate	TBEP	78-51-3	Phosphoric acid, tris(2-butoxyethyl) ester; tris(2-butoxyethanol) phosphate; *tris(2-butoxyethyl) phosphate*	Phosflex T-bep; Kronitex KP-140
Tri-*n*-butyl phosphate	TBP	126-73-8	Phosphoric acid, tributyl ester; *tributyl phosphate*	Disflamoll TB; Celluphos 4; Kronitex TBP
Tris(2-chloroethyl) phosphate	TCEP	115-96-8	Phosphoric acid, tris(2-chloroethyl) ester; trichloroethyl phosphate; *tris(2-chloroethyl) phosphate*	Celluflex; Disflamoll TCA; Celluflex CEF; Fyrol CEF; Niax 3CF; Genomoll P
Tris(1,3-dichloro-2-propyl) phosphate	TDCPP	13674-87-8	Phosphoric acid, tris(1,3-dichloro-2-propyl) ester; tris(2-chloro-1-(chloromethyl) ethyl phosphate; *tris(1,3-dichloropropan-2-yl) phosphate*	Emulsion 212; Fyrol FR-2; PF 38; CRP (fire-proofing agent)
Tris(2-ethylhexyl) phosphate	TEHP	78-42-2	Phosphoric acid, tris(2-ethylhexyl) ester; trioctyl phosphate; *tris(2-ethylhexyl) phosphate*	Amgard TOF; Disflamoll TOF; Flexol TOF; Kronitex TOF; Flexol plasticiser TOF
Triethyl phosphate	TEP	78-40-0	Phosphoric acid, triethyl ester; *triethyl phosphate*	-

Table 2. Substance identification data of the phosphate triesters (alphabetically ordered, except for TCP) (39, 59, 89, 99, 101, 185, 190, 243).

Common name	Abbrev.	CAS No.	Synonyms (*IUPAC name*)	Selected trade names
Isopropylated triphenyl phosphate	TIPP	68937-41-7	Triisopropylated phenyl phosphate; phenol, isopropylated, phosphate (3:1); *unspecific* This CAS No. has also been used for tris(4-isopropylphenyl) phosphate, *tris(4-propan-2-ylphenyl) phosphate*	Durad 100; Durad MP280(sup R) hydraulic fluid; Duran MP280(sup R); Durad 300; Kronitex 50; Kronitex 100, 200 and 300; Reofos 35, 50, 65, 95, 120; Proprietary G
		26967-76-0	Tri(isopropylphenyl) phosphate; tris(isopropylphenyl) phosphate This CAS No. has also been used for tris(2-isopropylphenyl) phosphate, *tris(2-propan-2-ylphenyl) phosphate*	
		72668-27-0	Tris(3-isopropylphenyl) phosphate; phenol, 3-(1-methylethyl)-, phosphate (3:1); *tris(3-propan-2-ylphenyl) phosphate*	
Tris(monochloropropyl) phosphate	TMCPP			Amgard TMCP; Hostaflam OP 820; Fyrol PCF; Antiblaze 80; AP 33; TCPP; FG 81155
Tris(1-chloro-2-propyl) phosphate		13674-84-5	Phosphoric acid, tris(2-chloro-1-methylethyl) ester; tris(2-chloroisopropyl) phosphate; 1-chloro-2-propanol phosphate (3:1); *tris(1-chloro-propan-2-yl) phosphate*	
Tris(2-chloropropyl) phosphate		6145-73-9	Phosphoric acid, tris(2-chloropropyl) ester; 2-chloro-1-propanol phosphate (3:1); *tris(2-chloropropyl) phosphate*	
Tris(3-chloropropyl) phosphate		26248-87-3 [c]	1-Propanol, 3-chloro-, phosphate (3:1); 3-chloro-1-propanol phosphate (3:1); *tris(3-chloropropyl) phosphate*	
Triphenyl phosphate	TPP	115-86-6	Phosphoric acid, triphenyl ester; *triphenyl phosphate*	Disflamoll TP; Celluflex TPP; Phosflex TPP; Reofos TPP; Kronitex TPP

[a] Mixture of isomers including TOCP (nowadays usually below 0.1 %.), TMCP, TPCP, and mixed tricresyl and dicresyl phosphate esters.
[b] Proposed to be deleted by the European Union.
[c] Mixed with 13674-84-5.

TCP Commercial tricresyl phosphate is a complex mixture containing tri-*meta*-cresyl phosphate (TMCP), tri-*para*-cresyl phosphate (TPCP) as well as mixed tricresyl and dicresyl phosphate esters. Theoretically, the total number of *tri*-cresyl phosphate isomers (symmetrical and mixed) is ten. The synthesis and composition of commercial TCP have changed over time (Chapter 4). Tri-*ortho*-cresyl phosphate (TOCP) occurs nowadays only as a contaminant in commercial mixtures and usually in concentrations below 0.1 % (215).

In its classification systems for hazardous substances, the EU has introduced modifications of two of the CAS descriptions for tricresyl phosphate chemicals, namely:

- CAS No. 78-30-8 tricresyl phosphate (containing *o-o-o*, *o-o-m*, *o-o-p*, *o-m-m*, *o-m-p* and *o-p-p* isomers). In the present document, this CAS No. is used for the *o-o-o* isomer only (TOCP).
- CAS No. 78-32-0 tricresyl phosphate (containing *m-m-m, m-m-p, m-p-p* and *p-p-p* isomers). In the present document, this CAS No. is used for the *p-p-p* isomer only (TPCP).

The reason for this change was to discourage use of the general TCP mixture CAS No. 1330-78-5 (which is proposed to be deleted) and encourage better disclosure of *ortho*-cresyl-containing mixtures. The new CAS numbers will assist in identifying those products that contain the toxic *ortho*-cresyl ingredients. Both the mono-*ortho* and the di-*ortho* cresyl isomers are more neurotoxic than TOCP (257).

The analysis of a commercial TCP mixture used in the studies performed by the National Toxicology Program (NTP) indicated 28 components, nine of which had peak areas greater than 2 % of the total chromatographic peak area. The concentrations of TMCP and TPCP were estimated to 21 % and 4 %, respectively, and that of TOCP to below 0.1 %. Two peaks representing 24 % and 30 % of the total chromatographic peak area were identified by mass spectrometry as tricresyl phosphate esters whose isomeric compositions could not be confirmed. The remaining five major peaks (2 %, 3 %, 3 %, 4 % and 5 %) were identified as dicresyl phosphate esters, but the isomeric composition could not be confirmed. Thus, the commercial TCP used in the NTP studies referred to in this document is a complex mixture consisting of 18 % dicresyl phosphate esters and 79 % tricresyl phosphate esters with 21 % TMCP, 4 % TPCP and no detectable TOCP (< 0.1 %) (174).

Analysis of TCP used in aircraft engine oils revealed a predominance of *meta*-(non-*ortho*-) cresyl isomers with *ortho*-cresyl phosphate isomers present almost exclusively as mono-*ortho*-tricresyl isomers (*o-m-m* and *o-m-p*) (42).

TBEP Tris(2-butoxyethyl) phosphate is a technical product that may contain about 3 % TBP with traces of 2-butoxyethanol and phosphoric acid as impurities (103).

TBP Tri-*n*-butyl phosphate is one of the trialkyl phosphate esters.

TCEP Tris(2-chloroethyl) phosphate belongs to the group of chlorinated alkyl phosphate esters.

TDCPP The commercial product tris(dichloropropyl phosphate) has predominantly branched substituent propyl groups in the "iso" orientation joined via the centre carbon, tris(1,3-dichloro-2-propyl) phosphate (CAS No. 13674-87-8). The alternate isomer, tris(2,3-dichloro-1-propyl) phosphate (CAS No. 78-43-3) exists only as a trace in commercial TDCPP because of steric hindrance from chlorine substitution on adjacent carbon atoms (102).

TEHP Tris(2-ethylhexyl) phosphate is one of the trialkyl phosphate esters.

TEP Triethyl phosphate belongs to the trialkyl phosphate esters.

TIPP Triisopropylated phenyl phosphate (with an unspecific molecular structure) has the CAS No. 68937-41-7. This CAS No. has also been used for a compound with three *para*-positioned isopropyl groups (tris(4-isopropylphenyl) phosphate). Tris(isopropylphenyl) phosphate has the CAS No. 26967-76-0, which has also been used for tris(2-isopropylphenyl) phosphate . The symmetrical *meta*-isomer tris(3-isopropyl phenyl) phosphate has the CAS No. 72668-27-0. The designation TIPP in this document refers rather to isopropylated triphenyl phosphates (with an unspecified number of isopropyl groups) and will if possible be specified in each study in this document. Isopropylated triphenyl phosphates are substituted with isopropyl groups at *ortho, meta* and/or *para* positions on one, two or three of the phenyl rings. Thus, the number of potential isomers is large. Commercial TIPP contains also other compounds such as TPP (27, 55, 251). The percentage of TPP varies with the grade of product and ranges from about 5 % to 50 %, with the most viscous products having the least amount of TPP. There are several commercial products of isopropylated triaryl phosphates. The most substituted product is Kronitex® 300 (CAS No. 67426-58-8) when compared to Kronitex® 50 (CAS No. 67426-57-7), Kronitex® 100 (CAS No. 66797-44-2) and Kronitex® 200 (CAS No. 96300-97-9) (251). An analysis of Kronitex® 50 and Kronitex® 100 showed TPP concentrations of 33 % and 18 %, respectively (167). A later analysis of one commercial isopropylated triphenyl phosphate (208) did not reveal any substantial proportion of triisopropylated phenyl phosphate (Table 3).

Table 3. Content of one commercial isopropylated triphenyl phosphate (208).

Component	%
TPP	24
Ortho-isopropylphenyl diphenyl phosphate	24
Ortho-para diisopropylphenyl diphenyl phosphate	18
Di(*ortho*-isopropylphenyl) phenyl phosphate	10
Di(isopropylphenyl) phenyl phosphate	10
Para-isopropylphenyl diphenyl phosphate	6
Isopropylphenyl diisopropylphenyl phenyl phosphate	7
Di(diisopropylphenyl) phenyl phosphate	< 1

TMCPP Tris(monochloropropyl) phosphates theoretically comprise four different symmetrical isomers, of which the three most common are presented in Table 1. Although tris(1-chloro-2-propyl) phosphate (CAS No. 13674-84-5) is the most abundant isomer in commercial products, companies have tended to refer to their product by the name tris(2-chloropropyl) phosphate (TCPP), though that name refers to CAS No. 6145-73-9. This has led to a considerable degree of uncertainty in the literature and toxicity databases as to the identity of the substance that has undergone toxicity testing. TMCPP toxicity testing has usually been carried out on commercial mixtures containing variable amounts of TMCPP isomers, which also include e.g. the asymmetrical isomers bis(1-chloro-2-isopropyl) (2-chloropropyl) phosphate (CAS No. 76025-08-6) and bis(2-chloropropyl) (1-chloro-2-isopropyl) phosphate (CAS No. 76649-15-5) (216). Therefore, the designation TMCPPs in this document refers to single isomers or to commercial mixtures containing variable amounts of TMCPP isomers. When possible, TMCPP isomers will be specified.

TPP Triphenyl phosphate is one of the triaryl phosphate esters. TPP may be a substantial part of commercial TIPP (Table 3) (55, 208).

3. Physical and chemical properties

The phosphate esters covered in the present document are mainly used as flame retardants and plasticisers. All of them except TPP, TMCP and TPCP are liquids at room temperature. Most have rather low vapour pressures and for some of them (TCP, TBEP and TEHP), the concentration in saturated atmosphere is below 1 ppm. Data on physical and chemical properties are presented in Table 4.

TCP (commercial) is an almost colourless liquid with a slightly aromatic odour. Based on vapour pressure, a saturated atmosphere contains around 0.1 ppm TCP. TOCP, TMCP and TPCP are all colourless. Pure TMCP is half-solid and TPCP a crystalline solid (99).

The pyrolytic degradation at 525 ^{o}C of two jet engine oils (Castrol 5000 and Exxon 2380) containing TCP resulted in the release of carbon dioxide and carbon monoxide, as well as a large number of volatiles. Although TCPs were found in both bulk oils as well as in the air, the presence of the very potent neurotoxin trimethyl propane phosphate could not be demonstrated. Trimethyl propane phosphate may be formed from TCP and trimethylolpropane esters, which are both common constituents in jet engine oils (246).

TBEP is a light-coloured, high-boiling, viscous liquid with a butyl-like odour under normal conditions. It is more soluble in non-polar than polar solvents (103).

TBP is a colourless and odourless liquid. It is thermally unstable and begins to decompose at temperatures below its boiling point. At 370 ^{o}C, TBP was ex-

tensively thermally degraded in air and the major generated component was butene (180). The weak bond of the molecule is the C-O bond and its splitting leads to butene and phosphoric acid. At about 700 °C with an excess of oxygen, complete combustion occurs with the formation of carbon dioxide and water (101).

TCEP is a clear, colourless to pale yellow liquid with a slight odour. It is stable to short-term exposure at 150 °C, but rapid decomposition occurs above 220 °C. The products of thermal decomposition are carbon monoxide, hydrogen chloride, 2-chloroethane and dichloroethane (102). At 370 °C, also vinyl chloride is formed (180).

TDCPP is a clear, viscous liquid, which is soluble in most organic solvents (102). Based on vapour pressure, a saturated atmosphere contains less than 13 ppm TDCPP. At 370 °C, the halogenated phosphate triester undergoes extensive thermal oxidative degradation. The major products formed are 1,3-dichloroprene, 1,2,3-trichloropropane, hydrogen chloride and acrolein (180).

TEHP is a viscous, colourless to light yellow liquid, which is almost odourless (103).

TEP is a colourless liquid (90). Based on vapour pressure, a saturated atmosphere contains about 400-500 ppm TEP.

TIPP In commercial products of isopropylated triphenyl phosphates, the percentage of TPP varies with the grade of product and ranges from about 5 % to 50 % with the most viscous products having the least amount of TPP (251).

TMCPP Variations in manufacturing methods result in commercial formulations that contain different proportions of the TMCPP isomers. Mixtures in which the linear forms are above trace levels tend to be pale yellow, whereas other mixtures are colourless (216). Thus, the most abundant isomer tris(1-chloro-2-propyl) phosphate is a colourless liquid (102). Based on vapour pressure, a saturated atmosphere contains less than 2 700 ppm.

TPP is a colourless, crystalline substance with a faint, aromatic odour. It begins to decompose at about 600 °C but is not completely degraded even at 1 000 °C in inert gas. Under these conditions, TPP yields aromatic hydrocarbons, oxygenated aromatic compounds and phosphoric oxides including phosphoric acids. With a large excess of air, complete combustion to carbon dioxide is accomplished within the temperature range 800-900 °C (100).

Table 4. Physical and chemical properties of the phosphate triesters. Substances are alphabetically ordered, except for tricresyl phosphate.

Common name	Abbre-viation	Boiling point (°C)	Melting point (°C)	Flash point (°C)	Density (g/ml) at 20-25 °C	Vapour pressure (Pa) at 25 °C	Solubility in water (mg/l) at 25 °C	Partition coefficient (log P octa-nol/water)	Conversion factor 1 ppm = x mg/m^3
Tricresyl phosphate [a]	TCP	265 [b], 420 [c] 241-255 (5.3h Pa) [d]	-33 [b, d]	257 [d]	1.16-1.17 [c, d]	8×10^{-5} [b] 1.33×10^{-2} (20 °C) [d]	0.36 [b, c, d]	5.11 [b, c, d]	15.1 [d]
Tri-*o*-cresyl phosphate	TOCP	410 [b, c, d], 415 [e]	11 [b, c, d, e]	225 op [e]	1.18 [e], 1.20 [c, d]	1.46×10^{-3} [e]	0.3 [d, e]	6.34 est [b]	15.1 [d]
Tri-*m*-cresyl phosphate	TMCP	260 (20 hPa) [b, c, d] > 290 [e]	25-26 [b, c, d, e]	225 op [e]	1.15 [c, d, e]	2.3×10^{-4} (20 °C) [e]	0.36 [e] Insoluble [c]	6.34 est [b]	15.1 [d]
Tri-*p*-cresyl phosphate	TPCP	244 (4.7 hPa) [c, d] 275-280 (27 hPa) [e] > 300 [f]	77.5 [b] 77-78 [c, d] 77.5-78 [e]	225 op [e]	1.17 [e] 1.24 [d] 1.25 [c]	3.49×10^{-6} [e] 4.4 (150 °C) [f]	0.0184 [e] 0.074 [d] 0.3 [b]	6.34 est [b]	15.1 [d]
Tris(2-butoxyethyl) phosphate	TBEP	200-230 (5.3 hPa) [d, e] 215-228 (5.3 hPa) [c] 221 (5.3 hPa) [b]	-70 [b, c, d, e]	210 appr. [d] 224 op [e]	1.02 [c, d, e]	2.8×10^{-5} [d] 1.6×10^{-4} (20 °C) [e]	1 100 [b, c, e] 1 100-1 300 (20 °C) [d]	3.75 [b, c]	16.5 [d]
Tri-*n*-butyl phosphate	TBP	289 decomp. [d, e] 289 [b, c]	-79 [b, e] -80 [d] < -80 [c]	146 op [e] 166 op [g] 193 [f]	0.973-0.983 [c, d, e]	0.151 [b, c] 0.8 (20 °C) [e]	280 [b, c] 600 [e] 400 (20 °C) [f]	4.0 [b, c, d]	10.9 [d]
Tris(2-chloroethyl) phosphate	TCEP	330 [b, c] 351 [d] 192 (13 hPa) [e]	-35 [b] -62- -55 [e] -55 [c]	202 cl [d] 232 op [e]	1.39 [c, e] 1.425 [d]	3.36×10^{-3} [e] 8.17 [b, c]	7 000 [b, c, e] (unspec. temp) 8 000 (20 °C) [d]	1.44 [b, c] 1.7 [d]	11.65 [c] 11.7 [d]
Tris(1,3-dichloro-2-propyl) phosphate	TDCPP	236-237 (6.7 hPa) [b, d] > 200 [e]	27 [b] -58 [h]	251 op [e] 252 op [c, d]	1.52 [d]	1.33 (30 °C) [d]	42 [h] 100 (30 °C) [d] 110 [e], 7 [b]	2.4 [h] 3.65 [b] 3.8 [d]	17.6 [d]
Tris(2-ethylhexyl) phosphate	TEHP	210 (5 hPa) [d] 220 (6.7 [d]/7 [e] hPa) 215 (5.3 hPa) [b, c]	-74 [b, c, d, e]	170 op [e, f] 190-195 [d]	0.92 [f] 0.93 [d, e] 0.92 (26 °C) [c]	1.1×10^{-5} [b, c]	1 000 [e] < 100 [d] 0.6 (24 °C) [b, c]	4.2 [d]	17.8 [d]

Table 4. Physical and chemical properties of the phosphate triesters. Substances are alphabetically ordered, except for tricresyl phosphate.

Common name	Abbre-viation	Boiling point (°C)	Melting point (°C)	Flash point (°C)	Density (g/ml) at 20-25 °C	Vapour pressure (Pa) at 25 °C	Solubility in water (mg/l) at 25 °C	Partition coefficient (log P octa-nol/water)	Conversion factor 1 ppm = x mg/m^3
Triethyl phosphate	TEP	215 [b, c, e]	-56 [b, c, e] -57 [f]	116 op [e] 130 [f]	1.07 [c, e]	39.3 [e], 52 [b, c] 10 (20 °C) [f]	11 150 [e] 500 000 [b, c]	0.8 [b, c]	7.4
Isopropylated triphenyl phosphate TIPP									
CAS No. 68937-41-7		220-270 [e] 220-270 (5.3 hPa) [i]	-12- -26 [e]	199 op [e] 199 cl [i] 255 op [k]	1.10-1.20 [e] 1.14 [k]	2.75×10^{-6} est [b] 34.6 (150 °C) [i]	0.7-2 [e] Insoluble [k]	4.9-5.2 [j]	-
CAS No. 26967-76-0		220-270 (5.3 hPa) [c, e]	-25 [c, e]	-	1.16 [c, e]	-	-	-	-
Tris(monochloropropyl) phosphate TMCPP									
Tris(1-chloro-2-propyl) phosphate		> 270 [b] 341.5 [e]	-40 [b] -42 [e]	185 cl 218 op [l]	1.29 [e]	2.7×10^{-3} est [b] < 689 [e]	1 200 [b] 1 600 [e]	2.59 [b, d]	13.4 [d]
Tris(2-chloro-1-propyl) phosphate		220 °C decomp. [m]	-65 [m]	220 op [m]	1.297 [m]	0.1 e, < 13 [m]	1 200 [e, m]	2.89 est [b]	13.4 [d]
Tris(3-chloropropyl) phosphate		-	-	-	-	6.4×10^{-4} est [b]	18.8 [e] 18.8 est [b]	3.11 est [b]	13.4 [d]
Triphenyl phosphate	TPP	220 (5 [f]/6.7 [d] hPa) 245 (15 hPa) [b, c, d] > 250 [e], 370 [n]	49-50 [c, d, e] 50.5 [b]	220 op [e] 220, 225 [d] > 230 [f]	1.21 (50 °C) [c] 1.21 [e]	8.4×10^{-4} [b, c] 1×10^{-3} [e]	1.9 [b, c, e]	4.59 [b, c] 4.61-4.76 [d]	13.3 [c, d]

[a] Commercial mixture containing TOCP (probably less than 0.1 %), TMCP and TPCP but also mixed tricresyl and dicresyl phosphate esters.
[b] (183), [c] (90), [d] (99-103), [e] (39), [f] (152), [g] (123), [h] regarded as the most reliable data by the US EPA (243), [i] (74), [j] (59), [k] (40), [l] (238), [m] (166), [n] (218).
Appr: approximately, cl: closed cup, EPA: Environmental Protection Agency, est: estimated, op: open cup.

4. Occurrence, production and use

The phosphate triesters included in this document do not occur naturally in the environment. They are used as flame retardants in polyvinyl chloride (PVC), flexible and rigid polyurethane foams, thermoset resins, thermoplastic materials, textile finishes, cellulosics, polyesters, and phenolic and hydraulic fluids. They are also used as plasticisers in polymers like PVC, cellulose acetate, polyester, acrylonitrile-butadiene-styrene, polystyrene, synthetic rubber and polyphenylene oxide resins. Phosphate triesters are also applied as plasticisers and flame retardants in products like paints, lacquers and varnishes. The chlorinated triesters (TCEP, TDCPP and TMCPP) are used in flexible and rigid polyurethane foams, rubber and textile coatings. They have been found in mattresses, wood preservation coatings, sound- and shock-absorbing materials, and foam fillers. Apart from being used as flame retardants, some phosphate triesters (e.g. TCP, TBP and TPP) are utilised as extreme pressure additives and antiwear agents in hydraulic fluids, lubricants, transmission oils and motor oils to prevent surface damage (145).

Commonly used trade names for the phosphate triesters are shown in Table 2. Table 5 presents the annual use of the chemicals as registered in the SPIN database (207), which provides data on the use of chemical substances in Norway, Sweden, Denmark and Finland. The project is financed by the Nordic Council of Ministers Chemical Group and the data are supplied by the Product Registries of the contributing countries. The most commonly used phosphate triester in the Nordic countries is tris(1-chloro-2-propyl) phosphate (TMCPP) with an annual use of approximately 2 000 tonnes, followed by TCEP, TEHP, TEP and TIPP with yearly uses of about 300 tonnes.

Some common uses of phosphate triesters in the Nordic countries are presented in Table 6.

TCP is usually produced by the reaction of synthetically prepared cresols (with known isomeric composition) with phosphorus oxychloride (99) to limit the formation of unwanted isomers (e.g. TOCP) and contaminants. Early manufacturing practices used petroleum or coal tar derived cresols. Commercial TCP is a complex mixture containing TMCP and TPCP but also mixed tricresyl and dicresyl phosphates. Nowadays, TOCP occurs only as a contaminant in commercial mixtures, usually at very low concentrations (< 0.1 %) (215).

TCP is used as a plasticiser in vinyl plastic manufacture, as a flame-retardant, a solvent for nitrocellulose, in cellulosic moulding compositions, as an additive to extreme pressure lubricants and as a non-flammable fluid in hydraulic systems (99). It is used in jet turbine engine oils in the formulation of lubricants as antiwear additive to enhance load-carrying capacity and tolerance to increasing speed of rotating or sliding motion (141). TOCP has also been used as a lead scavenger in gasoline (18).

The synthesis and composition of commercial TCP have changed over time, towards a reduction of the TOCP content. So-called Class 1 TCP was manufactured

Table 5. Registered annual use of the phosphate triesters in the Nordic countries in tonnes (207). Data are presented when available from at least three of the countries Denmark, Finland, Norway and Sweden.

Compound	CAS No.	2002	2003	2004	2005	2006	2007
TCP	1330-78-5	13	8	16	17	14	16
TOCP [a]	78-30-8	-	-	-	-	-	-
TMCP [b]	563-04-2	-	-	-	-	-	-
TPCP	78-32-0	0.5	0.7	0.8	0.4	3.6	1.5
TBEP	78-51-3	122	84	60	76	88	73
TBP	126-73-8	71	86	92	112	103	118
TCEP	115-96-8	1 315	1 298	2 424	1 110	454	342
TDCPP [c]	13674-87-8	-	-	-	-	-	-
TEHP	78-42-2	166	133	36	143	130	379
TEP	78-40-0	81	32	30	39	273	310
TIPP	68937-41-7	96	72	92	207	236	313
TMCPP	13674-84-5	1 841	2 037	1 949	1 727	3 225	1 857
TMCPP [d]	6145-73-9	-	-	-	-	-	-
TMCPP [e]	26248-87-3	-	-	-	-	-	-
TPP	115-86-6	107	96	116	69	115	149

-: Data are not available for reasons of confidentiality. Generally, data are kept confidential if the substance is a component in less than 4 preparations from less than 3 producers.

[a] Used in Denmark (amount < 0.1 tonnes/year), Norway and until 2003 in Sweden.

[b] Used in Sweden.

[c] Used in Denmark, Finland and until 2003 in Sweden.

[d] Used in Denmark (ca. 260 tonnes/year until 2002, and then ca. 10 tonnes/year) and in Sweden and until 2002 in Norway.

[e] Used in Denmark and until 2002 in Norway.

from a crude cresol mixture containing about 30 % *ortho*-cresol. This was the "torpedo oil" type responsible for numerous poisonings in Germany during World War II and shortly thereafter. It was about 8-10 times more toxic than TOCP itself. Class 2 TCPs were detected in two jet engine oils that were intentionally mixed into cooking oil and sold for food use in Morocco in 1958. The toxicity of the TCPs in the Moroccan oils (named B and C) was 50 and 25 %, respectively, of the "torpedo oil". The Class 3 TCPs were described by Henschler in 1958 as modern commercial preparations of greatly reduced *ortho*-cresol content (~3 %) (82). The Class 4 "conventional" TCPs are those commonly available from 1992 and the Class 5 "low-toxicity" TCPs are those commercially available from 1997 (141).

There was an at least 400-fold decrease in the neurotoxicity of TCP from World War II to the low-toxicity materials available today. The reduction in activity from Class 1 to Class 5 is associated with changes in the phenolic mixture used for synthesising TCP, the introduction of processing alternatives and improved methods of purification. Effort has focused on reducing the *ortho*-cresol content in the reaction mixture and in the final TCP product. The first commercial TCP was synthesised from a mixture containing approximately 25 % *ortho*-cresol (82), the TCP of Moroccan oils from a mixture containing approximately 12 % *ortho*-cresol, and the "modern" low-*ortho* commercial preparation from a mixture of approximately 3 % *ortho*-cresol. The reductions in *ortho*-cresol content correlate with a substantial lowering in the neurotoxicity of the synthesised TCPs. Hydrolysates of

currently (1990s) manufactured “low-toxicity” TCPs have extremely low levels of all *ortho* substituted phenols and xylenols and are composed almost entirely of *meta*- and *para*-cresols (141).

Mobil Jet Oil II is a synthetic oil product. The product is used worldwide and is manufactured by one facility in the United States (US). This oil has been essentially unchanged since its development in the early 1960s. The oil contains 3 % TCP, which is a blend of ten TCP isomers including TOCP plus other structurally similar compounds (257).

It is difficult to obtain data on the amount of TOCP in commercially available materials containing TCP marketed worldwide. However, conservative estimates of 0.1-1 % seem realistic (the concentration is usually below 0.1 %, see Chapter 2). This suggests that a product containing 3 % TCP would contain about 0.003-0.03 % TOCP. The ‘‘new generation’’ materials are claimed to have an even lower TOCP content, although data are sparse. Importantly, however, the focus of attention on the toxicity of TOCP has masked the study of the toxic potential of other *ortho*-cresyl isomers. It is known that the mono-*ortho* and the di-*ortho* isomers are more toxic than TOCP. The introduction by the EU of two new CAS numbers (Chapter 2) will assist in identifying products containing *ortho*-cresyl ingredients (257).

In a recent study, analysis of TCP in aircraft turbine engine oil revealed that the *ortho* isomers of TCP were present almost exclusively as mono-*ortho* tricresyl isomers in concentrations of 13-150 mg/kg oil (42).

TBEP is produced by reacting phosphorus oxychloride and butoxyethanol, and stripping hydrochloric acid and excess of butoxyethanol. Another production method uses the sodium salt of butoxyethanol (103).

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 plasticiser in synthetic rubber, plastics and lacquers. TBEP is widely used as a plasticiser in rubber stopper for Vacutainer tubes and plastic ware (103).

TBP is prepared by the reaction of phosphorus oxychloride with *n*-butanol (101). TBP is used as a solvent for cellulose esters, lacquers and natural gums, as a herbicide and as a defoaming agent for concrete and oil well drilling. It is used as a plasticiser in the manufacture of plastics and vinyl resins, an antifoaming agent mainly in paper manufacturing plants, in printing inks, and as an extractant in the dissolution process in nuclear fuel processing. Its major use is as a base stock in the formulation of the fire-resistant aircraft hydraulic fluids (79, 101). Some hydraulic fluids contain 70-80 % TBP (63). TBP is also used as a wetting agent in casein glue and as a pasting agent in pigment paste (145).

A novel non-ionic surfactant nanoemulsion designated 8N8 has been tested and shown to have bactericidal, virucidal and fungistatic activities. This emulsion is composed of an oil phase of TBP, soybean oil and Triton X-100, which is mixed with water (75). TBP has also been used for viral inactivation in immune serum globulins (10).

TCEP was historically used in polyurethane foams and systems, mainly for rigid foam but with minor use in flexible polyurethane (102). Among the Nordic countries, Norway had the highest registered use in 2001 and 2002 with 1 100 tonnes/year and Sweden the lowest with less than 20 tonnes/year (207).

TCEP is not recommended by producers for use as a flame retardant additive for use in textiles nor for use in block polyurethane foams because of the probability of its decomposition (102).

In a study measuring TCEP in indoor environments, the highest content was reported in an acoustic ceiling (68 g/kg). Lower concentrations were reported in polyurethane foam fillers (32 g/kg), polyurethane soft foam (20 g/kg) and wood preservation coatings (10 g/kg) (98).

TCEP has been used in Australia as flame retardant in acrylate and polyurethane preparations for sealing rock faces in underground coal mines (166).

TDCPP is produced by the reaction of phosphorus oxychloride and epichlorohydrin (102) and was first synthesised by chemists of the Stauffer Chemical Company in the 1950s. It was introduced as a flame retardant in the 1950s and was later given the commercial trade name Fyrol® FR-2. TDCPP was used as a flame retardant in children's and infants' sleepwear until May 1977, when it was withdrawn in the US from sales to the apparel market after published reports that it was mutagenic in bacteria (217).

Nowadays, TDCPP is used as a flame retardant mainly in polyurethane foams and other materials (102). In 2002, about 130 tonnes was used in Denmark (207). Mattresses for hospitals and prisons are commonly treated with TDCPP (145).

TEHP is prepared by the reaction of phosphorus oxychloride and 2-ethylhexanol (103). TEHP is used in PVC plastisols, as a flame retardant in cellulose acetate and as a solvent for certain chemical reactions (103).

TEP is used in ketene synthesis and as flame retardant and plasticiser in plastics industry. About three fourth of the annual production of TEP is used as a catalyst in the manufacture of ketene. In Finland, TEP is also registered as a component of a car paint repair product (237).

TEP released from polyurethane hard foam for building and indoor use was detected in an emission experiment. Emission rates decreased rapidly and after 168 hours, only traces of TEP could be determined (192).

TIPP often occurs together with TPP in commercial products. In commercial flame retardant products, the proportion of TPP may be in the range 4-40 % (243).

Table 6. Common uses of the phosphate triesters in the Nordic countries (207).

Common name	Abbreviation	CAS No.	Uses
Tricresyl phosphate	TCP	1330-78-5	Paints, lacquers and varnishes; lubricants and additives; adhesives, binding agents; flame retardants and extinguishing agents; surface treatment; softeners.
Tri-*o*-cresyl phosphate	TOCP	78-30-8	No data.
Tri-*m*-cresyl phosphate	TMCP	563-04-2	No data.
Tri-*p*-cresyl phosphate	TPCP	78-32-0	Paints, lacquers and varnishes; lubricants and additives; flame retardants and extinguishing agents; hydraulic fluids and additives.
Tris(2-butoxyethyl) phosphate	TBEP	78-51-3	Adhesives, binding agents; surface treatment; paints, lacquers and varnishes; surface-active agents; softeners; construction materials; cleaning/washing agents; colouring agents.
Tri-*n*-butyl phosphate	TBP	126-73-8	Surface-active agents; hydraulic fluids and additives; paints, lacquers and varnishes; fillers; process regulators; construction materials; colouring agents; lubricants and additives; solvents; cleaning/washing agents; adhesives, binding agents; softeners; corrosion inhibitor.
Tris(2-chloroethyl) phosphate	TCEP	115-96-8	Construction materials; flame retardants and extinguishing agents; adhesives, binding agents; insulating materials.
Tris(1,3-dichloro-2-propyl) phosphate	TDCPP	13674-87-8	Flame retardants and extinguishing agents.
Tris(2-ethylhexyl) phosphate	TEHP	78-42-2	Adhesives, binding agents; lubricants and additives; fillers; construction materials; paints, lacquers and varnishes; corrosion inhibitor; heat transferring agents.
Triethyl phosphate	TEP	78-40-0	Flame retardants and extinguishing agents; process regulators; construction materials; adhesives, binding agents; fillers; intermediates.
Isopropylated triphenyl phosphate	TIPP	68937-41-7	Lubricants and additives; hydraulic fluids and additives; paints, lacquers and varnishes; cutting fluids; construction materials; surface treatment; flame retardants and extinguishing agents; adhesives, binding agents.
Tris(1-chloro-2-propyl) phosphate	TMCPP	13674-84-5	Adhesives, binding agents; insulating materials; flame retardants and extinguishing agents; fillers; construction materials; paints, lacquers and varnishes; intermediates.
Tris(2-chloropropyl) phosphate	TMCPP	6145-73-9	Fillers; adhesives, binding agents; insulating materials.
Tris(3-chloropropyl) phosphate	TMCPP	26248-87-3	No data.
Triphenyl phosphate	TPP	115-86-6	Softeners; lubricants and additives; paints, lacquers and varnishes; non-agricultural pesticides and preservatives; construction materials; cutting fluids; surface treatment; adhesives, binding agents, flame retardants and extinguishing agents; hydraulic fluids and additives; insulating materials; reprographic agents.

TMCPP is produced by the reaction of phosphorus oxychloride and propylene oxide (102). The most abundant isomer in commercial products is the branched isomer, tris(1-chloro-2-propyl) phosphate (216).

TMCPP was commercialised in the mid-1960s and production increased by about 4 % per year the next 30 years (102). In 2002, Finland had the highest use (among the Nordic countries) with 1 000 tonnes/year and Sweden the lowest with 100 tonnes/year (207). The major use of TMCPP is as a flame retardant, mainly in polyurethane foams (102). The highest TMCPP level was reported from a polyurethane foam filler (180 g/kg). Lower concentrations were reported from polyurethane-containing carpet backing (13 g/kg), mattresses (1.5 g/kg) and wallpaper of glass fibre (1 g/kg) (98). TMCPP has been found to be emitted from upholstery at rates of up to 77 µg/m^2/hour (116).

TPP is produced from phosphorus oxychloride and phenol (100). TPP is used as a flame-retardant in phenolics and phenylene-oxide-based resins for the manufacture of electrical and automobile components, and as a non-flammable plasticiser in cellulose acetate for photographic films. Other uses of TPP are as a non-combustible substitute for camphor in celluloid, for impregnating roofing paper, and as a plasticiser in lacquers and varnishes. TPP is further found as a component of hydraulic fluids and lubricant oils (100). It is also used in artificial leather, thermoplastics and synthetic rubber (144).

5. Measurement and analysis of workplace exposure

Air sampling of the phosphate triesters requires a method capable of sampling both vapours and aerosols. The combination of an adsorbent (Chromosorb 106) and a 37 mm filter cassette with glass fibre filter was the best combination for mixed phase air sampling of some phosphate triesters originating from hydraulic fluids. The triaryl phosphates were recovered solely from the filter, while the trialkyl phosphates were recovered from both the filter and the adsorbent (204). Air samples may also be collected on solid-phase extraction (SPE) columns containing aminopropyl silica, which have been shown to be suitable adsorbents for organophosphorus compounds. The SPE sampling has been compared with sampling on borosilicate glass fibre filter. For TBP, TCEP, TDCPP and TPP, results were comparable. However, the concentration of TEP was almost 5-fold higher using the SPE adsorbent as compared to glass fibre filter. A probable explanation is that TEP has a higher vapour pressure and might evaporate from the filter during sampling (29, 211). Solid-phase microextraction (SPME) with e.g. polydimethylsiloxane sorbent has been employed for extraction and preconcentration of alkyl and aryl phosphates (104, 197). A molecularly imprinted SPE method for extracting the TPP metabolite diphenyl phosphate from aqueous solutions has been developed. Recoveries from urine extraction were higher than 70 % (164).

Analysis of phosphate esters is performed by gas chromatography (GC) with either nitrogen phosphorus detection (GC-NPD) (211), mass-spectrometry detection (GC-MS) (29, 232), atomic emission detection (GC-AED) (29) or electron capture detection (GC-ECD) (202). Following extraction and pre-concentration of alkyl and aryl phosphates by SPME, analysis by GC coupled to inductively coupled plasma mass spectrometry (GC-ICP-MS) was performed for phosphorus-specific determination of these compounds in human plasma. The detection limits for blood plasma were 17 ng/l for TBP, 240 ng/l for TCEP and 24 ng/l for TPP (197). Real-time aerosol mass spectrometry is capable of monitoring submonolayer coverage of TBP on the surface of micron-sized particles (133).

Organophosphate esters may occur in laboratory air and laboratory equipment can be contaminated (211). Application of the SPME-GC method presented above on plasma samples previously stored in PVC plasma bags revealed the presence of TBP and TPP (197). Some batches of sampling tubes containing coconut shell charcoal sorbent have been found to be contaminated with TMCPP and TDCPP (245).

6. Occupational exposure data

This chapter is divided in occupational exposure to phosphate triesters via airborne and via dermal exposure, respectively.

6.1 Airborne exposure

Air concentrations of phosphate triesters from European indoor environments (including homes) are presented in Table 7. The data are from Finland, Germany, Sweden and Switzerland. Levels exceeding 1 µg/m^3 were found in recycling of electronics (TCEP and TPP), in furniture workshops (TBP) and in vehicles and garages (TMCPP) (29, 30, 78, 98, 143-145, 163, 202, 212).

Additional studies are presented below.

Industry

TCP was collected close to the breathing zone of a bench worker using a synthetic oil containing 1-5 % TCP. The concentrations of TCP were 24 and 280 µg/m^3. No TOCP was detected (204).

In an unpublished report from a flexible polyurethane foam plant using TDCPP, nine static air samplers were used and the detection limit was 5 µg/m^3. In only 2 out of 9 samples were concentrations above the detection limit, one being 5 µg/m^3 and the other, near the removal of paper in a polyester line, 14 µg/m^3 (166).

The emission rate of TEP from polyurethane hard foam products was > 100 µg/m^2 hour at 24-hour testing. TEP decreased rapidly and after 168 hours only traces could be determined (192).

Sutton *et al* investigated the TPP concentration in the air of a TPP-manufacturing plant and found levels up to 30 000 µg/m^3 and a time-weighted average (TWA) of 3 500 µg/m^3. Most air samples were taken by drawing air through two gas washing

Table 7. Air concentrations (ng/m^3) of some phosphate triesters in indoor environments in Europe. The number of samples per site varies.

TCP	TBEP	TBP	TCEP	TDCPP	TEHP	TMCPP	TPP	Reference
Electronics recycling								
nd-810	nd-212	nd-100	nd-1 100	nd-450	nd-90	nd-510	nd-10 300	(163, 202)
Furniture workshop								
nd	nd	nd-1 200	nd -69	nd-38	nd	nd-131	nd-530	(163)
Industries								
nd-3	1-36	nd-29	nd-38	0.4-23	nd-2	1-32	nd-180	(145, 202, 212)
Offices								
nd-0.4	nd-15	nd-870	nd-730	nd-35	nd-14	nd-160	nd-82	(29, 30, 78, 144, 212)
Schools and other public buildings								
< 2.2	nd-3.3	< 0.2-64	2.0-590	nd-1.7	< 0.2-3.4	19-440	< 0.1-18	(29, 78, 143)
Hospitals, day care centres, etc.								
nd	1-55	3.7-350	nd-320	nd-150	nd-10	28-750	nd-1.1	(29, 144, 212)
Shops								
nd-0.2	nd-172	1.7-68	nd-29	nd-19	nd-2.8	nd-96	nd-13	(78, 144, 212)
In vehicles and garages								
nd	nd-15	nd-320	nd-9.4	nd-220	nd-18	nd-2 300	nd-3	(78, 212)
Homes								
nd	< 0.4-80	1-120	nd-600	nd-21	nd-2	7-210	nd-0.9	(98, 144, 212)

nd: not detected.

bottles arranged in series. TPP was estimated by ultraviolet spectrometry (218). These air levels are the highest reported of an organophosphate flame retardant.

Offices and homes

The average indoor concentrations of TBEP in Wichita, Kansas, US, and Lubbock, Texas, US, were 0.004 and 0.025 µg/m^3, mainly in fine aerosol particles. TBEP was not found in outdoor aerosol particles (253). In another US study, the mean concentration of TBEP in representative samples from seven offices was reported to be 0.015 µg/m^3 (103). The significance of floor polish, which may contain 1 % TBEP (165), as a source of these particles was suggested by the finding that the highest concentration (0.025 µg/m^3) was observed immediately following floor polishing work. The floor dust in a new office building in Austria contained 4.3-7.8 g TBEP/kg dust. After removal of the floor coating and wet cleaning, the floor dust contained 410 mg/kg and, after further 3 months, 90 mg/kg (95).

TCEP was detected in indoor air in German homes and schools. The 50th percentile was 0.010 and the 98th percentile 0.6 µg/m^3 (Table 7). The highest level was 6 µg/m^3 found in a school building with an acoustic ceiling containing 68 g TCEP/kg. The geometric means of TCEP and tris(1-chloro-2-propyl) phosphate (TMCPP) in domestic dust were 0.7 and 0.5 mg/kg, respectively. Since TCEP and tris(1-chloro-2-propyl) phosphate residues in domestic dust were assumed to be condensates arising from primary sources, spot check analysis of various indoor materials was performed. The results showed that soft foams, paints and wallpapers contained mainly TCEP. High levels of tris(1-chloro-2-propyl) phosphate were

found in polyurethane-containing carpet backing and foam fillers, 13 and 180 g/kg, respectively (98).

Airborne concentrations of TEHP were collected on filters simultaneously outdoors and indoors in Wichita, Kansas, US, during the autumn and early winter of 1981-1982. The average TEHP indoor concentration was 0.006 µg/m^3, whereas it was not detected in outdoor air (253). The mean concentration in representative samples of dust from seven office buildings in the US was 0.005 µg/m^3 (Weschler and Shields 1986, cited in (103)).

An indoor TEP air concentration of 0.2 µg/m^3 was measured in a newly built Japanese house (188).

Several phosphate triesters were analysed in settled house dust from indoor environments and in wipe test samples from computer screens and covers. Computer covers may contain 0.3-10 % (w/w) of TPP and may thus act as a source of TPP in indoor air (144). Samples taken above new running computer monitors contained on average 0.56 µg/m^3 (193).

Indoor air samples of phosphate triesters were taken from apartments and family houses in the Tokyo Metropolitan area. The means of both TBP and TPP were 0.010 µg/m^3 (179).

Personal air measurements were performed for 18 subjects representing different occupations: aircraft technicians, prison wardens, librarians, day care centre personnel and taxi drivers (see below). The highest exposures among prison wardens, librarians and day care centre workers were to TBEP, TCEP and TMCPP (Figure 2) (143).

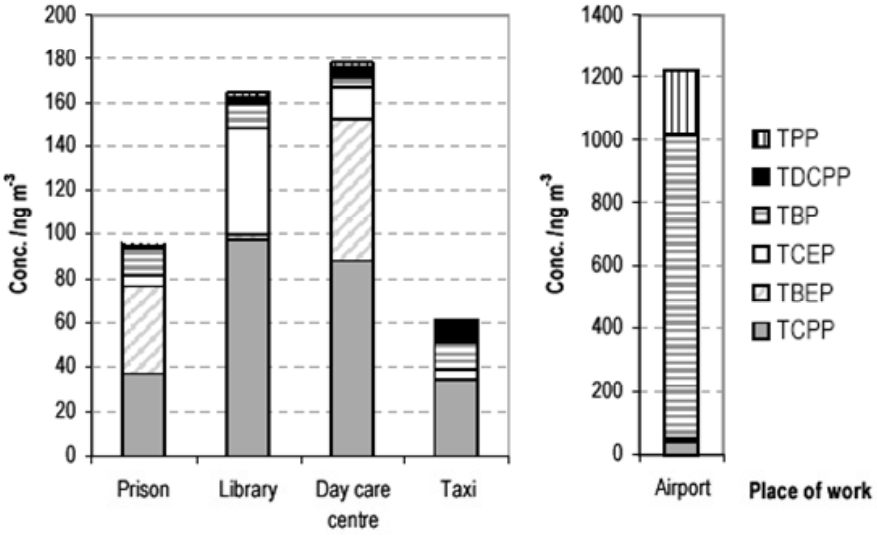


Figure 2. Occupational exposure levels of phosphate triesters as measured by personal air sampling and duplicate samples (with permission from Marklund) (143). TCPP corresponds to TMCPP (commercial mixture) in this document. Note the different scales in the two figures.

Transport

Among the occupations mentioned above, the aircraft technicians were exposed to much higher levels than all the other groups (Figure 2). They were predominately exposed to TBP at levels ranging from 0.27 to 2.1 µg/m^3, followed by TPP at an average level of 0.20 µg/m^3. The high exposure to TBP may be explained by a high proportion of TBP (19 %) in some hydraulic oils (Skydrol 500B4) (Table 8) (146). The taxidrivers were exposed mainly to TMCPP, i.e. tris-(1-chloro-2-propyl) phosphate (143).

In another study, the TBP concentrations in the breathing zone of aviation mechanics were 61 and 72 µg/m^3 (204).

A survey of cockpit air contamination in three aircraft types revealed TCP concentrations below 4 µg/m^3 with two exceptions (22 and 49 µg/m^3). Ground engine starts at high power gave rise to the highest concentrations. Other phosphate triesters (mainly TPP, triisobutyl phosphate and TEHP) were found at total levels below 6 µg/m^3 (76).

Two jet engine oils (Castrol 5000 and Exxon 2380) containing TCP were investigated regarding pyrolytic degradation at 525 °C. The heating resulted in the release of carbon dioxide and carbon monoxide as well as a large number of volatiles. Although TCP isomers were found in both bulk oils as well as in the air, the presence of the neurotoxic trimethyl propane phosphate that may be formed from TCP could not be demonstrated (246).

Some TCP isomers were measured in engine oils from motor bikes and cars and the two main isomers were TOCP and TMCP. Engine oils for motor bikes contained 1.7-7.3 µg TOCP/g oil and 1.5-6.8 µg TMCP/g oil. These isomers were

Table 8. Contents (µg/g) of some phosphate triesters measured in product samples (146).

Product	TCP [a]	TBP	TEHP	TPP
Waste oil from cars	< 0.3	< 0.5	4.2	1.0
Waste oil from lorries	< 0.3	< 0.5	< 0.3	0.8
Waste oil from road-construction machines	< 0.3	< 0.5	< 0.3	1.9
Waste oil from tractors	< 0.3	< 0.5	< 0.3	< 0.3
TurboSuper 10W-30 (engine oil)	< 0.3	< 0.5	< 0.3	< 0.3
Agrol Mendo 46 Bio (hydraulic oil)	< 0.3	< 0.5	< 0.3	< 0.3
BP Turbo oil 2380 (airport)	12 000	< 0.5	< 0.3	6.1
BP Turbo oil 2197 engine and accessory oil (airport)	6 300	< 0.5	< 0.3	8.9
Mobil Jet Oil II Synthetic jet engine oil (airport)	6 500	< 0.5	< 0.3	1.9
Kilfrost DF PLUS (80) (de-icing fluid, airport)	< 0.3	< 0.5	< 0.3	< 0.3
Skydrol 500B4 (hydraulic fluid, airport)	< 0.3	190 000	< 0.3	< 0.3
Kilfrost ABC-2000 (de-icing fluid, airport)	< 0.3	< 0.5	< 0.3	< 0.3
Binol Vegecool (hydroelectric power station)	< 0.3	< 0.5	< 0.3	< 0.3
Mobil DTE Heavy medium oil (hydroelectric power station)	160	< 0.5	< 0.3	< 0.3

[a] TCP was semi-quantified using TPP.

also found in exhaust gases from these vehicles. The concentrations were approximately the same for both isomers in exhaust from motor bikes (0.15-0.30 µg/m^3) and the proportion (TOCP/TMCP) was the same before and after combustion. The levels were somewhat lower in exhaust from cars (0.14 µg/m^3) (226).

Snow samples collected in northern Sweden at a road intersection and an airport indicated that traffic is a source of phosphate esters in the outdoor environment. TPP was identified in lubricants and in waste oil from vehicles, and thus, leakage of transmission and motor oils was a probable source of TPP found at the sampled sites. In the three samples from the airport, ten phosphate triesters were detected. TBP was the most abundant, at levels three orders of magnitude higher than in the reference sample (taken 3 km from the nearest road to ensure minimal influence from the local traffic), i.e. 25 compared to 0.019 µg/kg. The main source of TBP at the airport was aircraft hydraulic fluid. Analysis of background air and deposition samples indicated that some phosphate triesters are subject to long-range air transportation (146).

Summary

The air concentrations of individual phosphate triesters in homes, offices, hospitals, day care centres, schools and other public buildings have generally been below 1 µg/m^3. An exception was the higher level of TCEP (6 µg/m^3) in a school building equipped with an acoustic ceiling. The concentrations of TMCPP (in vehicles and garages) and of TBP (furniture workshop) have occasionally exceeded 1 µg/m^3. Higher levels of phosphate triesters have been reported for TCP for a bench worker (280 µg/m^3), for TBP among aviation mechanics (72 µg/m^3), for TDCPP in a polyester line (14 µg/m^3) and for TPP in electronics recycling (10 µg/m^3).

6.2 Dermal exposure

Dermal exposure is likely to contribute significantly to the systemic dose of phosphate triesters. Dermal exposure has, however, only been assessed from hand wash samples taken from two workers in a circuit board factory and in a furniture workshop. The highest mean concentrations were measured for TPP, which amounted to 3.3 and 24 µg/hands in the circuit board factory and in the furniture workshop, respectively. Lower concentrations were measured for TBP, TCP, TEHP and TDCPP (163). However, these results do not give any information regarding absorption.

Dermal exposure and uptake may be important when workers are exposed to different oils and fluids containing phosphate esters. The content of some phosphate triesters in different oils and fluids are presented in Table 8.

7. Toxicokinetics

7.1 Uptake

Since all phosphate triesters for which there are data are readily absorbed via the oral (TCP, TBP, TCEP, TDCPP, TMCPP) as well as the dermal route (TOCP, TBP, TDCPP), a high uptake is likely also if inhaled. However, inhalation uptake has not been studied to a great extent. The most important route of exposure is unidentified and may vary between phosphate triesters and work procedures.

TCP All three symmetrical isomers of TCP (TMCP, TPCP and TOCP) administered by gavage to rats at doses of 2, 20 and 200 mg/kg bw in corn oil were reported by the NTP to be well absorbed (174).

The absorption of a single dermal dose of 50 mg/kg bw of ^{14}C-labelled TOCP was studied in male cats. TOCP was applied to an unprotected, preclipped area on the back of the neck (approximately 10 cm^2). Three cats were sacrificed at 0.5, 1, 2, 5 and 10 days, respectively, after treatment. The skin at the dosing site was extracted with acetone. Within the first 12 hours, 73 % of the applied dose disappeared from the dosing site. A second phase had a slower rate with a half-time of 2 days. TOCP was absorbed from the skin and subsequently distributed throughout the body. Within the 10-day experimental period, approximately 28 % and 20 % of the applied dose were recovered in the urine and faeces, respectively (169).

Adult male European ferrets (*Mustela putorius furo*) were exposed to a single oral or dermal dose of 250, 500 or 1 000 mg TOCP/kg bw (214). The neurological effects observed (see Chapter 10.4) indicated a high dermal absorption.

Marzulli *et al* reported a dermal absorption rate of TOCP of 0.18 µg/cm^2/hour, using human skin *in vitro* (148). Applying the ECETOC procedure for evaluating skin notation (51), i.e. exposure of 2 000 cm^2 of skin (approximately corresponding to the skin of the hands and forearms) for 1 hour (equivalent to exposure of 250 cm^2 skin or 70 % of one hand for 8 hours) and using the above human *in vitro* data, a dermally absorbed dose of 0.36 mg of TOCP is obtained. This corresponds to 72 % of the amount absorbed by inhalation (0.5 mg) during 8-hour exposure at 0.1 mg/m^3 (the present 8-hour threshold limit value (TLV) adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) (4)), assuming 10 m^3 inhaled air during 8 hours and a pulmonary retention of 50 %. In conclusion, dermal exposure to TOCP may result in significant systemic exposure.

At least 41 % of a single oral dose of 7.8 mg/kg bw ^{14}C-TPCP in rats was excreted in the urine over 7 days following administration, indicating absorption of at least that part of the administered dose. At a higher dose (89.6 mg/kg bw), 12 % was found in urine after 7 days. As TPCP is also excreted through the bile, a higher absorption is possible (120).

In 1955, Treon *et al* studied the effects in rabbits of a 24-hour dermal exposure to seven commercial TCP mixtures. The minimum lethal dose varied between 0.4-0.6 ml/kg bw (500-750 mg/kg) and 1.6-3.2 ml/kg bw (2 000-4 000 mg/kg) for the different compounds (Treon *et al* 1955, cited in (215)). It should be remembered

that the TCPs from the 1950s were much more toxic than the TCPs from the 1990s.

TBEP No data were located.

TBP Male Wistar rats were given a single oral or intraperitoneal dose (14 mg/kg bw) of ^{14}C-labelled TBP. Within 24 hours after the oral administration, 50 % of the radioactivity was recovered in urine, 10 % in exhaled air and 6 % in faeces. Following the intraperitoneal injection, 70 % of the radioactivity was found in urine, 7 % in exhaled air and 4 % in faeces within 24 hours (220). The low faecal excretion rate indicates a very high uptake from the gastrointestinal tract.

In vitro investigation on isolated human skin has showed a good penetrating capacity. The average maximum steady-state rate of penetration through human skin *in vitro* was 10.8 µg/cm^2/hour (148). Applying the ECETOC procedure for skin notation (51) and using the above human data, a dermally absorbed dose of 21.6 mg of TBP is obtained. This corresponds to nearly 200 % of the amount absorbed (11 mg) during 8-hour inhalation exposure at the present TLV of 0.2 ppm (3) assuming 10 m^3 inhaled air during 8 hours and a pulmonary retention of 50 %. In conclusion, dermal exposure to TBP may result in significant systemic exposure.

TCEP Radiolabelled ^{14}C-TCEP was administered in a single oral dose of 50 µmol/ kg bw in olive oil to groups of 3-5 male Wistar rats. Absorption was calculated from the radioisotopic measurements of cumulative urinary excretion and cumulative exhalation performed for 7 days post-exposure, and of the amount in blood and tissues of rats sacrificed at 3, 6, 12, 24, 72 or 168 hours following administration. Absorption of radiolabelled TCEP was rapid and radiolabel was detected throughout the body as early as 3 hours post-administration. At 168 hours, 96 % of the administered oral dose had been excreted in the urine (94 %) and expired air (1.7 %) (154).

TDCPP Radioactive TDCPP was administered to rats orally at doses of 0.2, 2 and 20 µmol/kg bw. More than 90 % of given doses were absorbed from the gastrointestinal tract within 24 hours. TDCPP was also readily absorbed from the skin of rats. Administration of 2 µmol/kg bw applied in 60 µl methanol to a 4-cm^2 area of the shaved back of rats resulted in a blood concentration of 0.75 nmol/g after 4 hours. This concentration was one fourth of the concentration (3.05 nmol/g) measured in blood two hours after an equal intravenous dose (170).

Skin from the adult hairless female mouse was removed and mounted in flow-through diffusion cells. TDCPP penetrated the skin and 39-57 % of the applied dose was detected in the receptor fluid by 24 hours (92).

TEHP Nine male rats received a single aerosol exposure during 20 minutes of 720 or 910 mg/m^3 of ^{32}P-TEHP. The animals were killed post-exposure after 5 or 30

minutes, 1, 4, 17, 18, 24, 48 or 70 hours. Carcass radioactivity increased to a peak corresponding to 81 % retention at 48 hours post-exposure, followed by a decrease (140).

TEP and ***TIPP*** No data were located.

TMCPP Radiolabelled ^{14}C-tris(1-chloro-2-propyl) phosphate (99 % pure by GC) was administered in a single oral dose of 16.4 mg/kg bw (0.05 mmol/kg) in olive oil to groups of 3-5 male Wistar rats. Absorption was calculated from the radio-isotopic measurements of cumulative urinary excretion and cumulative exhalation 7 days post-exposure, and of the amount in blood and tissues of rats sacrificed at 3, 6, 12 hours as well as 1, 3 or 7 days following administration. Absorption of radiolabelled TMCPP was rapid. Radiolabel was detected throughout the body as early as 3 hours post-administration. At 7 days, 76 % of the administered oral dose had been excreted in the urine and in expired air or remained in the carcass. Another 22 % was excreted in the faeces. TMCPP, however, undergoes enterohepatic circulation and it is not clear if this proportion includes unabsorbed TMCPP, TMCPP excreted in the bile, or both. Therefore, at least 76 % was absorbed following oral administration to rats (154, 216).

TPP No data were located.

7.2 Distribution

Adipose tissue act as an important storage compartment for the phosphate tri-esters, as indicated by their lipophilic properties manifested by e.g. high octanol: water partition coefficients (Table 4). Some of the phosphate triesters have been detected in human adipose tissue (TBEP, TBP and TDCPP) and several also in human milk (TCP, TBEP, TBP, TCEP, TDCPP, TMCPP and TPP).

TCP The distribution of a single dermal dose of 50 mg/kg bw of ^{14}C-TOCP was studied in male cats. TOCP was applied to an unprotected, preclipped area on the back of the neck. TOCP was absorbed from the skin and subsequently distributed throughout the body. No radioactivity was detected in expired air. Generally, the highest concentrations of radioactivity were associated with bile, gall bladder, urinary bladder, kidneys and liver, and the lowest were found in the neural tissues, muscle and spleen. Furthermore, low levels of radioactivity were found in the spinal cord and brain. Chemical analyses showed that the parent compound was found primarily in the brain, spinal cord and sciatic nerve, while metabolites were primarily found in the liver, kidney and lung (169).

Twenty-four hours after oral administration of 89.6 mg/kg bw of ^{14}C-TPCP to rats, the highest concentrations of radioactivity were found in the intestine (including contents), followed by the stomach, adipose tissue, liver and kidneys (4-13-fold higher than blood concentrations). The lowest concentrations were

found in heart, muscle and brain. These levels were lower than those found in blood (120).

After a single oral dose of 50 mg radiolabelled TOCP to hens, the highest plasma concentration was found a half to one day after administration. The disappearance of TOCP followed monoexponential kinetics with a half-time of 2.2 days (219).

Male F344 rats were treated orally for 10 days with TOCP (50 mg/kg bw/day) and DNA was isolated from liver, kidney, lung, heart, brain and testes 1, 4, 7 and 28 days after giving the last dose. Analysis by ^{32}P-postlabelling revealed two adducts present in the DNA isolated from liver, kidney, lung and heart one day after giving the last dose. DNA adducts were not detected in the brain and testes. The adduct pattern after *in vivo* treatment with TOCP was identical with that found in bacteria and hepatoma cells treated with the metabolite 2-phenoxy-4H-1,3,2-benzo-dioxaphosphorin 2-oxide, the major adduct being a cytidine adduct and the minor an uridine adduct. Both DNA adducts persisted in the lungs for the entire observation period, whereas in the kidney only the cytidine adduct could be detected 28 days after the last dose of TOCP. In liver and heart, the adducts were detectable only on the first day after completion of the treatment. The results indicate that the compound may pose a genotoxic potential (151).

The highest TCP level found in pooled human milk samples collected 1997-2006 from Swedish primiparous women was 3.7 ng/g lipid. TOCP levels were below the detection limits, which was in the range 0.2-0.5 ng/g lipid (147).

TBEP was detected in 21 out of 68 male human adipose tissue samples and in 20 out of 47 female samples, obtained from autopsies from two Canadian cities (135). In a later study, TBEP was detected in human adipose tissue autopsy samples from three out of six Ontario (Canada) municipalities, based on a detection limit of 20 ng/g. Mean concentrations were 396 ng/g (range 320-483 ng/g) in Toronto and 173 ng/g (range, not detected-202 ng/g) in Cornwall (136).

TBEP was detected in breast milk samples from primiparous women. Levels of pooled samples collected between 1997 and 2006 varied between not detected to 63 ng/g lipid (147).

TBP In a Canadian study, 16 human adipose tissue samples were analysed post mortem. TBP was detected in one sample (9 ng/g adipose tissue, with a detection limit of 2 ng/g) (134).

The levels of TBP in pooled breast milk samples from Swedish primiparous women collected 1997-2006 were 11-57 ng/g lipid (147).

TCEP After intravenous TCEP administration (20 mg/kg bw), plasma clearance was investigated in F344 rats. The clearance of free TCEP from plasma was 30 ml/min/kg among anaesthetised males, 74 ml/min/kg among awaken males and 53 ml/min/kg among awaken females. The difference between anaesthetised and awaken male rats is presumably due to physiological effects of anaesthesia. There was no significant difference between awaken male and female rats (50).

^{14}C-labelled TCEP was administered in a single oral dose of 0.05 mmol/kg bw in olive oil to male Wistar rats. After 3 hours, the highest concentration of ^{14}C was found in the kidney (47 nmol/g tissue) followed by the liver (26 nmol/g tissue) and the lung (12 nmol/g tissue). The level in the brain was 6 nmol/g tissue (154).

Administration of TCEP by gavage (175, 350 or 750 mg/kg bw) to F344 rats showed that TCEP was readily distributed to all brain regions of males and females (83).

After a single oral dose of ^{14}C-labelled TCEP in rats, the biological half-times in blood were 14 hours (the first phase) and 54 hours (the second phase) (154).

TCEP levels of 2.1-8.2 ng/g lipid were reported in milk samples collected 1997-2006 from Swedish primiparous women (147).

TDCPP ^{14}C-labelled TDCPP was administered in a single oral dose of 50 µmol/kg bw in olive oil to male Wistar rats. After 3 hours, the highest concentration of ^{14}C was found in the liver (50 nmol/g tissue) followed by lung (26 nmol/g tissue) and kidney (24 nmol/g tissue) (154).

After intravenous administration of TDCPP to rats, the compound disappeared rapidly from plasma with a half-time of less than 5 minutes (139).

After a single oral dose of ^{14}C-labelled TDCPP in rats, the biological half-times in blood were 13 hours (the first phase) and 42 hours (the second phase) (154).

^{14}C-TDCPP was bound to DNA present in the liver of male CD-1 mice that were given a single intravenous dose of TDCPP at 94.4 µmol/kg bw and sacrificed 6 hours later. The level of TDCPP in liver DNA was estimated to 8.3 nmol/g. Traces of radioactivity were detected in kidney DNA but not in muscle. Larger amounts were detected in protein and low-molecular-weight RNA isolated from liver and kidney (157).

TDCPP was present in human adipose tissue autopsy samples from two out of six Ontario (Canada) municipalities, based on a detection limit of 1 ng/g. The mean concentration was 17 ng/g in Welland, the city with the highest level (136).

TDCPP was reported to range from 5 to 50 ppb in human seminal plasma analysed by negative-chemical-ionisation mass spectrometry (91).

In human milk, TDCPP levels from 1.6 to 5.3 ng/g lipid were detected (147).

TEHP Nine male rats received a single aerosol exposure during 20 minutes of 720 or 910 mg/m^3 of ^{32}P-TEHP. The animals were killed post-exposure after 5 minutes, 30 minutes, 1, 4, 17, 18, 24, 48 or 70 hours. TEHP or its metabolites were distributed into the lungs (peak of 13 % of total radioactivity after 5 minutes), brain and liver (9 and 16 %, respectively, after 30 minutes) and stomach content (64 % after 1 hour) (140).

TEP Weanling and adult female rats were administered 500 mg/kg bw of TEP intraperitoneally. The concentrations declined in the brain, with half-times of 8 hours for weanlings and 30 hours for adults, respectively (22).

TIPP No data were located.

TMCPP ^{14}C-labelled TMCPP was administered in a single oral dose of 50 µmol/kg bw in olive oil to male Wistar rats. After 3 hours, the highest concentration of ^{14}C was found in the liver (29 nmol/g tissue) and the kidney (27 nmol/g tissue) followed by the lung (9 nmol/g tissue). The concentrations in blood, heart, spleen, brain, testis, adipose tissue and muscle were all below 4 nmol/g tissue (154).

After a single oral dose of ^{14}C-labelled TMCPP in rats, the biological half-times in blood were 12 hours (first phase) and 59 hours (second phase), respectively (154).

In human pooled milk collected from Swedish women after delivery of their first babies in 1997-2006, levels of tris(1-chloro-2-propyl) phosphate were 22-82 ng/g lipid (147).

TPP has been analysed in plasma from 3 occupationally non-exposed individuals with duplicate samples. The concentrations varied between 120 and 150 ng/g plasma (111).

Analysis of pooled human milk samples showed TPP levels of 3.2-11 ng/g lipid (147).

7.3 Biotransformation

All investigated phosphate triesters are metabolised and several lose one of the ester moieties to form phosphate diesters.

TCP Many studies on the metabolism of TOCP are available. TOCP is metabolised to highly neurotoxic derivatives such as saligenin cyclic *o*-cresyl phosphate (Figure 3).There are no data to suggest that TMCP or TPCP is metabolised to neurotoxic metabolites. However, exposure to TCP mixtures containing isomers with one or two *ortho*-cresol groups could result in the formation of neurotoxic metabolites (109, 174). It has been shown that after a given dose of TOCP, the concentrations in plasma of both TOCP and its active metabolite saligenin-*o*-cresyl phosphate were much lower in the rat than in the hen. The plasma half-time of TOCP was also shorter in the rat compared to the hen. These facts might be one explanation for the differences between these two species in the susceptibility to TOCP induced organophosphorus-induced delayed neuropathy (OPIDN) (see Chapters 9-10) (219).

In rats, metabolism of ^{14}C-TPCP following oral administration of 7.8 or 89.6 mg/kg bw was found to involve successive oxidations and hydrolysis resulting in the production of *p*-hydroxybenzoic acid. The major urinary metabolites identified were *p*-hydroxybenzoic acid, di-*p*-cresyl phosphate and *p*-cresyl *p*-carboxyphenyl phosphate. The main biliary metabolites were di-*p*-cresyl phosphate, *p*-cresyl *p*-carboxyphenyl phosphate, and the oxidised triesters di-*p*-cresyl *p*-carboxyphenyl phosphate and *p*-cresyl di-*p*-carboxyphenyl phosphate. Faecal metabolites were

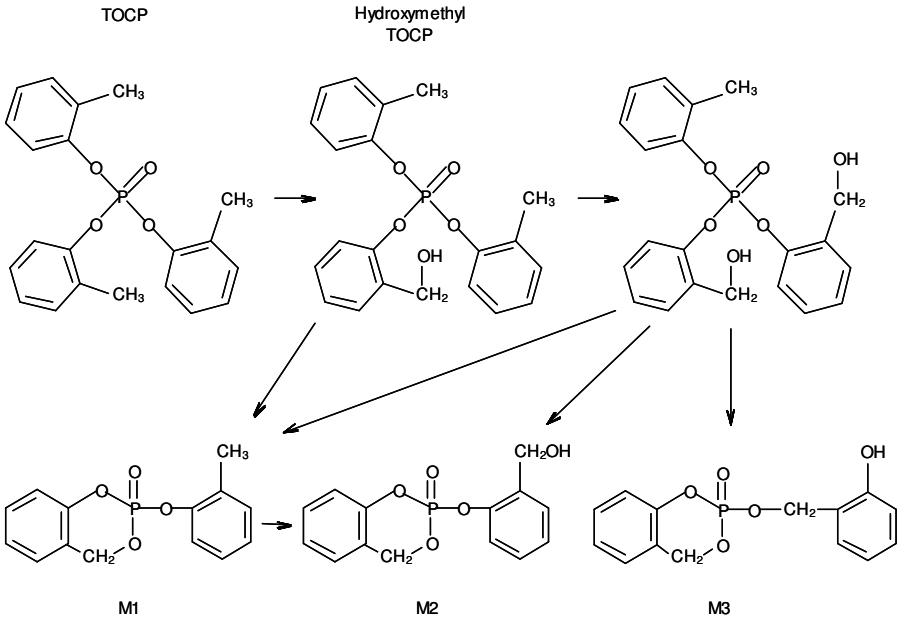


Figure 3. Proposed pathway for hydroxylation and cyclisation reactions in the metabolism of TOCP. M1 is saligenin-*o*-cresyl phosphate. M2 and M3 are also possible metabolites. Adapted from IPCS, 1990 (99).

similar to the biliary metabolites. $^{14}CO_2$ was found in expired air following administration and appeared to be formed through decarboxylation of *p*-hydroxybenzoic acid by intestinal microbes (120).

TBEP No data were located.

TBP The metabolic transformation of TBP was studied in male rats following oral and intraperitoneal administration of ^{14}C-labelled TBP. The first stage in the metabolic process was oxidation catalysed by cytochrome P450 (CYP) dependent monooxygenase. The generated hydroxyl groups were further oxidised to carboxylic acids and ketones. In urine, the major phosphorus-containing metabolites were dibutyl hydrogen phosphate, butyl dihydrogen phosphate and butyl bis(3-hydroxybutyl) phosphates (220).

TCEP In mice, several urinary metabolites of TCEP were identified such as bis(2-chloroethyl) carboxymethyl phosphate, bis(2-chloroethyl) hydrogen phosphate, and bis(2-chloroethyl)-2-hydroxyethyl phosphate glucuronide. The metabolism in rats was not induced or inhibited by nine daily doses of 175 mg/kg bw (24).

TCEP was metabolised by male and female human liver microsomes at a rate of 0.027 and 0.031 nmol/min/mg protein, respectively, and by male and female

human liver slices at a rate of 1.37 and 1.82 nmol/min/g liver slice, respectively. 2-Chloroethanol and bis(2-chloroethyl) hydrogen phosphate were found after exposing human liver slices to TCEP. The formation of 2-chloroethanol was lower in men than in women, 614 versus 2 118 pmol/min/g liver. In contrast, the formation of bis(2-chloroethyl) hydrogen phosphate was higher in men than in women, 404 versus 198 pmol/min/g liver. 2-Chloroethanol and bis(2-chloroethyl) hydrogen phosphate were the major metabolites formed, except in two human male subjects in which an unidentified metabolite constituted 29-38 % of the total TCEP metabolism. TCEP was not metabolised by plasma or whole blood from male or female human subjects (38).

TDCPP Following intravenous administration of 0.8 µmol ^{14}C-TDCPP to male Sprague Dawley rats, urine collected over 24-hour periods for 5 days contained a major metabolite, bis(1,3-dichloro-2-propyl) phosphate (BDCPP) (138, 139).

TDCPP was rapidly metabolised *in vitro* (by a NADPH-dependent microsomal mixed-function oxidase system and glutathione *S*-transferase from rat liver) to BDCPP; 1,3-dichloro-2-propanol, 3-chloro-1,2-propanediol; and one metabolite which was probably a glutathione conjugate (170, 194).

Gold and coworkers proposed an oxidative dealkylation of TDCPP to 1,3-dichloro-2-propanone analogous with the known metabolism of other related phosphate triesters (73), but this has not been shown.

TEHP No data were located.

TEP Pre-treatment with phenobarbital markedly increased the rate of disappearance of TEP from both plasma and brain in rats given 500 mg TEP/kg bw intraperitoneally (22).

Rats and mice were administered ^{32}P-labelled TEP orally or intraperitoneally. The de-ethylated compound ^{32}P-diethyl phosphate was found in urine (90 % of the radioactive material within 16 hours and nearly all over 96 hours) (110).

TIPP A single dose of 1 000 mg/kg bw of tri-*ortho*-isopropylphenyl phosphate was given by gavage to rabbits. In addition, a commercial product Reolube Hyd 46 (containing 35 % mono-*ortho*-isopropylphenyl diphenyl phosphate, 25 % di-*ortho*-isopropylphenyl phenyl phosphate, 10 % tri-*ortho*-isopropylphenyl phosphate and 7 % TPP) was gavaged to rabbits in a dose of 2 000 mg/kg bw. Cyclic metabolites of the three *ortho*-isopropylated phenyl phosphates were detected in rabbit bile (261).

TMCPP No data were located.

TPP was metabolised by a NADPH-independent mechanism by microsomes from rat liver homogenate, unlike many other phosphates. Diphenyl hydrogen phosphate was the only major metabolite of TPP in this *in vitro* study (194).

7.4 Excretion

Urinary excretion is generally the main pathway for excretion of phosphate triesters.

In rats given radiolabelled chloro-substituted phosphate triesters, the expired air contained higher proportions of radioactivity after exposure to the dichloro-substituted TDCPP (16 %) compared to the monochloro-substituted compounds tris(1-chloro-2-propyl) phosphate (8 %) and TCEP (2 %) (154).

TCP The excretion of a single, dermal dose of 50 mg/kg bw of ^{14}C-TOCP was studied in male cats. TOCP was applied to an unprotected, preclipped area at the back of the neck. No radioactivity was detected in the expired air. Within the 10-day experimental period, approximately 28 % and 20 % of the applied dose were recovered in the urine and the faeces, respectively (169).

Excretion of radioactivity following oral administration of ^{14}C labelled TMCP, TPCP or TOCP in rats at doses of 0.5, 2, 20 and 200 mg/kg bw was investigated by NTP. Radioactivity from TMCP was excreted primarily in the faeces at all dose levels. Radioactivity from TPCP was excreted primarily in the urine at 0.5 and 2 mg/kg and primarily in the faeces at 20 and 200 mg/kg. Radioactivity from TOCP was excreted primarily (70 %) in the urine at all doses tested (174).

Rats receiving ^{14}C-TPCP as a single oral dose of 7.8 mg/kg bw excreted 41 % of the dose of radioactivity in the urine, 44 % in the faeces, and 18 % in the expired air within 7 days. A majority of the excretion occurred within 24 hours. Rats with cannulated bile ducts excreted 28 % of the administered radioactivity in the bile during the first 24 hours. Rats treated in a similar manner with 89.6 mg/kg bw of ^{14}C-TPCP excreted 12 % of the administered radioactivity in the urine, 77 % in the faeces and 6 % in the expired air (120).

TBEP No data were located.

TBP Male Wistar rats were given a single oral or intraperitoneal dose (14 mg/kg bw) of ^{14}C-labelled TBP. Within 24 hours after the oral administration, 50 % of the radioactivity was recovered in urine, 10 % in exhaled air and 6 % in faeces. The total excretion after 5 days was 82 %. Following the intraperitoneal injection, 70 % of the radioactivity was found in urine, 7 % in exhaled air and 4 % in faeces within 24 hours. The total excretion after 5 days was 90 % (220).

TCEP Wistar rats were given an oral dose of 50 µmol TCEP/kg bw. Most of the ^{14}C-labelled TCEP was excreted by 24 hours, and by 7 days, less than 1 % remained in the tissues. Urinary excretion accounted for 96 %, faecal excretion for 6 % and expired air for 2 % of the label (154). The rapid urinary excretion was confirmed by Burka *et al*, who found 40 % of the label in urine within 8 hours after an oral dose of 175 mg ^{14}C-TCEP/kg bw in male and female rats. However the excretion rate was even higher among mice, which excreted > 70 % after the same dose (24).

TDCPP Following intraperitoneal administration of 0.8 µmol ^{14}C-TDCPP to male Sprague Dawley rats, urine collected over 24 hours contained a major metabolite, BDCPP. In rats receiving intravenous injection, approximately 96 % of the administered radiolabelled material was recovered in urine, faeces and exhaled air after completion of 5 days' collection. The urinary proportion was 54 %. More than half (62 %) of the urine proportion was BDCPP (138, 139).

In Wistar rats given 50 µmol TDCPP/kg bw, most of the ^{14}C-labelled TDCPP was excreted, and by 7 days less than 3 % remained in the tissues. Urine excretion accounted for 43 %, faecal excretion for 39 % and expired air for 16 % of the label (154).

Radiolabelled TDCPP (Fyrol FR-2) was distributed rapidly throughout the body in the rat following either oral or dermal administration or intravenous injection. About 80 % of the dose was eliminated within 24 hours. About 20 % of a total intravenous dose (2 µmol/kg bw) was exhaled as carbon dioxide during the first 24 hours in rats (170).

Minegishi *et al* measured biliary excretion of ^{14}C-TDCPP in cannulated rats for 48 hours following an oral dose of 50 µmol TDCPP/kg bw. Biliary radioactivity peaked at 4-6 hours after administration, and after 48 hours, biliary excretion accounted for approximately 40 % of the administered dose (154).

TEHP Rats were exposed to an aerosol of radioactive TEHP 720-910 mg/m^3 for 20 minutes. The faecal excretion was higher than the urinary excretion and at 17 hours after inhalation, the total excretion was 7 % (140).

TEP and ***TIPP*** No data were located.

TMCPP Wistar rats were given 50 µmol TMCPP/kg bw orally. Most of the ^{14}C-labelled TMCPP was excreted within 24 hours and by 7 days, less than 1 % remained in the tissues. Urinary excretion accounted for 67 %, faecal excretion for 22 %, and expired air for 8 % of the label (154).

Also biliary excretion of ^{14}C-TMCPP was measured in cannulated rats for 48 hours following the same oral dose. Biliary radioactivity peaked within 2 hours of administration and after 48 hour, biliary excretion accounted for approximately 45 % of the administered dose (154).

TPP The TPP metabolite diphenyl phosphate was measured in urine at a level of 80 µg/l in one aircraft technician (143).

7.5 Summary

All phosphate triesters investigated are readily absorbed via the oral as well as the dermal route and a high uptake via inhalation is likely.

The phosphate triesters are distributed throughout the body. Adipose tissue act as an important storage compartment for phosphate triesters as indicated by their lipophilic properties.

All phosphate triesters, for which there are data, are metabolised. Several phosphate triesters lose one of the ester groups to form phosphate diesters. Urinary excretion is generally the main pathway for excretion.

8. Biological monitoring

Biological monitoring is performed by measuring the parent chemical or its metabolites in blood, urine or exhaled air, or by measuring effects of the exposure. No studies correlating external exposure to biomarker levels were located.

8.1 Markers of exposure

Some of the phosphate triesters or their metabolites have been measured in blood, urine and exhaled air. Biological exposure monitoring would be valuable since skin absorption may be a major route of exposure.

However, contamination from rubber and plastic storage materials has to be considered. TBEP has been found in blood stored in Vacutainers with rubber stoppers (49, 65). Both TBP and TPP have been identified in plasma stored in PVC bags (197).

TPP was found in plasma from three, presumably occupationally non-exposed, individuals. The concentrations varied between 120 and 150 ng/g (approximately 100 µg/l) (111).

Diphenyl phosphate, a metabolite from TPP, was measured in urine at a level of 80 µg/l in one aircraft technician (143).

Diethyl phosphate was measured in urine among 1 133 children from the US National Health and Nutrition Survey (2000-2004). Almost half of the values were below the detection limit (47 %). The geometric mean was 4.7 nmol/l and the range was 0.4-5 902 nmol/l (19). Diethyl phosphate, however, is not only a metabolite of TEP but also of at least one organophosphorus pesticide, namely diazinon (15). The origin of the compound is therefore unknown.

8.2 Markers of effect

Some of the phosphate triesters inhibit the activity of cholinesterases, which are divided in two subgroups, acetylcholinesterase and unspecific cholinesterase.

Acetylcholinesterase is bound to cell structures in the regions of the cholinergic synapses, the grey substance of the central nervous system, the autonomic ganglions, the pre- and postganglionic sympathetic synapses, the motor endplates in muscles, as well as the parasympathetic postganglionic synapses, and in erythrocytes. This enzyme has the physiological function of rapid splitting of the transmitter acetylcholine into choline and acetic acid and thus to inactivate it.

The enzymes of the second subgroup, cholinesterases, are less specific and ubiquitously present in the organism. These unspecific cholinesterases, also called pseudocholinesterases or butyryl cholinesterases, are often measured in plasma or serum but occasionally also in other organs. Their concentration in plasma is 7-9 mg/l (46).

Determination of acetylcholinesterase inhibition provides a direct measure of a biological parameter for the damage, independent of the chemistry of the inhibitor. In particular, the determination of the inhibition of erythrocyte acetylcholinesterase has proved suitable for quantitative biological monitoring (46).

In contrast, the use of cholinesterase activity as evidence of exposure to organic phosphates is limited by the considerable range of normal plasma and serum cholinesterase activity (46).

The Food and Agriculture Organization of the United Nations and the World Health Organization considered a statistically significant inhibition of 20 % or more of brain or erythrocyte acetylcholinesterase to be of clear toxicological significance (67).

If the erythrocyte acetylcholinesterase activity decreases after exposure to the inhibitor to below 30 % of the individual reference value, clinical manifestations of an internal acetylcholine intoxication are to be expected. In Germany, the biological exposure limit for acetylcholinesterase inhibitors is a reduction of the acetylcholinesterase activity in the isolated erythrocytes to 70 % of the individual reference value (48).

Erythrocyte acetylcholinesterase activity mirrors the activity of neuronal cholinesterase. Erythrocyte acetylcholinesterase activity is recommended by ACGIH as a biological exposure index for both TOCP and TBP. Pre-exposure baseline determination (on two occasions at least three days apart) at the individual level is necessary because of the wide interindividual variation in acetylcholinesterase activity. Plasma cholinesterase is not recommended as an index of exposure (2).

More than half of a group of workers manufacturing TCP and other alkyl phenyl phosphates exhibited a decreased level of plasma cholinesterase (lower than 70 % of normal activity) but the erythrocyte cholinesterase level was normal (223).

No decreases in erythrocyte acetylcholinesterase and plasma cholinesterase levels were observed in more than 100 workers producing phosphate triester plasticisers, the final products being TOCP, tri-xylenyl phosphate and TPP (158).

In 1960, an outbreak of TOCP intoxications was reported in Bombay, India after the consumption of contaminated mustard oil. Erythrocyte acetylcholinesterase activity was considerably lower (50 %) early after the onset of clinical symptoms among 9 patients admitted to hospital. Consecutive determinations showed that the activity returned to normal after 3 months (260).

A statistically significant correlation between erythrocyte acetylcholinesterase activity and monocyte esterase activity was observed among 38 resin-processing operators exposed to some aryl phosphate esters (55). In a small group of TBP exposed workers, the monocyte esterase activity was not significantly decreased

(142). The monocyte esterase has not been further examined as a possible indicator of exposure.

9. Mechanisms of toxicity

The phosphate triesters in this document have different toxicological effects mediated by a variety of mechanisms.

9.1 Neurotoxicity

General
The clinical picture associated with inhibition of acetylcholinesterase leads to an accumulation of the transmitter substance in the tissues. Depending on the severity of the inhibition, the sequelae vary from the characteristic symptoms of parasympathetic stimulation to motor and central nervous cholinergic crisis. The parasympathetic symptoms comprise increased secretion from tear, sweat and salivary glands, as well as from mucous glands in the tracheobronchial tract, and stimulation of the smooth muscles of the bronchial tract (dyspnoea, bronchospasm), of the gastrointestinal tract (vomiting, diarrhoea, colic) and of the urogenital system (urinary incontinence) (46).

Nasal and oral discharge observed in animals exposed to high aerosol concentrations of TCP and Skydrol (TBP) may be a cholinergic effect as decreased levels of plasma cholinesterase were observed in these animals (81).

Organophosphorus-induced delayed neuropathy (OPIDN)
It has been known since the early 1930s that TOCP in man and hen induce a delayed neurotoxic effect characterised by ataxia and weakness of the limbs, 10-14 days after exposure (107). This delayed response is called organophosphorus-induced delayed neuropathy (OPIDN) and is characterised by a distal axonopathy in susceptible regions of the central and peripheral nervous systems. The primary lesion in OPIDN resides in distal regions of long axons where axonopathic events lead to distal degeneration of the neurite and secondarily of its myelin sheath (251).

Aldridge and others studied the relation between exposure to several organophosphorus compounds and OPIDN without finding a clear correlation between chemical structure and neurotoxicity (6-8). Later, Johnson presented structural characteristics of the aryl phosphates contributing to OPIDN (Section 10.4) and also proposed neurotoxic (or neuropathy) target esterase (NTE) to be a critical enzyme for inhibition by organophosphorus compounds capable of inducing OPIDN (108, 109).

Despite numerous studies, the NTE hypothesis has not advanced our understanding of the mechanism of OPIDN according to Abou-Donia (1). There are some arguments against this hypothesis: a) evidence for the involvement of NTE is only correlative, b) it has not been shown how inhibition and ageing of NTE leads to axonal degeneration, c) NTE, which is present in neuronal and non-

neuronal tissues and in sensitive and non-sensitive species, has no known biochemical or physiological function, d) some organophosphorus pesticides that produce OPIDN in humans do not inhibit or age NTE, e) NTE-knockout mice are sensitive to the development of OPIDN, indicating that this enzyme is not involved in the mechanisms of OPIDN (1).

Anomalous hyperphosphorylation of cytoskeletal elements is associated with OPIDN and has been proposed as a possible mechanism (1). An increase of cyclin-dependent kinase 5 and its activator has been observed in the spinal cord of hens treated with TOCP (248) and a decrease of some neurofilaments in the spinal cord (264) and in the sciatic nerve (265). Delayed polyneuropathy induced by TOCP could not be prevented completely by calcium, however, polyneuropathy and the dysfunction of nerves and muscles suffering from polyneuropathy can be alleviated, as long as calcium tonic is administered before the clinical signs develop (184).

In a study on chickens, there was no evidence for autoimmunity to have a causative role in the development of neurotoxic effects (250).

9.2 Carcinogenicity

TBP, TCEP, TDCPP and TEHP are carcinogenic in animal studies. Genotoxicity data for TCEP and TDCPP are inconclusive and it is thus unclear if genotoxicity is linked to the development of cancer. TBP and TEHP are not genotoxic. For TBP, inflammatory and proliferative mechanisms secondary to regeneration following ulceration and necrosis have been suggested (11). The presence of DNA adducts in several organs of rats exposed orally to TOCP indicates that this compound may pose a genotoxic potential (151).

9.3 Hormonal and reproductive effects

The constitutively active receptor (CAR) is a crucial regulator of genes encoding for enzymes active in drug and steroid oxidation, conjugation and transport. Chemical substances isolated from livers of untreated mice inhibited CAR-regulated transcriptional activity. The inhibitory substances were identified as di- and tri-isopropylated phenyl phosphates. However, when these compounds were tested for influence on responses regulated by human CAR, it was found that most of them did not inhibit but activated CAR (3-6-fold). Among steroid hormone receptors, the human androgen receptor was inhibited by TPP, mono-*para*-, and mono- and di-*ortho*-isopropyl phenyl phosphate (ca 40-50 %) and activated by di- and tri-*para*-isopropyl phenyl phosphate (2-fold). These results suggest steroid-dependent biological pathways that may contribute to hormonal and reproductive disturbances of some triaryl phosphates (88). In a competitive binding assay, the affinity of TPP to the androgen receptor was considered moderate (64).

An effect on sperms was observed after treatment of rats with TOCP. This effect was associated with a decrease of non-specific esterase activity in the testis and also with decreased NTE activity (206).

Activities of neutral cholesteryl ester hydrolase (an enzyme that converts cholesteryl esters to cholesterol in the uptake and storage pathways) and acyl coenzyme A:cholesterol acyl transferase (an enzyme that esterifies cholesterol to cholesteryl ester) were depressed in TCP treated rats. The inhibition of these enzymes most likely resulted in the striking accumulation of cholesteryl ester in cytoplasmic lipid droplets of adrenocortical and ovarian interstitial cells observed and in elevated intracellular cholesterol levels in adrenocortical cells (130).

10. Effects in animals and *in vitro* studies

The main effects observed in animal and *in vitro* studies are summarised in Table 15. A more extensive tabular presentation of the data is given in Appendix 1.

10.1 Irritation and sensitisation

After a single dermal exposure, the irritating effect of the phosphate triesters varied from no to moderate irritation. After instillations in the eyes, the effect varied from no irritation to moderate conjunctivitis (Table 15). Data on airway irritation are generally lacking.

TCP The skin of rabbits exposed for 24 hours to commercial mixtures of TCP at both lethal and sublethal doses showed mild inflammation and, in a few instances, focal acanthosis and slight hyperkeratosis. Repeated dermal exposure produced local skin inflammation. Inflammation was more severe in animals that died from treatment than among survivors (Treon *et al* 1955, cited in (215)).

Rabbits exposed to TCP aerosols at concentrations of 5 900 to 42 200 mg/m^3 for periods of 3 hours to 18 days had considerably increased nasal and oral discharge during and immediately following exposure, and respiratory difficulties were noted. Histopathological evaluation of the respiratory tract revealed mucosal irritation, including bronchitis, inflammation of the larynx and pulmonary oedema. Mortality was very high. The study is also described in Sections 10.2 and 10.4 (Broadhurst *et al* 1951, cited in (215)).

TBEP In three studies, TBEP was non-irritating to intact and abraded skin when applied topically to albino rabbits (Gabriel 1980c, Monsanto 1984b and Freeman 1991b, cited in (103)).

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 1 000 mg/kg bw/day, 5 days/week for 3 weeks. The unabraded dorsal clipped skin was used. The test sites were occluded for 6 hours after each exposure. The highest dose did not result in any adverse systemic effect. Local irritation, oedema and desquamation occurred at all dose levels. The skin irritation was dose-related and the severity progressed over time. Microscopic observations of the skin (1 000 mg/kg bw/day) showed squamous cell hyperplasia, hyperkeratosis, hair follicles

distended with keratin and surface accumulation of keratin, cellular debris, ulcers, inflammation, congestion and haemorrhages (Monsanto 1985e, cited in (103)). The results indicate that skin irritation arose when exposure reached several days or weeks.

In four studies, TBEP was non-irritating to the eyes of albino rabbits (Gabriel 1980b, Monsanto 1984b, Freeman 1991a and Hoechst 1988, cited in (103)). The doses were not reported.

TBP A single dermal application of 500 mg TBP to the intact or abraded skin of 6 rabbits produced severe irritation, inducing erythema and oedema in all the animals. Instillation of 100 mg TBP in the conjunctival sac of rabbits gave rise to mild irritation, which was noted 1-7 days following the application (FMC 1985a, cited in (101)).

When tested according to OECD guidelines, TBP was slightly irritating to the eyes of rabbits (Bayer 1986, cited by (79)).

TCEP In a study conducted according to modern protocol standards, 0.5 ml of TCEP was applied to the skin of 3 New Zealand White rabbits under semi-occlusive dressing for 4 hours. Slight erythema (grade 1) was observed in each animal on day 1 only (Liggett and McRae 1991c, cited in (102)).

In another study, 0.1 ml (140 mg) of TCEP was instilled into the eye of 3 New Zealand White rabbits. Slight conjunctival redness (grade 1) was observed in each animal on day 1 and in one animal on day 2 (Liggett and McRae 1991a, cited in (102)).

TDCPP The acute dermal irritation potential of TDCPP was investigated in 3 New Zealand White rabbits. Well-defined (score 2) erythema was observed in 2 animals 1 hour after patch removal, whereas the 3rd animal only showed very slight erythema. By 48 hours, the treated sites were normal. TDCPP was classified as irritant to rabbit skin (Cuthbert 1989b, cited in (102)).

Slight conjunctival redness and slight discharge were noted 1 hour after instillation in the eyes of New Zealand White rabbits. After 24 hours, all treated eyes were normal. It was concluded that TDCPP was slightly irritative to the rabbit eye (Cuthbert and Jackson 1990, cited in (102)).

TEHP was tested in 3 albino rabbits according to the OECD 404 test guideline. Well-defined erythema, slight to moderate oedema, crust formation and desquamation were observed. TEHP was classified as a moderate irritant to rabbit skin (Guest 1993a, cited in (103)).

A single dose of 250 mg undiluted TEHP applied to the clipped skin of rabbits produced moderate erythema, which persisted for a week. Repeated applications of 0.1 ml (90 mg), 5 days/week (10 or 20 applications) produced moderate erythema after the first application. Following the 5th application, all the animals exhibited moderate desquamation and a coriaceous condition. The fissures

generally cleared within three days, whereas other signs persisted. At the end of the observation period, thickening and severe hyperkeratosis of the skin were apparent (140).

TEHP was non-irritating when tested in the eyes of 3 albino rabbits according to the OECD 405 test guideline (Guest 1993b, cited in (103)).

TEHP was instilled into the conjunctival sac of one eye of each of 2 rabbits at dose levels from 0.01 to 0.5 ml (9-460 mg). Doses up to 0.05 ml (46 mg) produced slight conjunctivitis, while doses of 0.1 and 0.5 ml produced moderate conjunctivitis, which cleared up in 24 hours (140).

TEP No data were located.

TIPP Three male and 3 female Sprague Dawley rats were exposed to isopropylated triphenyl phosphate by dermal application (2 000 mg/kg bw). The test material was maintained in contact with the intact skin for 24 hours using an occlusive wrap. The skin was observed upon unwrapping and then again daily for 14 days. No irritation was observed (FMC 1990a, cited in (74)).

Isopropylated triphenyl phosphate (0.1 ml or 110 mg) was applicated on the shaved backs of 3 New Zealand rabbits. The test site was wrapped with gauze, which was covered with cheesecloth. The test material was in contact with the skin for 4 hours. The sites were scored at 4.5, 24, 48 and 72 hours after they were unwrapped using the method of Draize. No irritation was observed and the test substance was classified as non-irritating. The Primary Irritation Score was 0 (FMC 1990b, cited in (74)).

Eye irritation from isopropylated triphenyl phosphate was investigated in 9 rabbits. The treated eyes of 6 rabbits were unwashed through the 7-day observation period whereas the eyes of 3 rabbits were washed about 4 seconds after treatment. The treated eyes were examined at 24, 48, 72 hours and 7 days after treatment. There was no irritation in any of the treated eyes at any of the observation times (Food and Drug Research Laboratories 1975, cited in (74)).

Three New Zealand White rabbits were treated with 0.1 ml (110 mg) isopropylated triphenyl phosphate in their conjunctival sac of the right eye. Each treated eye was held closed for about one second after administration. The eyes were evaluated for irritation using the Draize method at 1, 24, 48 and 72 hours after dosing. Slight conjunctival redness was observed in two treated eyes 24 hours after dosing. The irritation had disappeared by the 48-hour observation. The Primary Eye Irritation Index was 1.3 at 24 hours and 0 at 48 and 72 hours. Thus, isopropylated triphenyl phosphate caused very slight irritation (FMC 1990c, cited in (74)).

TMCPP 0.5 ml (650 mg) of tris(1-chloro-2-propyl) phosphate was applied to the skin of 3 New Zealand White rabbits under semi-occlusive dressing for 4 hours. Slight erythema (grade 1) was noted in one animal on day 1 only. Thereafter, there were no signs of skin irritation (Liggett and McRae 1991d, cited in (102)).

In two different studies, 0.5 ml (approximately 650 mg each of Antiblaze 80 and tris(2-chloropropyl) phosphate, i.e. presumably tris(1-chloro-2-propyl) phosphate) was applied to two test sites, one abraded and one intact skin of the back of 6 New Zealand White rabbits under an occlusive binder for 24 hours. Sites were scored for irritancy at 24 and 72 hours after application. In both cases, the test material was classified as not irritative (Smithey 1980b, 1981b, cited in (102, 238)).

In another study, 0.1 ml (130 mg) of tris(1-chloro-2-propyl) phosphate was instilled into the eye of each of 3 New Zealand White rabbits. Slight conjunctival redness (grade 1) was seen in each animal on day 1 only. Thereafter, there were no signs of eye irritation (Liggett and McRae 1991b, cited in (102)).

In older studies, 0.1 ml (130 mg) of tris(2-chloropropyl) phosphate (presumably tris(1-chloro-2-propyl)) and of Antiblaze 80, respectively, was instilled into the eye of each of 6 New Zealand White rabbits. The test eyes remained unwashed and were evaluated for eye irritation 1, 24, 48 and 72 hours post-administration. The materials were considered as not irritant (Smithey 1980a, 1981a, cited in (102, 238)).

Unspecified TMCPP was examined using the Magnusson and Kligman method for possible contact sensitisation potential in guinea pigs. TMCPP produced no skin sensitisation (SafePharm 1979, cited in (102)).

TPP No significant skin irritation was observed when a gauze pad soaked with approximately 0.5 ml (600 mg) of a 70 % solution of TPP in alcohol was applied to the skin of mice for 72 hours (218).

The irritation potential of TPP on mucous membranes of the rabbit eye was determined according to the OECD guideline 405. The treated eyes were rinsed 24 hours after instillation. No sign of irritation was detected (Bayer 1990, cited in (240)).

Similar findings were recorded in a study employing 4 hours of treatment without rinse in 6 rabbits (group 1) and rinsing after 4 seconds in 3 additional rabbits (group 2). In group 1, conjunctival effects were observed in all 6 animals. These effects cleared during the 72-hour observation period. In group 2, no ocular effects were observed in any of the 3 animals. The material was found mildly and transiently irritating when not washed out (FMC 1975, cited in (240)).

A minimal irritating potential of TPP in 6 New Zealand White rabbits was also found when 100 mg was instilled into the conjunctival sac of the left eye. The eyelids were then held closed for 1 second. After 30 seconds, the compound was flushed out of the eyes of 3 of the rabbits. Very slight reactions were seen in 2/3 washed and 3/3 unwashed eyes 1 hour after compound application. The reactions were less severe at 24 hours although all washed and unwashed eyes were affected. All (3/3) washed eyes and 1/3 unwashed eyes were normal at 48 hours, 1 unwashed eye at 27 hours and the remaining unwashed eye at day 6. Slight opacity and damage to the surface epithelium was seen in 1 unwashed eye at 24 hours. This was no longer present at 48 hours. Minimal irritating potential of TPP in New

Zealand White rabbits was found (highest score 7, score 0-10 minimally irritant) (Ciba-Geigy 1983, cited in (240)).

10.2 Effects of single exposure

The oral lethal doses for 50 % of the exposed animals at single administration (LD_{50}s) of the phosphate triesters included in this presentation are generally above 1 000 mg/kg bw in the rat (Table 9) indicating a slight acute toxicity. The phosphate triesters are thus generally less acutely toxic than many organophosphorus pesticides, e.g. demeton, dichlorvos, mevinphos, parathion and terbufos for which the rat oral LD_{50} varies between 2 and 80 mg/kg (213).

The lethal concentrations for 50 % of the exposed animals at single inhalation exposure (LC_{50}) was investigated in rats for some phosphate triesters (TBEP, TDCPP, TEP and TMCPP) and was around 5 000 mg/m^3 or higher after 4-hour exposures.

In an *in vitro* study, several of the phosphate triesters (TCP, TBP, TDCPP and TPP) were shown to exert strong haemolytic activity in rabbit blood (195).

TCP Commercial TCP products were chemically not the same in the 1950s and 1990s (141) and the content of TOCP has decreased considerably over time.

In 1955, Treon *et al* studied the effects in rabbits of 24-hour dermal exposures to seven commercial TCP mixtures. The minimum lethal dose varied between 0.4-0.6 ml/kg bw (500-750 mg/kg) and 1.6-3.2 ml/kg bw (2 000-4 000 mg/kg) for the different mixtures. Lethal doses resulted in diffuse degenerative changes in

Table 9. Acute oral and dermal toxicity of phosphate triesters, LD_{50}s (g/kg bw).

Compound	Rat, oral	Hen, oral	Rabbit, dermal	Reference
TCP	> 15.8	> 10.0	> 7.9	(106)
TOCP	8.4		3.7	(106)
TBEP	4.7	> 5.0	> 5.0- > 10.0	(32, 33, 103)
TBP	1.4-3.2	1.5	> 3.1	(32, 33, 101, 106)
TCEP	0.4-3.6			(102, 235)
TDCPP	> 2.0			(102)
TEHP	> 10-37.1			(103)
TEP	1.1-1.6			(237)
TIPP [a]	> 15.8	> 1.0	> 7.9	(106)
TMCPP [b]	0.9-4.2 males 0.7-2.5 females		1.2- > 5.0	(102, 238)
TPP	3.5-10.8	> 5.0	> 7.9	(100, 106)

[a] Tri-*ortho*-isopropylphenyl phosphate. Data for some other isomers are given in Appendix IX.
[b] Presumably tris(1-chloro-2-propyl) phosphate or tris(2-chloro-1-propyl) phosphate.
LD_{50}: lethal dose for 50 % of the exposed animals at single administration.

the brain, liver and kidney, and oedema in the other viscera. Pathological changes were not observed in survivors (Treon *et al* 1955, cited in (215)).

Mortality was very high in rabbits exposed to TCP aerosols at concentrations of 5 900- 42 200 mg/m^3 for periods of 3 hours to 18 days. Rabbits had considerably increased nasal and oral discharge during and immediately following exposure and respiratory difficulties were noted. Diarrhoea was also seen (Broadhurst *et al* 1951, cited in (215)).

Rats were administered 10, 25, 50 or 100 mg TOCP/kg bw intraperitoneally in corn oil. After 18 hours, all animals were euthanised. No apparent morphological or histopathological changes were found in any tissues. A dose-dependent inhibition of fatty acid ethyl ester synthesising activity in the liver was observed starting already at 10 mg/kg bw. Similar results were also found for the plasma activity (153).

Adult Long Evans male rats were exposed to single oral doses of TOCP ranging from 145 to 3 480 mg/kg bw. Decreased body weight (transient at 145-1 160 mg/kg bw) was reported (181). The study aimed at studying OPIDN and is described in more detail in Section 10.4.

In an *in vitro* experiment investigating the haemolytic activity of various phosphate triesters, TCP was found to exhibit strong haemolytic toxicity. The concentration of TCP in rabbit blood necessary to lyse 50 % of the erythrocytes was 15 µM as compared to 350 µM for sodium *n*-dodecyl sulphate, which is a strong haemolytic substance (195).

In vitro, apoptosis was induced with 0.1 or 1 mM TOCP in SH-SY5Y human neuroblastoma cell cultures (28).

TBEP Groups of 5 male and 5 female Wistar rats were exposed for 4 hours to air TBEP concentrations of 3 300, 3 400 or 6 400 mg/m^3. No animal died but at all concentrations the animals exhibited depressed and irregular respiration, increased salivation, sneezing, unsteadiness and tremor. No dose-response information was presented. Symptoms cleared in most animals 9 days later. Body weights did not change and gross necropsy revealed no abnormalities. The 4-hour LC_{50} was above 6 400 mg/m^3 (Hoechst 1989, cited in (103)).

In another study in rats, LC_{50} was reported to be greater than 4 430 mg/m^3 (Mount 1991, cited in (103)).

In an *in vitro* experiment, the concentration of TBEP in rabbit blood necessary to lyse 50 % of the erythrocytes was higher (1 100 µM) as compared to that of the strongly haemolytic substance sodium *n*-dodecyl sulphate (350 µM) (195).

TBP Hens were given gelatin capsules of TBP with varying doses (from 500 to 5 000 mg) to determine LD_{50}, which was 1 500 mg/kg bw. Animals surviving the period of acute toxicity appeared normal thereafter (32, 33).

Male and female adult Sprague Dawley rats received 100, 325 and 1 000 mg/kg bw of TBP in corn oil by gavage. Mean body weight of male rats decreased significantly compared to controls at the high-dose level. Transient changes

attributable to the general toxicity were noted in forelimb grip strength and mean activity level only during the first 24 hours after the highest dose. On day 7 and 14, there were no differences between the groups. No treatment-related gross pathological findings in the animals were observed at necropsy (80).

Single intraperitoneal injections of 0.062-1 mmol/kg (16-270 mg/kg) of TBP in female rats caused a dose-related increase of β-glucuronidase activity in serum after 3 hours (221).

Intratracheal administration of 5 µl (5 mg) TBP (20 % in *n*-dodecane) in rats (body weight 280-300 g, estimated dose 17 mg/kg bw) resulted in an increase of the total cell number in bronchoalveolar fluid the first day compared to a control group. A mild inhibition of serum cholinesterase (20 %) was also observed on the first day only. The activities of superoxide dismutase and catalase were decreased to day 7 and those of glutathione peroxidase and glutathione reductase only on day 1. The malondialdehyde content was elevated to day 14. TBP caused moderate toxic injury of the lung parenchyma with depression of antioxidant enzymes and elevated lipid peroxidation (191).

In an *in vitro* experiment investigating the haemolytic activity of various phosphate triesters, the concentration of TBP in rabbit blood necessary to lyse 50 % of the erythrocytes was 250 µM as compared to 350 µM for sodium *n*-dodecyl sulphate, which is a strong haemolytic substance (195).

TCEP Reported LD_{50}s in rats were in the range 400-3 600 mg/kg bw (102, 235).

Cultured rabbit renal proximal tubule cells were exposed to TCEP. A concentration of 10 mg/l decreased cell viability (84 % of the control) but increased lactate dehydrogenase (150 % of the control). TCEP at 10 µg/l significantly increased cell cycle regulatory protein expression but slightly decreased DNA synthesis in primary cultured rabbit renal cells (186).

In an *in vitro* experiment, TCEP did not exhibit strong haemolytic toxicity. The concentration in rabbit blood necessary to lyse 50 % of the erythrocytes was 3 800 µM as compared to 350 µM for the strongly haemolytic sodium *n*-dodecyl sulphate (195).

TDCPP Slc/ddY mice were given a single oral intubation of TDCPP in olive oil and were observed for 14 days. Clinical signs included ataxia, hyperactivity and convulsion. LD_{50}s for male and female mice were 2 670 and 2 250 mg/kg bw, respectively (102, 114).

TDCPP was administered as an aerosol for 4 hours to groups of 5 male and 5 female rats. LC_{50} was greater than 5 220 mg/m^3 (Anderson 1990b, cited in (102)).

Strong haemolytic toxicity of TDCPP was reported in an *in vitro* study. The concentration in rabbit blood necessary to lyse 50 % of the erythrocytes was 71 µM as compared to 350 µM for the strongly haemolytic substance sodium *n*-dodecyl sulphate (195).

TEHP Wistar rats and Hartley guinea pigs were exposed to aerosols of TEHP. Rats were exposed to air concentrations of 283-460 mg/m^3 for 30-210 minutes without any mortality in any group of 10 animals. Guinea pigs were exposed to the same air concentrations for 30-180 minutes, with some mortality in each group. The mortality varied from 30 % (at 450 mg/m^3 for 30 minutes, 298 mg/m^3 for 60 minutes and 460 mg/m^3 for 60 minutes) to 80 % (at 287 mg/m^3 for 120 minutes) (140).

TEP The LC_{50} was greater than 8 817 mg/m^3 in rats exposed for 4 hours (237). A single intraperitoneal injection of TEP (1 mmol/kg, 180 mg/kg bw) in female rats (150-200 g) caused an increase of β-glucuronidase activity in serum after 3 hours, whereas the metabolite diethyl phosphate did not. The increase caused by TEP was less prominent compared to that caused by TBP (221).

In an *in vitro* experiment investigating the haemolytic activity of various phosphate triesters, TEP did not exhibit strong haemolytic toxicity in rabbit blood (195).

TIPP Five male and 5 female Wistar rats received a single oral dose of 20 000 mg/kg bw of isopropylated triphenyl phosphates. The animals were observed for 14 days, after which they were sacrificed, necropsied and their organs examined for gross lesions. No male rats died but 4 of the 5 females. No clinical signs were reported (Food and Drug Research Laboratories 1975, cited in (74)).

Three male and 3 female Sprague Dawley rats were exposed by dermal application to 2 000 mg/kg bw of isopropylated triphenyl phosphates. The test material was maintained in contact with the intact skin for 24 hours using an occlusive wrap. The skin was observed upon unwrapping and then again daily for 14 days. There was no mortality, no apparent effect on body weights, no observed irritation and no gross lesions at necropsy in any of the animals (FMC 1990a, cited in (74)).

TMCPP Acute oral LD_{50}s for TMCPP in rat have been reported in a series of studies and range between 931 and 4 200 mg/kg bw for males and between 707 and 2 500 mg/kg bw for females (102).

Inhalation studies with aerosols of TMCPP have been performed. The LC_{50} was reported to be above 4 600 mg/m^3 with an exposure duration of 4 hours (Mehlman and Singer 1981, Stauffer 1979, Anderson 1990a, cited in (102)).

Dermal LD_{50}s for rats were above 2 000 mg/kg bw (102). For rabbits, reported dermal LD_{50}s were approximately 1 200 to above 5 000 mg/kg bw (102, 238).

In an *in vitro* experiment, the concentration of tris(2-chloro-1-propyl) phosphate in rabbit blood necessary to lyse 50 % of the erythrocytes was 840 µM as compared to 350 µM for sodium *n*-dodecyl sulphate, which is a strong haemolytic substance (195).

TPP A commercial cresyl diphenyl phosphate preparation was analysed to contain approximately 35 % of TPP, 45 % of cresyl diphenyl phosphates, 18 % of dicresyl

phenyl phosphates and 2 % of TCP. The product was almost free of the *o*-cresyl isomers as revealed by the analysis of its alkaline hydrolysis products. Twenty-four hours after a single intraperitoneal injection (75, 150 or 300 mg/kg bw), an induction of microsomal CYPs in the liver of Wistar rats with a concomitant increase in the activities of mixed function monooxygenases was observed at the two highest doses and possibly also at 75 mg/kg bw. Morphology of hepatocytes investigated (for the 300 mg/kg-group only) by light and electron microscopy showed proliferation of smooth endoplasmic reticulum, enlargement of the nuclei and mitochondria with increased cristae. Hepatic morphology returned to normal 2 weeks after the treatment. The concentration of the phosphate esters in blood and liver decreased rapidly with only traces detected in blood after 24 hours (244). Other components than TPP may have contributed to the effects of this mixture. The study is also described in Section 10.4.

In a limited study, cats (n = 1-2) were given subcutaneous doses of 400, 700 or 1 000 mg/kg bw of TPP (99.99 % pure). At the lowest dose, one of two cats lost weight. Higher doses caused prostration. Complete necropsy (performed only at 700 mg/kg) revealed generalised vascular damage with perivascular oedema in many tissues. The liver displayed fatty change (256).

TPP exhibited strong haemolytic activity in an *in vitro* experiment. The concentration in rabbit blood necessary to lyse 50 % of the erythrocytes was 45 µM as compared to 350 µM for sodium *n*-dodecyl sulphate (a strong haemolytic substance) (195).

In another *in vitro* study, an inhibition of monocyte antigen presentation was observed at 1 µM in the test medium (58).

10.3 Effects of short-term exposure (up to 90 days)

Organ toxicity such as liver effects was observed after short-term exposure to some of the phosphate triesters (TBP, TCEP, TEP, TIPP, TMCPP and TPP).

TCP In an early study, groups of 3-4 female rabbits were exposed dermally to 0.25, 0.5, 1, 2 or 5 ml (300, 600, 1 200, 2 400 or 6 000 mg) of commercial TCP, 2 hours/day, 5 days/week for several weeks. Death was produced by doses as low as 0.25 ml (300 mg). Degenerative changes were seen in the brain, liver and kidneys of rabbits that died. Mild changes were also seen in the liver and kidneys of survivors (Treon *et al* 1955, cited in (215)). The study is also described in Section 10.4.

Groups of male and female F344 rats received daily oral doses of 400 mg/kg bw commercial TCP in sesame oil for 20, 40 or 60 days. The TCP was composed of mostly *p*- and *m*-isomers of TCP and other substances including substantial amounts of cresyl-xylyl, cresyl-ethylphenyl and ethylphenyl-xylyl phosphates. No TOCP was detected. Light microscopy revealed hypertrophy and lipidosis of adrenocortical (both sexes) and ovarian interstitial cells that progressed with duration of exposure (131).

Female rats received daily oral doses of 0 or 400 mg/kg bw of the same TCP mixture for 40 days. Adrenal glands and ovaries from TCP-treated rats were heavier than controls. Microscopic and biochemical studies revealed cholesteryl lipidosis composed of cholesteryl ester in the adrenal glands and ovaries in treated rats. The activity of neutral cholesteryl ester hydrolase (an enzyme that converts cholesteryl esters to cholesterol in the uptake and storage pathways) was inhibited by 97 % compared to that of controls, which most likely resulted in the striking accumulation of cholesteryl ester in cytoplasmic lipid droplets of adrenocortical and ovarian interstitial cells. The activity of acyl coenzyme A:cholesterol acyl transferase (an enzyme that esterifies cholesterol to cholesteryl esters) was depressed by 27 % compared to that of control adrenal glands, resulting in elevated intracellular cholesterol levels in adrenocortical cells (130).

Groups of 10 male Wistar rats were fed diets containing 0, 0.02, 0.05 or 0.1 g/kg of TCP (90 % *o-, m-* and *p*-isomers) for 6 weeks. Doses were estimated (215) to be 0, 2.4, 6 and 12 mg/kg bw/day, respectively. After 25 days of exposure, rats were immunised with tetanus toxoid. No clinical signs of toxicity were observed, and food and water intake, body weight and relative organ weights in treated rats were similar to controls. Serum antibody titres to tetanus toxoid were significantly reduced at 0.05 and 0.1 g/kg diet. Serum immunoglobulins (IgM and IgG) were significantly reduced at 0.1 g/kg while leukocyte and macrophage migration was inhibited at 0.05 and 0.1 g/kg. Thus, the results suggest that the immune system may be a sensitive target for TCP (14).

Adult male Long Evans rats were exposed to TOCP at 75, 150 or 300 mg/kg bw given 7 times orally in a 2-week period. Corticosterone was added to drinking water (400 µg/ml) for a total of 28 days in order to study the interaction of stress and exposure to TOCP. At the end of the 28-day testing period, the rats were sacrificed. The body weight was reduced at all TOCP doses and significantly so at 75 and 300 mg/kg bw. The thymus and spleen weights and cell counts were significantly reduced by corticosterone but not affected by TOCP (data only presented for the 300-mg/kg dose). The percentage of cells from thymus and spleen with specific markers (e.g. $CD4^+8^-$, $CD4^+8^+$, $CD4^-8^-$, $CD4^-8^+$) were not affected by TOCP, nor by corticosterone (53). The study is also described in Section 10.4.

TBEP In a 4-week study, diets containing 0, 0.5, 2, 7.5 or 15 g TBEP/kg were fed to male and female Sprague Dawley rats (corresponding to 0, 50, 200, 750, 1 500 mg/kg bw (44)). In males, no signs of toxicity were found in any group but there was a slight decrease in body weight and food consumption in females receiving diets containing 7.5 and 15 g/kg. No compound-related changes were observed at necropsy (Monsanto 1985b, cited in (103)).

TBP was administered by gavage to male and female Sprague Dawley rats for 14 consecutive days (0.14 and 0.42 ml/kg bw, i.e. 140 and 410 mg/kg bw). Effects were investigated at the end of the feeding period. Relative liver weights were increased in low-dose animals. Increased absolute liver weights and serum amylase

activity were found in high-dose animals. Histopathological examination (only performed in the high-dose group) revealed microscopic degenerative changes in 50 % of the seminiferous tubules of the testis in 1/4 rats. No other abnormal microscopic changes were observed (123).

Wistar male rats were fed pellet diets containing 0 or 5 g/kg of TBP for 9 weeks. The dietary levels correspond to approximately 500 mg/kg bw/day (44). Both absolute and relative liver weights increased after exposure as did relative weights of kidney and testes. Haematological parameters were not different from controls. Enzyme activities and all serum components were unaffected except urea nitrogen, which was increased (178).

In a 10-week toxicity study, male Wistar rats (n = 10-11/group) were given TBP (> 97 % purity) via the diet at doses of 5 and 10 g/kg (equivalent to approximately 0, 500 or 1 000 mg/kg bw/day (44)). The body weights and food consumption of the treated groups were significantly lower than those of the controls. In both treatment groups, increased relative brain, liver and kidney weights and decreased absolute brain and kidney weights were found compared to the control group. Clinical chemistry analysis showed significantly decreased serum glucose and increased urea concentrations at both dose levels, and increased total protein and cholesterol concentrations at the high dose. The activities of serum alanine and aspartate aminotransferase enzymes (ALAT and ASAT) and of alkaline phosphatase (ALP) were significantly decreased at both dose levels. The cholinesterase activity in the brain was significantly increased in both treatment groups, but no significant changes were observed in the serum or liver cholinesterase activities compared to the control group. The blood coagulation time of the treated groups was significantly prolonged at both dose levels (177). The study is also described in Section 10.4.

The dose-response of TBP for effects on urine and urothelium was evaluated in male Sprague Dawley rats (10/group) administered 0, 0.2, 0.7 and 3 g/kg in the diet (corresponding to approximately 0, 20, 70 and 300 mg/kg bw (44)) for 10 weeks. Urothelial effects were seen at the two highest doses but were most severe at 3 g/kg diet with ulceration and haemorrhage into the bladder lumen and, as a consequence, diffuse papillary and nodular hyperplasia. The bladder epithelial changes were reversible, but the ulcer repair process was accompanied by submucosal fibrosis (11). As the majority of TBP is metabolised, the cytotoxicity may be due to one or more of the metabolites. Supporting this hypothesis is the observation that dibutyl phosphate produces toxic and regenerative changes of the rat bladder similar to TBP (Chemicals Investigation Promoting Committee 1995, cited in (11)).

TCEP Groups of five F344/N rats of each sex received 22, 44, 88, 175 or 350 mg/kg bw of TCEP in corn oil by gavage 5 days/week with 12 doses over 16 days. No clinical signs of toxicity were observed. There was no significant differences in body weight between dosed and control animals. Mean absolute and relative kidney weights for males receiving 175 or 350 mg/kg bw were significantly greater than

those of controls, as were absolute and relative liver weights for high-dose females. Absolute and relative lung weights of females receiving 88-350 mg/kg bw were significantly decreased. No gross or histopathological lesions attributable to TCEP exposure were observed (173).

Groups of five mice of each sex received 44, 88, 175, 350 or 700 mg/kg bw of TCEP in corn oil by gavage 5 days/week with 12 doses over 16 days. Group mean body weights were similar to control values at the end of the study. Further, there were no chemical-related changes in absolute or relative organ weights. Gross or microscopic lesions were not observed (173).

TDCPP The effects of Fyrol FR-2 on immunological function and host susceptibility to infectious agents were examined following subcutaneous injections of 0.25, 2.5 or 25 mg/kg bw/day for 4 days. The treatment induced minimal changes regarding these endpoints only at the highest dose as indicated by decreased lymphoproliferative responses to mitogens and an increased incidence of tumours after tumour cell challenge. Histological examination revealed no significant lesions in the brain, vagina, uterus, liver, kidney, adrenals, spleen, bone marrow, lung or salivary gland (137). As pointed out by the US Environmental Protection Agency (EPA), there is some uncertainty as the test material, reported as Fyrol FR-2, was mis-identified by the authors as tris(2,3-dichloropropyl) phosphate (243).

No histological effects were observed in the liver, kidneys or gonads of rats given daily doses of 250 mg/kg bw for 10 days by gavage (review by Ulsamer *et al* (235)).

TEHP Rats were given oral doses of 110-1 550 mg TEHP/kg bw/day for 30 days. No effect on body weight was seen at 430 mg/kg. At the highest dose, weight loss was observed (Smyth 1948, cited in (103)).

Five rats (F344/N) and 5 mice ($B6C3F_1$) of each sex were administered 0, 375, 750, 1 500, 3 000 or 6 000 mg TEHP/kg bw in corn oil for 14 consecutive days. No animals died. The final mean body weights were lower among male rats that received 1 500 mg/kg bw or above and among female rats that received 3 000 mg/kg bw or above than among vehicle controls. There was no effect of body weight gain in mice (172).

TEP Male Wistar rats were fed pellet diets containing 0 or 5 g/kg for 9 weeks. The dietary concentrations correspond to approximately 500 mg/kg bw/day (44). Both absolute and relative liver and spleen weights as well as absolute weights of kidneys and testes increased after exposure. Leukocyte, erythrocyte counts, haemoglobin and serum component levels such as cholesterol, triglyceride, sodium and potassium were not different from controls. Further, the serum cholinesterase activity was also normal. Slight morphological changes were found in the liver. These included cytoplasmic vacuolisation, increases in the number of binucleated cells and enlargement of cell size (178).

TIPP Forty male and 40 female Sprague Dawley rats were treated with Kronitex® K-100 at doses of 1, 5 and 10 g/kg diet/day for 28 days (corresponding to approximately 100, 500 and 1 000 mg/kg bw/day (44)). Twelve rats died during the study but the mortality was not dose-related since 4 deaths occurred in the low-, 4 in the mid-, and 3 in the high-dose group. There was one death in the control group. Body weights were depressed only in the high-dose female rats. Routine haematological and clinical chemistry measurements were performed. Abnormal haematological values (not specified) were obtained from the high-dose animals and abnormal clinical chemistry measurements (not specified) from the mid- and high-dose animals. Urinalysis was normal for all animals. At necropsy, no gross lesions were observed. Realtive liver weights were increased in all dose groups. Kidneys and livers were examined microscopically and appeared normal (74).

TMCPP Groups of 5 female Wistar rats were given 0, 8, 40, 200 and 1 000 mg/kg bw of unspecified TMCPP in olive oil by gavage for 7 days. No abnormalities or mortality were observed except for one rat that died in the 1 000-mg/kg group. The only treatment-related effects were significant increases in the relative weights of the liver at 1 000 mg/kg and of the kidneys at or above 40 mg/kg (Kawasaki *et al* 1982, cited in (216)).

In a range-finding study, groups of 5 male Wistar rats received tris(1-chloro-2-propyl) phosphate (98 %) at doses of 0, 1, 10, 100 or 1 000 mg/kg bw by gavage in peanut oil for 7 days. There were no effects on mortality, clinical signs, body weight or food intake, and no effect on gross pathology (Bayer 1993, cited in (216)).

Groups of rats fed *ad libitum* for 14 days at levels of 4.2, 6.6, 10.6 and 16.6 g Fyrol PCF/kg diet presented minimal evidence of toxicity. The product contained ca 70 % tris(1-chloro-2-propyl) phosphate and ca 22 % tris(2-chloro-1-propyl) phosphate. The dietary levels correspond to 420, 660, 1 060, 1 660 mg/kg bw (44). No treatment-related changes were seen in haematology, clinical chemistry or cholinesterases activity. At the highest dose, increased relative and absolute liver weights in males were reported without concomitant histopathological changes (Stauffer 1980a, cited in (102, 238)).

TPP In a 35-day study, rats were exposed to dietary levels of 1 and 5 g/kg feed. High-dose animals exhibited increased relative liver weights and a slight depression of growth rate. Relative kidney weights were unaffected. No haematological effects (haemoglobin content, cell volume, erythrocyte and leukocyte counts and differential) were found (218). Doses were estimated to be approximately 100 and 500 mg/kg bw.

10.4 Neurotoxicity

Organophosphorus-induced delayed neuropathy (OPIDN) is a neurodegenerative disorder characterised by a delayed onset of prolonged ataxia and upper motor

neuron spasticity as a result of single or repeated exposures to organophosphorus esters. The neurological lesion is a central-peripheral distal axonopathy caused by chemical transection of the axon (known as Wallerian-type degeneration), followed by myelin degeneration of the distal portions of the long and large-diameter tracts of the central and peripheral nervous systems (1).

It is difficult to produce delayed neurotoxic effects in rodents even at repeated dosing (109). Thus, when studying OPIDN, the hen is the experimental animal of choice and is consequently used for testing in regulatory protocols (176, 242). This is due to the susceptibility of the hens, ease of handling, presence of clearly detectable clinical signs and lesions and the temporal similarity of its neuropathy to that of man. TOCP is used as a positive control as hens develop weakness and ataxia in 7-10 days, which progresses for 2-3 weeks. The severity and progression of these effects are scored and used for quantification of the clinical neuropathy associated with OPIDN (251). Different chicken strains seem to be more or less sensitive to TOCP regarding OPIDN (43).

In concluding that a chemical induces OPIDN, the US EPA states that at least two of the following three factors should be present: 1) evidence of the clinical disease, 2) typical nervous system lesions, and 3) appropriate degree of NTE inhibition (251). Despite numerous studies, however, the NTE hypothesis (Section 9.1) has not advanced our understanding of the mechanism of OPIDN according to Abou-Donia (1).

The structural features contributing to OPIDN have been studied and discussed (108, 109, 251). Among triaryl phosphates, the following structural characteristics are related to OPIDN:

- Esters having one or more rings substituted in the *ortho* position are neurotoxic provided that the *ortho*-alkyl group has at least one hydrogen atom on the α-carbon (the carbon attached to the phenyl ring).
- Further substitution in the phenyl ring containing the *ortho*-substituent greatly reduces the neurotoxicity by providing alternative degrading pathways. Thus, methyl groups in the *meta* or *para* positions, in addition to the *ortho* position, reduce neurotoxicity by opening a route to inactive excretable products. Further substitution in the other two rings of an *ortho*-substituted phosphate ester reduces neurotoxicity only slightly.
- The delayed neurotoxicity is greater in isomers having only one *ortho*-substituent, compared to the symmetrical tri-*ortho*-ester.
- The delayed neurotoxicity decreases as the substituent in the *ortho* position becomes larger and more branched. The *tert*-butyl group is unable to undergo the activation to the neurotoxic metabolite.
- Triaryl phosphate esters having no substituents are not neurotoxic.
- A substituent in the *para* position requires two hydrogen atoms on the α-carbon to produce neurotoxicity. Substituents in the *meta* position do not generally produce neurotoxicity. Mixed esters with some substituents in

both *meta* and *para* positions are less active than the symmetrical tri-*para*-esters.

TOCP is the most neurotoxic phosphate triester in this review and known to cause OPIDN. TCP (or derivates in its mixture) and the mono-*ortho*-derivate of isopropylated triphenyl phosphate (i.e. *ortho*-isopropyl phenyl diphenyl phosphate) can also cause OPIDN but are less potent. Pure TPP is not neurotoxic but commercial products may contain derivates generating OPIDN. Some other phosphate triesters in this document induce neurotoxic effects (TBEP, TCEP and TEP) although they do not produce OPIDN. TEP has a narcotic effect. In addition, TBP produced reduction of conduction velocity of the caudal nerve and morphological changes of the sciatic nerve in one study but other studies did not discover neurotoxic effects. Neurotoxicity at high doses has been reported after exposure to TDCPP and TMCPP. Inhalation exposure to TEHP was associated with a slight effect on performance in two dogs.

TCP Chemically, the commercial TCP mixtures have changed over time. The mixtures of the 1950s were more toxic and their content of TOCP was higher than those of later times (see Chapter 4) (141).

The effects of TOCP on brain NTE, spinal cord NTE, severity of clinical ataxia and neuropathology scores were investigated after single oral doses of 50, 90 or 500 mg/kg bw in hens. There was a clear dose-response on NTE inhibition, clinical ataxia and severity of nervous system lesions for the dose-range tested with effects starting already at the lowest dose (54).

Hens were treated with TOCP by gavage at single dosages of 375 and 750 mg/kg bw. Twenty-one days after treatment, the levels of neurofilament units in sciatic nerves were decreased at both dose levels (265).

In another experiment by the same research team, hens were given 750 mg/kg bw by gavage. Downregulation of neurofilament mRNA in the cerebral cortex was observed after 21 days (264).

Three strains of chicken were treated with TOCP by gavage. Babcock chickens were given a single dose of 800 mg/kg bw whereas Hy-line w36 and isobrown chickens were treated with 1 600 mg/kg bw. All groups exhibited decreased brain NTE (by 72-86 %) and plasma cholinesterase (by 40-60 %) activities after 24 hours. Brain cholinesterase activities were unaffected. Clinical signs of OPIDN were observed only among the isobrown chickens (43).

Adult male Long Evans rats were exposed to TOCP over a 63-day period in a setting of chronic stress. TOCP was administered in 14 gavage doses of 75, 150 or 300 mg/kg bw. To model aspects of chronic stress, corticosterone was added to the drinking water at 400 µg/ml. The major neuropathological change was the presence of axonal degeneration progressing to myelinated fibre degeneration, mainly in distal regions of selected fibre tracts and peripheral nerve, seen in animals sacrificed on experimental day 63. The cervical spinal cord and medullary levels of the sensory gracile fasciculus were most prominently affected. This axono-

pathy/fibre degeneration was dose-related at the 150- and 300-mg/kg bw levels (no effect at 75 mg/kg bw) and was associated with inhibition of the enzyme NTE in hippocampal tissue. Corticosterone did not appear to contribute to the neuropathic events or the enzyme inhibition. A cohort of high-dose rats was maintained on the corticosterone schedule (corticosterone or vehicle) without further exposure to TOCP for an additional 27 days. When these rats were examined on day 90, the nerve fibre degeneration had progressed in both groups administered the 300 mg/kg bw dose of TOCP, although hippocampal NTE had returned to control values (112).

Adult male Long Evans rats were exposed to TOCP at 75, 150 or 300 mg/kg bw given 7 times orally in a 2-week period. Corticosterone was added to drinking water (400 µg/ml) for a total of 28 days in order to study the interaction of stress and exposure to TOCP. At the end of the 28-day testing period, the rats were sacrificed. Decreased body weight and grip strength were elicited by TOCP and corticosterone. The body weight was reduced at all TOCP doses and significantly so at 75 and 300 mg/kg bw. A reduction of grip strength was observed only at the highest TOCP dose in combination with corticosterone. TOCP alone decreased acetylcholinesterase levels in erythrocytes and in several areas of the brain, e.g. cortex, hippocampus, basal forebrain and caudate putamen, at all dose levels. The NTE and carboxylesterase activities were also significantly reduced in the same areas of the brain at all doses. The glial fibrillary acidic protein in the cerebral cortex was significantly increased by both TOCP and corticosterone at all doses (53).

A rodent model of OPIDN was developed using adult Long Evans male rats exposed to TOCP. The rats were exposed to single doses of TOCP ranging from 145 to 3 480 mg/kg bw. Decreased body weight (transient at 145-1 160 mg/kg bw) was reported. The degree of NTE inhibition, measured at 20 and 44 hours and at 14 days post-exposure, correlated with the appearance of spinal cord pathology 14 days post-exposure in a separate group of similarly exposed rats. Dosages that inhibited mean NTE activity in spinal cord more than 72 % and in brain more than 66 % of control values produced marked spinal cord pathology 14 days post-exposure in more than 90 % of similarly dosed animals. In contrast, dosages of TOCP which inhibited mean NTE activity in the spinal cord less than 65 % and in the brain less than 57 % produced spinal cord pathology in less than 15 % of the animals. The NTE inhibition was non-significant at 145 and 290 mg/kg bw and became manifest at 580 mg/kg bw (181).

Adult male European ferrets (*Mustela putorius furo*) were exposed to a single oral or dermal dose of 250, 500 or 1 000 mg TOCP/kg bw. Corn oil served as the vehicle in the oral test and 95 % ethanol was the vehicle in the dermal test. In the dermal test, TOCP was applied to a 6 × 6 cm shaved area on the back of the neck. At 48 hours post-treatment, half of the animals in each group were killed by cervical dislocation for assessment of whole-brain NTE activity. The remaining 5 animals per group were observed and examined neurologically on a daily basis for 54 days. Of the animals dosed orally, only those in the 1 000 mg/kg bw group

showed clinical signs indicative of OPIDN. Ferrets dermally administered 250 and 500 mg/kg bw displayed variable degrees of hind limb weakness and ataxia. All ferrets dosed dermally with 1 000 mg/kg bw developed clinical signs characteristic of OPIDN ranging from ataxia to partial paresis. Small amounts of axonal degeneration were also noted in the dorsolateral part of the lateral funiculus and in the fasciculus gracilis of spinal cords in high-dose ferrets. The decrease of whole-brain NTE activity was dose-dependent (18, 25 and 46 %) after dermal dosing (214).

Socialised and non-socialised, stressed and unstressed male and female chickens were administered a single peroral TOCP dose of 360 mg/kg bw. TOCP induced a delayed neuropathy that caused ataxia in all the chickens. The ataxia was significantly more pronounced earlier in males than in females, although the sex difference became insignificant 18 days after dosing. Socialised chickens were ultimately more affected, with the most notable effects again seen in socialised males. This indicated that response to an organophosphate neurotoxicant was also dependent on sex and socialisation (175).

Hens received both TOCP (single dose of 0.5 ml equivalent to 600 mg/kg bw by gavage) and different nicotinic acid derivates. TOCP caused complete motor paralysis by day 15. A significant alleviation of ataxia was observed when these nicotinic acid compounds were administered daily for 10 days starting 2 days before treatment with TOCP. The onset of paralysis was delayed for several days by these agents, but complete prevention of the neurotoxic symptoms was not achieved. However, the mode of action of this alleviation is unknown (34).

White Leghorn cockerels given 25-800 mg/kg bw of TOCP orally exhibited paralysis (1/4 at the lowest dose, 4/4 at the highest doses). After administration of 1 000 mg/kg bw, a 67 % decrease of plasma cholinesterase activity was observed. Brain and spinal cord acetyl cholinesterase activity decreased with 14 and 32 %, respectively. No neurotoxic effects were observed in cockerels given TMCP or TPCP orally as single doses of 1 000 and 5 000 mg/kg bw or 1 000 mg/kg 5 times on alternate days (84).

In a review paper, Johnson summarised data showing that TOCP at single oral doses of 100-250 and 25-400 mg/kg bw was neurotoxic to the hen. In contrast, TMCP at single oral doses of 1 200 and 2 000-2 500 mg/kg bw was not. Repeated oral dosing of 1 000 mg/kg bw of TMCP (every 2nd day for 5 days) and 210 mg/kg bw for 20 days did not induce a neurotoxic response, whereas a higher total dose of 12 500 mg/kg bw did (presumably 500 mg/kg bw for 25 days) (94, 109). Hens administered TPCP exhibited no neurotoxic response after single doses (1 200 or 2 500 mg/kg) or after repeated dosages up to a total dose of 25 000 mg/kg bw (94, 109).

In a study evaluating neurotoxicological responses of a series of phosphate ester, a behavioural neurotoxic response was observed in 4/4 hens administered 300 mg/kg bw of TOCP for 5 days. Histology was not performed. TCP given to hens in oral doses of 10 000 mg/kg bw twice a day for 3 days resulted in both behavioural (6/6) and histological (6/6) neurotoxic responses (106) (Table 12).

In a review, Weiner and Jortner summarised the research (including non-peer reviewed industrial reports) on OPIDN of triarylphosphates. In one acute study, commercial undiluted TCP (Kronitex® TCP) was marginally neurotoxic to hens at levels of 150-300 mg/kg bw and higher. Another commercial TCP (Durad® 125L) also caused neurotoxic effects (251).

The neuropathic effects of TCP (mixed isomers), TOCP and TPCP were investigated on differentiating mouse N2a neuroblastoma cells. TCP inhibited the outgrowth of axon-like processes following exposures of 24 or 48 hours. Dose-response experiments indicated that TCP and TOCP exhibited similar sustained levels of toxicity after both 24 and 48 hours of exposure. The 50 % inhibitory concentration in the medium was 0.7 mg/l. By contrast, TPCP demonstrated a transient effect on the outgrowth of axon-like processes, which was detectable after 24 but not after 48 hours of exposure. The inhibitory effect on axon outgrowth of TOCP, but not TPCP, was enhanced in the presence of a microsomal activation system (68).

The NTP has performed 13-week and 2-year gavage and feed studies in rats and mice (described below and in Section 10.6). The TCP mixture comprised 18 % dicresyl phosphate esters and 79 % TCPs with 21 % TMCP and 4 % TPCP and no detectable TOCP (< 0.1 %) (174).

Groups of 10 male and 10 female F344/N rats and $B6C3F_1$ mice received TCP in corn oil by gavage at doses of 0, 50, 100, 200, 400 or 800 mg/kg bw for 13 weeks. All rats and mice survived at all dose levels. In mice, forelimb and hindlimb grip strength of 400- and 800-mg/kg males and females was significantly lower than for controls. Forelimb and hindlimb grip strength of 200-mg/kg females and hindlimb grip strength of 200-mg/kg males were also significantly lower than that of controls. There were significant dose-related decreases in serum cholinesterase activities in all dosed groups. The principal lesions occurred in the ovary, adrenal gland, spinal cord and sciatic nerve. Multifocal axonal degeneration of the spinal cord and sciatic nerve was observed in mice receiving 100 mg/kg bw or greater. The number of affected axons generally increased with dose. In rats, the only neurobehavioural measure affected by the exposure was a slight but significant reduction of hindlimb grip strength in female rats receiving 400 and 800 mg/kg bw (174).

Groups of 95 male and female F344/N rats and 95 male and 95 female $B6C3F_1$ mice were fed diets containing TCP for 105 weeks. Rats were fed diets containing 0, 0.075, 0.15 or 0.3 g/kg of the TCP mixture (estimated doses for males were 3, 6 or 13 mg/kg bw/day and for females 4, 7 or 15 mg/kg bw/day). An additional group of animals were given 0.6 g/kg in their diet for 22 weeks and then received only control feed. Hindlimb grip strength was significantly reduced in 0.3-g/kg males and in both sexes at 0.6 g/kg at the 3-month evaluation but not at the 9- and 15-month evaluations. At 9 months, serum cholinesterase activities of 0.15-g/kg males and 0.3-g/kg females were significantly lower than those of controls. At 15 months, serum cholinesterase in all exposed groups of females and in high-dose males were significantly lower than those in the controls (174).

Mice were fed diets containing 0, 0.06, 0.125 or 0.25 g/kg of the TCP mixture (estimated doses for males were 7, 13, 27 mg/kg bw/day and for females 8, 18 or 37 mg/kg bw/day). There were no effects on survival, feed consumption, body weight or clinical findings. Hindlimb grip strength was significantly reduced in the 0.25-g/kg females in the 3-month evaluation but not in the 9- and 15-month evaluations. Serum cholinesterase activities were significantly reduced in a dose-related manner in both sexes at and above 0.06 g/kg at all time points (174).

Hens were exposed to generic aviation engine oil containing 0.5, 1 or 3 % TCP (10, 20 or 60 mg/kg bw/day) by oral gavage 5 days/week for 10 weeks. One group of hens received 0.5 % TOCP (10 mg/kg bw/day) during the same time period. Higher incidences of clinical ataxia and ataxia of greater severity were observed in hens that received 3 % TCP (60 mg/kg bw/day TCP containing 0.24 mg/kg/day TOCP) than in hens that received 10 mg/kg bw/day TOCP in corn oil. A similar pattern was observed regarding inhibition of plasma cholinesterase, brain NTE, and spinal cord NTE activities (Table 10). Thus, the clinical findings and the enzyme inhibitor effects could not be explained by the content of TOCP in TCP. At 10 mg/kg bw of TCP, 1/30 died. None had ataxia or neuropathological lesions. Among animals exposed to 10 mg/kg bw of TOCP, there was no mortality or ataxia. Neuropathological lesions (moderate or severe) were present in 3/10 (70). Synthetic polyol-based lubricating oils containing 3 % of commercial TCP additive were evaluated for neurotoxicity in hens. Groups of 17-20 hens were administered the oils by oral gavage at a dose of 1 000 mg/kg, 5 days/week for 13 weeks. NTE activity in brain and spinal cord of hens dosed with the lubricating oils was not significantly different from saline controls after 6 weeks of treatment. After 13 weeks of dosing, brain NTE was inhibited 32-34 % in lubricant-treated hens. Clinical assessments of walking ability did not indicate any differences between the control group and lubricant-treated hens. Neuropathological examination revealed no alterations indicative of OPIDN. The authors concluded that the results indicated that synthetic polyol-based lubricating oil containing up to 3 % TCP had low neurotoxic potential and should not pose a hazard under realistic conditions of exposure (41).

Table 10. Percentage inhibition of plasma ChE, brain NTE and spinal cord NTE activities in hens given TCP or TOCP in engine or corn oil by oral gavage. Adapted from Freudenthal, 1993 (70).

Exposure (5 days/week, 10 weeks)	Daily dose (mg/kg bw/day)	Plasma ChE (%)	Brain NTE (%)	Spinal cord NTE (%)
Engine oil, 3 % TCP	60	49	77	62
Engine oil, 1 % TCP	20	27	55	34
Engine oil, 0.5 % TCP	10	23[a]	47	24
Engine oil, 0.5 % TOCP	10	41	68	52
Corn oil, 0.5 % TOCP	10	44	71	55
Engine oil, no TCP (control)	0	0	0	0

[a] Non-significant. All other values were significantly different from controls.
ChE: cholinesterase, NTE: neurotoxic or neuropathy target esterase.

In an early study, groups of 3-4 female rabbits were exposed dermally to 0.25, 0.5, 1, 2 or 5 ml (300, 600, 1 200, 2 400 or 6 000 mg) of a commercial TCP mixture for 2 hours/day, 5 day/week for several weeks. Death, which was produced by doses as low as 0.25 ml (300 mg), was preceded by ataxia and tremors. Degenerative changes were seen in the brain of rabbits that died (Treon *et al* 1955, cited in (215)). The study is also described in Section 10.3.

In another study from the 1950s, mortality was very high in rabbits exposed to TCP aerosols at concentrations of 5 900 - 42 200 mg/m^3 for periods of 3 hours to 18 days. The rabbits had considerably increased nasal and oral discharge during and immediately following exposure and respiratory difficulties. Diarrhoea was also seen. Delayed neuropathy was evident, progressing from hyperexcitability to tremors, gait impairment, and in several animals, paralysis of the hind legs. Serum cholinesterase was depressed (Broadhurst *et al* 1951, cited in (215)).

In continuous inhalation studies (36-163 days) conducted with a mist of a triaryl phosphate hydraulic oil (containing TCPs, trixylenyl phosphates and other trialkylphenyl phosphates and with an *ortho*-cresyl content less than 1.5 %) at concentrations of 1.8-110 mg/m^3, 23/27 White Vantress hens exhibited neurotoxic signs at 23-110 mg/m^3, whereas 13/14 birds exposed at 1.8-4.4 mg/m^3 appeared normal. At repeated exposures (8 hours/day, 5 days/week, 6 weeks), neurotoxic signs were noted at 50 mg/m^3 but not at 25 mg/m^3. Demyelination was not demonstrable in nerve tissue of hens exhibiting marked neurotoxicity. Inhalation data for dogs, rabbits, rats and monkeys are presented in Appendix I. Oral data in hens indicated that the minimally effective neurotoxic dosage was 4-5 times that of TOCP (201).

TBEP Groups of randomised female and male Sprague Dawley rats (in total 10 rats/sex, i.e. 1-4 animals/group) were administered a single oral dose of undiluted TBEP (1 000-3 200 mg/kg bw for females, 1 000-9 000 mg/kg bw for males). Physiological parameters were measured in surviving rats 3 weeks following TBEP administration. A significant reduction in caudal nerve conduction velocity was observed in females (1 750-3 200 mg/kg bw) and males (3 200-9 000 mg/kg bw). Light and electron microscopic examination of sciatic nerve sections showed degenerative changes in both myelinated and unmyelinated fibres of female (2 000 mg/kg) and male (6 800 mg/kg) groups. Advanced degeneration was observed only at the highest dose levels of both genders (3 200 mg/kg for females, 8 000 and 9 000 mg/kg for males). Although similar morphological changes were observed in both sexes, females were more susceptible than males to the toxic effects of this compound (127).

In a 14-day repeated dose study, female Sprague Dawley rats were given 0.8 or 1.12 ml/kg bw (800 or 1 140 mg/kg) and male rats 0.8 or 2.14 ml/kg bw (800 or 2 280 mg/kg) of TBEP. Electrophysiological measurements were made on days 15 and 28. A significantly decrease in body weight among low-dose females was observed at day 7 but not at day 14. The conduction velocity in the caudal nerve was significantly lower in high-dose females than in controls after 14 days. The

relative refractory period was longer in low- and high-dose males after 14 days. No morphological changes were found using light or electron microscopy (126).

In another study, male and female Sprague Dawley rats were given 0, 0.25 and 0.5 ml/kg bw (250 and 500 mg/kg) of TBEP, 5 days/week for 18 weeks. Observations were made after 6, 12 and 18 weeks. A few females (2/12) from the high-dose group showed transient muscular weakness and ataxia at the beginning of the experiment, which disappeared 4 weeks later. At the latter half of the study, almost all treated animals seemed affected by TBEP. Tremor, piloerection, lacrimation and increased urination were observed in the high-dose group. Electrophysiological changes were observed at 18 weeks in all dosed animals and included a significant reduction in nerve conduction velocity as well as increased refractory periods. Most of the treated animals exhibited some degeneration of myelin sheaths accompanied by axonal swelling and an advanced stage of degeneration in sciatic nerve, as examined by light and electron microscopy. There was no morphological sex difference. According to the authors, unmyelinated nerve fibres of rats fed TBEP were more affected than those of animals treated with TOCP (124).

In another study performed by the same research team, Sprague Dawley rats were dosed by gavage 0.25 or 0.5 ml TBEP/kg bw/day (250 or 500 mg/kg bw per day). At 18 weeks, there was a 5-7 % lower erythrocyte acetylcholinesterase activity in both dose groups compared to controls in males but not in females. Breathing difficulties and ataxia were observed in both dose groups though the low-dose group was less affected. Tremor, piloerection, lacrimation and increased urination were observed in the high-dose group (122).

Wistar rats (15/dose group) were given a diet containing 0, 0.3, 3 or 30 g/kg of TBEP for 14 weeks. The 0.3 mg/kg diet dose corresponded to 20 and 22 mg/kg bw for males and females, respectively. Suppression of body weight gain was observed in both sexes at 30 g/kg diet. Serum cholinesterase was significantly decreased in both sexes at 3 and 30 g/kg diet (189).

Sprague Dawley rats (20/sex/dose group) were fed diets containing 0.3, 3 and 10 g/kg of TBEP corresponding to 15, 150 and 500 mg/kg bw for 18 weeks. No clinical signs of neurotoxicity were observed. The only neurophysiological alteration observed was reduced caudal nerve conduction velocity in high-dose females. There were no treatment-related changes in peripheral nerve or spinal cord histopathology. In the groups exposed to 150 and 500 mg/kg bw, there was a decrease of plasma cholinesterase activity (Monsanto 1987a, b, cited in (103)).

Hens were killed 24 hours after a single dose of TBEP, TOCP or TBP, equal to the greater of either the LD_{50} or 5 000 mg/kg bw. TOCP resulted in heavy inhibition of the NTE activity but TBEP and TBP did not inhibit the NTE activity to an extent (> 70 %) which earlier was expected to result in OPIDN. TOCP and TBEP decreased plasma cholinesterase activities (Table 11) (32).

In an acute delayed neurotoxicity study in hens, two doses of 5 000 mg TBEP/kg bw were given 21 days apart. Another group of hens were given two dermal doses of 5 000 mg/kg bw. All animals survived. Each dose was followed by an atropine antidote treatment for 5 days. Two hens dosed orally had equivocal

Table 11. Effect of single doses of TOCP, TBEP and TBP on the activity of hen brain NTE, brain AChE and plasma ChE. Adapted from Carrington 1989 (32).

Compound	Single dose (mg/kg bw)	Brain NTE (%)	Brain AChE (%)	Plasma ChE (%)
Control		100	100	100
TOCP	750	8	88	28
TBEP	5 000	102	55	13
TBP	1 500	88	97	269

AChE: acetylcholinesterase, ChE: plasma cholinesterase, NTE: neurotoxic or neuropathy target esterase.

focal swollen axons in the spinal cord. No lesions were observed in the hens dosed dermally. The lesions seen in the control animals and those exposed to TBEP were of minimal severity and representative of spontaneously occurring nervous system lesions in hens of this age (32).

Groups of 5 male and 5 female Wistar rats were exposed for 4 hours to air TBEP concentrations of 3 300, 3 400 or 6 400 mg/m^3. No animal died but at all concentrations the animals exhibited depressed and irregular respiration, increased salivation, sneezing, unsteadiness and tremor. No dose-response information was presented. Symptoms cleared in most animals 9 days later. Body weights did not change and gross necropsy revealed no abnormalities (Hoechst 1989, cited in (103)).

In summary, TBEP was neurotoxic in rats but did not produce OPIDN in hens. Female animals seem to be more susceptible to the neurotoxic effects of TBEP but the results are not consistent.

TBP Male and female adult Sprague Dawley rats received TBP in corn oil by gavage as a single dose (100, 325 and 1 000 mg/kg bw) and repeatedly for 3 months (32.5, 100 and 325 mg/kg bw/day). Behavioural evaluations were performed in both studies and neuropathological evaluations in the 3-month study only. In the acute study, mean body weight gain decreased significantly compared to controls in males at 1 000 mg/kg bw. At the same dose level, transient changes attributable to the general toxicity were noted in forelimb grip strength and mean activity level during the first 24 hours after dosing. In the subchronic study, high-dose (325 mg/kg bw) males and females had significant body weight decreases. Some mortality also occurred at this dosage level. Postdosing salivation was observed rarely at 32.5 mg/kg bw, frequently in the mid-dose group and on almost all occasions at the highest dose. Motor activity levels and qualitative and quantitative functional observational battery measurements were comparable between treatment and control groups, and there were no gross or neurohistopathological findings indicative of treatment-related effects. Based on these study results, TBP was considered not neurotoxic to rats following either acute or subchronic exposures (80).

TBP was administered orally to male and female Sprague Dawley rats for 14 consecutive days at doses of 0.28 and 0.42 ml/kg bw (270 and 410 mg/kg bw). A significant reduction in conduction velocity of caudal nerve was observed in high-dose males. Electron microscopic examination of sciatic nerve showed

morphological changes such as retraction of Schwann cell processes surrounding unmyelinated fibres in both sexes of high-dose groups (125).

In a 10-week toxicity study, male Wistar rats (n=10-11/group) were given TBP (> 97 % purity) via the diet at doses of 5 and 10 g/kg (equivalent to approximately 0, 500 or 1 000 mg/kg bw/day (44)). The cholinesterase activity in the brain was significantly increased in both treatment groups, but no significant changes were observed in serum and liver cholinesterases activities compared to the control group (177).

Carrington and co-workers assessed the delayed neurotoxicity of some phosphate esters including TBP. To determine the dosage to be used, hens were given gelatin capsules of TBP of varying doses (from 500 to 5 000 mg) to determine LD_{50}, which was 1 500 mg/kg bw. The animals exhibited signs of cholinergic toxicity, including salivation, diarrhoea, and impaired respiration, which lasted for 2-4 days. Animals surviving the period of acute toxicity appeared normal thereafter and no clinical signs of OPIDN were observed. Enzyme activities were investigated in 5 hens 24 hours after a single oral dose of 1 500 mg/kg bw. The activity of brain NTE or of brain acetylcholinesterase in the treated group was not significantly different from the controls. Contrary to other phosphate triesters (TOCP and TBEP), TBP caused a significant increase of plasma cholinesterase activity (Table 11). In addition, 20 hens were given 2 oral doses of TBP gelatine capsules (98 % purity), equivalent to the LD_{50} (1 500 mg/kg bw), 21 days apart. Hens were treated with atropine sulphate (15 mg/kg bw) 3 times daily for 5 days following dosing to protect against cholinergic effects. The animals were killed 21 days after the second dose. The lesions seen in the control animals and those exposed to TBP were of minimal severity and representative of spontaneously occurring nervous system lesions in hens of this age. None of the hens exhibited treatment-related clinical signs or peripheral nerve, spinal cord or brain injury. The conclusion was that TBP do not produce OPIDN (32, 33).

Groups of approximately 10 hens were exposed orally to some phosphate esters. Undiluted corn oil solutions with 1 840 mg TBP were administered for two consecutive days. The birds (n = 9) were observed daily for possible neurotoxic reactions throughout the total 42-day test period. The hens were sacrificed on test day 42 and subjected to a gross pathologic and microscopic examination of the brain, sciatic nerve and spinal cord. No signs of neurotoxicity were observed regarding behaviour or histology (Table 12) (106).

Intratracheal administration of 5 µl (5 mg) TBP in rats (body weight 280-300 g, estimated dose 17 mg/kg bw) resulted in a mild inhibition of serum cholinesterase (20 %) on the first day only (191). The study is also described in Section 10.2.

Rats and rabbits were exposed to TBP concentrations in air up to 4.8 mg/m^3, 5 hours/day, 5 days/week for 4 months. The cholinesterase activity in erythrocytes or serum was unaffected. Exposure to 13.6 mg/m^3 caused a 33 % inhibition after 3 months (Kalinina 1971, cited in (47)). According to DFG, the study was insufficiently documented as there were no data for control animals, number or type of animals used or analytical monitoring of the exposure level (47).

Skydrol 500B-4 is a fire resistant hydraulic fluid composed of 80-90 % phosphate esters including dibutyl phenyl phosphate and TBP. Rats inhaled an aerosol of 0, 5, 100 and 300 mg/m^3, 6 hours/day, 5 days/week for 6 and 13 weeks. Nasal discharge was noted among 47/50 mid-exposure rats and 50/50 high-exposure rats during the first week of exposure. The incidence of the nasal discharge decreased over the course of the study. Plasma cholinesterase levels decreased significantly among high-exposure females but not among male rats (81).

In summary, TBP produced neurotoxic effects in one study in rats but has not produced OPIDN in hens.

TCEP The NTP has performed 16-day, 16- or 18-week and 2-year-studies in rats and mice administered TCEP by gavage (described also in Sections 10.3 or 10.6).

In the 16-day study, groups of five F344/N rats and B6C3F$_1$ mice of each sex received TCEP in corn oil by gavage 5 days/week with 12 doses over 16 days. Rats were given 0, 22, 44, 88, 175 or 350 mg/kg bw. No clinical signs of toxicity were observed. Serum cholinesterase activity was significantly reduced in female rats administered 175 mg/kg and 350 mg/kg. The activity was approximately 80 % of that of controls. No gross or histopathological lesions attributable to TCEP exposure were observed. Mice received 0, 44, 88, 175, 350 or 700 mg/kg bw. Mice given 350 or 700 mg/kg bw exhibited ataxia and convulsive movements during the first 3 days of dosing. The serum cholinesterase activities were not considered chemical-related. No effects on body or organ weights were observed and no histopathological lesions attributable to TCEP (173).

In the subchronic study, groups of ten F344/N rats of each sex received 0, 22, 44, 88, 175 or 350 mg/kg bw of TCEP in corn oil by gavage 5 days/week for 16 weeks (female) and 18 weeks (male). Female rats receiving 175 or 350 mg/kg bw experienced occasional periods of hyperactivity after dosing. Periodic convulsions were noted in high-dose females during week 12. Female rats receiving 175 or 350 mg/kg bw had serum cholinesterase activity levels that were 75 % or 59 % of the control value, respectively ($p < 0.01$). The serum cholinesterase activity was not reduced in male rats. Necropsy examination showed no gross lesions attributable to chemical exposure. However, necrosis of neurons of the hippocampus was observed histologically in the brains of 10/10 females and 2/10 males receiving 350 mg/kg TCEP and in 8/10 females receiving 175 mg/kg. In the more severe lesions, mineral deposits were present in the affected areas of the brain. In the high-dose females, neuronal necrosis was also observed in the thalamus (149, 173).

In the corresponding study on mice, groups of ten B6C3F$_1$ mice of each sex received 0, 44, 88, 175, 350 or 700 mg/kg bw of TCEP in corn oil by gavage 5 days/week for 16 weeks. Serum cholinesterase activities were not different from controls. Necropsy examination showed no gross lesions attributable to chemical exposure (173).

In the chronic study, groups of 60 male and 60 female F344 rats received 0, 44 or 88 mg TCEP/kg bw, 5 days/week by gavage for 103 weeks. At 103 weeks, there were no adverse effects on the body weight gain and no clinical signs of

toxicity. A marked increase in the incidence of degenerative lesions of the brain stem and cerebrum (thalamus, hypothalamus and basal ganglia) such as gliosis, haemorrhage, necrosis and mineralisation was noted at 88 mg/kg in approximately 40 % of females compared to 2 % of controls. Similar lesions occurred in a few male rats, but these lesions were not clearly related to exposure (150, 173).

TCEP was given to male ICR mice in order to study spontaneous ambulatory activity and to examine the neurochemical mechanism of this effect. The ambulatory activity was measured for 2 hours after exposure in 10-minute intervals. Single intraperitoneal injection of 200 mg/kg bw of TCEP increased ambulatory activity. No effect was seen at 50 mg/kg bw, whereas the activity was higher for the first 10 minutes after administration of the 100 mg/kg bw dose. Neither mecamylamine (nicotinic cholinergic antagonist) nor scopolamine (muscarinic cholinergic antagonist) affected the activity response to TCEP. On the other hand, diazepam (benzodiazepine agonist), muscimol (γ-aminobutyric acid (GABA)A agonist) and baclofen ((GABA)B agonist) all attenuated the effect of TCEP. Diazepam and muscimol blocked the increase of activity within the first 10 minutes after administration of TCEP. These drugs did not attenuate the activity increasing effect of scopolamine, suggesting that the mechanism of TCEP action is distinct from that of scopolamine. Muscimol and baclofen, but not diazepam, inhibited the activity increasing effect of the dopaminergic agonist apomorphine, suggesting that dopamine is involved in the control of activity and that GABA can affect activity through interaction with dopaminergic neurons. These results suggest that TCEP acts as a GABA antagonist and not as a cholinergic agonist, and that TCEP increases activity in ICR mice through a GABAergic mechanism (236).

Female F344 rats gavaged with a single dose of 275 mg TCEP/kg bw convulsed within 60-90 minutes and had extensive loss of CA1 hippocampal pyramidal cells when examined after 7 days. The seizure-related and neurohistological effects of TCEP were significantly attenuated by pre-treatment with atropine or chlordiazepoxide, suggesting that the hippocampal damage was related to the seizures produced by TCEP. In a second experiment, female rats were exposed to 275 mg/kg bw. Three weeks after dosing, the animals were trained on a spatial memory task in a water maze. The exposed rats were consistently impaired in performing a repeated acquisition task in the water maze. These data support the conclusion that the hippocampus is intimately involved in spatial memory in rats (230).

Single administration of TCEP (175, 350 or 700 mg/kg bw) induced seizures in rats. All animals receiving 700 mg/kg by gavage exhibited seizures within 1 hour after dosing. Most animals receiving 350 mg/kg also had seizures within 1 hour but not as severe as the high-exposed group. Seizures in females progressed over 12 hours and were occasionally noted 24 hours after dosing. Males experienced seizure activity within 1 hour after receiving 350 mg/kg but showed no signs of seizure activity 4 hours following dosing. Only mild occasional seizures were present at 175 mg/kg. In an experiment with repeated doses, all female rats dosed with 350 mg/kg/day showed seizures and died within 7 days. The authors concluded that the low levels of TCEP found in brain tissue at the time of seizures

indicated that TCEP is a potent neurotoxicant. There was no sex difference in the brain TCEP concentration (83).

White Leghorn hens (12 months old) were orally exposed to 420 mg TCEP/kg bw/day for 5 consecutive days. After 21 days of observation, there were no signs of neurotoxicity as compared to TOCP (positive control), which induced inability to walk, hypertension, ataxia and prostration (Bullock and Kamienski 1972, cited in (102)).

The neurotoxic effects of TCEP were evaluated in adult (12-14 months old) White Leghorn hens given 14 200 mg/kg bw of the chemical in corn oil followed 3 weeks later by a second dose. Four out of 18 treated hens died within 6 weeks of the first dose. No microscopic changes in brain, spinal cord or sciatic nerve were found. In a separate group of hens, the activities of brain NTE and plasma cholinesterase were determined 24 hours after the first dose of TCEP. Plasma cholinesterase activity was inhibited by 87 % and brain NTE activity by 30 %. No delayed neurotoxicity was observed (209).

In summary, TCEP was neurotoxic in rodents but did not produce OPIDN in hens. Female rats appear to be more sensitive regarding effects on the nervous system than males.

TDCPP Chicken (sex not given) exposed orally to TDCPP at doses of 600, 1 200, 2 400 or 4 800 mg/kg bw for 5 days exhibited leg and wing weakness at doses of 1 200 mg/kg or more and 100 % mortality at 4 800 mg/kg. TDCPP was estimated to have 5 % of the activity of TOCP in producing paralysis. No further details were given (102, 235).

White Leghorn hens, 12 months old, were orally exposed to 420 mg/kg bw of TDCPP for 5 consecutive days. After 21 days of observation, there were no signs of neurotoxicity, whereas TOCP, used as a positive control, induced inability to walk, ataxia and prostration (Bullock and Kamienski 1972, cited in (102)).

Groups of 50 male and 50 female Sprague Dawley rats received approximately 0, 5, 20 and 80 mg TDCPP/kg/day by dietary administration for 2 years. There was a slight decrease in plasma cholinesterase activity in females at 80 mg/kg, although erythrocyte acetylcholinesterase was unaffected. No further sex differences were reported (Aulette and Hogan 1981, cited in (102)). The study is also described in Section 10.6.

TEHP Hens were administered a single dose of 250, 500 or 1 000 mg TEHP/kg bw by gavage. The animals were observed for 2 months and examined for neurotoxicity twice weekly. No abnormalities in behaviour were detected. A single intramuscular injection of the same doses did not induce any signs of intoxication (Kimmerle 1958, cited in (103)).

TEHP was studied for its neurotoxic effects in four groups of female chickens who received a single dose into the crops as follows: 0, 500 or 2 500 mg TEHP/kg bw or 500 mg TOCP/kg bw as a positive control. The animals were observed for 4 weeks. The positive controls (TOCP) had apparent weight loss by the end

of the first week and muscular weakness and ataxia were evident by the 12th day. The chickens in the TEHP exposed group and unexposed controls appeared normal and maintained or gained weight throughout the study. There were no macroscopic or microscopic signs of neurotoxicity (140).

Two cats were administered 1.0 ml (926 mg) TEHP/kg bw by gavage, 5 days/week for 4 weeks. Measurements of erythrocyte acetylcholinesterase activity during the test period revealed no inhibitory effects (Bayer 1958, cited in (103)).

In a 3-month inhalation study, groups of 20 male guinea pigs each were exposed to TEHP aerosol for 6 hours/day, 5 days/week for a total of 60 exposures. The mean concentrations were 0, 1.6 and 9.6 mg/m^3. The mean particle size was 3.8 µm, respectively. Plasma and erythrocyte cholinesterase activities were unaffected in terminal blood samples. Histopathological examination of the spinal cord and sciatic nerve showed no pathologic changes (140).

In a similarly designed study, groups consisting of equal numbers of males and females and comprising 2 dogs and 2 rhesus monkeys were exposed to TEHP aerosols. Mean exposure levels during the 12-week period were 10.8, 26.4 and 85.0 mg/m^3, respectively. The median particle size was 4.4 µm. Plasma and erythrocyte cholinesterase activities were unaffected. No effects were detected in the performance of monkeys in a visual discrimination test. The performance of dogs trained in conditioned avoidance deteriorated as the exposure concentration increased. The percent missed avoidance was 18 % in the high-dose group, 10 % in the mid-dose group, 0 % in the low-dose group and 5.8 % in controls (140). The study is also described in Section 10.3.

In a 2-year NTP study, TEHP was administered 5 days/week for 103 weeks to groups of 50 male and 50 female F344/N rats and B6C3F$_1$ mice. Male rats received 2 000 or 4 000 mg/kg bw, female rats received 1 000 or 2 000 mg/kg bw and male and female mice received 500 or 1 000 mg/kg bw. No nervous system lesions were observed at histopathological examination (172). The study is described in more detail in Section 10.6.

TEP The narcotic effect of TEP was tested in rats and mice by intraperitoneal injections. The righting reflex was considered as "lost" when an animal remained on its back for 30 seconds or longer. The doses effective for 50 % of the exposed populations (ED_{50}s) for loss of righting reflex determined with rats were 333 mg/kg bw for females and 412 mg/kg bw for males. The durations of the loss of righting reflex were about equal in males and females. Brain cholinesterase activity was 85 % of normal one hour after administration of 500 mg/kg bw. The ED_{50} doses for loss of righting reflex was significantly higher for weanling rats compared to adult rats. Male mice were less sensitive than rats to narcosis produced by TEP. The ED_{50} for male mice was 600 mg/kg bw. Female mice were not tested (21). Weanling and adult rats regained their righting reflex when the plasma concentration of TEP was 0.8 µmol/0.2 µl after intraperitoneal administration of 500 mg/kg bw of TEP. The narcosis was shorter in weanlings as they regained their righting reflex after 11 minutes as compared to 36 minutes in adults (22).

TEP was given intravenously to female rats. 500 mg/kg bw resulted in deep anaesthesia for 4 minutes and weakness and incoordination for 2-3 hours. A doubled dose (1 000 mg/kg bw) resulted in deep anaesthesia with superficial respiration for about 1 hour and very pronounced weakness and dyspnoea for more than 12 hours. There were no cholinergic symptoms at any of the doses (247).

The serum cholinesterase activity was normal in Wistar male rats fed pellet diets containing 0 or 5 g/kg for 9 weeks (178) corresponding to approximately 500 mg/kg bw/day (44).

TIPP Tri-*ortho*-isopropylphenyl phosphate was given to hens. One oral dose of 600 mg/kg bw or 1 000 mg/kg bw for 4 days did not produce OPIDN. The 600-mg/kg bw dose produced a slight (12 %) decrease of NTE activity, whereas the 1 000-mg/kg bw doses had no effect on the NTE activity. A single dose of *ortho*-isopropylphenyl diphenyl phosphate at 1 200 mg/kg bw caused OPIDN and a 90 % decrease of NTE activity. Half the dose (600 mg/kg bw) caused an NTE activity decrease of 84 % with no OPIDN. Di-*ortho*-isopropylphenyl phenyl phosphate gave an ambiguous result regarding OPIDN at a single dose of 1 200 mg/kg bw and an 85 % decrease in NTE activity. The lower dose (600 mg/kg bw) caused no OPIDN and a 39 % decrease in NTE activity. Tri-*meta*-isopropylphenyl phosphate, tri-*para*-isopropylphenyl phosphate, di-*para*-isopropylphenyl phenyl phosphate and *para*-isopropylphenyl diphenyl phosphate given perorally to hens at 1 000 mg/kg bw as a single dose did not produce OPIDN (109).

Tri-*ortho*-isopropylphenyl phosphate and *para*-isopropylphenyl diphenyl phosphate were not neurotoxic when given to hens at a dose of 1 000 mg/kg bw and 10 000 mg/kg bw, respectively, twice daily for six days. However, hens receiving 1 000 mg/kg bw/day of *ortho*-isopropylphenyl diphenyl phosphate twice daily for six days exhibited signs of OPIDN (Table 12) (106).

Male Long Evans rats were given single oral doses of 2 000 mg/kg bw of 4 different triisopropylphenyl phosphate products from commercial suppliers or physiological saline for negative control. After 24 hours, the inhibition of serum cholinesterase activity was 81-90 % and that of brain NTE was 35-60 %. The corresponding inhibition for TOCP was 98 % and 93 %, respectively (141).

In a review, Weiner and Jortner summarised the research on organophosphate-induced delayed neurotoxicity of triarylphosphates. In general, commercial isopropylated triphenyl phosphates (Kronitex® 50, 100, 200, 300; see Chapter 2) were negative when tested at doses of 2 000-3 000 mg/kg bw in acute OPIDN hen studies. The most highly substituted product, Kronitex 300, did not produce signs of neurotoxicity in hens at doses of 2 000, 4 000 and 8 000 mg/kg bw and was thus not considered neurotoxic. At a higher dose (16 000 mg/kg bw), 3/10 exhibited minimal and transient ataxia with general signs of toxicity. Kronitex® 200 gave equivocal results when given as a single dose of 20 000 mg/kg bw (1/10 hens exhibited ataxia). Based on two acute hen OPIDN studies, it was concluded that the results on Kronitex® 100 did not reveal neurotoxicity when doses were at or below 2 000 mg/kg bw. The results at higher doses were considered difficult to

interpret because of e.g. inconsistent dose-response and excessive doses often producing general toxicity. Kronitex® 50 was administered orally in hens at doses of 2 000-8 000 mg/kg bw. The product showed weak neurotoxicity at 2000 mg/kg bw. Nervous system lesions were noted in hens dosed at 4 000, 6 000 and 8 000 mg/kg without a clear dose-response relationship. This product was chosen for a 90-day subchronic OPIDN study. Groups of 20 hens were administered doses of 0, 10, 20, 90 or 270 mg/kg bw of Kronitex® 50 in corn oil by gavage 5 days/week for 13 weeks. The NOAEL was 20 mg/kg bw/day. At 90 mg/kg bw, an increased incidence of ataxia (4/20) and lesions in the nervous system (5/10) were observed. At 270 mg/kg bw, the incidences of ataxia and lesions were higher (9/20 and 9/10, respectively) (251).

Reofos 65® is a mixture containing 23 % TPP, 33 % isopropylated triphenyl phosphate (24 % *ortho*-isopropylphenyl diphenyl phosphate, 8 % di-*ortho*-isopropylphenyl phenyl phosphate and 1 % tri-*ortho*-isopropylphenyl phosphate). Reofos 65® caused no clinical neurotoxic effect in hens after single oral doses of 5 000, 10 000 and 15 000 mg/kg bw. Redosing at day 22 did not result in clinical delayed neurotoxicity, but minor histopathological changes were found in the spinal cord at 10 000 and 15 000 mg/kg bw and in the peripheral nerves at all doses given (161).

Hens treated twice 3 weeks apart with doses of 12, 370 or 11 700 mg/kg bw of isopropylated triphenyl phosphate (described in Table 3) showed no clinical signs of delayed neurotoxicity and only mild signs of general toxicity. Furthermore, there were no neurohistological changes suggestive of delayed neurotoxicity. However, the mixture produced dose-dependent inhibitions of plasma cholinesterase and brain NTE activities (doses as above, and in addition 180 mg/kg bw) starting at 180 and 370 mg/kg bw, respectively (208).

To conclude, studies on mixed isopropylated triphenyl phosphates indicate that some induce OPIDN in hens but are less potent than TOCP.

TMCPP In a 90-day dietary study, male and female rats were given diets containing 0.8-20 g/kg (corresponding to approximately 40-1 000 mg/kg bw/day (44)) of Fyrol PCF containing ca 70 % tris(1-chloro-2-propyl) phosphate and ca 22 % tris(2-chloropropyl) phosphate. Brain, plasma or erythrocyte cholinesterase activities were unaffected by treatment (Stauffer 1981a, cited in (238)).

Groups of rats fed *ad libitum* for 14 days at levels of 4.2, 6.6, 10.6 and 16.6 g Fyrol PCF/kg diet (same composition as in the study above) presented no treatment-related changes in cholinesterases activity (Stauffer 1980a, cited in (102, 238)). The dietary levels correspond to 420, 660, 1 060, 1 660 mg/kg bw (44). The study is also described in Section 10.3.

The neurotoxic potential of Fyrol PCF or tri(2-chloropropyl) phosphate, i.e. presumably tris(1-chloro-2-propyl) phosphate, was evaluated in White Leghorn hens. A group of 18 hens received an initial oral dose of 13 200 mg/kg bw followed by the same treatment 3 weeks later. The animals were sacrificed 3 weeks after the second dose. No behavioural or histological evidence for delayed

neurotoxicity was seen. In a separate group of hens, there was no significant inhibition of brain NTE and plasma cholinesterase activities as determined 24 hours after the first dose of Fyrol PCF (209).

Adverse clinical signs including depression and intermittent muscle spasms were observed among rats after single oral dosing of 464 mg Fyrol PCF/kg bw. Higher dose levels (1 260 mg/kg bw in females and 2 000 mg/kg bw in males) induced spasms, salivation, ataxia and spasmodic jumping (Stauffer 1970, cited in (238)).

TPP White Leghorn cockerels given 500 mg/kg bw subcutaneously or 1 000 mg/kg bw orally did not exhibit paralysis. After oral dosing, a 35 % decrease of plasma cholinesterase activity 24 hours after administration was observed. Brain and spinal cord acetylcholinesterase activity decreased with 2 and 24 %, respectively (84).

Inhalation exposure of mice (n = 5-7) to 363 and 757 mg/m^3 for 2-6 hours resulted in slightly decreased whole blood cholinesterase activities, significant only after exposure to the highest level for 2 hours. The animals were prevented from preening and therefore ingestion of TPP. In addition, mice were administered single oral or intraperitoneal doses of TPP (0, 10, 50, 100, 200 and 500 mg/kg bw). After 4 hours, the cholinesterase (not specified) activity in whole blood decreased in all exposed groups. After oral dosing, the cholinesterase activities were 87, 89, 61, 54 and 30 %, respectively. The decrease in cholinesterase activity was more pronounced when corresponding doses (on weight basis) of TOCP were given. In 1-2 cats given a single intraperitoneal dose of TPP (100, 200, 300 and 400 mg/kg bw), neuromuscular signs were observed from 200 mg/kg bw (218).

In a limited study, cats (n = 1-2) were given subcutaneous doses of 400, 700 or 1 000 mg/kg bw of TPP (99.99 % purity). At the lowest dose, animals did not become ataxic. Histological examination did not reveal any evidence of axon degeneration or demyelination in the spinal cord at any dose level. Thus, there was no evidence of OPIDN. Plasma and erythrocyte cholinesterase activities (investigated in the 700-mg/kg group only) were not different from controls (256).

A group of 9 hens were exposed orally to 5 000 mg TPP/kg bw in corn oil (the maximum feasible dosage) twice a day for 6 days. Birds were observed daily for possible neurotoxic reactions throughout the total 42-day test period. Hens were sacrificed on test day 42 and subjected to gross pathologic and microscopic examinations of the brain, sciatic nerve and spinal cord. No signs of neurotoxicity or OPIDN were observed regarding behaviour or histology (Table 12) (106).

Table 12. Delayed polyneuropathy of some phosphate esters in hens (106).

Compound	Cumulative dose (g/kg bw)	Neurotoxic response (no. of positive/no. of birds)	
		Behaviour	Histology
TOCP	1.5	4/4	-
TCP	60	6/6	6/6
TBP	3.7	0/9	0/9
Tri-*ortho*-isopropyl phenyl phosphate	12	0/10	0/10
Ortho-isopropylphenyl diphenyl phosphate	12	4/9	5/9
TPP	60	0/9	0/9

Young male Sprague Dawley rats were fed diets containing TPP at levels of 0, 0.25, 0.50, 0.75 or 1.0 % for 4 months. The calculated average doses were 161, 345, 517 and 711 mg/kg bw/day. Treatment-related decrements in growth, in the absence of changes in food consumption, were found at all dietary levels from 0.5 % and above. At approximately monthly intervals, a battery of behavioural tests was used to assess different facets of neuromotor function including motility, balance, coordination and muscular strength. None of the behavioural measures used were affected by the treatment (203).

Wistar rats were administered a single intraperitoneal injection of a commercial cresyl diphenyl phosphate preparation (75, 150 or 300 mg/kg bw) containing approximately 35 % of TPP, 45 % of cresyl diphenyl phosphates, 18 % of dicresyl phenyl phosphates and 2 % of TCP. The product was almost free of the *o*-cresyl isomers as revealed by the analysis of its alkaline hydrolysis products. The plasma cholinesterase activity was significantly inhibited 4 and 24 hours (38 % and 26 %, respectively) after the injection of 300 mg/kg bw, but the effect levelled off. Injection of 150 mg/kg also caused a significant decrease, whereas 75 mg/kg did not. No effects on the activities of cerebral and muscle acetylcholinesterase were observed. The treatment (300 mg/kg) inhibited a brain diesterase (2',3'-cyclic nucleotide 3'-phosphohydrolase) throughout the 2-week observation period and was associated with demyelination in peripheral nerves (244). Other components than TPP may have contributed to the effects of this mixture. The study is also described in Section 10.2.

Effects of Reofos® 65, a mixture containing 23 % TPP and 33 % isopropylated triphenyl phosphate is described under the sub-heading TIPP.

Thus, pure TPP is not neurotoxic but commercial products may contain derivates generating OPIDN.

10.5 Mutagenicity and genotoxicity

In summary, TDCPP was genotoxic in bacterial tests, showed equivocal results in *in vitro* mammalian tests and negative results in standard *in vivo* tests. *In vitro* tests of mutagenicity regarding TCEP were inconsistent and an *in vivo* bone marrow micronucleus test gave equivocal results. TMCPP was not genotoxic in bacterial tests, showed negative results in *in vivo* tests, but some *in vitro* mammalian tests showed equivocal results. TCP, TBEP, TBP, TEHP, TEP, TIPP and TPP were negative in bacterial tests when the doses were below the bacteriotoxic effect.

TCP (100 to 10 000 µg/plate) was tested in two laboratories for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537. No induction of gene mutations was observed in either laboratory in any of the strains (174).

In cytogenetic tests with cultured Chinese hamster ovary (CHO) cells, TCP did not induce sister chromatid exchanges (SCEs) with (16-5 000 µg TCP/ml) or without (0.05-16 µg TCP/ml) Aroclor 1254-induced male Sprague Dawley rat liver S9. TCP did not induce chromosomal aberrations with (160-5 000 µg TCP/ml) or

without (50-5 000 µg TCP/ml) S9. No TCP-induced cell cycle delay was observed in either of these two assays (174).

Male F344 rats were treated orally for 10 days with TOCP (50 mg/kg bw) and DNA was isolated from liver, kidney, lung, heart, brain and testes 1, 4, 7 and 28 days after giving the last dose. Analysis by ^{32}P-postlabelling revealed that two adducts were present in the DNA isolated from liver, kidney, lung and heart 1 day after giving the last dose. DNA adducts were not detected in the brain and testes. The adduct pattern after *in vivo* treatment with TOCP was identical with that found in bacteria and hepatoma cells treated with the TOCP metabolite 2-phenoxy-4H-1,3,2-benzo-dioxaphosphorin 2-oxide (demethylated saligenin phosphate), the major adduct being a cytidine adduct and the minor an uridine adduct. Both DNA adducts persisted in the lungs for the entire observation period, whereas in the kidney only the cytidine adduct could be detected 28 days after the last dose of TOCP. In liver and heart, the adducts were detectable only on the first day after completion of the treatment. The results indicate that TOCP may pose a genotoxic potential (151).

TBEP was not mutagenic in a test performed with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 (concentrations not given) with and without metabolic activation (MacKeller 1978, cited in (103)).

TBEP (0, 50, 100, 500, 1 000, 5 000 and 10 000 µg/plate) was tested for mutagenic activity with *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 in the presence and absence of rat liver S9 metabolic system, in comparison with positive controls. TBEP did not cause any mutagenic response either with or without metabolic activation (Monsanto 1984c, cited in (103)).

TBEP was not mutagenic in a CHO/HPRT (hypoxanthine-guanine phosphoribosyl transferase) mammalian cell forward gene mutation assay at 50, 100, 150, 225 and 300 µg/ml with S9 or at 5, 50, 75, 100 and 130 µg/ml without S9 (Monsanto 1985a, cited in (103)).

TBP was tested for mutagenicity at concentrations up to 100 µl/plate (diluted with dimethyl sulfoxide) with *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1538 in the presence and absence of metabolic activation by Aroclor induced rat liver S9 fraction. TBP did not produce a positive response in any strain with metabolic activation. Strains TA1535, TA1537 and TA1538 without metabolic activation produced twice the number of revertants per plate compared to the solvent control for at least three of the five test concentrations, but no dose-response relationship was observed (US EPA 1978, cited in (101)).

TBP was tested for mutagenic effects in a *Salmonella*/microsome test both with and without S9 mix at doses of up to 12.5 mg/plate using four *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537. Doses up to 120 µg/plate produced no bacteriotoxic effects. At high concentrations, there was marked strain-specific bacterial toxicity so that only the range up to 500 µg/plate could be evaluated. There were no indications that TBP had any mutagenic effect (Bayer 1985, cited in (101)).

In a Russian study, TBP was reported to be mutagenic in the Ames test with *Salmonella typhimurium* strains TA1535 and TA1538 at concentrations of 500 and 1 000 µg/plate both with an without metabolic activation. No mutagenicity was noted at concentrations below 100 µg/plate (Gafieva and Chudin 1986, cited in (101)).

Testing TBP at doses of 97 to 97 000 µg/plate both with and without a metabolising system (S9 mix) on the *Salmonella typhimurium* strains TA98, TA100, TA1537 and TA1538 confirmed the lack of mutagenic activity (FMC 1985b, cited in (101)).

TBP was also tested for mutagenicity in four bacterial strains, *Salmonella typhimurium* TA102 and TA2638 and *Escherichia coli* WP2/pKM101 and WP2 *uvr*A/pKM101 at doses of 31-5 000 µg/plate. TBP was not mutagenic in this assay but was toxic at the highest doses (249).

Tests with TBP on *Escherichia coli* strains WP2, WP2uvrA, CM561, CM571, CM611, WP67 and WP12 showed no mutagenic effect after 48 or 72 hours of incubation at 37 ^{o}C (77).

TBP was not mutagenic when tested in the HPRT mutation assay in CHO cells, both with and without metabolic activation. Cell cultures were exposed for 5 hours at 0.05-0.11 µl/ml without activation and at 0.06-0.15 µl/ml with S9 activation. No increases of chromosome aberrations compared to negative controls were observed in metaphases evaluated 12 hours after treatment initiation in CHO cells exposed to TBP at 0.013-0.15 µl/ml for 10 hours without activation or at 0.01-0.15 µl/ml for 2 hours with S9 activation (presented as an abstract) (16).

TBP was not mutagenic in recessive lethal mutation tests in *Drosophila melanogaster* (77).

In an *in vivo* cytogenetics study, male and female rats were dosed orally with up to 1 200 mg/kg of TBP in corn oil. Bone marrow was collected and evaluated after 12, 24 and 36 hours. No increases in chromosome aberrations due to TBP were observed. TBP was not genotoxic *in vivo* under these conditions (presented as an abstract) (16).

TCEP was not mutagenic in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 at dose levels up to 5 000 µg/plate both with and without metabolic activation with Aroclor 1254 induced rat liver S9 (Simmon *et al* 1977, cited in (102)).

Negative results were obtained when TCEP was tested at doses of 3.3, 10, 33 and 333 µg/plate in liquid pre-incubation assays employing *Salmonella typhimurium* TA1535, TA1537, TA98 and TA100 both with and without a metabolic system from Aroclor 1254 induced rat liver or Syrian hamster liver S9 (Haworth *et al* 1983, cited in (102)).

In V79 cells, TCEP (1 µM-1 mM) did not induce DNA strand breaks in the alkaline version of the Comet assay neither without an external enzymatic metabolising system nor in the presence of rat liver S9 mix. No mutagenic potential

could be detected for TCEP in eight *Salmonella* strains using concentrations up to 1 mM in the presence or absence of S9 (71).

In contrast, TCEP at dose levels of 285, 755, 2 850 and 8 550 µg/plate produced a dose-related increase in mutations (with a maximum 7.6-fold increase of revertants over the control at 2 850 µg/plate) in *Salmonella typhimurium* TA1535 in the presence but not in the absence of metabolic system from Kanechlor 500-induced Wistar rat liver S9. The same doses produced a dose-related increase in mutations in TA100 with a maximum 1.8-fold increase in revertants at 2 850 µg/plate (Nakamura *et al* 1979, cited in (102)).

TCEP was tested for chromosomal aberrations and SCE in CHO cells both with and without an exogenous metabolism system from Aroclor 1254 induced Sprague Dawley rat liver. The test doses for the cells varied from 5 to 1 600 µg/ml. TCEP did not induce chromosomal aberrations. The results of the SCE test were regarded as equivocal because a positive response was seen only in one trial with S9 fraction at 500 and 1 600 µg/ml but was not observed in a repeated trial under the same conditions (Galloway *et al* 1987, cited in (102)).

TCEP (0, 500, 1 000 and 2 000 µg/ml) did not significantly increase the number of 6-thioguanine-resistant mutants in V79 hamster cells without S9 (190).

TCEP was tested for SCEs in V79 hamster cells in two separate experiments. The first experiment was performed at concentrations of 343, 490, 700 and 1 000 µg/ml. A statistical increase in the number of SCEs was noted at 700 and 1 000 µg/ml with S9 (3-methylcholantrene-induced rat liver) and at 700 µg/ml without S9 (1 000 µg/ml was not tested without S9). In the second experiment, TCEP was tested without S9 at 2 000 and 3 000 µg/ml and was positive at both concentrations. However, 3 000 µg/ml caused cytotoxicity (190).

In the presence of S9 from methylcholantrene-induced Wistar rat livers, TCEP at 900 and 1 500 µg/ml gave a negative result in a transformation assay using C3H10T1/2 cells (102).

A high level of transformation of Syrian hamster embryo cells was observed with TCEP at 400 and 500 µg/ml. The two highest concentrations (600 and 800 µg/ml) were cytotoxic and no transformation was seen at these concentrations (190).

TCEP caused a dose-related (343-1 000 µg/ml) increase in the incidence of SCEs in the Chinese hamster V79 cell line, but doses from 500 to 2 000 µg/ml did not induce mutations at the HPRT locus in the same cell line (190).

TCEP was administered intraperitoneally at dose levels of 62.5, 125 and 250 mg/kg bw to groups of male and female Chinese hamsters. No clear dose-dependent increase in the number of micronuclei isolated from bone-marrow cells was seen. However, in some of the dose groups an approximate doubling in the number of micronuclei was noted (in females at 62.5 and 125 mg/kg bw and in males at 250 mg/kg bw) (190).

TCEP gave a negative response in the w/w+ bioassay for somatic cell damage in *Drosophila melanogaster* when tested at doses of 2.5-40 mM (258).

TDCPP has been investigated several times in bacterial gene mutation studies using the *Salmonella*/microsome mutation test. The compound was tested (10-10 000 µg/plate) in 3 different laboratories using strains of TA100, TA1535, TA98, TA97 (2 laboratories) and TA1537 (2 laboratories) in the presence and absence of metabolic activation by S9. There was no evidence of mutagenicity in the absence of S9, but all 3 laboratories obtained some positive results in the presence of S9. Positives were reported in at least some of the laboratories for strains TA97, TA100 and TA1535 with both hamster and rat S9. All 3 laboratories reported positive findings in TA100 (160). Two other studies also found a mutagenic response in TA100 in the presence of metabolic activation at dose levels of 50-250 µg/plate (73) and 50-1 000 µg/plate (222), respectively. Brusick *et al* found no mutagenicity at doses of 50-200 µg/plate in strains TA1535 or G46 in the presence or absence of S9 but obtained different results in TA100 depending on the source of the S9 used in the assay. Mutagenic activity was seen with S9 from rat liver activated with Aroclor 1254 or phenobarbital but not with S9 from human or mouse liver activated in the same way (23).

Gold and coworkers proposed an oxidative dealkylation of TDCPP to 1,3-dichloro-2-propanone analogous with the known metabolism of other related phosphate triesters. This compound was shown to be a powerful direct-acting mutagen (73). The metabolite 1,3-dichloro-2-propanol was mutagenic without activation with S9 in *Salmonella typhimurium* strain TA100. The number of revertant colonies/plate increased linearly with dose when tested at dose levels of 100-1 000 µg/plate (139).

No mutagenic activity was noted in strains TA98, TA100, TA1535 and TA1537 incubated with untreated or β-glucuronidase-treated urine from TDCPP-treated mice (0.05, 0.17 or 0.5 ml/kg bw or 76, 260 or 760 mg/kg bw by gavage) (23, 102).

TDCPP did not induce gene mutations in the mouse lymphoma assay either in the absence or presence of various exogenous metabolic systems (S9 from rat or mouse liver induced with either Aroclor 1254 or phenobarbital) when tested up to a concentration causing a 50 % reduction in cell growth (23, 102).

V79 Chinese hamster lung cells were used in a mammalian point mutational assay. These cells were fortified with a microsomal activation system from phenobarbital-pretreated rats. No increase in the number of 6-thioguanine-resistant clones was observed using 0.02 mM TDCPP. Hepatocyte monolayer cultures derived from either untreated or phenobarbital-pretreated rats were used to study unscheduled DNA synthesis. TDCPP at 0.05 mM did not cause a significant genotoxic effect, whereas at 0.1 mM TDCPP, a moderate increase in response was observed with hepatocytes from untreated rats (222).

TDCPP was also tested for *in vitro* chromosome effects, i.e. chromosomal aberrations and SCEs, using mouse lymphoma (L5178Y) cells at concentrations up to those causing a 50 % reduction in growth rate. Tests were performed in the absence or presence of exogenous metabolic systems. The results for SCEs were equivocal, whereas those for chromosomal aberrations showed increased numbers (excluding gaps) with both metabolic activation systems (23, 102).

TDCPP did not induce primary DNA damage as measured indirectly as unscheduled DNA synthesis in a primary culture of rat hepatocytes (102, 255).

TDCPP did not induce morphological cell transformations in BALB/3T3 cells (0.02-0.31 µl/ml) in two independent tests in the absence of metabolic activation (23, 102).

TDCPP did not induce chromosomal aberrations in bone marrow cells of CD-1 mice following either a single oral gavage dose of 0.05, 0.17 or 0.5 ml TDCPP/kg bw (76, 260 or 760 mg/kg bw) or 5 consecutive daily oral exposures at the same dose levels with a harvest time of 6 hours after the last dose (23).

TDCPP did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (23).

TDCPP did not induce micronuclei in polychromatic erythrocytes in the bone marrow of either sex of mice that had been given a single dose of 2 000 mg/kg bw of TDCPP by a not specified route of administration. The ratio of normochromatic erythrocytes to polychromatic erythrocytes was not elevated at any of the sampling times (24, 48 and 72 hours post-dosing). As systemic toxicity was observed in the treated mice, TDCPP must have entered the blood circulation and thus the bone marrow cells must have been exposed to TDCPP or its metabolites (Thomas and Collier 1985, cited in (102)).

Male CD-1 mice received TDCPP as a single intravenous dose (94 µmol/kg bw). The results indicated that TDCPP could bind covalently to macromolecules, including DNA of liver and kidney (157).

TEHP was not mutagenic 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 (263).

Concentrations of TEHP of up to and exceeding the apparent solubility limit of 62.5 µl/l did not produce any increase of mutations in a mouse lymphoma assay. The assay was carried out with and without S9 from livers of Aroclor 1254-treated male F344 rats (162).

In vitro cytogenetic assays (SCEs and chromosome abberations) in CHO cells were carried out using concentrations of TEHP up to 251 µg/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. However, at 16.7 µg/ml and above there was severe cell cycle delay, which limited the number of cells available for analysis (105).

A mouse bone marrow micronucleus assay was carried out in male $B6C3F_1$ mice. The mice were given intraperitoneal TEHP injections of 500, 1 000 or 2 000 mg/kg bw on 3 consecutive days. Bone marrow was harvested at 24 hours after the last dose and was examined for micronucleus containing polychromatic erythrocytes (MN-PCEs). A significant dose-related increase in the number of MN-PCEs was observed in the bone marrow of treated mice. The assay was repeated in two further experiments using doses of 1 500 and 2 000 mg/kg bw in one and 2 000 and 3 000 mg/kg bw in the other. No increase in the number of MN-PCEs was de-

tected in either of these experiments. The authors concluded that the initial result was an artefact and that TEHP was not mutagenic in this assay (198).

An *in vivo* cytogenetic assay was carried out in male $B6C3F_1$ mice. The mice were given a single intraperitoneal injection of TEHP (dose not given). Bone marrow was harvested at 17 and 36 hours after the given injections. The number of chromosomal aberrations was not elevated in TEHP treated mice (199).

In an *in vivo* liver hepatocyte replicative DNA synthesis assay, male $B6C3F_1$ mice were given TEHP doses of 1 000 or 2 000 mg/kg bw by gavage. The mice were killed at 24, 39 and 48 hours after given doses. There was no evidence of increased replicative DNA synthesis in hepatocytes from treated mice (155).

TEP (313-5 000 µg/plate) was not mutagenic in four bacterial strains, *Salmonella typhimurium* TA102 and TA2638 and *Escherichia coli* WP2/pKM101 and WP2 *uvr*A/pKM101 (249).

Negative results were also reported in Ames tests conducted with *Salmonella typhimurium* strains (TA98, TA100, TA1535 and TA1537) in the absence or presence of rat and hamster liver S9 (262).

TEP did, however, induce gene mutations without metabolic activation in some bacteria, viruses and a yeast strain. For clarification of the endpoint gene mutation, a HPRT test in V79 cell cultures was done, which revealed a negative result with and without metabolic activation (237).

In an *in vitro* unscheduled DNA synthesis test on rat hepatocytes, TEP showed no DNA damaging effect. The results for *Drosophila melanogaster* in the limited documented recessive-lethal tests were contradictory, while *in vivo* studies on the mouse (cytogenetics in bone marrow, dominant lethal test) were negative (237).

TEP gave a positive dose-response in the w/w+ bioassay for somatic cell damage in *Drosophila melanogaster* when tested at doses of 2.5-10 mM (258).

TIPP was tested for mutagenicity in five strains of *Salmonella typhimurium* in presence and absence of a metabolic activating system. Five dose levels were used but were not described. TIPP was not mutagenic in this test. However, the reliability of these tests was not assignable according to Great Lakes Chemical Corporation (74).

TMCPP There was no clear evidence that commercial TMCPP products were genotoxic from a battery of assays for mutagenic and related effects. TMCPP produced no gene mutations in strains TA1535, TA1537, TA1538, TA97, TA98 and TA100 in *Salmonella*/microsome plate assays and one *Escherichia coli* nor in a yeast gene mutation assay in either the presence or absence of metabolic activation (Anonymous 1980, Kouri and Parmar 1977, Mehlman *et al* 1980, Nakamura *et al* 1979, Parmar 1977, Stauffer 1978b, Zeiger *et al* 1992, cited in (102)).

In V79 cells, tris(1-chloro-2-propyl) phosphate (1 µM-1 mM) did not induce DNA strand breaks in the alkaline version of the Comet assay neither without an

external enzymatic metabolising system nor in the presence of S9 mix. No mutagenic potential could be detected in eight *Salmonella* strains using concentrations up to 1 mM in the presence or absence of S9 (71).

One mouse lymphoma assay gave equivocal results with TMCPP (Anonymous 1981, cited in (102)) but a second mouse lymphoma assay was negative in the presence and absence of metabolic activation (Stauffer 1978c, cited in (102)). *In vitro* assays for unscheduled DNA synthesis in a primary culture of rat hepatocytes gave negative results (Bayer 1991b, cited in (102)), (255), whereas the results of the same test in an *in vitro* assay in WI-38 cells (Stauffer 1978a, cited in (102)) were equivocal in the presence and absence of metabolic activation.

Two out of three cell transformation assays in BALB/3T3 cells gave negative results with Fyrol PCF in the absence of metabolic activation (Stauffer 1978a, 1980b, cited in (102)), whereas the third was equivocal (Stauffer 1978d, cited in (102)).

TMCPP caused no chromosomal damage in bone marrow in three *in vivo* cytogenetic assays using oral or subcutaneous administration to rats and intraperitoneal administration to mice (Bayer 1991a, Stauffer 1978e, cited in (102)).

TPP did not demonstrate mutagenic activity in microbial assays using strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100) and *Saccharomyces cerevisiae* as indicator organisms (doses not given). All studies were carried out both with and without metabolic activation (Monsanto 1979, cited in (100)).

Negative results were also reported in Ames tests conducted with *Salmonella typhimurium* strains (TA98, TA100, TA1535 and TA1537) in the absence or presence of rat and hamster liver S9 (262).

TPP was also tested for its ability to induce mutations at the thymidine kinase locus in cultured L5178 mouse lymphoma cells (doses not given). When tested with or without metabolic activation, TPP did not induce a significantly increased frequency of mutations (Monsanto 1979, cited in (100)).

10.6 Effects of long-term exposure and carcinogenicity

Several of the phosphate triesters covered in this document have neoplastic potential in animal experiments (TBP, TCEP, TDCPP and TEHP) (Table 13). However, TCP does not seem to have such an effect. Some of the esters have not been properly tested.

TCP The NTP has performed 13-week and 2-year-studies in rats and mice administered TCP by gavage or in the diet. The TCP product contained 18 % dicresyl phosphate esters and 79 % TCPs (consisting of 21 % TMCP, 4 % TPCP, less than 0.1 % TOCP, and other unidentified TCPs) (174). The studies are described below and also in Sections 10.4 and 10.7.

Groups of 10 male and 10 female F344/N rats and $B6C3F_1$ mice received TCP in corn oil by gavage at doses of 0, 50, 100, 200, 400 or 800 mg/kg bw for 13

Table 13. Tumours and hyperplasia in animals exposed to phosphate triesters.

Species, sex	Tumours	Hyperplasia	Reference
TCP			
Rat, female	No neoplasms	Ovarian interstitial cells	(174)
Mouse, both sexes	No neoplasms	Gall bladder mucosal epithelium	(174)
TBP			
Rat, both sexes Rat, males		Urinary bladder epithelium Renal pelvis epithelium	(101, 121, 234)
Rat, both sexes	Transitional urinary cell carcinomas, urinary bladder papillomas	Urinary bladder epithelium	(13)
Mouse, males	Hepatocellular adenomas		(12)
TCEP			
Rat, both sexes	Renal tubule adenomas	Renal tubule	(173)
Mouse, both sexes	Renal tubule neoplasmas, Harderian gland adenomas	Renal tubule	(173)
Mouse, both sexes	Renal and hepatocellular adenomas/carcinomas, forestomach papillomas/ carcinomas and leukaemias	Renal tubule	(225)
TDCPP			
Rat, both sexes	Benign neoplastic liver nodules, liver carcinoma, renal cortical tumours	Renal tubule, bone marrow erythroid/myeloid	(102, 217)
Rat, female	Thyroid adenomas, adrenal cortical adenomas		
Rat, male	Benign testicular interstitial tumours, brain tumours		
TEHP			
Rat, males	Phaeochromocytomas of the adrenal gland		(172)
Mouse, both sexes		Thyroid follicular cell	
Mouse, female	Hepatocellular carcinoma		
TMCPP			
Rat, both sexes		Thyroid follicular cell (very mild)	(238)

weeks. All rats and mice survived. In the rats, final mean body weights of males receiving 200, 400 and 800 mg/kg bw were significantly lower than those of the controls. The principal lesions in rats occurred in the testis, ovary and adrenal glands (Section 10.7). Cytoplasmic vacuolisation of the adrenal cortex occurred in all exposed groups (50-800 mg/kg bw) and the severity increased with dose. The only neurobehavioural measure affected by the exposure was a slight but significant reduction of hindlimb grip strength in female rats receiving 400 and 800 mg/kg. Females given 200 mg/kg bw of TCP and higher and males given 400

mg/kg bw and higher had significantly lower haemoglobin concentrations in blood. In the mice, final mean body weights and mean body weight gains were significantly lower than those of the controls in males receiving 200, 400 and 800 mg/kg, and in females receiving 400 and 800 mg/kg. There were significant dose-related decreases in serum cholinesterases in all dosed groups. The principal lesions in mice occurred in the ovary, adrenal gland, spinal cord and sciatic nerve. The lesions in the ovary and adrenal gland were similar to those in rats. Female mice given 200 mg/kg bw TCP and higher had significantly lower haemoglobin concentrations in blood. Male mice given 400 mg/kg TCP and higher had a significantly lower mean cell haemoglobin levels but not lower haemoglobin concentrations. The male mice had also an increased number of reticulocytes at 400 and 800 mg/kg bw (174) as an expression of bone marrow stimulation.

In the diet study, groups of 10 male and 10 female F344/N rats were fed diets containing 0, 0.9, 1.7, 3.3, 6.6 or 13 g/kg of TCP for 13 weeks. The estimated delivered daily doses were 55, 120, 220, 430 and 750 mg/kg bw for males and 65, 120, 230, 430 and 770 mg/kg for females. All rats survived. Cytoplasmic vacuolisation of the adrenal cortex was observed in all exposed groups. Ovarian interstitial cell hypertrophy occurred in all exposed groups of females. Renal papillary oedema and renal papillary necrosis occurred in 13-g/kg diet males and in 6.6- and 13-g/kg diet females. Basophilic hypertrophy of the pituitary gland pars distalis and atrophy of the seminiferous tubules were observed in males receiving 3.3, 6.6 and 13 g/kg diet. Both males and females given 1.7 g/kg (120 mg/kg bw) TCP in the diet had an increased number of platelets in the blood. Female rats given 3.3 g/kg diet (230 mg/kg bw) and higher had significantly lower haemoglobin concentrations in blood. The effect was also seen in males at the highest dose level (174). B6C3F_1 mice were fed diets containing 0, 0.25, 0.5, 1.0, 2.1 or 4.2 g/kg of TCP for 13 weeks. The estimated delivered daily doses were 45, 110, 180, 380 or 900 mg/kg bw for males and 65, 130, 230, 530 and 1 050 mg/kg bw for females. Final body weights were reduced at the two highest dose levels. Lesions associated with chemical exposure occurred in the spinal cord, sciatic nerve, adrenal gland, gall bladder, ovary and kidney. Cytoplasmic vacuolisation of the adrenal cortex occurred in all exposed groups of females and in males exposed to 0.5-4.2 g/kg diet. Hyperplasia of the mucosal epithelium of the gall bladder was observed in males exposed to 0.5 g/kg or more and in females exposed to 1 mg/kg diet or more (174).

In the 2-year study, groups of 95 male and 95 female F344/N rats were fed diets containing 0, 0.075, 0.15 or 0.3 g/kg TCP. Approximately 50 animals/sex and dose group were exposed throughout the whole study period. The given dietary levels were estimated to deliver average daily doses of 3, 6 or 13 mg/kg bw in males and 4, 7 or 15 mg/kg bw in females. An additional group of animals were given 0.6 g/kg in their diet for 22 weeks and then received only control feed. Cytoplasmic vacuolisation of the adrenal cortex occurred in 0.6-g/kg males and 0.15-, 0.3- and 0.6-g/kg females at the 3-month evaluation. At 9 and 15 months, cytoplasmic vacuolisation occurred only in females, primarily in the 0.3 g/kg

group. Cytoplasmic vacuolisation of the adrenal cortex and ovarian interstitial cell hyperplasia occurred in 0.3-g/kg females exposed throughout the 2-year study and the incidence and severity were significantly increased at the end of the study. There were no chemical-related increases in the incidence of neoplasms among these groups of rats.

In the corresponding 2-year mouse study, groups of 95 male and 95 female $B6C3F_1$ mice were fed diets containing 0, 0.06, 0.125 or 0.25 g/kg of TCP. Approximately 50 animals/sex and dose group were exposed throughout the whole study period. The given dietary levels were estimated to deliver average daily doses of 7, 13 or 27 mg/kg bw in males and 8, 18 or 37 mg/kg bw in females. Ceroid pigmentation of the adrenal cortex occurred in all groups of mice including controls. The severity was markedly increased in females receiving 0.25 g/kg. Incidences of clear cell foci, fatty change, and ceroid pigmentation of the liver were significantly increased in males receiving 0.125 and 0.25 g/kg. There were no chemical-related increases in the incidence of neoplasms.

The NTP Task Group concluded that there was no evidence of carcinogenic activity of TCP in male and female F344/N rats or in male or female $B6C3F_1$ mice (174).

Male mice gavaged with 0, 5, 50 or 500 mg/kg bw of TOCP or 50 mg/kg bw of TMCP once a week for 13 weeks exhibited no effect on immunoglobulin levels and there was a non-dose-related suppression of lymphocyte proliferation (20).

TBEP Wistar rats were given a diet containing 0, 0.3, 3 or 30 g TBEP/kg for 14 weeks. There were 15 rats in each group. Suppression of body weight gain was observed in both sexes at 30 g/kg diet. Serum cholinesterase acitity decreased significantly in both sexes at 3 and 30 g/kg diet. Serum γ-glutamyl transferase activity was increased at 30 g/kg. After 5 weeks, serum amylase was significantly increased at 3 and 30 g/kg diet among males and at 30 g/kg among females. Absolute and relative liver weights in both sexes were significantly increased in the 30-g/kg groups after 5 and 14 weeks of exposure. Examination of the liver revealed moderate periportal hepatocyte swelling in males at 30 g/kg after 14 weeks of exposure, but this change was not found in males given 3 g/kg or less. The NOAEL for TBEP in the diet was 0.3 g/kg diet, corresponding to 20 and 22 mg/kg bw/day for males and females, respectively (189, 233).

In a gavage study, groups of 12 male and 12 female Sprague Dawley rats were given 0, 0.25 or 0.5 ml/kg bw (250 or 500 mg/kg) undiluted TBEP, 5 days/ week for 18 weeks. During the first week, 2 high-dose females showed muscular weakness and ataxia, which disappeared by the end of the 4th week. After about 7 weeks, nearly all animals exhibited some signs of toxicity. All treated animals appeared less active and one female rat 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 less affected. Tremors, piloerection, lacrimation and increased urination were observed in the high-dose group. After the last dose, the clinical signs decreased in intensity. High-dose females had significantly

elevated serum γ-glutamyl transferase levels. Haematological parameters were not different from controls and there were no differences between low- and high-dose groups of either sex. Animals were necropsied one week after the last dose. Liver weight was significantly increased in both treated groups. Kidney weight was increased by about 20 % in both dose-groups and significantly so in the high-dose group. Histopathological changes were confined to the heart of males in both dose groups. In the high-dose group (3/6) and in the low-dose group (2/6), animals had multiple foci of mononuclear cell infiltration, haemorrhages and/or myocardial fibre degeneration. These lesions were more severe in the high-dose group than in the low-dose group and were absent among controls. Two of six (2/6) high-dose, 3/6 low-dose rats and 1/6 control rat demonstrated multifocal interstitial fibrosis. The authors concluded that TBEP may have accelerated the development of focal myocarditis, which is a normal feature in older male Sprague Dawley rats (122, 124). The studies are also described in Section 10.4.

In an 18-week study, four groups of 20 male and 20 female Sprague Dawley rats were fed diets containing 0, 0.3, 3 or 10 g TBEP/kg. Body weight, food intake and clinical observations were similar in treated and control rats. In the groups exposed to 3 and 10 g/kg, there was an increase of serum γ-glutamyl transpeptidase and a decrease of plasma cholinesterase activity. Other haematological and clinical chemistry parameters were normal except for increased platelet counts in the highest dose group. Liver weight was increased in the highest dose group. Microscopic examination showed mild periportal hepatocellular hypertrophy and periportal vacuolisation in males receiving 3 and 10 g/kg in the diet. The NOAEL was 0.3 g/kg diet equivalent to 15 mg/kg bw/day and the LOAEL 3 g/kg diet equivalent to 150 mg/kg bw (Monsanto 1987a, cited in (103)).

TBP Male and female adult Sprague Dawley rats received TBP (32.5, 100 and 325 mg/kg bw) in corn oil by gavage for 13 weeks. Postdosing salivation was observed rarely at 32.5 mg/kg, frequently at 100 mg/kg and on almost all occasions in the high-dose animals. High-dose males and females had significantly decreased body weights. Some mortality was also observed at the two highest dose level (80). The study is also described in Section 10.4.

TBP was administered in the diet at concentrations of 0, 0.2, 0.7 or 3 g/kg to groups of 50 male and 50 female Sprague Dawley rats for 2 years. The mean daily intake was 9, 32 and 143 mg/kg bw for males and 12, 42 and 182 mg/kg bw for females. At the highest dose, body weight was decreased in both sexes. A dose-related increase in the incidence and severity of urinary bladder hyperplasia and the incidence of urinary bladder papillomas were evident in males and females receiving the 0.7 and 3 mg/kg diets. Transitional cell carcinomas were present in 6/49 males and 2/50 females and squamous cell carcinoma was present in 1/49 males in the group that received 3 g/kg (13).

TBP was administered in the diet at concentrations of 0, 0.15, 1 or 3.5 g/kg to groups of 50 male and 50 female CD-1 mice for 18 months. The mean daily intake was 29, 169 and 585 mg/kg bw for males and 24, 206 and 711 mg/kg bw for

females. A significant dose-related increase in absolute and relative liver weights was seen in both sexes receiving the two highest dietary concentrations (1 and 3.5 g/kg). The incidence of hepatocellular adenomas was significantly increased in males treated with 3.5 g/kg TBP in diet. No other tumours were associated with TBP administration in this study. No urinary bladder alterations occurred attributed to TBP administration. The NOAEL for chronic toxicity was 24-29 mg/kg bw for mice (12).

Groups of randomised female and male Sprague Dawley rats were divided into two dose groups and control groups with 12 rats per sex in each group. TBP was administered by gavage daily for 5 days/week over an 18-week period. Low-dose animals received 200 mg/kg bw throughout the experiment. High-dose animals received 300 mg/kg bw for the first 6 weeks followed by 350 mg/kg bw for the remaining 12 weeks. Histopathological examination of tissues revealed that all rats examined developed diffuse hyperplasia of the urinary bladder epithelium. Similar changes were not found in the control animals (121).

In a 2-generation reproduction study in rats, the LOAEL for parental toxicity was approximately 10-21 mg/kg bw/day, based on microscopic evidence of a very low incidence of urinary bladder epithelium hyperplasia and transient reductions in body weight (234). The study is described in detail in Section 10.7.

Sprague Dawley rats were fed diets containing 0, 0.008, 0.04, 0.2, 1 or 5 g/kg of TBP for 90 days (corresponding to approximately 0.4-250 mg/kg bw/day (44)). Clinical chemistry changes included increased serum γ-glutamyl transpeptidase levels in both sexes given 5 g/kg. Absolute and relative liver weights were increased in both sexes at this dose. Histopathological studies indicated TBP induced transitional cell hyperplasia in the urinary bladder of males given 1 or 5 g/kg and females given 5 g/kg diet (presented as an abstract) (Cascieri *et al* 1985, cited in (101)).

Skydrol 500B-4 is a fire resistant hydraulic fluid composed of 80-90 % phosphate esters including dibutyl phenyl phosphate and TBP. Rats inhaled an aerosol of 0, 5, 100 and 300 mg/m^3, 6 hours/day, 5 days/week for 6 or 13 weeks. Nasal discharge was noted among 47/50 mid-exposure rats and 50/50 high-exposure rats during the first week of exposure. The incidence of the nasal discharge decreased over the course of the study. In high-dose animals, increased absolute and relative liver weights and decreased haematocrit were observed. High-dose females also exhibited decreased body weights, plasma cholinesterase levels, erythrocyte counts and haemoglobin levels, and centrilobular hepatocellular hypertrophy (10/15) (81).

TCEP The NTP has performed 16- or 18-week and 2-year studies in rats and mice administered TCEP by gavage (173).

Groups of 10 F344/N rats of each sex were administered 0, 22, 44, 88, 175 or 350 mg/kg bw of TCEP in corn oil by gavage 5 days/week for 16 weeks (female) and for 18 weeks (male). There were deaths in the two highest dose groups (1 male receiving 175 mg/kg, 5 high-dose males and 3 high-dose females). Final mean body weights were generally similar among dosed and control male rats,

although the final mean body weight of surviving high-dose females was about 20 % greater than the control value. The final absolute and relative (organ-weight-to-body-weight and organ-weight-to-brain-weight ratios) weights of liver and kidney were significantly increased in high-dose males ($p = 0.01$) and in females receiving 44-350 mg/kg ($p = 0.01$). These differences were considered related to the administration of TCEP. Necropsy examination showed no gross lesions attributable to chemical exposure (173).

Groups of 10 mice of each sex were administered 0, 44, 88, 175, 350 or 700 mg/kg bw TCEP in corn oil by gavage 5 days/week for 16 weeks. There were no chemical-related deaths. Weight gain and group mean body weights at the end of the study were similar among dosed and control mice. The mean absolute and relative liver weights were significantly increased in females receiving 175-700 mg/kg bw and in males receiving 700 mg/kg bw. These increases were considered to be chemical-related. The absolute and relative testis weights of high-dose males were decreased relative to those of controls ($p = 0.01$). Male mice receiving 175-700 mg/kg bw had significantly reduced relative kidney weights ($p = 0.01$), but absolute kidney weights were significantly reduced in high-dose males only. Although necropsy examination showed no gross lesions attributable to chemical administration, epithelial cells with enlarged nuclei (cytomegaly and karyomegaly) were observed in the renal tubules in all males and females receiving 700 mg/kg bw of TCEP. These lesions were observed primarily in the proximal convoluted tubules of the inner cortex and outer stripe of the outer medulla and, to a lesser extent, in the straight portion of the loops of Henle in the outer medulla (173).

Groups of 60 male and 60 female F344 rats received 0, 44 or 88 mg/kg bw/day of TCEP, 5 days/week by gavage for 103 weeks. At 103 weeks, there were no adverse effects on the body weight gain and no clinical signs of toxicity. Reduced survival was noted in males and females at 88 mg/kg bw (males 51 % survival compared to 78 % in controls, females 37 % compared to 66 % in controls). In each group, 50 animals were examined microscopically. Non-neoplastic findings in the kidneys were hyperplasia (0/50, 2/50 and 24/50) in males and (0/50, 3/50, 16/50) in females. Neoplastic lesions were observed in the kidney; the frequency of adenomas was 1/50, 5/50 and 24/50 in males and 0/50, 2/50, 5/50 in females. In the brain, benign granular cell tumours were observed in 3/50 males at 88 mg/kg only. A slight increase in the incidence of thyroid adenomas was noted in males (1/50, 2/48, 3/50), and of carcinomas in males (0/50, 0/48, 2/50) and in females (0/50, 2/50, 3/50). Marginal increases in mononuclear cell leukaemia were also observed in dosed males and females. Leukaemia occurred with a significant positive trend in both sexes and the incidences in the high-dose groups were significantly greater than those in controls. However, the incidences in the dosed groups were within the range of NTP historical control groups and the marginal increases in leukaemia in both sexes were not considered to be clearly chemical-related (173) (also published in (150)).

Groups of 60 male and 60 female $B6C3F_1$ mice received 0, 175 or 350 mg/kg bw, 5 days/week by gavage for 103 weeks. The body weights of mice receiving

TCEP were not different from those of controls and there were no clinical signs of toxicity. Renal tubular neoplasms in male $B6C3F_1$ mice are rare (historical vehicle controls 8/2 183, 0.4 %). Due to this, the kidneys were further sectioned for a more profound microscopic examination. Thus, the incidences of renal tubule neoplasms in original and further sections combined were 1/50, 1/50 and 4/50. Focal hyperplasia in the kidneys was observed in one control, one 175 mg/kg bw female, two 350 mg/kg bw males and two 350 mg/kg bw females. Karyomegaly (nuclear enlargement) was observed in approximately 80 % of mice receiving 350 mg/kg bw and less frequently at 175 mg/kg bw. The incidence of neoplasms (adenoma or carcinoma) of the Harderian gland was not significantly greater in female mice than in controls (3/50, 8/50 and 7/50). However, if the animals in a 66-week study were added to the 103-week study, a significant trend was observed and the incidence in the high-dose group was significantly greater than that in controls (adenomas and carcinomas in 3/59, 8/60 and 10/60). This gland is located in the orbit behind the eye (173) (also published in (150)).

The NTP Task Group concluded that there was clear evidence of carcinogenic activity for male and female F344/N rats receiving TCEP as shown by increased incidences of renal tubule adenomas. There was equivocal evidence of carcinogenic activity for male and female $B6C3F_1$ mice shown by marginally increased incidence of renal tubule cell neoplasms and Harderian gland adenomas, respectively (173).

Groups of 50 male and 50 female Slc:ddy mice received approximately 0, 12, 60, 300 or 1 500 mg TCEP/kg bw by dietary administration (assuming 30 g body weight and 3 g/day food consumption) for 18 months. Histologically, hyperplasia, hypertrophy and karyomegaly were observed in the kidney of all treated animals. In addition, cysts of the kidneys, necrosis and interstitial fibrosis were reported in animals given 1 500 mg/kg bw per day. The number of tumour-bearing animals was increased at 300 among females and at 1 500 mg/kg bw in both sexes. An increased incidence of renal adenomas was noted in males (0/50, 0/49, 0/49, 2/49, 9/50) and females (0/49, 0/49, 0/50, 0/49, 2/50). In addition, there was an increased incidence of renal carcinomas in males (2/50, 0/49, 2/49, 3/47, 32/50) and females (1/50 at 1 500 mg/kg per day and zero in all other groups). In the liver, there was an increased incidence of adenomas in males (3/50, 4/49, 3/49, 10/47, 16/50) and in females (2/50 at 1 500 mg/kg bw with zero in all other groups). The incidences of leukaemia and forestomach tumours were also increased (102, 225).

TDCPP Slc:ddY mice (12 of each sex/group) were fed diets containing 0, 0.1, 0.4, 1.3, 4.2 or 13.3 g/kg diet for 3 months. The daily intake of TDCPP was reported to be 0, 13, 47, 171, 576 or 1 792 mg/kg bw for males and 0, 15, 62, 214, 598 or 1 973 mg/kg bw for females. The animals in the highest exposure group showed emaciation, rough hair and tremor, and all animals died within one month. Haemoglobin concentration was decreased in males and females by 13 % and 11 %, respectively, in the group fed the 4.2 g/kg diet. There was an increase in relative liver weight in males (significant at 1.3 and 4.2 g/kg diet with increases of 32 %

and 51 %, respectively) and females (significant at 0.4, 1.3 and 4.2 g/kg with increases of 16 %, 29 % and 51 %, respectively). There was also an increase in relative kidney weight in males (significant at 4.2 g/kg with an increase of 39 %) and females (significant at 1.3 and 4.2 g/kg with increases of 34 % and 40 %, respectively). Thus, the NOAELs for the increase in relative liver weight were 47 and 15 mg/kg bw for males and females, respectively. The LOAELs were 171 mg/kg bw in males and 62 mg/kg bw in females (102, 114).

Groups of 50 male and 50 female Sprague Dawley rats received approximately 0, 5, 20 and 80 mg TDCPP/kg bw/day by dietary administration for 2 years (Aulette and Hogan 1981, cited in (102)). At the highest dose level, body weight was reduced and kidney, liver and thyroid weights were increased. In males, also mortality increased. Neoplastic changes were observed in the liver, kidneys, testes, brain, thyroid and adrenals. In the liver, the occurrence of benign neoplastic nodules was 2/45, 7/48, 1/48, 13/46 in males and 1/49, 1/47, 4/46, 8/50 in females. The incidences of liver carcinoma were 1/45, 2/48, 3/48, 7/46 in males and 0/49, 2/47, 2/46, 4/50 in females. In the kidneys, the incidence of renal cortical tumours (benign and/or malignant) was 1/45, 3/49, 9/48, 32/46 in males and 0/49, 1/48, 8/48, 49/50 in females. An increased occurrence of hyperplasia in the renal convoluted tubules was observed in all groups of treated males (2/45, 10/49, 28/48 and 24/46) and females (0/49, 1/48, 3/48 and 22/50). At 80 mg/kg bw, also the incidence of chronic nephropathy was increased. The incidences of benign testicular interstitial tumours were 7/43, 8/48, 23/47 and 36/45. At 80 mg/kg bw, a slight increase in the incidence of brain astrocytomas was observed in males (4/46 versus 0/44 in controls) and a single oligodendroglioma was observed amongst males and females. At the same dose level, the occurrences in females of thyroid adenomas (5/49 versus 1/42 in controls) and of adrenal cortical adenomas (19/49 versus 8/48 in controls) were increased. In addition, a slight increase in the occurrence of parafollicular cell adenomas was noted in males (3/41 versus 0/40) and in females (4/49 versus 2/42) at 80 mg/kg bw. Erythrocyte values were reduced in males and females at 80 mg/kg bw. An increased incidence of bone marrow erythroid/myeloid hyperplasia was recorded at the same dose in males and females. No samples were taken from other treated groups.

It was concluded that TDCPP is carcinogenic at all exposure levels that were tested in both sexes of rats based on the increased occurrence of liver carcinomas. Kidney, testicular and brain tumours were also found. In addition, there were non-neoplastic adverse effects in bone marrow, spleen, testis, liver and kidney. Effects in the kidney and testis occurred at all exposure levels. Only the animals in the highest dose and control groups were evaluated for effects in the bone marrow and spleen. It was therefore impossible to determine the dose-response relationship for these effects (Aulette and Hogan 1981, cited in (102)). The data are apparently the same as those presented by Stauffer 1981b, cited in (217), and by Freudenthal and Henrich 2000 (69), although group sizes differ.

TEHP In a 3-month inhalation study, three exposed groups, each consisting of 2 dogs and 2 rhesus monkeys (equal numbers of each sex), were exposed to TEHP for 6 hours/day, 5 days/week for a total of 60 exposures. The mean concentrations (± standard deviations) of the exposure over the 12-week period were 10.8 (± 6), 26 (± 17) and 85 (± 33) mg/m^3. The median particle size was 4.4 µm. No mortality and normal increases in body weights were observed in dogs and monkeys. There were no treatment-related alterations in biochemical or haematological parameters or in organ function tests as compared to controls. The lungs of the monkeys were normal but the lungs of the dogs showed mild, chronic parenchymal inflammatory changes (140).

In another 3-month inhalation study, groups of 20 male guinea pigs were exposed to TEHP 6 hours/day, 5 days/week for 12 weeks. The mean concentrations (± standard deviations) of the two exposed groups were 1.6 (± 0.8) and 9.6 (± 1.5) mg/m^3. The median particle size was 3.8 µm. The high-dose guinea pigs showed significantly increased body weights in comparison to controls. Both exposed groups exhibited a lower kidney-to-body weight ratio than the controls. Gross pathological examination of the 2 guinea pigs which died during the 9th week of exposure showed extensive consolidation of lung tissue. However, when the surviving animals were sacrificed at the end of exposure, mildly congested lungs were noted in a quarter of the animals in the control group, whereas no abnormalities were observed in the treated groups. Histopathological alterations in the lung, liver and kidneys were not related to treatment. Sections of the spinal cord and sciatic nerve showed no pathologic changes. Activities of plasma and erythrocyte cholinesterase were unaffected in terminal blood samples (140).

The NTP has performed 13-week and 2-year gavage (in corn oil) studies in rats and mice (172). In the 13-week studies, groups of 10 F344 rats of each sex received 0, 250, 500, 1 000, 2 000 or 4 000 mg TEHP/kg bw for 5 days/week and groups of 10 mice of each sex received 0, 500, 1 000, 2 000, 4 000 or 8 000 mg TEHP/kg bw. In rats, mean body weights were depressed 5 % for males that received 4 000 mg/kg, and 10 % and 5 % for females at 2 000 mg/kg and 4 000 mg/kg, respectively. In male and female mice, body weight gain was suppressed by 7 and 5 %, respectively, at the highest dose level. No deaths were attributable to TEHP administration. Dose-related inflammatory lesions were observed in the gastric mucosa in all groups of mice but no other compound-related effects were observed in either species at necropsy (172) (briefly reported also in (117)).

In the chronic study, TEHP was administered 5 days/week for 103 weeks to groups of 50 male and 50 female F344/N rats and B6C3F$_1$ mice. Male rats received 2 000 or 4 000 mg/kg bw, female rats received 1 000 or 2 000 mg/kg bw. Male and female mice received 500 or 1 000 mg/kg bw. No compound-related clinical toxicity was observed in either sex or species. Decrease in body weight, compared to 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: control 2/50 (4 %), low-dose 9/50 (18 %) and high-dose 12/50

(24 %). Two phaeochromocytomas of the high-dose group were malignant. In two previous gavage studies in the same laboratory, the incidences of phaeochromocytomas among control males were 24 and 26 %. The overall historical incidence in this laboratory was 18 %. The incidence of phaeochromocytomas in dosed female rats was not significantly higher than in controls. There was a significantly positive trend for increased incidence of thyroid follicular cell tumours in male rats. However, the incidence in the dosed groups was not significantly higher than that in vehicle controls. Thus, this was not considered a positive effect.

In B6C3F_1 mice, TEHP caused a dose-related increase in the incidence of thyroid follicular cell hyperplasia in both males (0/49, 12/48, 24/47) and females. (1/44, 13/47, 12/46). In female mice, there was a dose-related increase in the incidence of hepatocellular carcinomas (0/48, 4/50, 7/50), which was statistically significant at the highest dose level. In male mice, the incidence of hepatocellular carcinomas was 9/50, 12/50, 12/49 (172) (also published in (117)).

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 incidence of phaeochromocytomas. There was no evidence of carcinogenicity in female rats or in male mice receiving TEHP. TEHP caused a dose-related increase in the incidence of thyroid follicular cell hyperplasia in male and female B6C3F_1 mice (172) (also published in (117)).

TEP and ***TIPP*** No data were located.

TMCPP In a 90-day dietary study, male and female rats (20/sex/group) were given diets containing 0.8-20 g/kg TMCPP (corresponding to approximately 40-1 000 mg/kg bw/day (44)). The substance given was Fyrol PCF containing ca 70 % tris(1-chloro-2-propyl) phosphate and ca 22 % tris(2-chloropropyl) phosphate. No mortalities and no treatment-related clinical signs were noted. Males and females given 20 g/kg diet showed significantly reduced body weights. Significantly increased absolute and relative liver weights were found in males of all groups and in females fed 7.5 or 20 g/kg. The mean kidney weights of males given 7.5 g/kg or greater were significantly increased relative to controls, while female rats were unaffected. Histopathologic and treatment-related change was seen in the livers of rats fed 20 g/kg, which was characterised by a very mild swelling of cells located in the periportal region of the hepatic lobule. Very mild cortical tubular degenerative changes were observed in the kidneys of males fed 7.5 and 20 g/kg and of females administered 20 g/kg. The sternal bone marrow of 3 rats administered 20 g/kg was observed to be very mildly hypoplastic. Very mild thyroid follicular hyperplasia was found in all males and in females given 20 g/kg. There were no treatment-related effects observed in haematology, clinical chemistry or in brain, plasma and erythrocyte cholinesterase activity. All histopathologic changes were considered reversible. According to the authors, the NOAEL for

male rats was 0.8 g/kg and for female rats 7.5 g/kg in the diet (increased liver weight was regarded as a non-adverse effect) (Stauffer 1981a, cited in (238)).

TPP Young male Sprague Dawley rats were fed diets containing TPP (98 % purity) at levels of 0, 2.5, 5, 7.5 or 10 g/kg for 4 months. The calculated average doses were 161, 345, 517 and 711 mg/kg bw/day. Treatment-related decrements in growth in the absence of changes in food consumption were found at all dietary levels from 5 g/kg and above. There were no effects in behavioural tests (203) (see Section 10.4).

Spartan Sprague Dawley rats were fed 0, 2.5, 5, 7.5 and 10 g TPP/kg diet for 120 days (corresponding to approximately 125, 250, 375 and 500 mg/kg bw (44)). The immunotoxicity evaluation included total protein, electrophoretic analysis of serum proteins, lymphoid organ weights in relation to growth, and histopathology, together with expanded immunohistochemical evaluation of B- and T-lymphocyte regions in the spleen, thymus and lymph nodes using immunoperoxidase staining. Assessment was made of the humoral response to a T-lymphocyte-dependent antigen, sheep red blood cells, and was begun at midterm of the feeding period for the primary response followed by secondary and tertiary booster immunisations at 3-week intervals. The kinetics of the response was measured by haemolysin assay of relative antibody titres at days 3, 4, 5 and 6 post-injection. No significant effects on the response were noted for either sex at any of the dose levels tested. The only effects observed were a decreased rate of growth in males at high levels of TPP and increased levels of α- and β-globulins (85).

There was no increased incidence of lung adenomas after 24 weeks in male mice given 1-18 intraperitoneal injections of 20, 40 or 80 mg/kg bw/dose of TPP (purity 95-99.9 %) (229).

10.7 Reproductive and developmental toxicity

Reproductive and developmental toxicity studies are summarised in Table 14. Several of the phosphate triesters have shown effects on reproduction or development in animal studies (TCP, TOCP, TCEP, TDCPP and TMCPP). TOCP affects testicular function in rats at low doses (10 mg/kg bw) and this compound may be responsible for the effects seen after exposure to TCP containing less than 9 % of TOCP. TDCPP exposure to rats caused atrophy of the seminal vesicle and decreased secretory product at all dose levels starting at 5 mg/kg bw. However, these effects were not confirmed in rabbits. In one study, there was equivocal evidence of an affect on development from TPP exposure. The data on TEP is regarded insufficient. No information has been found regarding TEHP and TIPP.

Table 14. Summary of reproductive and developmental toxicity in animal studies.

Dose range, mg/kg bw/day	Exposure duration	Species, sex	NOAEL, mg/kg bw/day	LOAEL, mg/kg bw/day	Outcome at the NOAEL/LOAEL	Reference
TCP						
3, 6, 13	104 weeks	Rat, males	13	-	No significant lesions of the genital systems.	(174)
4, 7, 15	104 weeks	Rat, females	4	7	Minimal to mild ovarian interstitial cell hyperplasia (dose-dependent).	(174)
7, 13, 27	105 weeks	Mouse, males	27	-	No significant lesions of the genital systems.	(174)
8, 18, 37	105 weeks	Mouse, females	37	-	No significant lesions of the genital systems.	(174)
50, 100, 200, 400, 800	13 weeks	Rat and mouse, both sexes	- 200	50 400	Ovarian interstitial cell hypertrophy (dose-dependent). Atrophy of the seminiferous tubules.	(174)
55, 120, 220, 430, 750	13 weeks	Rat, males	220	430	Atrophy of the seminiferous tubules.	(174)
62.5, 124, 250	14 weeks	Mouse, both sexes	-	62.5	In F_1, reduced sperm motility (47 % vs. 72 % in controls) and increase of abnormal sperms (4 % vs. 3 %).	(35, 128)
			62.5	124	In F_0, increase of dead pups.	
65, 120, 230, 430, 770	13 weeks	Rat, females	-	65	Ovarian interstitial cell hypertrophy and interstitial inflammation.	(174)
65, 130, 230, 530, 1 050	13 weeks	Mouse, females	230	530	Bilateral cytoplasmic vacuolisation of the ovarian interstitial cells.	(174)
100, 200 (<9 % TOCP)	8 weeks	Rat, males	- 100	100 200	Increase of abnormal sperms (19 vs. 6 % in controls). Reduction of sperm concentration, motility and velocity. Histopathologic changes in the testes and epididymides.	(31)

Table 14. Summary of reproductive and developmental toxicity in animal studies.

Dose range, mg/kg bw/day	Exposure duration	Species, sex	NOAEL, mg/kg bw/day	LOAEL, mg/kg bw/day	Outcome at the NOAEL/LOAEL	Reference
200, 400 (<9 % TOCP)	14 days prior to breeding, 10 days breeding, gestation until postnatal day 21	Rat, females	-	200	Fertility rate severely affected. Proportion of littering 45 % vs. 95 % in controls. Overall breeding success 38 % vs. 75 % in controls. Mean litter size 9.6 vs. 11.3 in controls. Diffuse vacuolar cytoplasmic alteration of ovarian interstitial cells.	(31)
400	20, 40 and 60 days	Rat, both sexes	-	400	Hypertrophy and lipidosis of ovarian interstitial cells. Degeneration of seminiferous tubules.	(131)
400	135 days	Rat, both sexes	-	400	Decreased fertility index, number of litters born and number of pups per litter. 100 % infertility in males.	(132)
TOCP						
10, 25, 50, 75, 100	9 weeks	Rat, males	-	10	Significant decrease of non-specific esterase activity in testis. Normal testicular morphology. 0.25 % abnormal sperms vs. 0.17-0.19 % in controls.	(205)
			-	25	Normal array of germ cells appeared disorganised. 1.20 % abnormal sperms vs. 0.17-0.19 % in controls. 16 % amorphous sperms vs. 0 % in controls.	
			-	50	Pathologic testicular histology. 34 % abnormal sperms vs. 0.17-0.19 % in controls. 39 % amorphous sperms vs. 0 % in controls. No observable motile sperm.	
87.5, 175, 350 [a]	Gestation days 6-18	Rat, females	-	87.5	Increased foetal weight at all doses but no difference between exposed groups.	(231)
			175	-	No indication of teratogenic effect (no effect on pre-implantation loss or resorption, no increase of visceral or skeletal variations). No maternal toxicity.	

Table 14. Summary of reproductive and developmental toxicity in animal studies.

Dose range, mg/kg bw/day	Exposure duration	Species, sex	NOAEL, mg/kg bw/day	LOAEL, mg/kg bw/day	Outcome at the NOAEL/LOAEL	Reference
100-1 600	2 weeks	Rat, males		100	Decreased epididymal sperm density and disruption of the seminiferous epithelium.	(205)
150	3 weeks	Rat, males	-	150	Complete absence of germinal cells in the testis. Irreversible testicular lesion.	(206)
TBEP						
250, 500, 1 500	Gestation days 6-15	Rat, females	1 500	-	No effects on foetal resorption, foetal viability, post-implantation loss, total implantations or the incidence of foetal malformations.	(103) [b]
TBP						
13-21, 44-70, 193-316 [c]	Prebreed, during mating and gestation (13 weeks) until postnatal day 21	Rat, F_1 both sexes	13-21	44-70	Occasional postnatal weight reduction (F_2), which was consistent at 193-316 mg/kg bw. Maternal toxicity.	(234)
12-17, 41-60, 178-266 [c]	As above	Rat, F_0 both sexes	41-60	178-266	Consistent postnatal weight reduction (F_1). Maternal toxicity.	(234)
0, 100, 200, 400, 800	Gestation days 7-17	Rat, females	100	200	Maternal weight gain reduction (adjusted for gravid uterus). Maternal toxicity. Dose-finding study.	(168)
0, 62.5, 125, 250, 500	Gestation days 7-17	Rat, females	250	500	Increase of rudimentary lumbar ribs. Maternal toxicity.	(168)
50, 150, 400	Gestation days 6-18	Rabbit, females	150	400	No foetotoxicity or teratogenicity. Maternal and embryotoxicity (presented as an abstract).	(196)
188, 375, 750	Gestation days 6-15	Rat, females	375	750	Reduced foetal body weights and delayed ossi-fication. Maternal toxicity (presented as an abstract).	(196)

Table 14. Summary of reproductive and developmental toxicity in animal studies.

Dose range, mg/kg bw/day	Exposure duration	Species, sex	NOAEL, mg/kg bw/day	LOAEL, mg/kg bw/day	Outcome at the NOAEL/LOAEL	Reference
TCEP						
22, 88, 175	13 weeks	Rat, males		22-175	Decreased sperm motility. Level at which effect appeared unknown.	(159)
44, 175, 700	13 weeks	Mouse, both sexes		44-700	Increase of abnormal sperms. Level at which effect appeared unknown.	(159)
50, 100, 200	Gestation days 7-15	Rat, females	200	-	No teratogenic effects (no increase of foetal death, no malformations, and normal development). Maternal toxicity (7/30 died).	(115)
175, 350, 700	14 weeks	Mouse, both sexes	175	350	Decreased number of litters per pair (8 %). Decreased number of live pups per litter (20 %).	(36)
0.5, 1.5 mg/m^3 (inhalation)	4 months	Rat, males	-	0.5 mg/m^3	Testicular toxicity (decreased sperm counts and sperm motility and abnormal sperm morphology).	(200)
			0.5 mg/m^3	1.5 mg/m^3	Decreased fertility (increased pre- and post-implantation loss, decreased litter sizes).	
TDCPP						
5, 20, 80	12 or 24 months	Rat, males	-	5	Atrophy of the seminal vesicle and decreased secretory product at all dose levels (the results of the 2 references seem to be based on the same dataset although group sizes differ).	(102, 217)[d]
			5	20	Benign interstitial tumours in testis (also at 80 mg/kg).	
2, 20, 200	12 weeks	Rabbit, males	200	-	No effect on mating behaviour, fertility, sperm quality or quantity (presented as an abstract).	(254)
25, 50, 100, 200, 400	Gestation days 7-15	Rat, females	200	400	Foetotoxicity (increased number of foetal deaths). Severe maternal toxicity.	(227)
25, 100, 400	Gestation days 6-15	Rat, females	100	400	Increased resorptions and foetal mortality. Maternal toxicity.	(243)[e]

Table 14. Summary of reproductive and developmental toxicity in animal studies.

Dose range, mg/kg bw/day	Exposure duration	Species, sex	NOAEL, mg/kg bw/day	LOAEL, mg/kg bw/day	Outcome at the NOAEL/LOAEL	Reference
TEHP						
No data						
TEP						
125, 625	Not given	Rat, females	625	-	No evidence of teratogenic potential. Maternal toxicity.	(237)
335, 670	Not given	Rat, both sexes	335	670	Reduction of litter size. No maternal toxicity.	(237)
TIPP						
No data						
TMCPP (Unspecified)						
6, 70, 625	Gestation days 0-20	Rat, females	-	6	Dose-related increases in the incidence of missing 13th ribs and cervical ribs. No maternal toxicity.	(216) [f]
TPP						
166, 341, 516, 690 [g]	13 weeks (from 4 weeks post weaning through mating and gestation	Rat, both sexes	- 690	166 -	Increased number of soft tissue variations. Equivocal evidence of developmental toxicity. No effect on fertility.	(252)

[a] 28 % maternal deaths at 350 mg/kg bw.
[b] Monsanto 1985d, cited in (103).
[c] Approximate doses for females. Doses for males are presented in the text.
[d] Aulette and Hogan 1981, cited in (102) and Stauffer 1981b, cited in (217).
[e] Hazleton 1978, cited in (243).
[f] Kawasaki *et al* 1982, cited in (216).
[g] Daily intake during pregnancy.

TCP Male rats gavaged with 100-1 600 mg/kg bw/day for 14 days of TOCP exhibited decreased epididymal sperm density and disruption of the seminiferous epithelium in all treated animals (205).

A subchronic 63-day study (reflecting the 49-day length of the rat seminiferous epithelium cycle plus the 14-day transit time of spermatids through the epididymis) was initiated. Dose-dependent (10-100 mg TOCP/kg bw/day) decreases in cauda epididymal sperm motility and density, testicular enzyme activities and alterations in sperm morphology were observed. The 10-mg/kg dose caused a significant decrease of non-specific esterase activity in testis. There was a normal testicular morphology and a slight increase of abnormal sperms, 0.25 % versus 0.17-0.19 % in controls. At 25 mg/kg bw, a significant decrease of non-specific esterase activity in testis was observed. The normal array of germ cells appeared disorganised. There was an increase of abnormal sperms (1.20 % versus 0.17-0.19 %) and amorphous sperms (16 % versus 0 % in controls). The 50-mg/kg dose caused a significant decrease of non-specific esterase activity in testis and a pathologic histology. There was an increase of abnormal (34 % versus 0.17-0.19 %) and amorphous sperms (39 % versus 0 %) and a significant decrease of motile sperms. At the doses 50, 75 and 100 mg/kg bw, there were no observable motile sperms. Concurrent pair-fed controls (matched to the highest dose group, 100 mg/kg/day) indicated that weight loss from TOCP administration had contributed minimally to the testicular toxicity. Plasma α-tocopherol acetate (vitamin E) and testosterone concentrations were unaffected. TPCP, the non-neurotoxic structural analogue of TOCP, produced a slight decrease of testosterone levels but no effect on sperm quality at 100 mg/kg bw. According to the authors, a minimum effective dose for observable testicular toxicity was determined to be 10-25 mg TOCP/kg bw. The data suggest that TOCP interferes with spermatogenic processes and sperm motility (205).

Eight male F344 rats were given 150 mg/kg bw of TOCP in corn oil for 21 successive days. The animals were allowed to recover for 98 days (two cycles of the seminiferous epithelium) with no further treatment. Complete absence of germinal cells in the testis was observed in all treated animals. Thus, this treatment caused an irreversible testicular lesion (206).

Pregnant Long Evans rats were gavaged with 87.5, 175 or 350 mg/kg bw/day TOCP throughout organogenesis, i.e. from gestation days 6 through 18 (Day of sperm = Day 0). The highest dose tested (350 mg/kg bw) was lethal in 28 % of the dams, whereas no maternal deaths or toxicity were observed in the 87.5- or 175-mg/kg dose groups. There were no significant differences noted among the experimental and control groups for preimplantation loss or resorption. Foetal weights for both sexes in the TOCP groups were significantly greater than in the control group, however, no difference among the TOCP groups was observed. There was no difference regarding number of implants/litter, preimplantation loss and resorption between treated and controls. Malformation rates were too low to warrant statistical analysis. Numerous soft tissue and skeletal variations were observed in both control and TOCP-treated groups and there were no significant

differences in the frequency of variations between the dose groups. The results of this study indicate that TOCP is not teratogenic in the Long Evans rat (231).

In studies by NTP (detailed below), F344/N rats and $B6C3F_1$ mice were gavaged or fed diets with a complex mixture of 18 % dicresyl phosphate esters and 79 % TCPs. Two of the TCPs were indentified as TMCP (21 %) and TPCP (4 %) with no detectable TOCP (< 0.1 %).

In a sub-chronic toxicity study (described also in Section 10.6), groups of 10 male and 10 female F344/N rats and $B6C3F_1$ mice received TCP in corn oil by gavage at doses of 0, 50, 100, 200, 400 or 800 mg/kg bw for 13 weeks. All animals survived. In rats, ovarian interstitial cell hypertrophy occurred in all dosed female groups. Atrophy of the seminiferous tubules occurred in males receiving 400 and 800 mg/kg. In mice, ovarian interstitial cell hypertrophy and adrenal cortex cytoplasmic vacuolisation occurred in all dosed female groups (174).

In a similar study, groups of 10 male and 10 female F344/N rats were fed diets containing 0, 0.9, 1.7, 3.3, 6.6 or 13 g/kg of TCP for 13 weeks. The estimated delivered daily doses were 55, 120, 220, 430 and 750 mg/kg bw for males and 65, 120, 230, 430 and 770 mg/kg bw for females. Ovarian interstitial cell hypertrophy and interstitial inflammation occurred in all exposed groups of females. Basophilic hypertrophy of the pituitary gland pars distalis and atrophy of the seminiferous tubules occurred in male rats receiving 6.6 and 13 g/kg diet (174).

$B6C3F_1$ mice were fed diets containing 0, 0.25, 0.5, 1.0, 2.1 or 4.2 g/kg of TCP for 13 weeks. The estimated delivered daily doses were 45, 110, 180, 380 or 900 mg/kg bw for males and 65, 130, 230, 530 and 1 050 mg/kg bw for females. At the two highest doses, bilateral cytoplasmic vacuolisation of the interstitial ovarian cells was observed (174).

In a chronic toxicology and carcinogenesis study (described also in Section 10.6), groups of 95 male and 95 female F344/N rats were fed diets containing 0, 0.075, 0.15 or 0.3 g/kg of TCP for 2 years. The estimated delivered daily doses were 3, 6 and 13 mg/kg bw for males and 4, 7 and 15 mg/kg bw for females. Ovarian interstitial cell hyperplasia was observed after 3 months (6/10 versus 0/10) in the 7 mg/kg bw group of females but not later. These changes were observed at all interim evaluations at the dose 15 mg/kg bw (174).

In a corresponding 2-year study, $B6C3F_1$ mice were fed diets containing 0, 0.06, 0.125 or 0.25 g/kg TCP (corresponding to average daily doses of 7, 13 or 27 mg/kg bw in males and 8, 18 or 37 mg/kg bw in females). There were no significant lesions of the genital systems of males or females (174).

Swiss CD-1 mice were exposed to TCP using the reproductive assessment by continuous breeding protocol (RACB). The TCP mixture contained 21 % TMCP, 4 % TPCP and < 0.1 % TOCP. Overall, pure or mixed *ortho-, meta-, para*-tricresyl isomers composed 75 % of the total, with the remainder composed of dicresyl phenyl and di- and tricresylxylyl phosphates. TCP was mixed into the feed at 0, 0.5, 1 or 2 g/kg. The estimated doses of TCP were 62.5, 124 and 250 mg/kg bw/day. The fertility index was not changed in the animals consuming the high-concentration feed. However, the number of litters per pair decreased in a dose-

related fashion, and the proportion of liveborn pups and their weight were significantly decreased in the high-dose group. A crossover mating trial demonstrated impaired fertility in both males and females exposed to 2 g TCP/kg diet, with a greater effect in females. Histopathology of the F_0 pairs revealed dose-related seminiferous tubule atrophy and decreased testis and epididymal weights in the high-dose males, while the female reproductive tract showed no histopathological changes. There were dose-related changes in the adrenals of both sexes, and body weight was depressed in both sexes at the highest concentration. The last litter was reared by the dam until weaning, after which dosed feed was provided to the F_1 mice at the same concentrations as their parents had consumed. The last litter born in the 98-day breeding phase was reared to age 74 days and then mated within the control and two of the treatment groups (0, 0.5 and 1 g TCP/kg) (there were too few offspring in the 2 g/kg group). There was a decrease in the fertility index in the 1 g/kg group and a decreased proportion of liveborn and number of liveborn pups per litter. At necropsy, sperm concentration and morphology in the F_1 males were normal at termination, although motility was decreased in both the 0.5 and the 1 g/kg diet groups compared to controls. These data show that TCP impaired fertility in both sexes of mice in the F_0 generation and affected sperm motility at even the lowest dose in F_1 males (62.5 mg/kg bw) (35, 128).

In a later review of reproductive toxicants tested within the NTP, TCP was ranked as a highly toxic chemical with an effect observed at 62 mg/kg bw/day (156), a level based on the above mentioned study (35, 128).

Long Evans rats were exposed to TCP containing less than 9 % TOCP, the remainder being a mixture of TPCP, TMCP and other tri-cresyl isomers. Male Long-Evans rats received 0, 100 or 200 mg/kg bw and females received 0, 200 or 400 mg/kg bw of TCP in corn oil by gavage. The 100-mg/kg bw males were mated with 200-mg/kg females, and 200-mg/kg males were bred with 400-mg/kg females. Males were dosed for 56 days and females for 14 days prior to breeding and throughout the 10-day breeding period. Following breeding, the males were necropsied and evaluated for sperm parameters and reproductive tract histopathology. Females were dosed throughout gestation and lactation. Pups and adult females were necropsied on postnatal day 21. No clinical signs of toxicity or body weight depression were observed among male or female rats. Sperm concentration, motility and progressive movement were decreased for 200-mg/kg males. A dose-dependent increase in abnormal sperm morphology was observed for males in both TCP dose groups. The percent of sperm-positive females per group was unchanged but the number of females delivering live young was severely decreased by TCP exposure. Litter size and pup viability were decreased in the 400-mg/kg dose group. Pup body weight and developmental landmarks were unaffected by TCP exposure. Histopathologic changes were observed in the testes and epididymides of male rats at 200 mg/kg. A dose-dependent diffuse vacuolar cytoplasmic alteration of ovarian interstitial cells was observed in female rats (31).

Male and female F344 rats received single daily oral doses of 400 mg/kg bw of TCP in sesame oil for 20, 40 and 60 days (the is study also described in Section

10.3). There was a significant increase of cytoplasmic lipidosis in ovarian interstitial and adrenocortical cells in females. In males, there were decreased testicular weights and degeneration of the seminiferous tubules (131).

In another study by the same research team, groups of breeding F344 rats received single daily oral doses of 400 mg/kg bw of TCP in sesame oil for up to 135 days beginning 7 days prior to pairing. A naive control group allowed to breed but not dosed or handled daily demonstrated that daily dosing and handling of the rats had no effect on reproduction. The fertility index, number of litters born and number of pups per litter were significantly decreased in rats exposed to TCP. A crossover mating experiment between exposed and vehicle controls demonstrated that TCP caused 100 % infertility in males, whereas no effects were observed in females. Both sexes in the crossover experiment exhibited significant decreases in terminal body weights and increases in adrenal gland and liver weights. TCP-dosed males had significantly decreased testicular and epididymal weights. TCP-dosed females had increased ovarian weights (132).

TBEP was administered by gavage in corn oil to three groups of 25 mated Charles River CD female rats at dose levels of 0, 250, 500 or 1 500 mg/kg/day on gestation days 6-15. The treatment had no effect on foetal resorption, foetal viability, post-implantation loss, total implantations or the incidence of foetal malformations. The NOAEL was the highest dose level tested, 1 500 mg/kg bw (Monsanto 1985d, cited in (103)). In an earlier range-finding study, maternal weight loss was observed in animals receiving 2 000 but not 1 000 mg/kg bw/day (Monsanto 1985c, cited in (103)).

TBP was administered by gavage to male and female Sprague Dawley rats at doses of 0.14 and 0.42 ml/kg bw (140 and 410 mg/kg) for 14 consecutive days. Effects were investigated at the end of the feeding period. Histopathological examination was only performed in the high-dose animals. Microscopic degenerative changes were found in 50 % of the seminiferous tubules of the testis in one out of four rats (123). The study is described also in Section 10.3.

Thirty CD Sprague Dawley rat weanlings of each sex (F_0) were exposed to TBP in the diet *ad libitum* at 0, 0.2, 0.7 or 3 g/kg for 10 weeks and then randomly mated within groups for 3 weeks with continued exposure. The approximate ranges for daily TBP consumption for males during the prebreed period were 11-18 mg/kg bw for F_0 (10-21 for F_1) at 0.2 g/kg diet, 38-65 (36-72 for F_1) mg/kg bw at 0.7 g/kg diet, and 160-264 (166-328 for F_1) mg/kg bw at 3 g/kg. For females, the approximate ranges were 12-17 mg/kg bw for F_0 (13-21 for F_1) at 0.2 g/kg diet, 41-60 (44-70 for F_1) mg/kg bw at 0.7 g/kg diet, and 178-266 (193-316 for F_1) mg/kg bw at 3 g/kg diet. During gestation (gestation days 0-20), female daily TBP consumption was approximately 13 mg/kg bw for F_0 and F_1 at 0.2 g/kg diet, 47 (45 for F_1) mg/kg bw at 0.7 g/kg diet, and 214 (217 for F_1) mg/kg bw at 3 g/kg diet. During lactation (postnatal days 0-21), the female daily TBP consumption was approximately 26 mg/kg bw for F_0 (31 for F_1) at 0.2 g/kg diet, 94 (107 for F_1)

mg/kg bw at 0.7 g/kg diet, and 404 (502 for F_1) mg/kg bw at 3 g/kg diet. F_0 parents and 10 F_1 weanlings/sex/dose were necropsied and adult reproductive organs, urinary bladders (both sexes), kidneys (males) and livers (females) were evaluated histologically. Thirty F_1 weanlings/sex/dose continued exposure for 11 weeks and were bred as described above. F_1 parents and F_2 weanlings, 10/sex/dose, were then necropsied as described above. Adult toxicity was observed in both sexes and generations at 0.7 and 3 g/kg diet. Observations included reduced body weights, weight gain and feed consumption, urinary bladder epithelial hyperplasia (both sexes), renal pelvis epithelial hyperplasia (only at 3 g/kg diet, males) and centrilobular liver hypertrophy (females). At 0.2 g/kg diet (10-21 mg/kg bw), transient reductions in body weight were observed in F_0 and F_1 females, and urinary bladder epithelial hyperplasia in F_0 males and females and in F_1 males. There was no evidence of reproductive toxicity, of reproductive organ pathology or of effects on gestation or lactation at any dose tested. Postnatal toxicity was evidenced by consistent reductions in F_1 and F_2 pup body weights at 3 g/kg diet and occasional weight reductions in F_2 litters at 0.7 g/kg diet and was associated with maternal toxicity observed at these doses and during the postnatal period. The weight reductions were observed from postnatal day 1. According to the authors, the NOAEL for reproductive toxicity was at least 3 g/kg diet and the NOAEL for postnatal toxicity was approximately 0.2 g/kg diet (234).

In a developmental toxicity study, pregnant New Zealand White rabbits were given TBP (100 % purity) in corn oil at doses of 0, 50, 150 or 400 mg/kg bw/day by gavage on gestational days 6-18. The animals were sacrificed on gestational day 30. Maternal - and embryotoxicity were suggested at 400 mg/kg bw, with no observations of foetotoxicity or teratogenicity in any dosage group. Groups of pregnant Wistar rats (24/group) received TBP (100 % purity) in corn oil at doses of 0, 188, 375 or 750 mg/kg bw/day by gavage on gestational days 6-15. On gestational day 20, the animals were euthanised. Maternal toxicity was observed at all dosages. Only the dams administered 750 mg/kg bw displayed mortality. Significant foetotoxic effects, delayed ossification and reduced foetal body weights were observed in the 750-mg/kg dosage group only. TBP was not teratogenic or embryotoxic in the rat (presented as an abstract, no further details were given) (196).

In a dose-finding study, pregnant Wistar rats were treated orally on gestation days 7-17 with TBP in olive oil at 0, 100, 200, 400 and 800 mg/kg bw/day. All pregnant rats died after five or six consecutive doses of 800 mg/kg bw. In the teratological study, the doses were 0, 62.5, 125, 250 and 500 mg/kg bw/day. The NOAEL for maternal toxicity was considered by the authors to be 62.5 mg/kg bw because of significant decreases in maternal body weight gain found at 200 mg/kg in the dose-finding study. There were no significant differences between the groups in the incidence of dead or resorbed foetuses, the number of living foetuses and the body weights of living foetuses of both sexes. The incidence of rudimentary lumbar rib increased significantly at 500 mg/kg bw. There were two cases of malformations but the incidence was not significantly increased (168).

TBP was injected into the yolk sac of eggs from Leghorn hens and was reported to be slightly teratogenic at a high dose (5 mg/egg) in this test (187). The lack of details in the study precludes a sound conclusion on TBP teratogenicity.

TCEP was given to mice by gavage at doses of 44, 175 and 700 mg/kg bw. The study was a regular 13-week study to which sperm morphology and vaginal cytology examinations were added. Decreased weights of epididymis and testis were recorded and an increase of abnormal sperms in one or more dose groups compared to a control group. Rats were given TCEP by gavage at 22, 88 and 175 mg/kg bw for 13 weeks and a decrease of sperm motility was noted in one or more dose groups compared to a control group (159). The study does not reveal at which dose the effect appears.

TCEP was suspended in olive oil and administered by oral intubation to groups of 23-30 Wistar rats at dose levels of 50, 100 and 200 mg/kg bw during gestation days 7 through 15. No changes in maternal body weight gain, food consumption, and general appearance were observed at 50 and 100 mg/kg bw. A marked suppression of food consumption and maternal body weight gain with toxic symptoms such as piloerection and general weakness was seen in the 200-mg/kg group and 7 out of 30 dams died. There was no evidence of an increase in foetal death or of malformations attributable to the treatment with TCEP at any dose levels examined. In the postnatal examination, the development of the offsprings in all groups examined was well maintained, without any disorders attributable to the treatment in morphological examination and in some functional tests. The authors concluded that TCEP had no teratogenic effect in rats under the present experimental conditions, although the compound elicited maternal toxicity at the highest dose (115).

TCEP was tested for its effects on reproduction and fertility in Swiss CD-1 mice using a continuous breeding protocol (RACB). Data from a 2-week dose-range-finding study were used to set exposure concentrations for the continuous cohabitation phase (14 weeks) at 175, 350 and 700 mg/kg bw by gavage in corn oil. Body weights of treated animals were not different from those of controls. There were significant effects on reproduction. The number of litters per pair was significantly reduced in the mid- and high-dose groups by 8 and 63 %, respectively. Only 2 of 18 pairs of high-dose mice delivered a third litter compared to 37 of 38 controls. The number of live pups per litter was reduced by 20 and 32 % in the mid- and high-dose groups, respectively, although pup viability, sex ratio and body weight remained unchanged. Cumulative days to deliver each litter were increased in the high-dose group only, an effect which started at the second litter (40 days from the start of cohabitation for controls to deliver their second litter versus 66 days for high-dose mice).

The last litter from all dose groups was reared by the dam and monitored for viability and growth. There were no pups at the high dose. Although dam weight was reduced by approximately 7 % in the middle dose group compared to control, there were approximately 50 % fewer pups per litter, so pup weight gain during nursing was greater in the middle dose group than in controls.

After the crossover mating, the control and high-dose F_0 mice were killed and necropsied. In males, body weight was unchanged, absolute testis weight was reduced by approximately 30 %, and relative liver weight and kidney weight was increased by 15 % and decreased by 20 %, respectively. Epididymal sperm density was reduced by approximately 30 %, motility was reduced by more than 50 % and abnormal forms increased from a control value of 9 to 31 %. In high-dose F_0 females, body weight was unchanged and relative kidney weight was reduced by approximately 10 %. Oestrous cyclicity was unchanged.

F_1 adults were killed and necropsied. Mid-dose males weighed 6 % more than controls but there were no other changes seen at necropsy. Female body weights did not differ across groups nor were organ weights or oestrous cycle parameters different. Microscopically, there were more liver changes in middle dose males than in controls, an effect not seen in females. There were no other significant microscopic lesions.

These data showed clear effects of TCEP on murine reproduction, manifest as fewer and smaller litters. At least at the high dose, the effect occurred primarily in the males. In both generations, doses that caused hepatic changes also reduced fertility. Whether the converse occurs (fertility changes at doses that do not affect the liver or kidneys) is unknown because of the lack of necropsy data for the F_0 middle dose group (36, 37).

In a poorly reported inhalation study, male rats were continuously exposed to 0.5 or 1.5 mg TCEP/m^3 for 4 months. Testicular toxicity was seen at both exposure levels, with more severe effects at the highest level. There were decreased sperm counts, decreased sperm motility and abnormal sperm morphology. Histology of the testes showed an increased number of spermatogonia but decreased numbers of sperm in the later stages of development. When the treated males were mated there was decreased fertility at 1.5 mg/m^3 with increased pre- and post-implantation loss and decreased litter sizes (200).

TDCPP In a fertility study, male rabbits were given TDCPP orally at 2, 20 or 200 mg/kg bw/day for 12 weeks. There were significant treatment-related increases in liver and kidney weights in the highest dose group. The treatment did not affect mating behaviour, fertility, sperm quality or quantity. No histopathological lesions were reported in testes or epididymides (presented as an abstract) (254).

Male Sprague Dawley rats were fed 0, 5, 20 or 80 mg/kg bw/day in the diet for 12 or 24 months. In the seminiferous tubules, there was a slight increase in occurrence of oligospermia (35/57, 31/60, 45/60, 51/56), eosinophilic material in the tubular lumen (2/57, 4/60, 12/60, 11/56), sperm stasis (5/57, 5/60, 11/60, 14/56) and periarteritis nodosa (5/57, 10/60, 19/60, 16/56). In the epididymides, males given 80 mg/kg bw had an increased incidence of oligospermia and degenerated seminal products. The lowest TDCPP dose of 5 mg/kg bw caused atrophy of the seminal vesicle and decreased secretory product. These effects were also observed at higher doses (Stauffer 1981b, cited in (217)).

Groups of 50 male rats received approximately 0, 5, 20 or 80 mg/kg bw of TDCPP by dietary administration for 2 years. In the seminiferous tubules, there was a slight increased occurrence of germinal epithelium atrophy and oligospermia (30/43, 29/48, 42/47, 44/45), eosinophilic material in the tubular lumen (2/43, 4/48, 12/47, 11/45), sperm stasis (5/43, 5/45, 11/47, 14/45) and periarteritis nodosa (5/43, 10/48, 19/47, 14/45). There was also an increase of benign testicular interstitial tumours nodulus (7/43, 8/48, 23/47, 36/45). Seminal vesicle atrophy and decreased secretory products were reported in all treated groups. In the epididymides, males given 80 mg/kg bw had an increased incidence of oligospermia and degenerated seminal products (Aulette and Hogan 1981, cited in (102)). The data are apparently the same as those presented above by Stauffer 1981b, cited in (217), and by Freudenthal and Henrich 2000 (69), although group sizes differ.

Female Wistar rats were given 25, 50, 100, 200 or 400 mg/kg bw by oral intubation on gestation days 7-15. In the 400-mg/kg group, there was severe maternal toxicity with markedly suppressed maternal body weight gain and food consumption. Eleven out of 15 dams died. In the 200-mg/kg group, a significant increase in relative kidney weight by 15 % in the dams was observed. There was no evidence of an increased number of foetal deaths, of abnormal foetal development or of malformations at an exposure of 200 mg/kg or less. The highest dose (400 mg/kg) was associated with a significantly higher incidence of foetal death. In this study, the NOAEL and LOAEL for maternal toxicity were 100 mg/kg bw and 200 mg/kg bw, respectively. The NOAEL and LOAEL for foetotoxicity were 200 and 400 mg/kg bw, respectively. In postnatal examination performed at dose levels of 200 mg/kg and below, the development of offspring appeared well without any appreciable change in functional tests. The authors concluded that TDCPP had no teratogenic effect in rats under the present experimental conditions, although the compound elicited maternal and foetal toxicity at the highest dose, 400 mg/kg bw (102, 227).

Pregnant Sprague Dawley rats (20/group) received 0, 25, 100 or 400 mg/kg bw per day by gavage on gestation days 6-15. Maternal toxicity manifested as clinical signs, reduced food consumption and transient reductions in body weight was observed at 100 and 400 mg/kg bw. TDCPP had no effect on implantation efficiency or mean number of corpora lutea. Treatment at 400 mg/kg significantly increased the number of resorptions and reduced foetal viability. Decreased skeleton development in the highest dose group was related to growth retardation and decreased foetal size. The incidence of malformations were not treatment-related (Hazleton 1978, cited in (243)).

TEHP No data were located.

TEP In an early study using a small number of rats, the litter size was reduced after repeated feeding of both sexes at 670 mg/kg bw/day, although no symptoms of poisoning were described in the parent animals. The NOAEL for effects on the litter size was 335 mg/kg/bw/day. Neither testicular weights nor the histological

investigation of the testes revealed any remarkable findings (highest dose 6 700 mg/kg bw) (237).

In a 28-day study with doses up to 1 000 mg/kg bw, no effect on testicular weight was observed (237).

A teratogenic study in rats showed no evidence of a teratogenic potential up to the highest dose of 625 mg/kg bw (NOAEL for developmental toxicity). At the highest dose, there was reduction of body weight gain, food intake and faeces excretion as signs of maternal toxicity (NOAEL 125 mg/kg bw/day) (237).

In the UNEP review (237) from which the above data were taken, no further details were given and references were not adequately presented.

TIPP No data were located.

TMCPP Groups of 11-14 pregnant female Wistar rats were fed a diet containing 0, 0.1, 1 or 10 g/kg TMCPP (not specified) during gestation days 0-20. The intake of TMCPP was estimated to 0, 6, 70 and 625 mg/kg bw/day. Some dams were sacrificed on gestation day 20, and the foetuses were examined for skeletal or visceral abnormalities. Litters born naturally from groups of five to seven dams were culled to eight neonates each and monitored for 4 weeks. TMCPP had no effect on food consumption or body weight gain in dams. TMCPP did not affect the number of implants, the number of resorptions or the number or weight of live foetuses. No foetuses died or had obvious external malformations. The incidence of skeletal or visceral malformations in foetuses from treated litters was not statistically different from controls. However, dose-related increases in the incidence of missing 13th ribs and cervical ribs were observed in treated foetuses. Delayed ossification of sternebra was observed in all groups. Treatment *in utero* had no effect on growth or survival of weanlings up to postnatal day 28 (Kawasaki *et al* 1982, cited in (216)).

A group of 18 adult White Leghorn hens received an initial oral dose of 13 200 mg/kg bw of Fyrol PCF followed by the same treatment 3 weeks later. The animals were sacrificed 3 weeks after the second dose. Egg production ceased shortly after the first dose and there was severe loss of feathers (209).

TPP Male and female Sprague Dawley rats were fed dietary levels of 0, 2.5, 5, 7.5 or 10 g TPP/kg from 4 weeks post weaning for 91 days through mating and gestation. At these dietary levels, the daily intake of TPP during pregnancy was 0, 166, 341, 516 and 690 mg/kg bw, respectively. No adverse effect on fertility was observed. All treated groups had significantly more foetuses with moderate hydroureter than the control group. However, the high baseline incidence exhibited in the control group and lack of clear dose-related response make the biological significance of this finding unclear. The average number of foetuses having at least two soft-tissue variations was significantly higher in all dose groups except the highest. However, the proportion of litters with foetuses having at least two soft-tissue variations was 7 % (controls), 24 % (166 mg/kg), 41 % (341

mg/kg) 32 % (516 mg/kg) and 18 % (690 mg/kg). The authors concluded that TPP exposures had no toxic effects on mothers or offspring at these dosages. No significant increases in the incidence of anomalies were seen in the treated groups as compared to the control values (252). NEG notes that the lack of dose-response may not be so such a spurious finding, since the spacing of doses is rather small. If the dose-response curve is shallow, one may not expect obvious variation with dose, taking general variation into account. The results of the study are classified as equivocal.

10.8 Summary

A condensed summary of main effects reported in animal or *in vitro* studies of flame retardant phosphate ester exposures is presented in Table 15.

Table 15. Main effects of phosphate triesters in animal and *in vitro* studies.
Symbols used: + clear effect, (+) slight effect, +/- inconclusive, - no clear indication of effect.

Compound	Irritation		Neurotoxicity		Genotoxicity	Cancer	Reproductive and developmental toxicity		Target organ for critical effects [a]
	Skin	Eye	OPIDN (in hens)	Other			Fertility	Development	
TCP	(+)	No data	+		-	-	+	+	
TOCP	No data	No data	+		No data [b]	No data	+	-	
TBEP	(+)	-	-	+	-	No data	No data	-	Liver
TBP	+	(+)	-	(+) [c]	-	+	-	-	
TCEP	(+)	(+)	-	+	+/-	+	+	-	Liver, kidney
TDCPP	+	(+)	-	(+) [c]	+/-	+	+	-	
TEHP	+	-	-	(+) [c]	-	+	No data	No data	
TEP	No data	No data	No data	+	-	No data	Insufficient data	Insufficient data	Liver, spleen, kidney, testes
TIPP	- [d]	(+) [d]	+/- [e]		Insufficient data	No data	No data	No data	Liver [f]
TMCPP	- [g]	(+) [g]	- [g]	(+) [c, g]	- [h]	No data	No data	(+)	
TPP	-	-	-	-	-	No data	-	+/-	

[a] Effects other than neurotoxicity, cancer/hyperplasia, reproductive and developmental toxicity.
[b] No standard genotoxicity tests available, but DNA adducts were present in several organs after *in vivo* oral exposure of rats.
[c] Minor effect or effect shown in one high-dose study.
[d] Isopropylated triphenyl phosphate.
[e] Tri-*ortho*-, tri-*meta*- and tri-*para*-isopropylphenyl phosphates are considered not to be neurotoxic, but other isomers (e.g *ortho*-isopropylphenyl diphenyl phosphate) found in commercial products may cause OPIDN.
[f] Kronitex® 100.
[g] Fyrol PCF.
[h] Different commercial TMCPP products.

11. Observations in man

11.1 Irritation and sensitisation

Respiratory and eye irritation data are lacking. Skin irritation data are presented below.

TCP Mild irritation after initial contact with TCP formulations in patch tests on volunteers was reported by Broadhurst *et al* 1951, cited in (215).

Totally 230 patients with occupational dermatitis in the metallurgic industry in Spain were studied with a standard patch test (10 % TCP in olive oil). The proportion of tests positive to TCP was 2.6 % (9). In Finland, totally 839 patients were patch tested with a 5 % TCP solution and none reacted (228).

In Germany, 199 metalworkers were patch tested with a 5 % TCP solution because of suspected metalworking fluid dermatitis. No positive reactions were seen (72).

A patient with eczema gave a strong reaction to the surgical tape used in applying patch test, which was the result of sensitivity to TCP (tested with a 5 % solution). This patient also reacted to TPP (182).

TBEP A repeat human insult patch test on a panel of 209 volunteers was undertaken by Monsanto. In the 3-week induction period, 0.2 ml of TBEP was applied for 24 hours to occluded skin 4 times/week. During the 4th week, 4 similar applications were made to previously untreated skin. During induction, minimal irritation was observed in 9 of the individuals. The irritation was only observed once or twice during the 12 applications. There was no dermal reaction to the challenge applications. The results indicate minimal skin irritation and no sensitising potential (Monsanto 1984a, cited in (103)).

TBP In an occlusive skin irritation test, TBP was irritating when tested as a 75 % solution in lanoline for 3 hours. When applied as 50 % and 25 % solutions in lanoline for 24 hours, mild irritation and no irritation, respectively, were reported (German Chemical Society 1995, cited by (79)). TBP has been shown to have an irritant effect on the skin and mucous membranes in humans (101).

Patches with a solution containing less than 25 % TBP were applied 15 times on alternate days on the skin of 53 volunteers. No reactions were observed 24 hours after the final patch. Thus, there was no evidence of sensitisation (Monsanto 1980, cited by (79)).

One case of sensitisation to TBP was reported among 42 patients with furniture-related dermatitis (129).

TCEP and ***TDCPP*** No data were located.

TEHP No irritant effects were seen after 24 hours of exposure to a TEHP-saturated cotton swab placed on the skin of the forearm of 6 volunteers. A piece (2

cm^2) of PVC plastic containing 40 % TEHP was placed on the arm of 8 volunteers for 72 hours. Slight redness but no irritation was observed (Kimmerle 1958, cited in (103)).

TEP No data were located.

TIPP Skin irritation was not reported among workers exposed to hydraulic fluids containing isopropylated triphenyl phosphate (27, 113).

TMCPP No data were located.

TPP Allergic contact dermatitis has been reported after exposure to TPP in cellulose acetate films (86), glues (25) and spectacle frames (26, 182). Between 1950 and 1962, 15 out of 23 192 (0.065 %) patients in Denmark showed positive reactions when tested with discs of cellulose acetate film plasticised with 7-10 % TPP. Approximately 2 250 (out of the 23 192) were re-examined by routine patch tests after an interval of years. Two or possibly three patients with chronic eczema had been sensitised to the cellulose acetate film as a result of the patch test (86). In Finland, totally 343 patients were patch tested with a 5 % TPP solution and none reacted (228).

Probable cross-reactivity between triphenyl phosphite and TPP has been observed (87).

11.2 Effects of single and short-term exposure

TCP There are many reported cases of human poisoning, mostly from TCP contamination of food-stuffs. Occupational poisoning, usually resulting from dermal exposure, has also been reported. Around 60 000 people have been poisoned worldwide. The *ortho* isomer of TCP is generally regarded as the responsible toxic agent (99). Mono-*ortho* and di-*ortho* isomers are even more neurotoxic than TOCP (257). Short-term symptoms after ingestion might involve vomiting, abdominal pain and diarrhoea. These clear up and a symptom-free interval follows lasting from 5 to 21 days. This interval is followed by soreness of the muscles below the knees and numbness of the toes and fingers lasting several days and followed by weakness of the toes and bilateral foot-drop. After another interval of about 10 days, weakness of the fingers and wrist-drop follow. This paralysis is usually not as severe as that in the feet and legs. In the upper extremities, paralysis does not extend above the elbows. The thigh muscles may be involved in advanced cases (93).

There is considerable variation in the sensitivity of individuals to TOCP. Severe symptoms were reported with a TOCP dose of 0.15 g in one individual, while others were unaffected by 1-2 g (259). There is also considerable variation in the rate of recovery from poisoning. Some patients recover completely, whereas others are still severely affected years later, after apparently similar exposure (99).

In 1960, 58 cases of TOCP-poisoning were reported in Bombay, India and 32 patients were investigated in hospital. The patients had been using mustard oil for cooking and massaging the body for years. TOCP was detected in 49 out of 344 samples of oil obtained from shops in the areas, and the concentrations varied from 0.7 to 32.5 mg per 100 g oil. As the contaminated oil did not differ from regular cooking oil in smell or taste, it was not possible to establish the interval between consumption of the toxic oil and the first symptoms. The clinical features were similar to those reported in previous outbreaks of TOCP poisoning. Cholinesterases in blood were measured in 9 patients. Erythrocyte acetylcholinesterase was reduced by about 50 % shortly after onset of clinical symptoms and reached normal values after 3 months. Plasma cholinesterase showed a transient increase reaching a maximum in about a month and then gradually decreased, reaching the normal range after a period of 3-6 months (260). No information was presented regarding duration of exposure.

One of the latest outbreaks of toxic neuropathy was reported in July 1988 from India. About 600 victims were reported to Vidya Sagar Hospital, Calcutta, of which 343 were admitted. Some rapeseed oil samples were contaminated with TCP to the extent of 22-57 % (210).

TBEP No data were located.

TBP Workers exposed to 15 mg/m^3 of TBP complained of nausea and headache (Mastromatteo, personal communication to ACGIH (3)).

TCEP, TDCPP, TEHP, TEP, TIPP, TMCPP and ***TPP*** No data were located.

11.3 Effects of long-term exposure

TCP Three workers manufactured TCP with a high content of TOCP and also handled TPP. They performed similar working tasks and developed polyneuritis. All eventually returned to work (94). The first worker was 41 years of age and exposed for 2.5 years while manufacturing TOCP and TPP. Six months before admission, the process was speeded up and he worked every Sunday instead of one in four. For 2 days he suffered from abdominal pain and diarrhoea and 5 days later he could not walk properly. The disability progressed until he was unable to stand without support. One year after admission, he was completely recovered and returned to work.

The second worker was 30 years old and exposed for 8 months prior to admission. He worked 63 hours/week. After 5 months, he complained of cramp-like pains in the thighs, calf muscles and toes. Later he experienced weakness of feet and only walked with difficulty. He made slow progress and after 3.5 years only slight residual signs of neuropathy were present.

The third worker was 38 years old and exposed for 6 months prior to admission. During this time he complained of cramp-like pains in his hands, which started after he had been lifting heavy drums. He had diarrhoea and noticed some days

later that his toes dragged along the ground and that his feet slapped down as he walked. He suffered from severe pain in his calf muscles and in his hands. The weakness of his legs gradually became worse. He was discharged after ten months in hospital, able to walk with no evidence of foot drop (94).

All the 3 men worked in a room 7.5 × 3.5 m with a height of 3.5 m that was totally enclosed during the hours of darkness due to black-out regulations, although it was provided with a vent. During daylight, windows and doors were open. Crude TCP entered tanks at a temperature of about 60 °C. The TCP was immediately cooled with added cold water. Measurements of air concentrations were performed later but arranged in such a way as to represent the working conditions of interest. The measured air concentrations were 0.55-1.7 mg/m^3 and the TOCP content of the finished product was about 60 % (94). Thus, the roughly calculated exposure to TOCP would be about 0.33-1.0 mg/m^3. However, dermal exposure could have a great impact on body burden and consequently invalidate the apparent relation between air concentrations and response.

The clinical picture of TOCP poisoning resulting in permanent disability was demonstrated by a 27-year old man who had manufactured *meta* and *para* isomers of TCP for use as plasticisers. The final product contained less than 1 % TOCP but 6-10 % was present during manufacturing. The first symptoms appeared after 5 months of exposure, being general malaise, anorexia, nausea, vomiting and aching of the lower limbs. His condition deteriorated and 3 months after the onset of symptoms, a coarse static tremor involving head, trunk and upper limbs had developed and he was unable to feed himself. Blurring of vision progressed slowly and there were flexor spasms of the lower limbs and progressive muscular wasting. Fifteen months after the first symptoms he was discharged from the hospital ward. He had spasticity and ataxia of the lower limbs and was unable to walk without assistance. Tremor of his hands was less severe and he was able to feed and shave himself. The clinical findings indicated that the lesions were present in the pyramidal and spinocerebellar tracts and in the cerebellum, and the patient was likely to remain permanently and almost totally disabled (17).

Totally 34 out of approximately 40 men in a plant manufacturing a number of organic phosphates including TCP were investigated in a cross-sectional study. Twenty-eight men worked in the production and six belonged to the clerical and laboratory staff. Among the production workers, 5 of 28 had neuromuscular symptoms and signs (hypoesthesia, decreased vibratory sense and sluggish reflexes) (versus 0/6 in controls), 25/28 had respiratory symptoms (versus 3/6) and 14/28 had gastrointestinal symptoms (nausea, heartburn and vomiting) (versus 1/6). Some of the symptoms may be associated with exposure to the irritant phosphorus chloride. There was no depression of erythrocyte acetylcholinesterase activity. Sixteen workers exhibited a depressed plasma cholinesterase activity (70 % of normal or lower), although no correlation was observed between degree or duration of exposure and cholinesterase activity. There was no correlation between gastrointestinal or neuromuscular symptoms and depressed cholinesterase activity. The men in production manufactured triaryl phosphates containing mixtures of TPP,

TCP and trixylyl phosphates and sometimes phosphates of higher alkyl substituted phenols. The air concentrations varied from 0.27 to 3.4 mg/m^3 reported as TCP, although this chemical also contained other trialkyl phenyl phosphates varying after what was manufactured. The content of TOCP varied up to 20 %. Absorption through the skin may have occurred throughout the whole factory and the workers' gloves and clothes were contaminated with TCP. There was no cafeteria or lunch-room and consequently workers ate either in a smoke shed or on the job. The average length of exposure was 8.9 years and 16 men were exposed for 10 years or more (223, 224). Assuming a TOCP content of 20 %, the calculated air concentration of TOCP would be in the range 0.05-0.68 mg/m^3. Intraindividual comparisons of plasma cholinesterase activities (activity prior to exposure compared to activity during exposure) were not reported and thus the presented plasma activities are of limited value (see Section 8.2).

TBEP No data were located.

TBP In a poorly described study, a group of 12 plant workers exposed to TBP for 7-30 hours during a workweek was studied. Exposure was not measured and occurrence of symptoms not presented. Blood samples were drawn at the end of the workweek. No significant difference in monocyte non-specific esterase staining was found between the exposed group and controls (142). The monocyte esterase activity is discussed in Section 8.2.

TCEP A single human case report has been presented. A 5-year old girl developed neurological effects, which was later associated with repeated exposure to TCEP present in household timber (600 mg/kg wood). Clinical signs included weakness in arms and abdominal muscles and abnormalities in electromyogram and nerve conduction velocities. Following a further 9 months of exposure, the child was admitted to hospital with dystelectatic pneumonia where a diagnosis of spinal muscle dystrophy with tetraparesis was established. After cessation of exposure neurological impairment was still evident after several months, despite an improvement in her health status. However, no functional abnormalities were reported 2 years post-exposure (personal communication to NICNAS (166)). The evidence in favour of a causal association between TCEP exposure and the neurological disorder in this case is meagre.

TDCPP In a retrospective cohort study, mortality in 289 workers manufacturing TDCPP was examined. The cohort included all male workers employed for 3 months or more in a manufacturing plant in the US during 1956-1977. The participants were followed until 1980. Overall mortality in the cohort was 75 % of the normally expected for the male population in the US. Air samples were not taken at the time of exposure but breathing zone samples were taken from other job classifications in 1981 and all contained less than 0.4 µg/m^3 (7 ppb) of TDCPP. Three cases of lung cancer were found versus 0.8 expected. All three decedents

were moderate to heavy smokers. The increase of the number of workers with lung cancer was not significant and its association with TDCPP exposure remains unclear due to the small size of this study and to possible exposure to other chemicals (Stauffer 1983b, cited by (102)).

During 1981, workers at a TDCPP manufacturing plant in the US had their health assessed in physical examinations. Potentially exposed workers (totally 93) were compared to 31 non-exposed workers who were matched for age, alcohol consumption and smoking habits. Exposed workers had a 2-fold increase in the prevalence of "abnormal" electrocardiograms, but fewer exposed workers had a history of heart disease. The prevalence of minor respiratory disease was slightly increased in exposed workers. The results of the study did not reveal any significantly increased morbidity in workers exposed to TDCPP (Stauffer 1983a, cited by (102)).

TEHP and ***TEP*** No data were located.

TIPP A 48-year-old mechanic was daily and heavily exposed to hydraulic fluids containing isopropylated triphenyl phosphate, which exact composition was not known. For two years, he was testing hydraulic systems in ships. His underwear was often completely soaked with the fluid and his hands and forearms were always wet by the fluid. During the months preceding development of his symptoms he used hydraulic fluid containing about 0.5 % isopropylated triphenyl phosphates. According to the supplier's analyses it contained less than 50 ppm TOCP. At vacation he noticed weakness in his hands and forearms, which developed 2 weeks after last exposure. He returned to work but the weakness in his hands made it impossible to work. Nerve conduction velocities in some nerves were decreased. Electromyography showed marked reduction of motor unit potentials. After 3 years, his symptoms had improved only slightly. A cross-sectional examination of 8 other men exposed to hydraulic fluids and 8 controls showed differences in electromyography but not in nerve conduction velocities or other values measured in a clinical examination. The study indicated a possible association between heavy occupational exposure to hydraulic fluids and isopropylated triphenyl phosphate and polyneuropathy (113).

In a Danish study, a 27-year old mechanic worked with pump oil for pressure testing. After some years, he developed paresis of both legs as well as thumb and index finger bilaterally. Chemical analysis showed that the oil contained 23 % TPP, 24 % mono (*ortho*-isopropylphenyl) diphenyl phosphate, 8 % bis(*o*-isopropylphenyl) phenyl phosphate and 1 % tris(*o*-isopropylphenyl) phosphate (27).

Totally 38 resin-processing operators were exposed to a mixture of 30 % TPP, 40 % monoisopropyl triphenyl phosphate, and 30 % of diisopropyl triphenyl phosphate, triisopropyl triphenyl phosphate and higher congeners. They were compared with 33 males between 20 and 50 years who were full-time employees or students. The erythrocyte acetylcholinesterase activity was significantly lower among the exposed than in the comparison group but the plasma cholinesterase

activity did not differ. There was a significant correlation between the erythrocyte acetylcholinesterase activity and the monocyte esterase activity (55). There was no quantitative information of exposure in the study.

A case-control study was conducted at an automotive carburetor plant to investigate potential triaryl phosphate exposures associated with a cluster of 18 cases exhibiting neurological symptoms resembling multiple sclerosis. Symptom onset was between 1970 and 1985. Four controls per case were selected randomly from the plant population. From work histories and telephone interviews, cumulative exposures for 10 chemical or process categories were computed based on rank estimates of exposure levels. Two hydraulic fluid products containing high concentrations of triaryl phosphates were used at the plant during 1965-1982. Six stationary 4-hour samples for total particles contained aryl phosphates in the range 0.04-0.15 mg/m^3. There were significantly increased relative risks associated with die-casting and organophosphate exposures. However, if exposure to die-casting and organophosphates was defined as ever working in the main die-casting department or ever having a job classification assigned to the high-exposure category, no cases qualified. According to the authors, the study is hampered by uncertainties of exposure assessment, by the small number of cases, and by the inability to pursue further clinical neurological evaluation (50 % of the cases were seen only at initial diagnosis). The intriguing unanswered question is whether some of the diagnosed multiple sclerosis cases actually represent delayed neuropathy caused by organophosphate exposure (119). Out of 13 distinct aryl phosphates detected, TPP and isopropylphenyl diphenyl phosphate were identified at air levels of 0.057 and 0.013 mg/m^3 (100, 241). No further studies regarding the tentative association between organophosphate exposure and multiple sclerosis were located.

TMCPP No data were located.

TPP There was no evidence of adverse clinical effects in 32 men regularly engaged in the manufacture of TPP and exposed for 2-10 years (mean 7.4 years) to TPP mist and dust. A significant reduction (8.5 %) of erythrocyte cholinesterase activity was found in a sub-group of 11 men as compared to a non-exposed group of 9 persons. There was no difference regarding plasma cholinesterase levels. TPP measurements were performed over a period of 8 years and the estimated weighted average air concentration was 3.5 mg/m^3 (218).

12. Substance summaries with dose-effect and dose-response relationships

In this chapter, a summary of the toxicological database for each substance is presented. A more extensive presentation of dose-effect and dose-response relationships is found in Appendix 1 (Tables I-XI). Generally, most data originate from animal studies, whereas the human database is limited.

TCP and TOCP (Tables I-II)

Commercial TCP is a complex mixture. The content of TOCP has decreased considerably over time and TOCP occurs today only as contaminant (usually below 0.1 %).

TOCP is easily absorbed via the oral as well as the dermal route, which presumably applies also to TMCP and TPCP. The acute toxicity of TCP and TOCP in animals is low (measured as LD_{50}). Occupational dermatitis with positive reactions to TCP is reported. TCP caused slight irritation in patch tests in volunteers. Eye irritation has not been studied.

TOCP is highly neurotoxic, whereas TMCP and TPCP are not. Exposure to TOCP causes OPIDN with delayed central and peripheral neuropathy and inhibits cholinesterases and NTE activities. Numerous cases of human poisoning and polyneuritis involving accidental or occupational exposure of TCP have been reported. Severe symptoms were reported following ingestion of 0.15 g TOCP, while other individuals showed no toxic effect after ingesting 1-2 g. There is also considerable variation in the rate of recovery from poisoning after apparently similar exposure (259). These findings may be due to a variation in the individual sensitivity and/or differences in chemical composition of commercial TCP products. Both the pure TOCP and isomeric mixtures are considered major hazards to human. As pointed out by Winder and Balouet, mono-*ortho* and di-*ortho* isomers are even more neurotoxic than TOCP (257).

TCP air concentrations of 0.55-1.7 mg/m^3 were associated with polyneuritis during the manufacture of TCP with a high content of TOCP and presence also of other compounds. The persons with polyneuritis were also manufacturing TPP (94). The calculated approximate exposure to TOCP was 0.33-1.0 mg/m^3.

In 28 production workers exposed to mixtures of TPP, TCP and trixylyl phosphates and sometimes phosphates of higher alkyl substituted phenols, neuromuscular symptoms and signs were more common than in clerical and laboratory staff (5/28 versus 0/6). There was no depression of erythrocyte acetylcholinesterase activity. Sixteen workers exhibited a depressed plasma cholinesterase activity (70 % of normal or lower), although no correlation was observed between degree or duration of exposure and the enzyme activity. The air concentrations varied from 0.27 to 3.4 mg/m^3 reported as TCP, although this chemical also contained other trialkyl phenyl phosphates varying after what was manufactured. The content of TOCP varied up to 20 % (223, 224). Assuming a TOCP content of 20 %, the calculated air concentration of TOCP would be in the range 0.05-0.68 mg/m^3.

In these two industrial studies, dermal exposure may have had a great impact on body burden, which may have invalidated the relation between air concentrations and response.

In animals, TCP/TOCP has been shown to have reproductive and developmental effects. The available data do not indicate a carcinogenic potential of TCP. TOCP has not been tested for carcinogenicity or in standard *in vitro* and *in vivo* genotoxicity tests. However, the presence of DNA adducts in several organs of

rats given oral doses of TOCP (50 mg/kg bw/day) indicate that the compound may pose a genotoxic potential (151).

Regarding commercial TCP, inhibition of brain and spinal cord NTE was reported in hens gavaged with 10 mg/kg bw of TCP for 10 weeks. Cytoplasmic vacuolisation of the adrenal cortex was observed in female rats after exposure to TCP at daily gavage doses of 15 mg/kg bw for 2 years (174). The overall LOAEL is 6-7 mg/kg bw/day. Reduced serum antibody titres as well as inhibition of leukocyte and macrophage migration were reported in rats at 6 mg/kg bw after immunisation with tetanus oxide (14). The study was considered preliminary by the authors and no other data confirming an immunotoxic effect of TCP were located. At 7 mg/kg bw, decreased activity of serum cholinesterase (rats and mice) and minimal to mild ovarian interstitial cell hyperplasia were observed (rats). The effects could not be attributed to TOCP (< 0.1 %) and the causative agent is not known. Two of the TCPs were identified as TMCP (21 %) and TPCP (4 %) (174).

The critical effects of TOCP are neurotoxicity (inhibition of brain and spinal cord NTE and plasma cholinesterase activities in hens) (70) and reproductive toxicity (decreased non-specific esterase activity in testis and increase of abnormal sperms in rats) (205) observed at 10 mg/kg bw/day (overall LOAEL), the lowest dose tested.

TBEP (Table III)

The acute animal toxicity of TBEP is slight. TBEP was non-irritating to the rabbit eye in four studies but doses were not given. The results indicate that skin irritation arise when exposure reach several days or weeks. Human data indicate minimal skin irritation and no sensitising potential of TBEP.

TBEP was not mutagenic in bacterial or mammalian tests, but no tests for chromosomal damage were located. No carcinogenicity studies were found. No adverse effects on the foetuses were reported from one study of female rats (Monsanto 1985d, cited in (103)). Other aspects of reproductive toxicity have not been studied.

TBEP does not cause OPIDN but has been associated with neurotoxicity in rats. Electrophysiological changes were observed in all animals dosed with 250 and 500 mg/kg bw for 18 weeks and included a significantly reduced nerve conduction velocity. Most treated animals exhibited some degeneration of myelin sheaths accompanied by axonal swelling and an advanced stage of degeneration in the sciatic nerve. Unmyelinated nerve fibres of rats fed TBEP were more affected than those of animals treated with TOCP. In male rats, TBEP may have accelerated the development of focal myocarditis, which is a normal feature in older male Sprague Dawley rats (122, 124). At similar levels, reduced activities of serum cholinesterase (200 and 220 mg/kg bw/day, in males and females) (189, 233) and erythrocyte cholinesterase (250 mg/kg bw) were observed in rats (122).

Subchronic animal studies have shown that TBEP affects the liver, and hepatotoxicity is considered to be the critical effect. Based on an 18-week repeated dose study in rats, the NOAEL for liver effects is 15 mg/kg bw/day and the LOAEL 150

mg/kg bw/day (increased serum γ-glutamyl-transpeptidase and decreased plasma cholinesterase activity, and mild periportal hepatocellular hypertrophy and periportal vacuolisation) (Monsanto 1987a, cited in (103)).

Rats exposed to airborne TBEP (3 300 mg/m^3) for 4 hours exhibited depressed and irregular respiration, increased salivation, sneezing, unsteadiness and tremor (Hoechst 1989, cited in (103)).

TBP (Table IV)

TBP is easily absorbed through the human skin *in vitro*. The acute toxicity in animals is slight. TBP is an irritant of the eyes, mucous membranes and skin of experimental animals and humans. There was no evidence of sensitisation in volunteers patch tested with TBP.

TBP produced a reduction of conduction velocity of the caudal nerve and morphological changes of the sciatic nerve in one study (125), whereas other studies did not discover neurotoxic effects. TBP has not produced OPIDN. Plasma cholinesterase levels were affected in some studies but no consistent trend was observed.

In a 2-generation reproduction study in rats, no treatment-related histopathologic lesions in the reproductive organs were seen in males given up to 160 mg/kg bw/day or in females given up to 178 mg/kg bw/day for 13 weeks. Parental toxicity was observed at 10-21 mg/kg bw based on microscopic evidence of a very low incidence of urinary bladder epithelium hyperplasia and transient reductions in body weight (234). An overall animal LOAEL of approximately 15 mg/kg bw is obtained from this study. Non-significant increased incidences of urinary bladder hyperplasia were also observed in a 2-year dietary study in rats at 32 mg/kg bw/day in males and 42 mg/kg bw/day in females. At 143 mg/kg bw/day, the hyperplastic changes increased and a significant increase in the frequency of bladder papillomas and transitional cell carcinomas was observed in males. In female rats, hyperplastic changes and a significant increase of bladder papillomas were observed at 182 mg/kg bw/day. The NOAELs were 9 and 12 mg/kg/day for male and female rats, respectively (13). Another study showed a significant increase of hepatocellular adenoma in male mice at 585 mg/kg bw/day for 18 months (12). Overall, studies both *in vitro* and *in vivo* indicate that TBP is not genotoxic. Thus, TBP is presumably a non-genotoxic carcinogen in rats and mice. The oncogenicity may be related to a toxic metabolite (13).

Nasal discharges were observed in rats exposed to 100 mg/m^3 Skydrol 500B-4 (mixture of dibutyl phenyl phosphate and TBP) (81).

Workers exposed to 15 mg/m^3 of TBP have complained of nausea and headache (3). However, the extent of dermal exposure is not known. This study indicates a LOAEL of approximately 15 mg/m^3. This level seems to be significantly lower than those causing effects in animals.

TCEP (Table V)

TCEP seems to have a slight or moderate animal acute toxicity and be slightly irritating to eyes and skin.

TCEP is neurotoxic but does not cause OPIDN. Forty % of female rats given 88 mg/kg/day for 103 weeks had a marked increase of degenerative lesions of the brainstem and cerebrum compared to 2 % in controls. Similar lesions occurred in a few male rats but these lesions were not clearly chemical-related (173).

No firm conclusion can be drawn regarding the mutagenic effect of TCEP, although most studies were negative. TCEP has shown to be carcinogenic in rats (44 mg/kg bw, lowest dose tested, renal tubule adenomas) (150, 173), and there is evidence of carcinogenic activity in both male and female mice (300 mg/kg bw, leukaemia, hepatocellular adenomas/carcinomas) (102, 225). The mechanism of carcinogenicity is unknown.

Repeated oral dosing of TCEP had an effect on liver and kidney. The NOAEL was 22 mg/kg bw/day and the LOAEL was 44 mg/kg bw/day for increased liver and kidney weights in female rats (149, 173).

Studies in mice and rats have shown adverse affects on fertility (35, 159). In rats given TCEP by gavage (22, 88 and 175 mg/kg bw) for 70 days, a decrease of sperm motility was noted in one or more dose groups compared to a control group (159). Unfortunately, the study does not reveal in which dose group the effect was observed.

Thus, the critical effects of TCEP are carcinogenicity and kidney and liver effects, which has appeared at 44 mg/kg bw (overall LOAEL). The level at which reproduction toxicity occurs is unknown.

TDCPP (Table VI)

The acute toxicity of TDCPP in animals is low. TDCPP was classified as irritant to rabbit skin in one study and slightly irritative to rabbit eye in another one (102).

An increased liver weight in female mice was reported at 62 mg/kg bw/day for 3 months (102, 114). In a 2-year study, mortality in male rats was increased at 80 mg/kg bw and body weight gain was reduced in both sexes. A slight increase in plasma cholinesterase was also observed in females at the same level, whereas erythrocyte acetylcholinesterase was unaffected (Aulette and Hogan 1981, cited in (102)).

Leg and wing weakness was reported in chickens exposed to 1 200 mg/kg bw or more for 5 days (235), whereas hens exposed 5 days to lower levels of 420 mg/kg bw exhibited no signs of neurotoxicity (Bullock and Kamienski, cited in (102)).

The chemical was genotoxic in bacterial tests and showed equivocal or negative results in *in vitro* and *in vivo* mammalian tests. TDCPP was carcinogenic in both sexes of rats.

No foetotoxicity and no teratogenicity was observed in rats at an oral dose of 200 mg/kg bw. At 400 mg/kg bw/day, foetotoxicity was observed in the presence of maternal toxicity (11/15 dams died) (227), an observation also made in another study (Hazleton 1978, cited in (243)).

The critical effects are cancer and male reproduction toxicity. The overall LOAEL is 5 mg/kg bw/day (lowest dose tested). At this level, a slight increase of liver carcinomas, renal cortical tumours and atrophy of the seminal vesicle and

decreased secretory product were observed in rats. At higher levels, also testicular and brain tumours were found (Aulette and Hogan 1981, cited in (102), Stauffer 1981b, cited in (217), and (69)).

The epidemiological studies of TDCPP exposed workers are inconclusive.

TEHP (Table VII)

The acute toxicity in rats is low. TEHP has been classified as a moderate irritant to rabbit skin (Guest, 1993a, cited in (103)). However, no irritation was observed in 6 or 8 volunteers after 24 or 72 hours of exposure, respectively, to TEHP placed on the skin of the arm (Kimmerle 1958, cited in (103)). In a study performed according to OECD guidelines, TEHP was non-irritating to the rabbit eye (103).

Studies on reproductive and developmental toxicity have not been located.

TEHP was not mutagenic in bacterial or mammalian test systems. There was, however, some evidence of carcinogenicity in female mice based on the increase in hepatocellular carcinomas (dose levels were 500 and 1 000 mg/kg bw) and equivocal evidence of carcinogenicity in male rats based on the incidence of phaeochromocytomas of the adrenal gland (2 000 and 4 000 mg/kg bw). Male and female mice also exhibited a dose-related increase in the incidence of thyroid follicular cell hyperplasia (172).

OPIDN has not been observed in hens or chickens (Kimmerle 1958, cited in (103)), (140). However, signs of neurotoxicity were observed in 2 dogs exposed for 6 hours/day, 5 days/week for 12 weeks to mean concentrations of 10.8, 26 and 85 mg/m^3. The performance of the dogs trained in conditioned avoidance deteriorated as the exposure concentration increased. The percent missed avoidance was 0 %, 10 % and 18 % in the exposure groups and 5.8 % in controls. Thus, the overall NOAEL for this compound is 10 mg/m^3 and the overall LOAEL 26 mg/m^3 (140).

TEP (Table VIII)

Overall, the toxicological data base is poor. Oral or dermal acute toxicity data in animals are lacking as are data on irritation and sensitisation. Overall, the weight of evidence from genotoxicity studies is negative. Long-term animal studies were not available.

TEP has a narcotic effect, but has not been tested in hens regarding OPIDN. The ED_{50} in rats for loss of righting reflex after intraperitoneal injection was 333 mg/kg bw for females and 412 mg/kg bw for males (21).

The available reproductive and developmental toxicity data are insufficient and poorly reported. The litter size was reduced after repeated feeding of both sexes of rats at 670 mg/kg bw/day. There was no effect on the litter size at 335 mg/kg bw/day. A teratogenic study in rats showed no evidence of a teratogenic potential up to the highest dose of 625 mg/kg bw/day. At the highest dose, however, a reduction of body weight gain, food intake and faeces excretion as a sign of maternal toxicity were observed (no such effects at 125 mg/kg bw/day) (237).

The critical effects are increases in absolute and relative liver and spleen weights as well as in absolute weight of kidneys and testes in rats after exposure

for 9 weeks to dietary concentrations corresponding to approximately 500 mg/kg bw/day (overall LOAEL) (178).

TIPP (Table IX)

Unspecified isopropylated triphenyl phosphate was not irritating to skin of rats and rabbits, and not or only slightly irritating to the rabbit eye. The fact that TIPP is not a well-defined chemical makes interpretation of the data in general difficult. However, some studies have been performed with pure and well-defined components. Tri-*ortho*-isopropylphenyl phosphate had a slight acute toxicity in animals. Tri-*ortho*-isopropylphenyl phosphate and *para*-isopropylphenyl diphenyl phosphate were not neurotoxic when given to hens at doses of 1 000 mg/kg bw and 10 000 mg/kg bw, respectively, twice daily for 6 days. However, hens receiving 1 000 mg/kg bw of *ortho*-isopropylphenyl diphenyl phosphate twice daily for 6 days exhibited signs of OPIDN (106). In another study, a single dose of *ortho*-isopropylphenyl diphenyl phosphate at 1 200 mg/kg bw caused OPIDN, whereas half the dose (600 mg/kg bw) did not. Di-*ortho*-isopropylphenyl phenyl phosphate gave an ambiguous result regarding OPIDN at a single dose of 1 200 mg/kg bw, whereas tri-*ortho*-isopropylphenyl phosphate did not produce OPIDN at a single oral dose of 600 mg/kg bw or 1 000 mg/kg bw for 4 days. Single oral doses of 600 mg/kg bw of mono-, di- and tri-*ortho*-isopropylphenyl phosphate reduced NTE activities by 84, 39 and 12 %, respectively, as measured one day after dosing (109).

In a review, different commercial isopropylated triphenyl phosphates did not produce OPIDN in hens when tested at single doses of 2 000-3 000 mg/kg bw. However, one product was evaluated in a 90-day subchronic OPIDN study at doses of 0, 10, 20, 90 and 270 mg/kg bw/day of Kronitex® 50. At 90 mg/kg bw, an increased incidence of ataxia and lesions in the nervous system were observed. The NOAEL was 20 mg/kg bw/day (251). One of the commercial products that did not produce OPIDN caused a dose dependent inhibition of plasma cholinesterase and brain NTE activities in hens starting at 180 and 370 mg/kg bw, respectively (208).

Increased relative liver weight was observed in rats administered 100 mg/kg bw of Kronitex 100® via diet for 28 days (Foster 1976, cited in (74)).

No long-term (chronic) animal studies were found.

One Swedish and one Danish mechanic developed weakness in hands and legs after mainly dermal exposure to isopropylated triphenyl phosphates (27, 113). The Danish mechanic was exposed to an oil containing 23 % TPP, 24 % *ortho*-isopropylphenyl diphenyl phosphate, 8 % bis(*ortho*-isopropylphenyl) phenyl phosphate and 1 % tris(*ortho*-isopropylphenyl) phosphate (27). Exposure levels were not known.

TMCPP (Table X)

The acute toxicity of commercial TMCPP products was low in rats and rabbits. Tris(1-chloro-2-propyl) phosphate seems to cause only mild or no eye and skin irritation. Unspecified TMCPP produced no skin sensitisation in a study examining contact sensitisation potential. TMCPP was not mutagenic in bacterial

tests or in mammalian *in vitro* tests and caused no chromosomal damage in bone marrow after *in vivo* administration to rats and mice. No long-term animal studies were located.

TMCPP has not been associated with OPIDN. However, adverse clinical signs including depression and intermittent muscle spasms were observed among rats given a single oral dose of 464 mg Fyrol PCF/kg bw (Stauffer 1970, cited in (102, 238)).

Increased absolute and relative liver weight in male rats were reported in a 90-day study at 40 mg/kg bw of Fyrol PCF (Stauffer 1981a, cited in (238)).

In female rats given 0, 8, 40, 200 and 1 000 mg/kg bw of unspecified TMCPP by gavage for 7 days, the only treatment-related effects were significant increases in the relative weights of the kidneys at or above 40 mg/kg bw and of the liver at 1 000 mg/kg (Kawasaki *et al* 1982, cited in (216)).

Pregnant Wistar rats were given 0, 6, 70, and 625 mg/kg bw/day of unspecified TMCPP during gestation days 0-20. The treatment did not affect the number of implants, the number of resorptions or the number or weight of live foetuses. No foetuses died or had obvious external malformations. The incidence of skeletal or visceral malformations in foetuses from treated litters was not statistically different from controls. However, a dose-related increase in the incidences of missing 13th ribs and cervical ribs were observed in the foetuses (Kawasaki *et al* 1982, cited in (216)). An overall LOAEL of 6 mg/kg bw is obtained from this study.

TPP (Table XI)

Animal data indicate that TPP has a slight acute toxicity. TPP does not possess an irritation potential on the skin based on a study in mice. The eye irritation potential is low. No animal data regarding skin sensitisation were located. Contact dermatitis in humans due to TPP has been described but is uncommon. In more recent studies, TPP has not produced OPIDN or exhibited signs of causing neurotoxicity in animals. Long-term (chronic) studies are missing. Genotoxicity tests *in vitro* yielded negative results (Monsanto 1979, cited in (100)) but studies of chromosomal aberrations were not available. No adequate carcinogenicity studies were located.

TPP may affect development. There was a significant increase of the number of foetuses having at least two soft-tissue variations in rats dosed 166 mg/kg bw/day compared to controls (252), a finding classified as equivocal.

In a 35-day rat study, a dose of 500 mg/kg bw/day produced an increase of relative liver weights and a slight depression of body weight gain (218). A reduced body weight gain was also seen in rats exposed for 4 months to 345 mg/kg bw/day. Body weight gain was not affected at 161 mg/kg bw/day (203).

The critical effect of TPP is a reduction of erythrocyte acetylcholinesterase activity, which has been observed in both animals and humans. Mice exhibited a dose-dependent reduction (11-70 %) after single exposures to 10, 50, 100, 200 and 500 mg/kg bw. In men, there was no evidence of adverse clinical effects after

exposure for 2-10 years to TPP mist and dust. However, a significant reduction (8.5 %) of erythrocyte acetylcholinesterase activity was found in a sub-group regularly engaged in the manufacture of TPP at an estimated average air concentration of 3.5 mg/m^3 (LOAEL) (218). This level seems to be significantly lower than those causing effects in animals.

13. Previous evaluations by national and international bodies

TCP

International Programme on Chemical Safety (IPCS), 1990

IPCS concluded that the neurotoxic symptoms involve initial inhibition of cholinesterases and subsequent delayed neuropathy characterised by severe paralysis. The committee stated that it was impossible to establish a safe level of exposure because of considerable variation among individuals in sensitivity to TOCP. It was also noted that severe symptoms had been reported from the ingestion of 0.15 g of TOCP, that animal studies showed considerable variation among species in the response to TOCP, and that humans appear to be particularly sensitive. It was also noted that irritant and allergic dermatitis had been reported.

Both the pure *ortho* isomer and isomeric mixtures containing TOCP were therefore considered major hazards to human health and exposure to the compound trough dermal contact or inhalation should be minimised (99).

American Conference of Governmental Industrial Hygienists (ACGIH), 2001

ACGIH noted that TOCP may be absorbed through the skin and may exert frank toxicity upon ingestion. It was also stated that exposure to TOCP causes central and peripheral neuropathies with paralysis of the distal muscles of the upper and lower extremities and that air concentrations between 0.55 and 1.7 mg/m^3 had been associated with polyneuritis. Reduced cholinesterase activity had been related to air concentrations from 0.27 to over 3 mg/m^3. A TLV of 0.1 mg/m^3 with a skin notation was recommended for occupational exposure to TOCP. ACGIH considered TOCP not classifiable as a human carcinogen (4). Erythrocyte acetylcholinesterase activity has been recommended by ACGIH as a biological exposure index for TOCP (2).

Subcommittee on Flame-Retardant Chemicals, Committee on Toxicology, Board on Environmental Studies and Toxicology, Commission on Life Sciences, US National Research Council, 2000

The subcommittee concluded that the neurobehavioural effects and neuropathological findings in the NTP studies were consistent with TCP-induced delayed neuropathy and not cholinesterase inhibition.

The subcommittee identified the adrenal gland and ovarian lesions in female rats and adrenal and liver lesions in female mice that occurred at 7 mg/kg/day to be the key critical effect for deriving an oral reference dose for TCP. Supporting

data were available from subchronic, reproductive and developmental toxicity studies, but studies of reproductive function did not identify a NOAEL for TCP.

It was further concluded that extensive human experience with TCP including poisonings of tens of thousands of people over the past 100 years had produced no evidence that oral exposure to TCP can cause cancer in humans and that no evidence for the carcinogenicity of TCP was found in rats or mice chronically exposed to this compound for two years in their diet (174). Available genotoxicity studies including assays for mutagenicity, cytogenetic effects and DNA damage found no evidence that TCP produces genotoxic effects. Therefore, TCP was considered not likely to be carcinogenic (215).

TBEP

International Programme on Chemical Safety (IPCS), 2000

IPCS concluded that the acute systematic mammalian toxicity and irritation potential are low and that several subchronic animal studies had shown that the liver is the target organ for TBEP toxicity. It was further stated that one study in male rats suggested that TBEP might cause focal myocarditis. Neurotoxic effects in rats after single exposures were considered inconsistent. In rats given repeated doses by gavage, decreased nerve conduction velocity was observed. TBEP 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 NOAEL for liver effects was reported to be 15 mg/kg bw/day, while the LOAEL was 150 mg/kg bw/day. It was noted that bacterial and mammalian cell tests for gene mutation gave negative results, but that no tests for chromosomal damage had been reported and, in addition, that the long-term toxicity and carcinogenicity of TBEP had not been studied. IPCS stated also that teratogenicity was not observed in one study of rats and that other aspects of reproductive toxicity had not been reported (103).

TBP

International Programme on Chemical Safety (IPCS), 1991

It was stated that the available information did not permit an assessment of the risk presented by TBP as a potential carcinogen, neurotoxic agent or dermal sensitiser. Observations relating to hyperplasia of urinary bladder epithelium in rats, neurotoxicity signs in rats, and sensitisation of guinea pigs were considered inadequate to evaluate the hazardous potential of TBP for human health. IPCS noted that no tumour development had been observed in rats, that TBP did not produce delayed neurotoxic effects in hens and that no adequate data were available on the effects of TBP on reproduction.

IPCS concluded that there were no reports that TBP has effects on occupationally exposed humans other than headache, nausea, and symptoms of skin, eye and mucous membrane irritation, and further, that no cases of poisoning among the general population had been reported.

The committee stated that there was no indication from animal studies of a neurotoxic effect comparable to OPIDN and that systemic toxicity in humans following acute exposure was likely to be low.

From *in vitro* test results, TBP was not considered to be mutagenic.

IPCS stated further that TBP is absorbed through the skin and dermal exposure should be minimised. The likelihood of long-term effects in occupationally exposed humans was considered small (101).

American Conference of Governmental Industrial Hygienists (ACGIH), 1992

ACGIH summarised that TBP is an irritant of the eyes, mucous membranes and skin of experimental animals and humans and that repeated oral administration of TBP had caused pathological changes in the rat bladder epithelium.

Given the scanty data, it was considered difficult to assign a TLV for TBP. ACGIH argued that the LD_{50} of TBP was about the same as that for TPP but, contrary to TPP, TBP irritates skin and is a narcotic. According to ACGIH, TBP is a weak cholinesterase inhibitor as compared with TPP. Given the absence of epidemiologic data on TBP, it was argued that the same TLV for both TBP and TPP seemed justified. Accordingly 0.2 ppm (2.2 mg/m^3) was recommended as a TLV (3) and erythrocyte acetylcholinesterase activity was recommended as a biological exposure index for TBP (2).

Deutsche Forschungsgemeinschaft (DFG), 2002

The committee identified the bladder as the target organ of the toxic and carcinogenic effects of TBP in the rat and noted that, in this organ, local cell damage with reversible hyperplastic, proliferative and necrotic changes had been observed. It was also noted that papillomas and, in particular in male animals, transitional cell carcinomas were found in long-term studies as a result of the damage to the bladder. In the liver, an increase in hepatocellular adenomas was observed, in particular in mice, but no carcinomas. Based on the results from the long-term studies and the negative results in the genotoxicity studies, the tumours were thought to be caused by direct cell damage and not by a genotoxic mechanism.

The committee concluded that local irritation and systemic effects of TBP must be taken into consideration in derivation of a MAK value and that in particular the toxic effects on the bladder were of importance for the systemic effects. It was noted that slight hyperplasia of the bladder epithelium had been observed even after TBP concentrations as low as about 10-20 mg/kg bw/day and that the NOAELs found in a 13-week study and a 24-month study were 15 and 9 mg/kg bw/day, respectively. For man, a dose of 9 mg/kg bw/day would correspond to a concentration in air of 63 mg/m^3, assuming a body weight of 70 kg and a volume of air inhaled in 8 hours of 10 m^3.

DFG stated further that TBP had been tested in studies of developmental toxicity with rats and rabbits and that embryotoxic and foetotoxic effects were observed only after doses that were toxic to the dams. The NOAEL for developmental toxicity in the rat was identified as 250 mg/kg bw/day and in the rabbit as 150 mg/kg bw/day (47).

In Germany, TBP has a skin notation indicating percutaneous absorption. TBP is classified as a substance with carcinogenic potential for which a non-genotoxic mode of action is of prime importance and genotoxic effects play no or most a minor part provided the MAK value (11 mg/m^3) is observed. TBP belongs to pregnancy risk group C, indicating no reason to fear damage to the embryo or foetus when the MAK value is observed (48).

United Nations Environmental Programme (UNEP) in its Screening Information Datasets (SIDS) for High Volume Chemicals, 2004

UNEP regarded the toxicology database as large and well documented, and that there were adequate data with which to evaluate the potential hazard to human health of this compound. In inhalation studies on rats and rabbits, depressed cholinesterase levels were observed at the highest concentration 13.6 mg/m^3, an effect that was reversible. Overall, the results of the rodent dietary/gavage studies consistently showed cellular and/or weight changes in the liver, kidney and bladder. In the rat, the NOAEL was 9 mg/kg bw/day in males and 12 mg/kg/day in females for cytotoxicity/hyperplasia in the urinary bladder. In an 18-month dietary study using CD-1 mice, the NOAEL was 28.9 mg/kg/day for females and 24.1 mg/kg per day for males, the lowest dose tested. TBP did not affect reproductive performance in a two-generation feeding study in rats (NOAEL > 225 mg/kg bw per day). Developmental and teratogenic toxicity was observed only at levels at which maternal toxicity was observed. In three separate teratology experiments (two with rats and one with rabbits), teratogenic (delayed ossification and rudimentary ribs) and developmental (reduced foetal weights) were observed only at maternally toxic doses and only in rats. The increased incidence of rudimentary lumbar ribs at doses of 500 mg/kg bw/day was considered to be an effect of maternal toxicity and not a result of teratogenicity. The lowest NOAEL for developmental toxicity from these studies was 720 mg/kg bw/day based on an increased incidence of rudimentary lumbar ribs. However, the lowest NOAEL for maternal toxicity was 62.5 mg kg bw/day.

TBP was considered an animal carcinogen when administered in doses greater than 9 mg/kg bw/day in rats or 24 mg/kg bw/day in mice. Overall, the results of both *in vitro* and *in vivo* genotoxicity studies indicated that TBP is not genotoxic. A mechanistic study in rats found that the effects of TBP on the bladder were reversible upon withdrawal of treatment and thus likely due to the direct urothelial cytotoxicity of the chemical itself (or its metabolites) and not a result of urinary changes.

It was noted that the neurotoxicity of TBP had been studied in several species including the rat, hen and rabbit. In these studies, TBP produced either no signs of neurotoxicity or only slight or transient effects on measured endpoints. TBP was judged irritating to the skin and eye of humans and laboratory animals but not to cause sensitisation in humans. The primary exposure to TBP was considered to be through dermal contact in the occupational setting. Based on this exposure route

and the NOAEL levels reported, UNEP concluded that the most likely effect of TBP exposure is irritation of the skin and eyes (239).

Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands, 2005

The committee stated that human and animal data suggest a significant skin penetration ability. In humans, TBP was considered irritating to the skin, the eyes, the mucous membranes and the respiratory tract. In short-term toxicity studies in rats and mice, the urinary bladder, the liver and the kidneys were regarded as the target organs. In long-term studies (2 years), the bladder was identified as the target organ showing increased incidence of urinary bladder hyperplasia, papillomas and transitional cell carcinomas. The carcinogenic effects showed a clear threshold at 33-42 mg/kg bw. The long-term NOAEL was 9 and 12 mg/kg bw/day for male and female rats, respectively. The NOAEL for neurotoxicity was > 325 mg/kg bw/day in a 13-week study.

The committee concluded that TBP is a non-genotoxic carcinogen in rats and mice and that tumours were only observed at dose levels associated with toxic, proliferative effects.

Based on a 2-generation reproduction study in rats, the NOAEL for reproductive toxicity was identified as 225 mg/kg bw/day and that for postnatal toxicity as 53 mg/kg bw/day. The LOAEL for parental toxicity was considered to be 15 mg/kg bw/day, based on microscopic evidence of a very low incidence of urinary bladder epithelium hyperplasia. In developmental toxicity studies, no developmental effects were observed at dose levels that did not cause maternal toxicity. The committee concluded that the NOAELs for maternal and developmental toxicity were 115 and 250 mg/kg bw/day in the rat and 150 and 400 mg/kg bw/day in the rabbit.

Based on the above data, the committee took the 2-generation rat study demonstrating a parental LOAEL of 15 mg/kg bw/day as starting point in establishing a health-based recommended occupational exposure limit. The committee recommended a health-based occupational exposure limit for TBP of 2 mg/m^3 (0.18 ppm) as an 8-hour TWA (79).

Since the amount that may be absorbed through the skin is more than 10 % of the amount taken up by inhalation, the committee recommended a skin notation.

Environment Canada, 2009

Environment Canada concluded that a critical effect for the characterisation of risk to human health for TBP is carcinogenicity. It was argued that tumours in the urinary bladder were observed in male and female rats following dietary exposure at the highest dose tested and that tumours in liver were also observed in male mice. It was further noted that TBP did not show any genotoxicity from bioassays in bacteria, cultured mammalian cells or animals and that mechanistic study and evaluations by international and other national agencies suggest that TBP is a non-genotoxic carcinogen and that tumors are associated with cytotoxicity and proliferative effects (57).

European commission
The European commission has classified TBP as a carcinogen (Category 3: limited evidence of a carcinogenic effect) (61, 62).

TCEP
International Agency for Research on Cancer (IARC), 1990 and 1999
In 1990, IARC evaluated TCEP regarding its carcinogenicity and concluded that there was inadequate evidence for the carcinogenicity of TCEP in experimental animals. There were no data available from studies of humans and the overall evaluation of TCEP was group 3, i.e. TCEP was not classifiable as to its carcinogenicity to humans (96). In 1999, IARC made a re-evaluation. There was now limited evidence for the carcinogenicity of TCEP in experimental animals. However, the overall evaluation was not changed (97).

International Programme on Chemical Safety (IPCS), 1998
The committee noted that the low volatility of TCEP precludes significant exposures from air. It was further assumed that exposure to TCEP from food, drinking water and air will not present an acute hazard to the general population. IPCS concluded that TCEP, in repeat dose studies, caused adverse effects on the brain (hippocampal lesions in rats), liver and kidneys. The NOAEL was 22 mg/kg bw/day and the LOAEL 44 mg/kg bw/day for increased weights of liver and kidneys in rats. TCEP was considered not teratogenic but to adversely affect the fertility of male rats and mice. The genetic toxicity data were considered ambiguous. TCEP was regarded to be carcinogenic in rats and mice. The committee concluded that a very high oral dose of TCEP caused some inhibition of plasma cholinesterase and brain NTE in hens but did not cause OPIDN and that a high dose of TCEP in rats caused convulsions, brain lesions and impaired performance in a water maze. However, because of the low exposure, the risk of adverse health effects from TCEP to the general population was expected to be very low (102).

Commentary by the authors of the present document regarding the carcinogenicity assessments made by IARC and IPCS
IARC (96, 97) did not include the study in mice by Takada *et al* (225) in the evaluations and consequently tumours were observed in only one species (rat) (173). IPCS included both studies and thus concluded that TCEP has caused benign and malignant tumours at various organ sites in rats and mice (102).

Environment Canada, 2009
Based on weight of evidence and taking into consideration more recent data, the critical effects for the characterisation of risks to human health for TCEP were considered to be carcinogenicity and impaired fertility. Carcinogenic effects included kidney tumours in rats and mice, thyroid tumours in rats, and liver, forestomach and Harderian gland tumours and leukaemia in mice. Mixed results were obtained in the limited *in vivo* and *in vitro* genotoxicity assays in mammalian

cells. However, based on the range of tumours observed in multiple species of experimental animals for which the modes of induction have not been elucidated, it could not be precluded that TCEP induces tumours via a mode of action involving direct interaction with genetic material.

Non-neoplastic effects were also observed in the liver and kidneys of rats and mice in short-term repeated-dose and long-term studies. In was added that TCEP impaired fertility in mice and induced testicular toxicity in both mice and rats. Based on comparison of estimated exposures to TCEP in Canada with the critical effect level for non-cancer effects, a dose that was also associated with increased incidences of tumours in a long-term study in rats, and taking into account the uncertainties in the databases on exposure and effects, it was considered that the resulting margins of exposure may not be adequately protective of human health.

On the basis of the carcinogenic potential of TCEP, for which there may be a probability of harm at any exposure level, as well as the potential inadequacy of the margins between estimated exposure and critical effect levels for non-cancer effects, it was concluded that TCEP is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health (56).

European commission

The European commission has classified TCEP as a carcinogen (Category 3: limited evidence of a carcinogenic effect) and as toxic to reproduction (Category 2: substances which should be regarded as if they impair fertility in humans) (60-62).

TDCPP

International Programme on Chemical Safety (IPCS), 1998

IPCS concluded that the low volatility of TDCPP precludes significant exposures from air and that exposure to TDCPP from food, drinking water and air will not present an acute hazard to the general population. It was referred to a 3-month study in mice, in which an exposure of approximately 1800 mg/kg bw/day caused death within one month. The NOAEL for the study was 15.3 mg/kg bw/day and the LOAEL for increased liver weight was 62 mg/kg bw/day. The potential for TDCPP to affect human male reproductive ability was judged unclear, in view of testicular toxicity in rats but a lack of effect on male reproductive performance in rabbits. A teratology study on rats showed foetotoxicity at an oral dose of 400 mg/kg bw/day. The NOAEL and LOAEL for maternal toxicity were 100 mg/kg and 200 mg/kg bw/day, respectively. No teratogenicity was seen.

TDCPP was considered genotoxic in bacterial tests and in some *in vitro* mammalian tests. However, it was judged not sufficiently tested for mutagenicity *in vivo*. TDCPP was found to be carcinogenic in rats. The mechanism of carcinogenicity had not been elucidated. The exposure level leading to the residues found in humans was said to be unknown. However, because of the low exposure, the risk was expected to be low (102).

Subcommittee on Flame-Retardant Chemicals, Committee on Toxicology, Board on Environmental Studies and Toxicology, Commission on Life Sciences, US National Research Council, 2000

The subcommittee found statistically significant atrophy and decreased secretory product of the seminal vesicles in male rats fed diets containing 5 mg TDCPP/kg-day (lowest dose tested) or greater. Using this as the critical effect and the LOAEL of 5 mg/kg/day, the oral reference dose was derived by applying a composite uncertainty factor 1 000 (extrapolating from animals to humans) yielding an oral reference dose of 0.005 mg/kg/day. The subcommittee stated a moderate confidence that the derived oral reference dose would protect against noncancer toxic effects in most persons. However, the subcommittee noted the presence of some uncertainty in the threshold dose associated with testicular and seminal vesicle effects after life-time exposure in rodents.

It was further stated that *in vitro* data suggested that TDCPP is mutagen in the presence of liver S9 fraction, initiates DNA repair and is clastogenic and that these findings suggested that TDCPP (or one of its metabolites) is DNA-reactive. Therefore the subcommittee concluded that linear extrapolation is appropriate for estimating cancer risk in the low dose range.

TDCPP is released from upholstery to ambient air and the average exposure concentration to TDCPP particles estimated by the subcommittee was used for cancer assessment. An inhalation cancer potency value was not available for TDCPP. Therefore a provisional inhalation cancer potency value was derived from oral cancer potency data. Multiplication of the TDCPP exposure estimate of 0.48 $\mu g/m^3$ for particles times the provisional cancer potency value of $1.71 \times 10^{-5}/\mu g/m^3$ produced an estimated lifetime cancer risks of 8.2×10^{-6}, which suggested that the cancer risk associated with the inhalation of TDCPP particles was negligible at the given upholstery concentrations and the exposure parameters in the worst-case exposure scenario. However, the subcommittee noted that exposure to TDCPP by this route may need further evaluation (217).

United States Environmental Protection Agency (EPA), 2005

The US EPA noted that mild reversible irritation of the conjunctiva was observed when TDCPP was applied to the rabbit eye, that it was a non-irritant when applied for four hours and a mild irritant when applied for 24 hours to rabbit skin. It was considered not a skin sensitiser in guinea pigs. It was concluded that the results of genotoxicity tests *in vivo* (mutation in *Drosophila*, chromosomal aberration in mice) were negative, but that positive results were reported in several *in vitro* assays (mutagenicity in bacterial and mammalian cells, chromosomal aberration). An increased tumour incidence was observed in rats exposed to TDCPP in the diet. Several studies gave no evidence of acute cholinergic toxicity, inhibition of neurotoxic esterase (NTE) or delayed neurotoxicity. The available reproductive toxicity data were judged inadequate. However, chronic toxicity data indicated a LOAEL of 5 mg/kg/day for atrophy and decreased secretory product of the seminal vesicles (243).

TEHP

International Programme on Chemical Safety (IPCS), 2000

According to IPCS, occupational exposure to TEHP is likely to be by the dermal route during manufacture (accidental exposure) and from the use of some products. The committee stated that the compound is absorbed dermally in experimental animals but that no information was available on its kinetics or metabolism via this route. Dermal exposure could not, therefore, be quantified but was expected to be low. In a study of human volunteers, no skin irritation was reported. Inhalation exposure in the office environment has been measured to be 10 ng/m^3 or less.

Given the reported LOAEL for thyroid hyperplasia of 357 mg/kg bw/day in mice, the risk to the general population was considered very low. It was considered unlikely that TEHP poses a significant carcinogenic risk to humans. It was noted that neurotoxicity studies had been conducted in several species and that TEHP caused no alteration in activity of erythrocyte or plasma cholinesterases but that no studies of delayed neurotoxicity were reported. The risk to those exposed occupationally was also considered to be very low, although this could not be quantified (103).

Note: The authors of the present document have not found the bases for the IPCS conclusion on dermal absorption in animals or for the reported LOAEL for thyroid hyperplasia.

TEP

United Nations Environmental Programme (UNEP) in its Screening Information Datasets (SIDS) for High Volume Chemicals, 1998

For toxicological endpoints, UNEP identified NOAELs of 1 000 mg/kg bw for subacute toxicity, of 625 mg/kg bw/day for teratogenicity and of about 335 mg/kg bw for fertility effects. Due to missing data on carcinogenicity, a comprehensive description of the toxic effects of TEP was not considered possible. On the basis of all data on genotoxicity, a mutagenic effect of TEP was not assumed. The committee concluded that the substance is harmful with a narcotic effect and, at high doses, show certain neurotoxic properties (inhibition of cholinesterase) without indicating delayed neurotoxicity. The human dose estimated by UNEP from an 8-hour inhalation exposure at 0.5 mg/m^3 was < 0.071 mg/kg bw based on a respirator volume of 10 m^3 and a body weight of 70 kg. On the basis of the known facts and properties, a low concern for risk was to be expected to the human health or the environment (237).

TIPP

United States Environmental Protection Agency (EPA), 2005

The US EPA noted that many of the available health effect studies were conducted with commercial mixtures that commonly contained TPP as well as Proprietary G (triaryl phosphate, isopropylated). Toxicity studies on acute inhalation, acute dermal and eye irritation, skin sensitisation, genotoxicity, reproduction, and development were all judged inadequate to meet the endpoints. There was no available

data on cancer. In an acute study on a defined Proprietary G mixture, significant suppression of both brain neurotoxic esterase and plasma cholinesterase levels was reported. According to EPA, the majority of studies suggested that delayed neurotoxicity may result from exposure to oral doses in excess of 1 000 mg/kg (243).

TMCPP

International Programme on Chemical Safety (IPCS), 1998

Tris(1-chloro-2-propyl) phosphate CAS No. 13674-84-5.

The committee concluded that the low volatility of TMCPP precludes significant exposures via air and that exposure to TMCPP from food, drinking water and air will not present an acute hazard to the general population. It was further stated that rabbit eye and skin irritancy studies indicated that TMCPP is either non-irritant or mildly irritant. A skin sensitisation study showed that TMCPP has no sensitising properties. It was noted that reproductive toxicity, immunotoxicity and carcinogenic potential had not been investigated. The results of *in vitro* and *in vivo* mutagenicity studies investigating an appropriate range of end-points indicated that TMCPP is not genotoxic. IPCS noted that there was no evidence of delayed neurotoxicity in hens when two oral doses (each 13 200 mg/kg bw) were given 3 weeks apart. Although toxicological data from long-term studies were considered limited, because of low exposure to TMCPP the risk of adverse effects to the general population was considered negligible (102).

Subcommittee on Flame-Retardant Chemicals, Committee on Toxicology, Board on Environmental Studies and Toxicology, Commission on Life Sciences, US National Research Council, 2000

In the evaluation, TMCPP referred to commercial mixtures containing variable amounts of TMCPP isomers.

The database on dermal toxicity was considered inadequate for developing a dermal reference dose. The duration of all available dermal studies was only 24 hours. The committee noted that *in vivo* genotoxicity studies of TMCPP were lacking but that all of the *in vitro* tests of genotoxicity yielded negative results.

The committee noted that no mortality or abnormalities were observed in groups of five female rats given 0, 8, 40, 200 and 1 000 mg/kg bw of TMCPP by gavage for 7 days, except for one rat that died in the 1 000 mg/kg group. The only treatment-related effects were significant increases in the relative weights of the liver (1000 mg/kg) and the kidneys (40 mg/kg). No chronic or subchronic studies in humans or animals had been located that could provide the basis for developing an inhalation reference concentration or oral reference dose for TMCPP, nor had long-term studies in humans or animals that could be used to assess the carcinogenic potency of TMCPP by any route of exposure. Data on the effects of TMCPP exposure on reproduction were also not available (216).

United Nations Environmental Programme (UNEP) in its Screening Information Datasets (SIDS) for High Volume Chemicals, 2000

As TMCPP (Tris(1-chloro-2-propyl) phosphate, CAS No. 13674-84-5) has low volatility at ambient temperature and pressure and is produced in a closed system, exposure to workers was expected to be minimal, as was exposure to the workers during the processing of the chemical as a flame retardant in rigid and flexible foam.

It was further stated that TMCPP showed low acute toxicity following oral, dermal or inhalation exposures, was a slight skin and eye irritant and not genetically active. Repeated dose studies showed no adverse effects. TMCPP was considered neither neurotoxic nor teratogenic. Pharmacokinetic data indicated a rapid elimination, 89 % within 72 hours. Therefore, adverse effects from any accidental exposure would not be expected (238).

TPP

Deutsche Forschungsgemeinschaft (DFG), 1990

TPP was found to be associated with a low degree of toxicity in different species after oral, dermal, subcutaneous and inhalatory administration. The irritation potential of skin, eye and mucous membranes of the respiratory tract was considered low. A strong skin resorption was not expected. It was noted that studies of chronic effects were missing. It was further said that the neurotoxicity of TPP had been discussed and that more recent studies had not detected neurotoxic effects *in vivo*. However, a previous study observed an inhibition of neurite outgrowth by TPP, a result characteristic for neurotoxic phosphate esters.

According to DFG, the single cases of sensitisation from TPP containing products were not convincing.

To what extent the low immunotoxicity in rats can be extrapolated to humans was not possible to estimate. Other studies had shown a cytotoxic potential of TPP.

In order to establish an OEL for humans, the animal studies were regarded as insufficient. The only human study was considered difficult to interpret due to insufficient data. Further studies, particularly regarding neurotoxicity *in vivo*, were considered necessary to perform (45).

International Programme on Chemical Safety (IPCS), 1991

It was stated that animal data indicated a low toxicity, that TPP produced no irritant effect on animal skin and that contact dermatitis due to TPP had been described. Despite an early report to the contrary, TPP was not considered neurotoxic in animals or man. The committee identified the NOAEL on mothers and offspring from a 90-day rat study of 690 mg/kg per day. It was noted that both exposure of the general population and occupational exposure to TPP were low. TPP was considered not mutagenic. It was concluded that the available data indicated no hazard to humans (100).

The American Conference of Governmental Industrial Hygienists (ACGIH), 2001
ACGIH stated that TPP has a low toxicity in experimental animals after oral, dermal or subcutaneous exposures, and is a limited cholinesterase inhibitor in animals and humans. It was noted that no evidence of neurological disease or other abnormalities were reported among workers exposed to TPP at a concentration of 3.5 mg/m^3 for an average of 7.4 years. A TLV of 3 mg/m^3 was recommended for occupational exposure. Sufficient data were not available to recommend a skin notation (5).

United States Environmental Protection Agency (EPA), 2005
It was noted that TPP caused mild reversible irritation primarily of the conjunctiva when administered to the rabbit eye but was not a skin irritant. It was also noted that a skin sensitisation study on guinea pigs was negative but that a few human cases of allergic dermatitis had been reported. A study of reproduction and development in rats exposed for 91 days prior to mating and continuing through mating until day 20 of gestation was said to partially satisfy the reproductive screening component of the current guideline, but was considered not fully adequate, primarily because it lacked histopathology of male and female reproductive organs. Findings relevant to reproduction were the absence of significant differences in number of corpora lutea, implants, implantation efficiency, viable foetuses, and number of early or late deaths at dietary levels as high as 1.0 % TPP (690 mg/kg bw/day). Because both sexes were treated and there were no effects on litter size (as measured by number of viable foetuses), the study was said to provide some evidence that fertility is not affected by TPP in the rat. The body weights of the females fed the 1.0 % diets were slightly but significantly lower than those of controls on day 0 of gestation. Given a lack of dose response and uncertain biological significance of the slight foetal changes in this study, the highest dose level (1.0 % TPP in the diet, 690 mg/kg bw/day) was regarded as a possible NOAEL for foetotoxicity. TPP did not produce teratogenic effects in this study. According to the committee, this study suggested a minimal LOAEL for decreased body weight gain of 1.0 % TPP in the diet (690 mg/kg bw per day) for the dams.

It was noted that three studies of gene mutation *in vitro* reported negative results, that these studies, two in bacteria and one in mammalian cells, predated the relevant guidelines but were conducted in a manner similar to them, and together, characterised the gene mutation *in vitro* endpoint. It was further stated that studies of chromosomal aberrations were not available, however, and were needed for adequate characterisation of the genotoxicity endpoint. The available carcinogenicity data were judged inadequate. There was no evidence of acute cholinergic toxicity or of delayed neurotoxicity (243).

United Nations Environmental Programme (UNEP) in its Screening Information Datasets (SIDS) for High Volume Chemicals, 2006
Acute toxicity after oral and dermal administration was considered low: acute oral administration in rats, mice, rabbits and guinea pigs produced LD_{50} values in a range from 3 000 to above 20 000 mg/kg bw. One study in mice with limited

documentation gave a value of 1 320 mg/kg bw. After dermal application, an LD_{50} of above 7 900 mg/kg bw was established in rabbits. The committee stated that no valid studies were available regarding the acute inhalation of TPP, that TPP did not possess an irritation potential on the skin and that the irritation potential of TPP on the mucous membrane of the eye is very low. It was noted that no animal data regarding skin sensitisation were available and that there were few human case reports showing evidence of skin sensitisation. The incidence of skin sensitisation was considered very low.

Based on the available data, the toxicity after repeated oral treatment of rats with TPP was considered low. A 35-day study using doses of up to 350 mg/kg bw/day produced a slight depression of body weight gain and an increase of liver weights at the highest dose. An estimated dose of ~ 70 mg/kg bw/day in the diet was without any effect.

It was stated that three 4-month studies with doses of up to 1 % in the diet (~ 700 mg/kg bw/day) confirmed the effect on growth. Whereas body weight gain was depressed only at the highest dose of 1 % in two studies, a decrease was observed even at 0.5 % in another study. The general well-being as well as neurotoxic or immunotoxic parameters were not affected in any of the dose groups. Therefore, the overall NOAEL for these studies was 161 mg/kg bw/day due to reduced body weight gain. The low toxicity was confirmed also after dermal exposure of 100 and 1 000 mg/kg bw/day in rabbits for 15 days without any sign of toxicity besides a depression of acetylcholinesterase as the only dose-related effect. The committee considered the toxicological relevance of this effect hard to evaluate since quantitative data as well as the purity of the test material were not available. It was pointed out that neurotoxicity was a potential adverse effect of many organophosphates, but also noted that pure TPP did not induce immediate nor delayed neuropathy in available studies in hens and cats. Further, the committee noted that the findings of a decreased activity of cholinesterase and paralysis predominantly in cats in older studies indicating a neurotoxic potential were not reproduced in later studies and may be due to contamination of the tested samples by other organophosphorus esters. At the high doses of TPP used, even small concentrations of impurities might have sufficient activity.

Tests for gene mutations in bacterial as well as yeast and mammalian cells were said not to reveal any sign of mutagenicity, and an unscheduled DNA synthesis test in Syrian hamster fibroblast cells showed no genotoxic effect. The committee stated that there were no data concerning chromosomal aberration and no findings indicating any adverse effects on fertility or the development of the foetus up to the highest tested dose level of 1 % in the diet (~700 mg/kg bw/day) in the rat treated for 4 months during gametogenesis prior to mating and throughout mating and gestation. The mouse lung adenoma assay gave no indication of a carcinogenic potential (240).

14. Evaluation of human health risks

14.1 Assessment of health risks

This document comprises a number of phosphate triesters with flame retardant properties. The main groups are triaryl, trialkyl and tris(chloroalkyl) phosphate esters. The phosphate triesters differ widely in physical properties as well as in toxicological profiles and toxic potency. The major well-established clinical effect in humans is the delayed neurotoxicity caused by ingestion of tricresyl phosphate (TCP) contaminated food-stuff. In general, however, human data for these substances are scarce, particularly on occupational inhalation exposure.

The vapour pressures for these compounds are generally low and a high human exposure to vapour is therefore not likely. However, aerosols may be generated under hot or pressurised conditions and phosphate triesters may also be adsorbed to other air pollutants.

Two of the phosphate triesters (TOCP and TBP) have been shown to be easily absorbed through the human skin *in vitro* and many are absorbed through the skin of animals. A high absorption by inhalation is likely although this route has not been studied to a great extent. The combination of low vapour pressure at normal temperatures and a high skin uptake leads to the assumption that skin absorption may have a greater impact than absorption by inhalation.

14.1.1 Irritation and sensitisation

The phosphate triesters covered in this document are not strong irritants although several of the substances cause a slight to moderate eye and skin irritation. Respiratory irritation data are generally lacking.

Some of the phosphate triesters (TCP, TBEP, TBP and TPP) have been patch tested in patients with contact dermatitis or among volunteers. Positive responses were uncommon for TCP, TBEP and TPP even in groups exceeding 200 persons.

14.1.2 Neurotoxicity

Organophosphorus-induced delayed neuropathy (OPIDN) has been associated with exposure to some triaryl phosphates. There are three main types of triaryl phosphates in this document, triphenyl phosphate (TPP), tricresyl phosphate (TCP) and isopropylated triphenyl phosphates (TIPP). The most well-known and feared of these compounds is the tri-*ortho*-isomer of TCP (TOCP), which has been associated with around 60 000 cases of poisoning worldwide. TOCP is thus highly neurotoxic, whereas tri-*meta*- and tri-*para*-cresyl phosphate (TMCP and TPCP) are not. It has been shown in hens that engine oil containing 3 % commercial TCP (0.24 mg/kg bw/day of TOCP) was more neurotoxic than engine oil containing 0.5 % TOCP (10 mg/kg bw/day TOCP), which indicates that commercial TCP may contain other neurotoxic compounds. It is known that triphenyl phosphate esters with one or two methyl group in the *ortho* positions, e.g. *ortho*-cresyl diphenyl phosphate, are more neurotoxic than TOCP.

The pure compounds TPP and the tri-*ortho*-, tri-*meta*- and tri-*para*-isopropylphenyl phosphates are not neurotoxic. However, commercial products of these compounds may contain other isomers with a potency to cause OPIDN (shown for *ortho*-isopropylphenyl diphenyl phosphate).

Other neurotoxic effects, not characterised as OPIDN, have been reported in animals for all other phosphate triesters except TPP.

Some phosphate triesters act as cholinesterase inhibitors. Erythrocyte acetylcholinesterase activity mirrors the activity of neuronal cholinesterase and is recommended by ACGIH as a biological exposure index for both TOCP and TBP. Pre-exposure baseline determination for the individual (on two occasions at least three days apart) is necessary because of the wide interindividual variation in acetylcholinesterase activity (2). Decreases of plasma cholinesterase levels were observed after varying doses to animals of TCP, TOCP, TBEP, TCEP, TIPP and TPP. Plasma cholinesterase is, however, not recommended as an index of exposure due to the considerable range of normal activity and daily fluctuations in humans (2).

14.1.3 Cancer

Some phosphate triesters (TBP, TCEP, TDCPP and TEHP) have shown carcinogenic effects in animal experiments. Genotoxicity data for TBP and TEHP are negative, whereas those for TCEP and TDCPP are inconclusive. Several of the esters have not been properly tested for cancer.

There is only one epidemiological study addressing cancer. Among 289 workers manufacturing TDCPP, a statistically non-significant increase of lung cancer was observed. No firm conclusion can be drawn from this study.

14.1.4 Reproduction

Some of the phosphate triesters are toxic to the male reproductive system as shown in animal studies (TCP, TOCP, TCEP and TDCPP). In females, ovarian interstitial cell hyperplasia, hypertrophy and lipidosis, as well as decreased fertility have been observed after TCP exposure.

Some of the compounds have also exhibited developmental toxicity (TCP and TMCPP). In addition, there is equivocal evidence from one study that TPP has an adverse effect on foetal development. TEHP and TIPP have not been studied.

No human data have been located.

14.1.5 Organ toxicity

Several of the phosphate triesters have exhibited adverse effects on liver and kidney at relatively low levels. Liver or kidney toxicity (such as increased organ weights or hypertrophy) is considered the critical effect for TBEP, TCEP and TEP, in some cases in combination with other effects. In addition, increased relative liver weight is the critical effect for one commercial product of isopropylated triphenyl phosphate. Cytoplasmic vacuolisation of the adrenal cortex was observed after exposure to TCP.

14.2 Groups at extra risk

There are some indications that female animals may be more sensitive to the neurotoxic effects of TBEP and TCEP. There is a shortage of systematic studies regarding sex-differences of neurotoxic effects partially due to the regulatory protocols of using hens for studying OPIDN.

It has been reported from several studies that erythrocyte acetylcholinesterase and plasma cholinesterase activities are significantly lower (approximately 10 %) in women than in men. A lower activity of these enzymes would increase the effects of cholinesterase inhibitors. Plasma cholinesterase activities may be depressed in pregnant women and in individuals with liver disease, heart disease, allergic conditions and neoplasms (171).

It has also been shown that a small sub-population possesses genetically determined variants in their plasma cholinesterase resulting in very low activity levels and may thus be more sensitive to some of the phosphate triesters (171).

14.3 Scientific basis for an occupational exposure limit

There are insufficient human or animal data to establish dose-effect/dose-response relationships between airborne concentrations of the phosphate triesters and critical effects. The combination of low vapour pressure and a high dermal penetration rate implies that skin exposure may contribute significantly to the systemic dose and that dermal uptake may even be more important than inhalation.

The major concerns from exposure to the phosphate triesters covered in this document are neurotoxicity, cancer, reproduction toxicity, and liver and kidney effects. Some of the neurotoxic esters are cholinesterase inhibitors. Commercial products of TCP, TIPP and TPP may contain other derivates of triaryl phosphates associated with neurotoxicity such as OPIDN.

NOAELs and LOAELs for critical effects in animals after oral dosing of phosphate triesters covered in this document are presented in Table 16. For most of the phosphate triesters, no NOAELs could be identified. The NOAELs identified (TBEP, TBP and one commercial product of TIPP) are in the range 9-20 mg/kg bw. Identified LOAELs range from 5 to 600 mg/kg bw. The overall LOAEL for TEHP is 26 mg/m^3 based on inhalation.

Human inhalation data are few. A reduction of erythrocyte acetylcholinesterase activity was found in men manufacturing TPP at an estimated average air concentration of 3.5 mg/m^3. Workers exposed to 15 mg/m^3 of TBP complained of headache and nausea. These air levels correspond to 0.5 and 2.1 mg/kg bw, respectively, assuming 100 % uptake by inhalation, no dermal uptake and 10 m^3 inhaled air during 8 hours. Thus, these human effect levels seem significantly lower than those causing effects in animals, however, the extent of dermal exposure is unknown.

Table 16. Overall NOAELs and LOAELs in animals for phosphate triesters covered in this document (summarised from Appendix 1, Tables I-XI).

Phosphate triester	NOAEL [a] mg/kg bw/day	LOAEL [a] mg/kg bw/day	Critical effects	Key reference
TCP	-	6-7	Inhibition of serum cholinesterase in rats and mice and mild interstitial ovarian cell hyperplasia in rats. Immunotoxicity in rats.	(14, 174)
TOCP	-	10	Inhibition of plasma cholinesterase, brain and spinal cord NTE, and neuropathological lesions in hens. Decreased non-specific esterase in testis and slight increase of abnormal sperms in rats.	(70, 205)
TBEP	15	150	Increased serum γ-glutamyl-transpeptidase, decreased plasma cholinesterase and mild periportal hepatocellular hypertrophy and periportal vacuolisation in rats.	(103)
TBP	9	15	Urinary bladder hyperplasia and reduced body weight in rats.	(13, 234)
TCEP	-	44	Renal tubular hyperplasia and adenomas, and increased liver and kidney weights in rats.	(149, 150, 173)
TDCPP	-	5	Renal tubular hyperplasia. Neoplastic changes in the liver, kidneys and testes. Atrophy and decreased secretory products from seminal vesicle. All effects in rats.	(102, 217)
TEHP	10 mg/m^3	26 mg/m^3	Decreased performance in conditional avoidance test in dogs after inhalation exposure.	(140)
	-	500	Thyroid follicular hyperplasia and some evidence of carcinogenicity in female mice.	(172)
TEP	-	500	Increased absolute and relative liver and spleen weights and increased absolute weights of kidney and testes, and slight morphological changes in the liver in rats.	(178)
TIPP				
Tri-*ortho*-isopropylphenyl phosphate		600	12 % decrease of NTE after single dose in hens.	(109)
Di-*ortho*-isopropylphenyl phenyl phosphate		600	39 % decrease of NTE after single dose in hens.	
Ortho-isopropylphenyl diphenyl phosphate		600	84 % decrease of NTE after single dose in hens.	
Kronitex® 50	20	90	Ataxia and nervous system lesions in hens.	(251)
Kronitex® 100	-	100	Increased relative liver weight in rats.	(74)
TMCPP	-	6	Developmental effects (increased incidence of missing 13th ribs and cervical ribs) in rats.	(216)
TPP	-	10	13 % reduction of whole blood cholinesterase activity (not specified) in mice.	(218)

[a] Oral repeated dosing unless otherwise stated.

LOAEL: lowest observed adverse effect level, NOAEL: no observed adverse effect level, NTE: neurotoxic or neuropathy target esterase.

15. Research needs

There is a lack of data on human exposure and of the correlation between biomarkers of exposure and effects. Such information would be valuable to establish dose-response relations as absorption by skin may be more important than absorption by inhalation.

There is also a need for studies on sensitive groups and sex differences.

Long-term animal studies are lacking for several compounds such as TBEP, TEP, TIPP, TMCPP and TPP.

16. Summary

Sjögren B, Iregren A, Järnberg J. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 143. Phosphate triesters with flame retardant properties.* Arbete och Hälsa 2010;44(6):1-220.

This document comprises the following phosphate triesters:

Tricresyl phosphate	TCP	Triethyl phosphate	TEP
Tris(2-butoxyethyl) phosphate	TBEP	Triisopropylated phenyl phosphate/ isopropylated triphenyl phosphate	TIPP
Tri-*n*-butyl phosphate	TBP		
Tris(2-chloroethyl) phosphate	TCEP	Tris(monochloropropyl) phosphate	TMCPP
Tris(1,3-dichloro-2-propyl) phosphate	TDCPP	Triphenyl phosphate	TPP
Tris(2-ethylhexyl) phosphate	TEHP		

The phosphate triesters are mainly used as flame retardants and plasticisers. They differ widely in physical properties as well as toxicological profiles and toxic potency. Most of these esters have low vapour pressures and are presumably absorbed to a substantial degree by the skin. The dermal exposure route may therefore be more important than inhalation.

Human toxicological data on the phosphate triesters are scarce, particularly regarding occupational inhalation exposure. Based on animal data, the critical effects vary depending on substance and include cholinesterase inhibition, neurotoxicity, cancer, reproductive toxicity, and liver and kidney toxicity.

Organophosphorus-induced delayed neuropathy (OPIDN) has been associated with exposure to some triaryl phosphates. The most well-known example is the TCP isomer tri-*ortho*-cresyl phosphate (TOCP), which has been associated with numerous cases of poisoning worldwide. The TOCP content is therefore kept at a very low level in commercial phosphate ester products of today. Commercial products of TCP, TIPP and TPP may, however, contain other triaryl phosphates associated with OPIDN. Several other phosphate triesters have shown other (non-OPIDN) neurotoxic effects in animals.

Some of the esters covered in this document exhibit carcinogenic effects in animals (TBP, TCEP, TDCPP and TEHP), whereas TCP shows no such potential. The other esters have not been properly tested.

The lowest observed adverse effect levels (LOAELs) of the phosphate triesters range from 5 to 600 mg/kg bw/day. The no observed adverse effect levels (NOAELs), only identified for TBEP, TBP and one commercial product of TIPP, are in the range 9-20 mg/kg bw/day.

Key words: cancer, flame retardant, neurotoxicity, occupational exposure limit, organophosphorus-induced delayed neuropathy (OPIDN), phosphate esters, reproductive toxicity, review, risk assessment, skin absorption

17. Summary in Swedish

Sjögren B, Iregren A, Järnberg J. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 143. Phosphate triesters with flame retardant properties.* Arbete och Hälsa 2010;44(6):1-220.

Detta dokument omfattar följande fosfattriestrar:

Trikresylfosfat	TCP	Trietylfosfat	TEP
Tris(2-butoxietyl)fosfat	TBEP	Triisopropylerad fenylfosfat/	TIPP
Tri-*n*-butylfosfat	TBP	isopropylerad trifenylfosfat	
Tris(2-kloretyl)fosfat	TCEP	Tris(monoklorpropyl)fosfat	TMCPP
Tris(1,3-diklor-2-propyl)fosfat	TDCPP	Trifenylfosfat	TPP
Tris(2-etylhexyl)fosfat	TEHP		

Fosfattriestrarna används huvudsakligen som flamskyddsmedel och mjukgörare. Dessa ämnen skiljer sig i såväl fysikaliska egenskaper som toxikologisk profil och potens. De flesta estrarna har lågt ångtryck och tas troligen väsentligen upp via huden, varför hudupptag kan vara viktigare än inandning.

Överlag är data på människa knapphändiga, speciellt med avseende på yrkesmässig exponering via inandning. Djurförsök har visat att de kritiska effekterna, som varierar beroende på ämne, inkluderar kolinesteras-hämning, neurotoxicitet, cancer och effekter på reproduktion, lever och njure.

En viss typ av neurotoxicitet, så kallad ”organophosphorus-induced delayed neuropathy” (OPIDN), har satts i samband med exponering för vissa triarylfosfater. Det mest kända och fruktade exemplet är TCP-isomeren tri-*orto*-kresylfosfat (TOCP) som associerats med ett stort antal förgiftningsfall i världen. TOCP-innehållet är därför mycket lågt i dagens kommersiella fosfatesterprodukter. Kommersiella produkter med TCP, TIPP och TPP kan dock innehålla andra triarylfosfater som relaterats till OPIDN. Flera andra fosfattriestrar har i djurförsök orsakat neurotoxiska effekter som inte är OPIDN.

Några av ämnena har orsakat cancer i djurförsök (TBP, TCEP, TDCPP, TEHP), dock inte TCP. De andra estrarna är inte testade.

Identifierade lägsta effektnivåer (LOAEL) är 5-600 mg/kg kroppsvikt/dag. Icke-effektnivåer (NOAEL), endast identifierade för TBEP, TBP och en kommersiell produkt med TIPP, är 9-20 mg/kg kroppsvikt/dag.

Nyckelord: cancer, flamskyddsmedel, fosfatester, hudupptag, hygieniskt gränsvärde, neurotoxicitet, organophosphorus-induced delayed neuropathy (OPIDN), reproduktionstoxicitet, riskbedömning, översikt

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20. Data bases used in search of literature

The major literature searches were performed in November 2004. The following databases were used:

Arbline
Cheminfo
CISDOC
HSELINE
MHIDAS
NIOSHTIC2
PubMed
RILOSH
RTECS
STN
Toxline

A final search in Toxline and PubMed was performed in November 2009.

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Appendix 1. Dose-effect and dose-response relationships in animals

Table I Tricresyl phosphate (TCP)

Table II Tri-*o*-, tri-*m*-, and tri-*p*-cresyl phosphate (TOCP, TMCP, TPCP)

Table III Tris(2-butoxyethyl) phosphate (TBEP)

Table IV Tri-*n*-butyl phosphate (TBP)

Table V Tris(2-chloroethyl) phosphate (TCEP)

Table VI Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)

Table VII Tris(2-ethylhexyl) phosphate (TEHP)

Table VIII Triethyl phosphate (TEP)

Table IX Triisopropylated phenyl phosphate/isopropylated triphenyl phosphate (TIPP)

Table X Tris(monochloropropyl) phosphate (TMCPP)

Table XI Triphenyl phosphate (TPP)

Table I. Dose-effect and dose-response relationships in animals after exposure to tricresyl phosphate (TCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Single dose						
Kronitex TCP						
75	Oral	Hen	4 females	-	Ataxia in 0/4, 21 days post-dosing.	(251)
150	Oral	Hen	4 females	-	Ataxia in 1/4, 21 days post-dosing. Same result at 300 mg/kg bw.	(251)
400	Oral	Hen	4 females	-	92.5 % inhibition of brain NTE at 24 hours post-dosing.	(251)
Durad 125L (< 0.2 % TOCP)						
2 000	Oral	Hen	11 females	-	Ataxia in 0/10. Nervous system lesions in 4/7. Significantly reduced activities of NTE in brain (45 %) and in spinal cord (83 %) at 48 hours post-dosing. Brain cholinesterase not inhibited.	(251)
TCP mixture (2.2 % TOCP)						
7 900	Dermal	Rabbit, albino		-	LD_{50} > 7 900 mg/kg bw.	(106)
10 000	Gavage	Hen	Females	-	LD_{50} > 10 000 mg/kg bw.	(106)
15 800	Gavage	Rat		-	LD_{50} > 15 800 mg/kg bw.	(106)
Multiple doses						
2.4 (90 % *o, m, p*)	Oral, in diet	Rat, albino	10 males	6 weeks	Rats immunised with tetanus toxoid after 25 days of exposure. No effect on serum antibody titres. No signs of cholinergic or delayed neurotoxic effects.	(14, 215)
4 [a]	Oral, in diet	Rat	53 females	2 years	No cytoplasmic vacuolisation of the adrenal cortex, no hyperplasia, no chemical-related increases in the incidence of neoplasms.	(174)
6 [a]	Oral, in diet	Rat	50 males	2 years	No cytoplasmic vacuolisation of the adrenal cortex, no hyperplasia, no chemical-related increases in the incidence of neoplasms. Same results at 3 mg/kg bw.	(174)
6 (90 % *o, m, p*)	Oral, in diet	Rat, albino	10 males	6 weeks	Rats immunised with tetanus toxoid after 25 days of exposure. Significantly reduced serum antibody titres. Inhibition of leukocyte and macrophage migration. No signs of cholinergic or delayed neurotoxic effects.	(14, 215)

Table I. Dose-effect and dose-response relationships in animals after exposure to tricresyl phosphate (TCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
7 [a]	Oral, in diet	Rat	50 females	2 years	Serum cholinesterase activity significantly lower compared to controls at 3, 9 and 15 months (also seen at 15 mg/kg bw). Cytoplasmic vacuolisation of the adrenal cortex but not significantly different from controls. Minimal to mild ovarian interstitial cell hyperplasia; significant at 3 months (6/10 vs. 0/10 in controls).	(174)
7 [a]	Oral, in diet	Mouse	49 males	2 years	Serum cholinesterase activity significantly lower compared to controls at 3, 9 and 15 months (also seen at 13 and 27 mg/kg bw). Slight increase of ceroid pigmentation of adrenal cortex at 3 months (3/10 vs. 0/8 in controls); no increase at 2 years (47/49 vs. 48/52). Harderian gland adenomas in 1/49 vs. 0/52.	(174)
8 [a]	Oral, in diet	Mouse	50 females	2 years	Serum cholinesterase activity significantly lower compared to controls at 3, 9 and 15 months (also seen at 18 and 37 mg/kg bw). Harderian gland adenomas in 3/50 vs. 5/50 in controls.	(174)
10 (0.04 TOCP)	Gavage, engine oil	Hen	30 females	10 weeks	Mortality in 1/30. None had ataxia. Inhibition of plasma cholinesterase 23 %, brain NTE 47 % and spinal cord NTE 24 % at week 6 (last two significant). Neuropathological lesions (> grade 2) in 0/11.	(70)
12 (90 % *o, m, p*)	Oral, in diet	Rat, albino	10 males	6 weeks	Rats immunised with tetanus toxoid after 25 days of exposure. Significantly reduced serum antibody titres, IgM and IgG. Inhibition of leukocyte and macrophage migration. No signs of cholinergic or delayed neurotoxic effects.	(14, 215)
13 [a]	Oral, in diet	Mouse	49 males	2 years	Slight increase of ceroid pigmentation of the adrenal cortex at 3 months (3/10 vs. 0/8 in controls); no increase at 2 years (49/49 vs. 48/52). Significant increase of clear cell foci, fatty change and ceroid pigmentation in liver. Harderian gland adenomas in 2/49 vs. 0/52.	(174)
13 [a]	Oral, in diet	Rat	50 males	2 years	Serum cholinesterase activity significantly lower compared to controls at 3, 9 and 15 months. Hindlimb grip strength significantly reduced at 3 months. No increase in the incidence of neoplasms at this or lower (3 or 6 mg/kg bw) levels.	(174)

Table I. Dose-effect and dose-response relationships in animals after exposure to tricresyl phosphate (TCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
15 [a]	Oral, in diet	Rat	50 females	2 years	Cytoplasmic vacuolisation of the adrenal cortex significantly increased (36/50 vs. 15/51 in controls). Ovarian interstitial cell hyperplasia significantly increased (15/50 vs. 0/51). Lesion characterised by increase in size and possibly number of interstitial cells. No increase in the incidence of neoplasms at this or lower (4 or 7 mg/kg bw) levels.	(174)
18 [a]	Oral, in diet	Mouse	48 females	2 years	Ceroid pigmentation of the adrenal cortex in most exposed and control mice but the severity was increased among exposed in a dose-related manner. No Harderian gland adenomas (0/48 vs. 5/50 in controls).	(174)
20 (0.08 TOCP)	Gavage, engine oil	Hen	30 females	10 weeks	Mortality in 2/30. None had ataxia. Significant inhibition of plasma cholinesterase (27 %), brain NTE (55 %) and spinal cord NTE (34 %) activities at week 6. Neuropathological lesions (> grade 2) in 1/9.	(70)
27 [a]	Oral, in diet	Mouse	50 males	2 years	Significant increase of ceroid pigmentation of the adrenal cortex at 3 months (6/10 vs. 0/8 in controls); no increase at 2 years. Significant increase of clear cell foci, fatty change and ceroid pigmentation in liver. Significant increase of Harderian gland adenomas (5/50 vs. 0/52). No increased incidence of neoplasms at this or lower (7 or 13 mg/kg bw) levels.	(174)
Ca 30	Oral, in diet	Rat	10 males, 9 females	22 weeks	Cytoplasmic vacuolisation of the adrenal cortex in both sexes.	(174)
37 [a]	Oral, in diet	Mouse	51 females	2 years	Ceroid pigmentation of the adrenal cortex in most exposed and control mice but the severity was increased among exposed in a dose-related manner. Significant decrease of Harderian gland adenomas (0/51 vs. 5/50 in controls). No increase in the incidence of neoplasms at this or lower (8 or 18 mg/kg bw) levels. Reduced hindlimb grip strength at 3 (but not at 9 and 15) months.	(174)
45 [a]	Oral, in diet	Mouse	10 males	13 weeks	No clinical findings. No cytoplasmic vacuolisation of the adrenal cortex. No neurotoxic effects.	(174)

Table I. Dose-effect and dose-response relationships in animals after exposure to tricresyl phosphate (TCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
50 [a]	Gavage, corn oil	Rat	10/sex	13 weeks	Significant increase of cytoplasmic vacuolisation of the adrenal cortex in both sexes and ovarian interstitial cell hypertrophy. Also seen at 100, 200, 400 and 800 mg/kg bw (dose-dependent). No neurotoxic effects.	(174)
50 [a]	Gavage, corn oil	Mouse	10/sex	13 weeks	Significant increase of cytoplasmic vacuolisation of the adrenal cortex in both sexes and ovarian interstitial cell hypertrophy. Decreased serum cholinesterase activity. Same effects also seen at 100, 200, 400 and 800 mg/kg bw (dose-dependent). No neurotoxic effects.	(174)
55 [a]	Oral, in diet	Rat	10 males	13 weeks	Significant increase of cytoplasmic vacuolisation of the adrenal cortex. Also seen at 120, 220, 430 and 750 mg/kg bw (dose-dependent). No neurotoxic effects.	(174)
60 (0.24 TOCP)	Gavage, engine oil	Hen	30 females	10 weeks	Mortality in 4/30. 22/30 had ataxia. Significant inhibition of plasma cholinesterase (49 %), brain NTE (77 %) and spinal cord NTE (62 %) activities at week 6. Neuropathological lesions (> grade 2) in 10/11.	(70)
62.5 < 0.1 % TOCP	Oral, in diet	Mouse	20/sex	14 weeks	F_0 and F_1 treated with the same dose. Significant decrease of motile sperms (47 % vs. 72 % in controls). Significant increase of abnormal sperms (4 % vs. 3 %).	(35)
65 [a]	Oral, in diet	Rat	10 females	13 weeks	Significant increase of cytoplasmic vacuolisation of the adrenal cortex and ovarian interstitial cell hypertrophy and inflammation. Also seen at 120, 230, 430 and 770 mg/kg bw (dose-dependent). No neurotoxic effects.	(174)
65 [a]	Oral, in diet	Mouse	10 females	13 weeks	Significant increase of cytoplasmic vacuolisation of the adrenal cortex. Also seen at 130, 230, 530 and 1 050 mg/kg bw (dose-dependent). No neurotoxic effects.	(174)
100 [a]	Gavage, corn oil	Mouse	10/sex	13 weeks	Significant increase of multifocal axonal degeneration in the spinal cord in females.	(174)

Table I. Dose-effect and dose-response relationships in animals after exposure to tricresyl phosphate (TCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
100 <9 % TOCP	Gavage, corn oil	Rat	12 males	66 days	Significant increase of abnormal sperms (19 % vs. 6 % in controls).	(31)
110 [a]	Oral, in diet	Mouse	10 males	13 weeks	Significant increase of cytoplasmic vacuolisation of adrenal cortex. Also seen at 180, 380 and 900 mg/kg bw (dose-dependent). No neurotoxic effects.	(174)
124 <0.1 % TOCP	Oral, in diet	Mouse	20/sex	14 weeks	Significant increase of dead pups.	(35)
180 [a]	Oral, in diet	Mouse	10 males	13 weeks	Significant increase of hyperplasia of gallbladder mucosal epithelium. No neurotoxic effects.	(174)
200 [a]	Gavage, corn oil	Rat	10/sex	13 weeks	Significant weight reduction in males. Significantly lower blood haemoglobin concentrations in females. No neurotoxic effects.	(174)
200 [a]	Gavage, corn oil	Mouse	10/sex	13 weeks	Significant weight reduction in males. Significant increase of multifocal axonal degeneration of spinal cord and sciatic nerve in both sexes. Reduced grip strength in both sexes (fore- and hindlimb in females and hindlimb in males).	(174)
200 <9 % TOCP	Gavage, corn oil	Rat	12 males	66 days	Significantly reduced weight of epididymis. Reduction of sperm concentration, motility and velocity. Significant increase of abnormal sperms (66 % vs. 6 % in controls). Histopathological changes in the testes and epididymides.	(31)
200 <9 % TOCP	Gavage, corn oil	Rat	24 females	14 days prior to breeding, breeding, lactation and weaning until day 21	Males on dose 100 mg/kg bw were bred with females in this group. Fertility rate severely affected. The percent of sperm positive females littering was 45 % vs. 95 % in controls. Overall breeding success 38 % vs. 75 %. Mean litter size 9.6 vs. 11.3. Diffuse vacuolar cytoplasmic alteration of ovarian interstitial cells.	(31)
220 [a]	Oral, in diet	Rat	10 males	13 weeks	Significant increase of basophilic hypertrophy of pituitary gland.	(174)
230 [a]	Oral, in diet	Rat	10 females	13 weeks	Significant weight reduction.	(174)

Table I. Dose-effect and dose-response relationships in animals after exposure to tricresyl phosphate (TCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
230 [a]	Oral, in diet	Mouse	10 females	13 weeks	Significant weight reduction. Significant increase of hyperplasia of gallbladder mucosal epithelium.	(174)
250 <0.1 % TOCP	Oral, in diet	Mouse	20/sex	14 weeks	Seminiferous tubule atrophy and decreased testis and epididymal weights. In females, no histopathological changes in the reproductive tract. Significant increase of dead pups and a decrease of number of liveborn pups per litter. Crossover mating trial revealed significant impaired fertility in both sexes, with a greater effect in females.	(35)
380 [a]	Oral, in diet	Mouse	10 males	13 weeks	Increase (non-significant) of axonal degeneration of spinal cord and sciatic nerve. Reduced forelimb grip strength.	(174)
400 (no TOCP detected)	Gavage, sesame oil	Rat	3/sex/group	20, 40 or 60 days	Hypertrophy and lipidosis present in ovarian interstitial cells and adrenocortical cells by 20 days. The lipid deposition was progressive with duration of exposure. Significantly decreased weight of testis after 60 days exposure. Degeneration of the seminiferous tubules by 40-60 days and decrease in sperm density in the epididymis.	(131)
400 (no TOCP detected)	Gavage, sesame oil	Rat	12 females	40 days	Adrenal glands and ovaries heavier than controls. Cholesteryl lipidosis composed of cholesteryl ester in the adrenal glands and ovaries. Neutral cholesteryl ester hydrolase activity inhibited by 97 % compared to that of controls. Acyl coenzyme A: cholesterol acyl transferase activity depressed by 27 % compared to that of control adrenal glands, resulting in elevated intracellular cholesterol levels in adrenocortical cells.	(130)
400 (no TOCP detected)	Gavage, sesame oil	Rat	20 pairs	Up to 135 days	Fertility index and number of litters born significantly decreased. Significantly decreased testicular and epididymal weights. Increased ovarian weights. Crossover mating with vehicle controls resulted in 100 % infertility in treated males but did not affect reproduction in females. Decreased body weight and increased liver and adrenal weights in both sexes.	(132)

Table I. Dose-effect and dose-response relationships in animals after exposure to tricresyl phosphate (TCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
400 [a]	Gavage, corn oil	Rat	10/sex	13 weeks	Significant weight reduction in males and atrophy of seminiferous tubules in the testis. Reduced hindlimb grip strength in females. Significantly lower haemoglobin concentrations in both sexes. Same effects also seen at 800 mg/kg bw (with significant weight increase in females).	(174)
400 [a]	Gavage, corn oil	Mouse	10/sex	13 weeks	Significant weight reduction. Significant increase of multifocal axonal degeneration of spinal cord and sciatic nerve. Increased number of reticulocytes in males. Same effects also seen at 800 mg/kg bw.	(174)
400 <9 % TOCP	Gavage, corn oil	Rat	24 females	14 days prior to breeding, breeding, lactation + weaning until day 21	Males on dose 200 mg/kg bw were bred with females in this group. Fertility rate severely affected. The percent of sperm positive females littering was 5 % vs. 95 % in controls. Overall breeding success was 0 % vs. 75 %. Mean litter size 3.0 vs. 11.3. Diffuse vacuolar cytoplasmic alteration of ovarian interstitial cells.	(31)
430 [a]	Oral, in diet	Rat	10 males	13 weeks	Significant weight reduction. Significant increase of basophilic hypertrophy of pituitary gland. Atrophy of seminiferous tubules in the testis.	(174)
430 [a]	Oral, in diet	Rat	10 females	13 weeks	Significant weight reduction. Significant increase of renal papillary oedema and necrosis. Same effects also seen at 770 mg/kg bw.	(174)
530 [a]	Oral, in diet	Mouse	10 females	13 weeks	Significant weight reduction. Significant increase of axonal degeneration of spinal cord and sciatic nerve and of ovarian interstitial cell hypertrophy and inflammation. Reduced fore- and hindlimb grip strength. Significant increase of hyperplasia of gallbladder mucosal epithelium. Same effects also seen at 1 050 mg/kg bw.	(174)
750 [a]	Oral, in diet	Rat	10 males	13 weeks	Significant weight reduction, increase of basophilic hypertrophy of pituitary gland and increase of renal papillary oedema and necrosis. Atrophy of seminiferous tubules in the testis. Reduced hindlimb grip strength.	(174)
900 [a]	Oral, in diet	Mouse	10 males	13 weeks	Significant weight reduction, increase of axonal degeneration of spinal cord and sciatic nerve, and regeneration of renal tubules. Reduced fore- and hindlimb grip strength.	(174)

Table I. Dose-effect and dose-response relationships in animals after exposure to tricresyl phosphate (TCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
1 000 [b]	Gavage, lubricating oil	Hen	17-20 females	13 weeks	Significantly inhibited brain NTE (32-34 %) at the end of exposure. Walking ability did not differ compared to controls. No sign of OPIDN.	(41)
10 000	Gavage	Hen	6 females	Twice per day, 3 days	Hens were sacrificed on day 42. Behavioural neurotoxic response in 6/6. Histological neurotoxic response in 6/6.	(106)
Multiple exposures, aerosol, MMD 2 µm						
1.8 mg/m^3 [c]	Inhalation	Hen	4 females	141 days [d]	Signs of neurotoxicity in 1/4 at day 101.	(201)
4.4 mg/m^3 [c]	Inhalation	Hen	3 females	108 days [d]	No signs of neurotoxicity at this level or at 2.2 and 4.3 mg/m^3.	(201)
4.4 mg/m^3 [c]	Inhalation	Monkey	6	108 days [d]	No signs of neurotoxicity at this level or at 4.3 mg/m^3.	(201)
23 mg/m^3 [c]	Inhalation	Hen	4 females	163 days [d]	Signs of neurotoxicity in 1/4.	(201)
25 mg/m^3 [c]	Inhalation	Hen	6 females	6 weeks	No signs of neurotoxicity. Increased body weight.	(201)
25 mg/m^3 [c]	Inhalation	Dog rabbit monkey	2 3 3	6 weeks	No signs of neurotoxicity. Increased body weight in dogs and rabbits. Reduced body weight in monkeys.	(201)
50 mg/m^3 [c]	Inhalation	As above	As above	6 weeks	No signs of neurotoxicity. Reduced body weight in all animals.	(201)
50 mg/m^3 [c]	Inhalation	Hen	6 females	6 weeks	Signs of neurotoxicity in 3/6. Reduced body weight.	(201)
34 mg/m^3 [c]	Inhalation	Hen	3 females	156 days [d]	Signs of neurotoxicity in 3/3.	(201)
34 mg/m^3 [c]	Inhalation	Rabbit	3	156 days [d]	No signs of neurotoxicity (same result at 1.8, 2.2, 4.3, 4.4 and 23 mg/m^3).	(201)
102-103 mg/m^3 [c]	Inhalation	Rabbit	5	41 or 52 days [d]	Hind leg paralysis in 5/5.	(201)
102-110 mg/m^3 [c]	Inhalation	Hen	20 females	36-99 days [d]	Signs of neurotoxicity in 19/20 on days 22-29.	(201)
110 mg/m^3 [c]	Inhalation	Rat	50	36 days [d]	No signs of neurotoxicity at this or lower (1.8, 23, 34, 102 mg/m^3) levels.	(201)

LD_{50}: lethal dose for 50 % of the exposed animals at single administration, MMD: mass median diameter, NTE: neurotoxic or neuropathy target esterase, OPIDN: organophosphorus-induced delayed neuropathy.

[a] Commercial TCP consisting of 18 % dicresyl phosphate and 79 % tricresyl phosphate esters (including 21 % TMCP, 4 % TPCP and < 0.1 % TOCP).

[b] 80 % TCP with < 0.5 % TOCP or 100 % TCP with < 1 % TOCP.

[c] Triaryl phosphate hydraulic oil containing TCPs (< 1.5 % *ortho*-cresyl phosphates), trixylenyl phosphates and other trialkylphenyl phosphates.

[d] Continuous exposure.

Table II. Dose-effect and dose-response relationships in animals after exposure to tri-*o*-, tri-*m*- and tri-*p*-cresyl phosphate (TOCP, TMCP and TPCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
TOCP Single dose						
10	Intraperitoneal, corn oil	Rat	5 males	-	Inhibition of fatty acid ethyl esterase synthesising activity in plasma (dose-dependent) and liver and of *p*-nitrophenyl acetate hydrolysing activity in liver. Also seen at 25, 50 and 100 mg/kg bw.	(153)
25	Gavage	Hen	Females	-	Neurotoxic response.	(109)
25	Gavage	Chicken	4 males	-	Paralysis in 1/4. The same effect seen at 50-400 mg/kg bw in a dose-related manner.	(84)
50	Oral, corn oil	Hen	8-9 females	-	Ataxia; score 2 (scale 0-8) on days 9-21 post-dosing. Nervous system lesions; score < 1 (scale 0-4) on day 21. 70 % inhibition of brain NTE 48 hours post-dosing.	(54)
90	Oral, corn oil	Hen	8-9 females	-	Ataxia; score 3 (scale 0-8) on days 9-21 post-dosing. Nervous system lesions; score 1 (scale 0-4) on day 21. 85 % inhibition of brain NTE 48 hours post-dosing.	(54)
145	Gavage	Rat	5 males	-	Transient weight loss during the first 72 hours No effect on CNS or PNS 14 days post-exposure. Non-significant NTE inhibition in spinal cord or brain at 20 or 44 hours; in spinal cord 24 % and in brain 18 % at 44 hours.	(181)
250	Gavage	Hen	Females	-	Neurotoxic response. 96 % inhibition of brain NTE activity.	(109)
250	Gavage, corn oil	Ferret (E)	5 males	-	No deficits regarding OPIDN within 54 days. 23 % inhibition of brain NTE 48 hours post-exposure.	(214)
250	Dermal, ethanol, 6 × 6 cm shaved area	Ferret (E)	5 males	-	2/5 had slight leg weakness with slight change in normal walking behaviour at days 51 and 53. 18 % inhibition of brain NTE 48 hours post-exposure.	(214)
290	Gavage	Rat	5 males	-	Transient weight loss during the first 72 hours. 7.5 % had spinal cord damage 14 days post-exposure. Non-significant NTE inhibition in spinal cord or brain at 20 or 44 hours; 40 % in spinal cord and 36 % in brain at 44 hours.	(181)

Table II. Dose-effect and dose-response relationships in animals after exposure to tri-*o*-, tri-*m*- and tri-*p*-cresyl phosphate (TOCP, TMCP and TPCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
360	Oral, corn oil	Chicken	6/sex	-	Delayed neuropathy that caused ataxia in all chickens (socialised and non-socialised, stressed and unstressed) within 32 days. Ataxia significantly more pronounced earlier in males. No sex difference 18 days after dosing.	(175)
375	Gavage, corn oil	Hen	6 females	-	Decrease of neurofilament subunits in sciatic nerve after 21 days. Also seen at 750 mg/kg bw.	(265)
500	Oral, corn oil	Hen	8-9 females	-	Ataxia; score 8 (scale 0-8) on days 9-21 post-dosing. Nervous system lesions; score 4 (scale 0-4) on day 21. 90 % inhibition of brain NTE 48 hours post-dosing.	(54)
500	Gavage, corn oil	Ferret (E)	5 males	-	No deficits regarding OPIDN within 54 days. 37 % inhibition of brain NTE 48 hours post-exposure.	(214)
500	Dermal, ethanol, 6×6 cm shaved area	Ferret (E)	5 males	-	4/5 had slight leg weakness with slight change in normal walking behaviour at days 23-27. 3/5 had leg weakness with some reluctance to walk at days 42-49. 25 % inhibition of brain NTE 48 hours post-exposure.	(214)
580	Gavage	Rat	5 males	-	Transient weight loss during the first 72 hours. 15 % had spinal cord damage 14 days post-exposure. Significant NTE inhibition in spinal cord (65 %) and brain (57 %) at 44 hours.	(181)
600	Gavage, corn oil	Hen	Females	-	Complete motor paralysis by day 15 (no symptoms before 10 days after treatment). Several nicotinic acid derivates significantly alleviated the ataxia.	(34)
750	Gavage	Hen	5 females	-	Downregulation of neurofilament mRNA in the cerebral cortex after 21 days.	(264)

Table II. Dose-effect and dose-response relationships in animals after exposure to tri-*o*-, tri-*m*- and tri-*p*-cresyl phosphate (TOCP, TMCP and TPCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
750	Oral, gelatin capsule	Hen	30 females	-	Axonal lesions characteristic of Wallerian-type degeneration in peripheral nerves and also multifocal axonal swelling, fragmentation and loss of myelin staining in all hens 21 days after treatment. In the spinal cord, multifocal axonal swelling in the lateral and ventral columns. Axonal swellings in the lateral white tracts of the medulla oblongata in 8 hens. Brain NTE was 8 %, brain acetylcholinesterase 88 % and plasma cholinesterase 28 % of normal value after 24 hours.	(32)
800	Gavage	Chicken, Babcock	8	-	Decrease of brain NTE by 80 % and plasma cholinesterase by 40 % (recovery of levels after 28 days). No change of brain cholinesterase. No clinical signs of OPIDN after 28 days.	(43)
835	Gavage	Rat	5 males	-	Transient weight loss during the first 72 hours. 90 % had spinal cord damage 14 days post-exposure. Significant NTE inhibition in spinal cord (72 %) and brain (66 %) at 44 hours.	(181)
1 000	Gavage, corn oil	Ferret (E)	5 males	-	3/5 had slight leg weakness with slight change in normal walking behaviour at days 21-27. 2/5 had leg weakness with some reluctance to walk at day 30. 26 % inhibition of brain NTE 48 hours post-exposure.	(214)
1 000	Dermal, ethanol, 6 × 6 cm shaved area	Ferret (E)	5 males	-	5/5 had slight leg weakness with slight change in normal walking behaviour at days 11-21. 4/5 had leg weakness with some reluctance to walk at days 13-27. 3/5 had mild ataxia with unsteadiness in gait and movement and minor loss of coordination at days 16-25. 5/5 had severe ataxia with unsteadiness and loss of coordination at days 18-39. 3/5 had slight paresis with inability to stand at days 39-49. Degenerating axons in the spinal cord. 46 % inhibition of brain NTE 48 hours post-exposure.	(214)

Table II. Dose-effect and dose-response relationships in animals after exposure to tri-*o*-, tri-*m*- and tri-*p*-cresyl phosphate (TOCP, TMCP and TPCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
1 000	Gavage	Chicken	5 males	-	Decrease of plasma cholinesterase activity by 67 % and brain and spinal cord acetylcholinesterase activities by 14 and 32 %, respectively.	(84)
1 160	Gavage	Rat	13 males	-	Transient weight loss during the first 72 hours. 100 % had spinal cord damage 14 days post-exposure. Significant NTE inhibition in spinal cord and brain at 20 and 44 hours; in spinal cord 75 % and in brain 85 % at 44 hours.	(181)
1 600	Gavage	Chicken, Hy-line w36	8	-	Decrease of brain NTE by 72 % and plasma cholinesterase by 58 % after 24 hours (recovery of levels after 28 days). No change of brain cholinesterase. No clinical signs of OPIDN after 28 days.	(43)
1 600	Gavage	Chicken, Isabrown	8	-	Decrease of brain NTE by 86 % and plasma cholinesterase by 60 % after 24 hours (recovery of levels after 28 days). No change of brain cholinesterase. Ataxia in 6/8 of the chickens as clinical signs of OPIDN after 28 days.	(43)
2 320	Gavage	Rat	13 males	-	Decreased body weight. 100 % had spinal cord damage 14 days post-exposure. Significant NTE inhibition in spinal cord and brain at 20 and 44 hours; 91 % in spinal cord and 98 % in brain at 44 hours. Similar result at 3 480 mg/kg bw.	(181)
3 700	Dermal	Rabbit, albino		-	LD_{50}.	(106)
8 400	Gavage	Rat		-	LD_{50}.	(106)

Table II. Dose-effect and dose-response relationships in animals after exposure to tri-*o*-, tri-*m*- and tri-*p*-cresyl phosphate (TOCP, TMCP and TPCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
TOCP Multiple doses						
10	Oral, engine oil	Hen	30 females	10 weeks	No mortality. None had ataxia. Significant inhibition of plasma cholinesterase (41 %), brain NTE (68 %) and spinal cord NTE (52 %) activities at end of week 6. Neuropathological lesions (> grade 2) in 3/10. Degenerative changes graded in severity scale; 1 none, 2 mild, 3 moderate, 4 severe.	(70)
10	Oral, corn oil	Hen	30 females	10 weeks	No mortality. 3/30 had ataxia. Significant inhibition of plasma cholinesterase (44 %), brain NTE (71 %) and spinal cord NTE (55 %) activities at end of week 6. Neuropathological lesions (> grade 2) in 7/10.	(70)
10	Gavage, corn oil	Rat	10 males	9 weeks	Significant decrease of non-specific esterase activity in testis (also seen at 25, 50, 75 and 100 mg/kg bw). Normal testicular morphology. 0.25 % abnormal sperms vs. 0.17-0.19 % in controls.	(205)
25	Gavage, corn oil	Rat	10 males	9 weeks	The normal array of germ cells appeared disorganised. 1.20 % abnormal sperms vs. 0.17-0.19 % in controls. 16 % amorphous sperms vs. 0 %.	(205)
50	Oral, corn oil	Rat	8 males	10 days	Analysis of DNA isolated from liver, kidney, lung, heart, brain and testis 1, 4, 7 and 28 days after the last dose revealed two types DNA-adducts in the samples isolated from liver, kidney, lung and heart 1 day post-dosing. Both DNA-adducts persisted in the lungs for the entire observation period.	(151)
50	Gavage, corn oil	Rat	10 males	9 weeks	Pathologic testicular histology. 34 % abnormal sperms vs. 0.17-0.19 % in controls. 39 % amorphous sperms vs. 0 %. No observable motile sperms.	(205)
75	Gavage	Rat	6 males	14 days, every other day	Decrease of erythrocyte acetylcholinesterase activity. Reduction of acetylcholinesterase, NTE and carboxylesterase activities in brain. Increased glial fibrillary acidic protein in the cerebral cortex. Reduced body weight at all doses (75, 150, 300 mg/kg bw) and significantly at 75 and 300 mg/kg bw.	(53)

Table II. Dose-effect and dose-response relationships in animals after exposure to tri-*o*-, tri-*m*- and tri-*p*-cresyl phosphate (TOCP, TMCP and TPCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
75	Gavage	Rat	3-6 males	7 weeks, every other day, days 1-15 and 35-49	No degeneration of myelinated fibres in medullary gracile fasciculus. No peripheral nerve fibre degeneration.	(112)
75	Gavage, corn oil	Rat	10 males	9 weeks	Decrease in germ cell numbers. 39 % abnormal sperms vs. 0.17-0.19 % in controls. 32 % amorphous sperms vs. 0 %. No observable motile sperms.	(205)
87.5	Gavage, corn oil	Rat	10 females	Gestation days 6-18	Foetal weights significantly increased. No increase of visceral or skeletal variations. No maternal deaths or toxicity. No effect on preimplantation loss or resorption. Same results at 175 mg/kg bw.	(231)
100	Gavage, corn oil	Rat	10 males	2 weeks	Decreased epididymal sperm density and disruption of the seminiferous epithelium (dose-related effects seen also at 200, 400, 800, 1 600 mg/kg bw).	(205)
100	Gavage, corn oil	Rat	10 males	9 weeks	Decrease in germ cell numbers. Epididymis was devoid of any sperms. 46 % abnormal sperms vs. 0.17-0.19 % in controls. 33 % amorphous sperms vs. 0 %. No observable motile sperms.	(205)
150	Gavage	Rat	6 males	2 weeks, every other day	Decrease of erythrocyte acetylcholinesterase activity. Reduction of acetylcholinesterase, NTE and carboxylesterase activities in brain. Same effects also seen at 300 mg/kg bw.	(53)
150	Gavage, corn oil	Rat	8 males	3 weeks	Animals recovered for 98 days. Complete absence of germinal cells in the testis. Irreversible testicular lesion.	(206)
150	Gavage	Rat	3-6 males	7 weeks, every other day, days 1-15 and 35-49	Minor myelinated fibre degeneration in medullary gracile fasciculus. No peripheral nerve fibre degeneration.	(112)
300	Gavage	Rat	6 males	2 weeks, every other day	Thymus and spleen weights and cell counts not affected (data not reported for 75 and 150 mg/kg bw). Reduced grip strength when combined with corticosterone.	(53)

Table II. Dose-effect and dose-response relationships in animals after exposure to tri-*o*-, tri-*m*- and tri-*p*-cresyl phosphate (TOCP, TMCP and TPCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
300	Gavage	Rat	3-6 males	7 weeks, every other day, days 1-15 and 35-49	Prominent myelinated fibre degeneration in medullary gracile fasciculus. Peripheral nerve fibre degeneration. Lesions more pronounced at day 76 compared to day 49.	(112)
300	Gavage	Hen	4 females	5 days	Neurotoxic response in all animals.	(106)
350	Gavage, corn oil	Rat	18 females	Gestation days 6-18	28 % mortality among dams. Foetal weights significantly increased. No effect on preimplantation loss or resorption. No increase of visceral or skeletal variations.	(231)
500	Gavage, corn oil	Mice	5 males	Once a week for 13 weeks	No effect on immunoglobulin levels. Non-dose-related suppression of lymphocyte proliferation.	(20)
TMCP Single dose						
1 200	Gavage	Hen	Females	-	No neurotoxic response. 7 % inhibition of brain NTE activity.	(109)
2 000-2 500	Gavage	Hen	Females	-	No neurotoxic response.	(109)
5 000	Gavage	Chicken	2 males	-	No neurotoxic response.	(84)
TMCP Multiple doses						
50	Gavage, corn oil	Mice	5 males	Once a week for 13 weeks	No effect on immunoglobulin levels. Non-dose-related suppression of lymphocyte proliferation.	(20)
210	Gavage	Hen	Females	20 days	No neurotoxic response.	(109)
500	Gavage	Chicken	2 males	25 days	Neurotoxic response (considerable weakness of the legs). After 6 additional days, respiratory paralysis developed.	(94, 109)
1 000	Gavage	Chicken	2 males	5 days, every other day	No neurotoxic response.	(84)

Table II. Dose-effect and dose-response relationships in animals after exposure to tri-*o*-, tri-*m*- and tri-*p*-cresyl phosphate (TOCP, TMCP and TPCP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
TPCP Single dose						
1 200	Gavage	Hen	Females	-	No neurotoxic response. No inhibition of brain NTE activity.	(109)
2 500	Gavage	Hen	Females	-	No neurotoxic response.	(109)
5 000	Gavage	Chicken	2 males	-	No neurotoxic response.	(84)
TPCP Multiple doses						
100	Gavage, corn oil	Rat	10 males	9 weeks	Slight decrease (25 %) of testosterone levels but no effect on sperm quality.	(205)
260	Gavage	Hen	Females	18 days	No neurotoxic response.	(109)
500	Gavage	Hen	Females	15 days	No neurotoxic response.	(109)
500	Gavage	Chicken	2 males	50 days	No neurotoxic response.	(94)
1 000	Gavage	Chicken	2 males	5 days, every other day	No neurotoxic response.	(84)

CNS: central nervous system, E: European, LD_{50}: lethal dose for 50 % of the exposed animals at single administration, NTE: neurotoxic or neuropathy target esterase, OPIDN: organophosphorus-induced delayed neuropathy, PNS: peripheral nervous system.

Table III. Dose-effect and dose-response relationships in animals after exposure to tris(2-butoxyethyl) phosphate (TBEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Single dose						
1 000	Gavage	Rat	10 males	-	No signs of toxicity.	(127)
1 500	Gavage	Rat	10 females	-	No signs of toxicity. Same result at 1 000 mg/kg bw.	(127)
1 750	Gavage	Rat	3 females	-	Slight tremors and piloerection the first 3 days. Significantly decreased nerve conduction velocity.	(127)
2 000	Gavage	Rat	2 females	-	Slight tremors and piloerection the first 3 days. Significantly decreased nerve conduction velocity. Degenerative changes in both myelinated and unmyelinated fibres.	(127)
3 200	Gavage	Rat	1 female	-	Abnormal gait, piloerection, tremors, diarrhoea and increased urination the first week. Significantly decreased nerve conduction velocity. Advanced nerve fibre degeneration.	(127)
3 200	Gavage	Rat	4 males	-	Significantly decreased nerve conduction velocity. Retraction of the Schwann cell processes.	(127)
4 700	Oral	Rat		-	LD_{50}.	(103) [a]
5 000	Oral, gelatin capsule	Hen	5 females	-	Significant decrease of brain acetylcholinesterase (55 % of controls) and plasma cholinesterase (13 % of controls) activities. No change of brain NTE activity. $LD_{50} > 5\ 000$ mg/kg bw.	(32, 33)
5 000	Dermal	Rabbit		-	$LD_{50} > 5\ 000$ mg/kg bw.	(103) [b]
6 800	Gavage	Rat	4 males	-	Slight tremors and piloerection the first 3 days. Significantly decreased nerve conduction velocity. Degenerative changes in both myelinated and unmyelinated fibres.	(127)
8 000	Gavage	Rat	4 males	-	Abnormal gait, piloerection, tremors, diarrhoea, and increased urination the first week. Significantly decreased nerve conduction velocity. Advanced nerve fibre degeneration. Effects also seen at 9 000 mg/kg bw.	(127)
10 000	Dermal	Rabbit		-	$LD_{50} > 10\ 000$ mg/kg bw.	(103) [c]

Table III. Dose-effect and dose-response relationships in animals after exposure to tris(2-butoxyethyl) phosphate (TBEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Single exposure, aerosol						
3 300 mg/m^3	Inhalation	Rat	5/sex	4 hours	No animal died but all exhibited depressed and irregular respiration, increased salivation, sneezing, unsteadiness and tremor. These symptoms cleared in most animals 9 days later. Body weights did not change and gross necropsy revealed no abnormalities. Same observations at 3 400 and 6 400 mg/m^3, i.e. LC_{50} > 6 400 mg/m^3.	(103) [d]
4 430 mg/m^3	Inhalation	Rat		4 hours	LC_{50} > 4 430 mg/m^3.	(103) [e]
Multiple doses						
10	Dermal	Rabbit	6/sex	3 weeks	The test sites were occluded for 6 hours after each exposure. Local irritation, oedema, atonia and desquamation. Also seen at 100 and 1 000 mg/kg bw (dose-related). No adverse clinical signs of systemic pharmacological or toxicological effects.	(103) [f]
15	Oral, in diet	Rat	20/sex	18 weeks	No effect on haematological or clinical chemistry parameters. No effects on liver.	(103) [g]
20 (males) 22 (females)	Oral, in diet	Rat	7 males, 8 females	14 weeks	No effect on the liver, the indicated critical organ.	(189, 233)
100	Gavage, corn oil	Rat	10/sex	2 weeks	No biochemical, haematological or histopathological changes. Same result at 1 and 10 mg/kg bw.	(118)
150	Oral, in diet	Rat	20/sex	18 weeks	Increased serum γ-glutamyl-transpeptidase and decreased plasma cholinesterase activities. Mild periportal hepatocellular hypertrophy and periportal vacuolisation in males. No clinical signs of neuro-toxicity, nor at 15 mg/kg bw.	(103) [g]
200	Oral, in diet	Rat	Both sexes	4 weeks	No signs of toxicity (including body weight or food consumption). Same result at 50 mg/kg bw.	(103) [h]
200 (males) 220 (females)	Oral, in diet	Rat	7 males 8 females	14 weeks	Significant decrease of serum cholinesterase activity in both sexes. Significant increase of serum amylase activity in males.	(189, 233)

Table III. Dose-effect and dose-response relationships in animals after exposure to tris(2-butoxyethyl) phosphate (TBEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
250	Gavage	Rat	12/sex	18 weeks	Almost all animals affected at the 2nd half of the experiment. Difficulty in breathing and ataxia. Significant increase of liver weight in females. Significantly lower erythrocyte acetylcholinesterase activity (5 %) and uric acid concentration (40 %) compared to controls and myocardial necrosis with inflammatory cell infiltration and haemorrhages in males. No haematological effects.	(122)
250	Gavage	Rat	12/sex	18 weeks	Almost all animals affected at the 2nd half of the experiment. Some difficulty in breathing and ataxia. Decreased nerve conduction velocity in caudal nerve after 6 weeks. Sciatic nerve showed presence of degenerating myelin sheaths accompanied by axonal swelling. No morphological sex differences.	(124)
500	Oral, in diet	Rat	20/sex	18 weeks	Increased serum γ-glutamyl-transpeptidase and decreased plasma cholinesterase activities. Mild periportal hepatocellular hypertrophy and periportal vacuolisation in males. Increased platelet counts. Increased liver weight. Reduced caudal nerve conduction velocity in females. No treatment related changes in peripheral nerve or spinal cord histopathology.	(103) [g]
500	Gavage	Rat	12/sex	18 weeks	During the 1st week, 2 females showed muscular weakness and ataxia that disappeared 4 weeks later. Tremor, piloerection, lacrimation and increased urination. Significantly lower erythrocyte acetylcholinesterase activity (7 %) and uric acid concentration (~40 %) compared to controls and myocardial necrosis with inflammatory cell infiltration and haemorrhages in males. Significant increase of relative liver weights in both sexes. Significant increase of amylase and γ-glutamyl transferase activities in females. No haematological effects.	(122)

Table III. Dose-effect and dose-response relationships in animals after exposure to tris(2-butoxyethyl) phosphate (TBEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
500	Gavage	Rat	12/sex	18 weeks	During the 1st week 2 females showed muscular weakness and ataxia, that disappeared 4 weeks later. Also neurotoxic effects as at 250 mg/kg bw but more advanced degeneration as indicated by lamellated electron dense inclusions in unmyelinated nerve fibres. No morphological sex differences.	(124)
750	Oral, in diet	Rat	Both sexes	4 weeks	No signs of toxicity in males. Slight decrease in body weight and food consumption in females. Same results at 1 500 mg/kg bw. No compound related changes observed at necropsy.	(103) [h]
800	Gavage	Rat	10/sex	2 weeks	Slightly (non-significant) decreased nerve conduction velocity in caudal nerve in females. Significantly increased relative refractory period in males. No sign of morphological changes in sciatic nerve.	(126)
1 000	Dermal	Rabbit	6/sex	3 weeks	The test sites were occluded for 6 hours after each exposure. Squamous cell hyperplasia, hyperkeratosis, erosion ulcers, inflammation, congestion and haemorrhages.	(103) [f]
1 000	Gavage, corn oil	Rat	Females		No maternal weight loss (dose-range-finding study).	(103) [i]
1 140	Gavage	Rat	10 females	2 weeks	Significantly decreased nerve conduction velocity in caudal nerve. No sign of morphological changes in sciatic nerve.	(126)
1 500	Gavage, corn oil	Rat	25 females	Gestation days 6-15	No effect on foetal resorption, foetal viability, post-implantation loss, total implantations or foetal malformations. Same results at 250 and 500 mg/kg bw.	(103) [j]
2 000	Gavage, corn oil	Rat	Females		Maternal weight loss (dose-range-finding study).	(103) [i]
2 000 (males) 2 200 (females)	Oral, in diet	Rat	7 males 8 females	14 weeks	Suppression of body weight gain. Significant increase of liver weights. Significant decrease of serum cholinesterase and significant increases of serum γ-glutamyl transferase and amylase activities. Moderate periportal hepatocyte swelling in males.	(189, 233)
2 280	Gavage	Rat	10 males	2 weeks	Significantly increased relative and absolute refractory periods. No sign of morphological changes in sciatic nerve.	(126)

Table III. Dose-effect and dose-response relationships in animals after exposure to tris(2-butoxyethyl) phosphate (TBEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
5 000	Oral, gelatin capsule	Hen	20	Twice, 21 days apart	All survived. 2 hens had equivocal focal swollen axons but the changes were not considered to differ from controls. No lesions in peripheral nerves.	(32, 33)
5 000	Dermal	Hen	20	Twice, 21 days apart	No lesions in the spinal cord or in peripheral nerves.	(32, 33)

LC_{50}: lethal concentration for 50 % of the exposed animals at single administration, LD_{50}: lethal dose for 50 % of the exposed animals at single administration.
All studies below cited in (103):
[a] Monsanto 1984b.
[b] Gabriel 1980a.
[c] FMC 1976.
[d] Hoechst 1989.
[e] Mount 1991.
[f] Monsanto 1985e.
[g] Monsanto 1987a, b.
[h] Monsanto 1985b.
[i] Monsanto 1985c.
[j] Monsanto 1985d.

Table IV. Dose-effect and dose-response relationships in animals after exposure to tri-*n*-butyl phosphate (TBP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Single dose						
16	Intraperitoneal, corn oil	Rat	4	-	Increase of β-glucuronidase in serum (×1.6). No effect on serum cholinesterase.	(221)
17	Intratracheal, dodecan	Rat	30	-	Increased total cell number and protein in bronchoalveolar lavage fluid day 1 post-exposure. Decreased serum cholinesterase activity on day 1 post-exposure.	(191)
100	Gavage, corn oil	Rat	12/sex	-	No reported signs from the nares, no effects on motor activity. Dose-related reduction of motor activity (significant at 1 000 mg/kg bw).	(80)
270	Intraperitoneal, corn oil	Rat	4	-	Increase of β-glucuronidase in serum (×50). No effect on serum cholinesterase activity.	(221)
325	Gavage, corn oil	Rat	12/sex	-	Staining/discharge at the muzzle and nares. Dose-related reduction of motor activity (significant at 1 000 mg/kg bw).	(80)
1 000	Gavage, corn oil	Rat	12/sex	-	Reduced motor activity. Lower activity based on Functional Observation Battery. One female died. Lower body weight increase among males. Decreased forelimb grip strength. Increased palpebral closure and grooming in females.	(80)
1 400-3 200	Oral	Rat		-	LD_{50}.	(101, 106)
1 500	Oral	Hen	5 females	-	LD_{50}. No change of NTE or acetylcholinesterase activities in brain. Significant increase of plasma cholinesterase (269 % of controls).	(32, 33)
3 100	Dermal	Rabbit		-	LD_{50} > 3 100 mg/kg bw.	(106)
Multiple doses						
9	Oral, in diet	Rat	50 males	2 years	Urinary bladder hyperplasia in 3/50 vs. 3/50 in controls. No neoplasms.	(13)
10	Oral, in diet	Rat	Both sexes	13 weeks	No histopathological changes or clinical chemistry changes (presented as an abstract).	(101) [a]

Table IV. Dose-effect and dose-response relationships in animals after exposure to tri-*n*-butyl phosphate (TBP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
12	Oral, in diet	Rat	50 females	2 years	Urinary bladder hyperplasia in 1/50 vs. 1/50 in controls. No neoplasms.	(13)
10-21	Oral, in diet	Rat	30 F_1 males	11 weeks during pre-breed period + mating, gestation, lactation	No mortality. No treatment-related clinical observations (same results observed at 36-72 and 166-328 mg/kg bw). Urinary bladder epithelial hyperplasia in 2/28 vs. 0/29-30 in controls. No renal pelvic epithelial hyperplasia.	(234)
11-18	Oral, in diet	Rat	30 F_0 males	10 weeks during pre-breed period + mating, gestation, lactation	No mortality. No treatment-related clinical observations (same results observed at 38-65 and 160-264 mg/kg bw). Urinary bladder epithelial hyperplasia in 1/30 vs. 0/29-30 in controls. No renal pelvic epithelial hyperplasia.	(234)
12-17	Oral, in diet	Rat	30 F_0 females	10 weeks during pre-breed period + mating, gestation, lactation	No mortality. No treatment-related clinical observations (same results observed at 41-60 and 178-266 mg/kg bw). Transient reductions in body weight. Urinary bladder epithelial hyperplasia in 2/30 vs. 0/29-30 in controls. No hepatic centrilobular hypertrophy.	(234)
13-21	Oral, in diet	Rat	30 F_1 females	11 weeks during pre-breed period + mating, gestation, lactation	No mortality. No treatment-related clinical observations (same results observed at 44-70 and 193-316 mg/kg bw). Transient reductions in body weight. No urinary bladder epithelial hyperplasia. No hepatic centrilobular hypertrophy.	(234)
20	Oral, in diet	Rat	10 males	10 weeks	No effects on urinary chemistry and no urothelial changes in the bladder.	(11)
24	Oral, in diet	Mouse	50 females	18 months	No effect on body weight. No tumours related to treatment.	(12)
29	Oral, in diet	Mouse	50 males	18 months	No effect on body weight. No tumours related to treatment.	(12)
31	Oral, in diet	Rat	30 F_1 females	Lactation days 0-21	No mortality. No treatment-related clinical observations (same results at 107 and 502 mg/kg bw). Reduction of F_2 pup body weights per litter at postnatal day 14.	(234)
32.5	Oral, in diet	Rat	50 males	2 years	Urinary bladder hyperplasia in 12/49 vs. 3/50 in controls. Urinary bladder papillomas in 2/49 vs. 0/50.	(13)

Table IV. Dose-effect and dose-response relationships in animals after exposure to tri-*n*-butyl phosphate (TBP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
32.5	Gavage, corn oil	Rat	12/sex	13 weeks	Rarely post-dosing salivation.	(80)
36-72	Oral, in diet	Rat	F_1 males	11 weeks during pre-breed period + mating, gestation, lactation	Urinary bladder epithelial hyperplasia in 16/30 vs. 0/29-30 in controls. No renal pelvic epithelial hyperplasia.	(234)
38-65	Oral, in diet	Rat	F_0 males	10 weeks during pre-breed period + mating, gestation, lactation	Urinary bladder epithelial hyperplasia in 22/30 vs. 0/29-30 in controls. No renal pelvic epithelial hyperplasia.	(234)
41-60	Oral, in diet	Rat	F_0 females	10 weeks during pre-breed period + mating, gestation, lactation	Urinary bladder epithelial hyperplasia in 21/30 vs. 0/29-30 in controls. Hepatic centrilobular hypertrophy in 3/30 vs. 0/29-30.	(234)
42	Oral, in diet	Rat	50 females	2 years	Urinary bladder hyperplasia in 5/49 vs. 1/50 in controls. Urinary bladder papillomas in 1/49 vs. 0/50.	(13)
44-70	Oral, in diet	Rat	F_1 females	11 weeks during pre-breed period + mating, gestation, lactation	Reduction of body weight and body weight gain. Urinary bladder epithelial hyperplasia in 21/30 vs. 0/29-30 in controls. Hepatic centrilobular hypertrophy in 1/30 vs. 0/29-30.	(234)
45 (F_1) 47 (F_0)	Oral, in diet	Rat	F_1 and F_0 females	Gestation days 0-20	No mortality. No effect on reproductive indices, mating and fertility indices. Same results at 13 mg/kg bw.	(234)
50	Oral, in diet	Rat	Both sexes	13 weeks	Transitional cell hyperplasia in the urinary bladder of males (presented as an abstract).	(101) [a]
62.5	Gavage, olive oil	Rat	20	Gestation days 7-17	No maternal toxicity. No foetotoxicity.	(168)

Table IV. Dose-effect and dose-response relationships in animals after exposure to tri-*n*-butyl phosphate (TBP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
70	Oral, in diet	Rat	10 males	10 weeks	No effect on urinary chemistry. Bladder effects: increased occurrence of simple hyperplasia, non-significant increase of nodular and papillary hyperplasia, and erosion, ulceration and haemorrhage.	(11)
94	Oral, in diet	Rat	30 F_0 females	Lactation days 0-21	No mortality. No treatment-related clinical observations. No reduction of body weight and weight gain. Same results at 26 mg/kg bw.	(234)
100	Gavage, olive oil	Rat	20	Gestation days 7-17	No effect on maternal body weight gain. No foetotoxicity (dose-range finding study).	(168)
100	Gavage, corn oil	Rat	12/sex	13 weeks	Frequently post-dosing salivation. 2 males and 1 female died.	(80)
107	Oral, in diet	Rat	30 F_1 females	Lactation days 0-21	Reduction of body weight and weight gain. Reduction of F_2 pup body weights per litter at postnatal days 1 and 21.	(234)
125	Gavage, olive oil	Rat	20	Gestation days 7-17	No significant effect on maternal body weight gain. No foetotoxicity. Same result at 62.5 and 100 mg/kg bw.	(168)
140	Gavage	Rat	10/sex	2 weeks	No effect on absolute liver weight but significant increase of relative liver weight.	(123)
143	Oral, in diet	Rat	50 males	2 years	Significantly lower body weight gain. Increase of urinary bladder hyperplasia (17/49 vs. 3/50 in controls). Significant increase of urinary bladder papillomas (23/49 vs. 0/50) and transitional cell carcinomas (6/49 vs. 0/50).	(13)
150	In corn oil, probably gavaged	Rabbit		Gestation days 6-18	No foetotoxicity or teratogenicity. Same results at 50 mg/kg bw (presented as an abstract).	(196)
160-264	Oral, in diet	Rat	30 F_0 males	10 weeks during pre-breed period + mating, gestation, lactation	Reduction of body weight and weight gain. Urinary bladder epithelial hyperplasia in 30/30 vs. 0/29-30 in controls. Renal pelvic epithelial hyperplasia in 2/30 vs. 0/29-30. No hepatic centrilobular hypertrophy.	(234)

Table IV. Dose-effect and dose-response relationships in animals after exposure to tri-*n*-butyl phosphate (TBP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
166-328	Oral, in diet	Rat	30 F_1 males	11 weeks during pre-breed period + mating, gestation, lactation	Reduction of body weight and weight gain. Urinary bladder epithelial hyperplasia in 30/30 vs. 0/29-30 in controls. Renal pelvic epithelial hyperplasia in 10/30 vs. 0/29-30. No hepatic centrilobular hypertrophy.	(234)
169	Oral, in diet	Mouse	50 males	18 months	Increased absolute and relative liver weight. No effect on body weight. No tumours related to treatment.	(12)
178-266	Oral, in diet	Rat	30 F_0 females	10 weeks during pre-breed period + mating, gestation, lactation	Reduction of body weight and weight gain. Urinary bladder epithelial hyperplasia in 30/30 vs. 0/29-30 in controls. Hepatic centrilobular hypertrophy in 28/30 vs. 0/29-30. No renal pelvic epithelial hyperplasia.	(234)
182	Oral, in diet	Rat	50 females	2 years	Significantly lower body weight gain. Increase of urinary bladder hyperplasia (29/49 vs. 1/50 in controls). Significant increase of urinary bladder papillomas (11/49 vs. 0/50).	(13)
188	Gavage, corn oil	Rat		Gestation days 6-15	Maternal toxicity. No foetotoxicity or teratogenicity. Same result at 375 mg/kg bw (presented as an abstract).	(196)
193-316	Oral, in diet	Rat	30 F_1 females	11 weeks during pre-breed period + mating, gestation, lactation	Reduction of body weight and weight gain. Urinary bladder epithelial hyperplasia in 30/30. Hepatic centrilobular hypertrophy 25/30. No renal pelvic epithelial hyperplasia.	(234)
200	Gavage, olive oil	Rat	5	Gestation days 7-17	Reduced maternal weight gain. Reduced body weight of living female foetuses (dose-range finding study).	(168)
200	Gavage	Rat	12/sex	18 weeks	Diffuse hyperplasia of the urinary bladder epithelium. Also seen at 300 mg/kg bw.	(121)
206	Oral, in diet	Mouse	50 females	18 months	Increased absolute and relative liver weight. No effect on body weight. No tumours related to treatment.	(12)

Table IV. Dose-effect and dose-response relationships in animals after exposure to tri-*n*-butyl phosphate (TBP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
214 (F_0) 217 (F_1)	Oral, in diet	Rat	30 F_0 and 30 F_1 females	Gestation days 0-20	No treatment-related clinical observations. Reduction of body weight and weight gain. No effect on reproductive indices, mating and fertility indices.	(234)
250	Gavage, olive oil	Rat	20	Gestation days 7-17	Reduced maternal weight gain. No foetotoxicity.	(168)
250	Oral, in diet	Rat	Both sexes	13 weeks	Increased absolute and relative liver weights, serum γ-glutamyl transpeptidase levels, and transitional cell hyperplasia in the urinary bladder (presented as an abstract).	(101) [a]
270	Gavage	Rat	4/sex	2 weeks	Increased absolute and relative refractory periods in the caudal nerve. Morphological changes of the sciatic nerve.	(125)
300	Oral, in diet	Rat	10 males	10 weeks	Increased bladder weight. Decreased urinary osmolality and creatinine concentrations. Increased occurrence of simple hyperplasia and nodular and papillary hyperplasia of the bladder. Erosion, ulceration and haemorrhage of the bladder. Occasional foci of squamous metaplasia, indicating chronic inflammation. No treatment-related histopathological effects on kidney or stomach at this dose or at 20 or 70 mg/kg bw.	(11)
325	Gavage, corn oil	Rat	12/sex	13 weeks	Moderate to severe post-dosing salivation. 3 males and 4 females died. Muzzle-region and urogenital staining in some rats. Decreased body weight gain. No effect in Functional Observation Battery. No effect on motor activity. No neurohistopathological effect.	(80)
375	Gavage, corn oil	Rat	Females	Gestation days 6-15	Maternal toxicity. No foetotoxicity or teratogenicity. Same results at 188 mg/kg bw (presented as an abstract).	(196)
400	Gavage, olive oil	Rat	5	Gestation days 7-17	Reduced maternal weight gain. Transient piloerection and salivation (dose-range finding study).	(168)

Table IV. Dose-effect and dose-response relationships in animals after exposure to tri-*n*-butyl phosphate (TBP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
400	Gavage, corn oil	Rabbit	Females	Gestation days 6-18	Maternal and embryotoxicity suggested. No foetotoxicity or teratogenicity (not observed at 50 or 150 mg/kg bw either (presented as an abstract).	(196)
404	Oral, in diet	Rat	30 F_0 females	Lactation days 0-21	Reduction of body weight and weight gain. Reduction of F_1 pup body weights per litter. No mortality. No treatment-related clinical observations.	(234)
410	Gavage	Rat	4/sex	2 weeks	Increased absolute refractory periods in the caudal nerve in females. Significant reduction in conduction velocity in caudal nerve in males. Retraction of Schwann cell processes surrounding unmyelinated fibres in the sciatic nerve in both sexes.	(125)
410	Gavage	Rat	10/sex	2 weeks	Significant increase of absolute liver weight in both sexes. Significant increase of triglycerides and amylase in females. Significant increase of amylase, bilirubin and erythrocyte acetylcholinesterase in males. 1/4 males showed microscopic degenerative changes in 50 % of the seminiferous tubules. No other microscopic changes.	(123)
500	Oral, in diet	Rat	Males	10 weeks	Decreased body weight gain and food consumption. Increased relative brain, kidney and liver weights and decreased absolute brain and kidney weights. No effect on cholinesterase activity in serum or liver but increased activity in brain. Increased blood coagulation time. Decreased serum glucose and increased urea concentrations. Decreased activities of serum ALAT, ASAT and ALP. (At 1 000 mg/kg bw, the same results were obtained and in addition increased total protein and cholesterol in serum).	(177)
500	Oral, in diet	Rat	8 males	9 weeks	Increased absolute and relative liver weights and increased relative weights of kidney and testes. Haematological parameters not different from controls. Enzyme activities and all serum components unaffected except increased urea nitrogen levels.	(178)

Table IV. Dose-effect and dose-response relationships in animals after exposure to tri-*n*-butyl phosphate (TBP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
500	Gavage, olive oil	Rat	20 females	Gestation days 7-17	Reduced maternal weight gain. Piloerection, wetting of abdominal hair with urine and salivation. Increased incidence of rudimentary lumbar ribs.	(168)
502	Oral, in diet	Rat	30 F_1 females	Lactation days 0-21	Reduction of body weight and weight gain. Reduction of F_2 pup body weights per litter.	(234)
585	Oral, in diet	Mouse	50 males	18 months	A slight increase in mortality. 10 % decrease of body weight gain. Increased absolute and relative liver weight. Increased incidence of hepatocellular adenomas in male mice (10/50 vs. 3/50 in controls). No urinary bladder alterations.	(12)
711	Oral, in diet	Mouse	50 females	18 months	10 % decrease of body weight gain. Increased absolute and relative liver weight. No urinary bladder alterations.	(12)
750	Oral, in diet	Rat	Females	Gestation days 6-15	Increased mortality among dams. Delayed ossification and reduced foetal body weights (presented as an abstract).	(196)
800	Gavage, olive oil	Rat	5 females	Gestation days 7-17	All animals died after 5-6 doses. Marked reduction of maternal weight gain (dose-range finding study).	(168)
1 500	Oral, gelatin capsules	Hen	20 females	2 doses 21 days apart	4 died after the 1st dose and 2 after the 2nd. Only lesions of minimal severity and representative of spontaneously occurring nervous system lesions in hens of this age. None of the hens exhibited treatment-related clinical signs or peripheral nerve, spinal cord or brain injury.	(32, 33)
1 840	Oral	Hen	9 females	2 days	No neurotoxic response regarding behaviour or histology.	(106)

Table IV. Dose-effect and dose-response relationships in animals after exposure to tri-*n*-butyl phosphate (TBP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Multiple exposures, aerosol						
4.8 mg/m^3 [b]	Inhalation	Rat, rabbit		4 months	No effects on cholinesterase activities in erythrocytes or serum. Exposure to 13.6 mg/m^3 caused a 33 % inhibition after 3 months. According to DFG (47), the study was insufficiently documented (no data for control animals, number or type of animals used or analytical monitoring of the exposure level).	(47) [c]
5 mg/m^3 [d]	Inhalation MMAD not analysed	Rat	25/sex	6 or 13 weeks	No effect on body weight. No salivation (10 animals/sex exposed for 6 weeks and 15 animals/sex for 13 weeks).	(81)
100 mg/m^3 [d]	Inhalation MMAD 2.9 µm	Rat	25/sex	As above	Nasal discharge in 47/50; decreasing over time. Salivation in 2/50 the first week.	(81)
300 mg/m^3 [d]	Inhalation MMAD 3.3 µm	Rat	25/sex	As above	Nasal discharge in 50/50, decreasing over time. Salivation from 40 % the first week. Increased absolute and relative liver weights and decreased haematocrit in all animals. Decreased body weights and plasma cholinesterase levels, erythrocyte counts and haemoglobin levels and centrilobular hepatocellular hypertrophy (10/15) in females.	(81)

DFG: Deutsche Forschungsgemeinschaft, LD_{50}: lethal dose for 50 % of the exposed animals at single administration, MMAD: mass median aerodynamic diameter, NTE: neurotoxic or neuropathy target esterase.

[a] Cascieri *et al*, 1985, cited in (101).

[b] No information of physical state of TBP.

[c] Kalinina 1971, cited in (47).

[d] Skydrol 500B-4 containing TBP and dibutyl phenyl phosphate.

Table V. Dose-effect and dose-response relationships in animals after exposure to tris(2-chloroethyl) phosphate (TCEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Single dose						
50	Intraperitoneal	Mouse	10 males	-	No effect on ambulatory activity (2 hours observation).	(236)
100	Intraperitoneal	Mouse	10 males	-	Ambulatory activity significantly higher the first 10 min after treatment compared to control but returned to control level quickly. Also seen at 200 mg/kg bw.	(236)
175	Gavage	Rat	3/sex	-	Mild, occasional seizures.	(83)
275	Gavage	Rat	Females	-	Convulsive activity within 60-90 minutes. Extensive loss of CA1 hippocampal pyramidal cells. Impaired acquisition of a reference memory task in a water maze.	(230)
350	Gavage	Rat	3/sex	-	Most animals had seizures within 1 hour (females more affected than males).	(83)
430-794	Oral	Rat	Females	-	LD_{50} (three different lots).	(235)
501	Oral	Rat	Males	-	LD_{50}. Spasmodic contractions and acute depression.	(235)
700	Gavage	Rat	3/sex	-	All animals exhibited seizures consisting of rearing and "wet dog shakes" within 1 hour.	(83)
800	Gavage	Rat	5/sex	-	No clinical signs of toxicity or microscopic pathology abnormalities.	(102) [a]
1 000	Gavage	Rat	5/sex	-	1/5 females died on day 2. Piloerection, increased salivation, hunched posture, abnormal gait, lethargy, laboured respiration, ptosis, and pale extremities among all animals. No clinical signs of toxicity or micro-scopic pathology abnormalities. LD_{50} calculated to be 1 150 mg/kg bw.	(102) [a]
1 230	Oral	Rat		-	LD_{50}.	(102)
1 260	Gavage	Rat	5/sex	-	4/5 males and 4/5 females died by day 4. Clinical signs as at 1 000 mg/kg bw. No clinical signs of toxicity in surviving animals from day 4 onwards. No microscopic pathology abnormalities.	(102) [a]

Table V. Dose-effect and dose-response relationships in animals after exposure to tris(2-chloroethyl) phosphate (TCEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
3 600	Oral	Rat	5/sex	-	LD_{50}.	(102) [b]
14 200	Oral	Hen	Females	-	Significant decrease of plasma cholinesterase (87 %) and brain NTE (30 %) activities. No signs of delayed neurotoxicity.	(209)
Multiple doses						
12	Oral	Mouse	50/sex	18 months	Number of tumour-bearing animals not significantly different from controls, 38/49 vs. 34/50 in controls (males) and 28/49 vs. 30/49 (females).	(102, 225)
22 [c]	Gavage, corn oil	Rat	10/sex	16 (females) or 18 (males) weeks	No effects on organ weights. 1/10 males and 2/10 females died due to gavage trauma.	(149, 173)
44 [c]	Gavage, corn oil	Rat	5/sex	5 days/week, totally 12 doses	All rats survived. No effect on body or organ weights. No histopatho-logical lesions attributable to TCEP. Normal serum cholinesterase activity. Same results at 22 mg/kg bw.	(173)
44 [c]	Gavage, corn oil	Rat	10/sex	16 (females) or 18 (males) weeks	Significant increase in absolute and relative liver and kidney weights in females. Also seen at 88, 175 and 350 mg/kg bw.	(149, 173)
44 [a]	Gavage	Rat	50/sex	2 years	No effects on body weight gain and no clinical signs of toxicity. No degenerative lesions of the brain. Renal tubular hyperplasia in males (2/50 vs. 0/50 in controls) and females (3/50 vs. 0/50). Renal tubular adenomas in males (5/50 vs. 1/50, $p = 0.083$) and females (2/50 vs. 0/50).	(150, 173)
60	Oral, in diet	Mouse	50/sex	18 months	Number of tumour-bearing animals not significantly different from controls, 39/49 vs. 34/50 in control (males) and 33/50 vs. 30/49 (females).	(102, 225)
88 [c]	Gavage, corn oil	Rat	5/sex	5 days/week, totally 12 doses	Significantly decreased organ weights including absolute and relative lung weights in females. All rats survived. No effect on body weight. No histopathological lesions attributable to TCEP. Normal serum cholinesterase activity.	(173)

Table V. Dose-effect and dose-response relationships in animals after exposure to tris(2-chloroethyl) phosphate (TCEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
88 [c]	Gavage, corn oil	Mouse	10/sex	16 weeks	No effects on body, liver or kidney weights. Same results at 44 mg/kg bw.	(149, 173)
88 [c]	Gavage	Rat	50/sex	2 years	Reduced survival. No effects on body weight gain and no clinical signs of toxicity. Increased incidences of renal tubular hyperplasia in males (24/50 vs. 0/50 in controls) and females (16/50 vs. 0/50), renal tubular adenomas in males (24/50 vs. 1/50, $p < 0.001$) and females (5/50 vs. 0/50, $p = 0.003$) and thyroid gland follicular cell adenomas or carcinomas in males (5/50 vs. 1/50, $p = 0.087$) and females (4/50 vs. 0/50, $p = 0.014$). Significant increase of degenerative lesions in brain in over 40 % of the females. Similar lesions occurred in a few males, but these lesions were not clearly chemical related.	(150, 173)
100	Gavage	Rat	23-30	Gestation days 7-15	No changes in maternal body weight gain and food consumption. No increase in foetal death or malformations. Same results at 50 mg/kg bw.	(115)
175 [c]	Gavage, corn oil	Mouse	5/sex	5 days/week, totally 12 doses	No effect on body or organ weights. No histopathological lesions attributable to TCEP. Normal serum cholinesterase activity. Same results at 44 and 88 mg/kg bw.	(173)
175 [c]	Gavage, corn oil	Rat	5/sex	5 days/week, totally 12 doses	All rats survived. No effect on body weight. Significantly increased absolute and relative kidney weights in males. No histopathological lesions attributable to TCEP. Serum cholinesterase activity decreased (20 %) in females but not in males. Similar results at 350 mg/kg bw.	(173)
175 [c]	Gavage, corn oil	Rat	10/sex	16 (females) or 18 (males) weeks	In females, significantly decreased serum cholinesterase (25 %) and increased incidence of lesions in the hippocampal region of the brain (8/10).	(149, 173)
175 [c]	Gavage	Rats	10	13 weeks	Decreased sperm motility in one or more dose groups compared to a control group. It is not clear at which dose level the effects appeared (22, 88 or 175 mg/kg bw).	(159)

Table V. Dose-effect and dose-response relationships in animals after exposure to tris(2-chloroethyl) phosphate (TCEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
175 [c]	Gavage, corn oil	Mouse	10/sex	16 weeks	Significantly increased liver weight in females and significantly decreased relative kidney weights in males. Same effects also seen at 350 mg/kg bw.	(149, 173)
175 [c]	Gavage	Mouse	50/sex	2 years	No effects on body weight gain and no clinical signs of toxicity. Significant increase of karyomegaly (nuclear enlargement) in renal tubular cells in males (16/50 vs. 2/50 in controls) and in females (5/49 vs. 0/50).	(150, 173)
175	Gavage, corn oil	Mouse	20/sex	14 weeks	No effect on reproduction.	(36)
200	Gavage	Rat	23-30	Gestation days 7-15	7/30 dams died. Maternal food consumption markedly suppressed with toxic symptoms such as piloerection and general weakness. No increase in foetal death or malformations. No developmental effects attributable to the treatment shown in morphological examination and functional tests.	(115)
300	Oral in diet	Mouse	50/sex	18 months	Number of tumour-bearing animals significantly increased in females (39/49 vs. 30/49 in controls) but not in males (39/47 vs. 34/50). Significant increase of leukaemia in females (9/49 vs. 1/49) and of hepatocellular adenomas/carcinomas in males (12/47 vs. 4/50).	(102, 225)
350 [c]	Gavage, corn oil	Rat	5/sex	5 days/week, totally 12 doses	All rats survived. No effect on body weight. Increased absolute and relative kidney weights in males. Increased absolute and relative liver weights in females. No histopathological lesions attributable to TCEP. Serum cholinesterase activity decreased (20 %) in females but not in males.	(173)
350	Gavage, corn oil	Mouse	5/sex	5 days/week, totally 12 doses	Ataxia and convulsive movements during the first 3 days. No effect on body or organ weights. No histopathological lesions attributable to TCEP. Normal serum cholinesterase activity. Same results at 700 mg/kg bw.	(173)

Table V. Dose-effect and dose-response relationships in animals after exposure to tris(2-chloroethyl) phosphate (TCEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
350 [c]	Gavage, corn oil	Rat	10/sex	16 (females) or 18 (males) weeks	Significant increase in relative liver and kidney weights in both sexes. *Females:* Serum cholinesterase significantly decreased (41 %). Increased incidence of lesions in the hippocampal region of the brain (10/10). The severity increased with dose. Lesions consisted predominantly of loss of CA1 pyramidal neurons of the hippocampus. Neuronal necrosis in the thalamus. Periodic convulsions during week 12. Increased (~20 %) body weight. 3 deaths. *Males:* Significant decrease in body weight. 5 deaths.	(149, 173)
350 [c]	Gavage	Mouse	50/sex	2 years	No effects on body weight gain and no clinical signs of toxicity. Significant increase of karyomegaly (nuclear enlargement) in renal tubular cells in males (39/50 vs. 2/50 in controls) and in females (44/50 vs. 0/50). Increase of hepatocellular adenomas and carcinomas (33/50 vs. 26/50, p = 0.087) in males. Increase of Harderian gland adenomas and carcinomas (10/60 vs. 3/59, p = 0.049) in females.	(150, 173)
350	Gavage, corn oil	Mouse	20/sex	14 weeks	Number of litter/pair reduced by 8 %. Number of live pups/litter reduced by 20 %.	(36)
420	Oral, probably gavage	Hen		5 days	No signs of neurotoxicity (TOCP used as positive control) during the 21-day observation period.	(102) [d]
700 [c]	Gavage, corn oil	Mouse	10/sex	16 weeks	Significantly increased liver weights in both sexes. Significantly decreased kidney and absolute and relative testis weights in males. Mild cytomegaly and karyomegaly of the epithelium of the kidney tubules in all mice.	(149, 173)
700 [c]	Gavage	Mouse	10 males	13 weeks	Decreased weights of epididymis and testis and an increase of abnormal sperms in one or more dose groups compared to a control group. It is not clear at which dose level the effects appeared (44, 175 or 700 mg/kg bw).	(159)

Table V. Dose-effect and dose-response relationships in animals after exposure to tris(2-chloroethyl) phosphate (TCEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
700	Gavage, corn oil	Mouse	20/sex	14 weeks	Number of litter/pair reduced by 63 %. The number of live pups/litter reduced by 32 %, although pup viability, sex ratio and weight remained unchanged. Only 2/18 pairs delivered a third litter vs. 37/38 in controls. Increase in cumulative days to deliver each litter.	(36)
1 500	Oral in diet	Mouse	50/sex	18 months	Number of tumour-bearing animals significantly increased in males (50/50 vs. 34/50 in controls) and in females (41/50 vs. 30/49). Significant increase of leukaemia (9/50 vs. 1/49) and of forestomach tumours (papilloma/squamous cell carcinoma) (7/50 vs. 0/49) in females. Significant increase of hepatocellular adenoma/carcinoma (19/50 vs. 4/50) and of renal cell adenoma/carcinoma (41/50 vs. 2/50) in males. Cysts of the kidneys, necrosis and interstitial fibrosis.	(102, 225)
14 200	Oral	Hen	18	2 doses 21 days apart	Four hens died. Egg production ceased and the birds lost feathers. Histological examination of nerve sections showed similar changes as in the control group. No evidence for OPIDN.	(209)
Multiple exposures, airborne						
0.5 mg/m^3	Inhalation	Rat	Male	4 months	Testicular toxicity at this level and at 1.5 mg/m^3 (study inadequately reported).	(200)

LD_{50}: lethal dose for 50 % of the exposed animals at single administration, NTE: neurotoxic or neuropathy target esterase, OPIDN: organophosphorus-induced delayed neuropathy.

[a] Kynoch and Denton 1990, cited in (102).

[b] Gardner 1987, cited in (102).

[c] 98 % TCEP.

[d] Bullock and Kamienski, cited in (102).

Table VI. Dose-effect and dose-response relationships in animals after exposure to tris(1,3-dichloro-2-propyl) phosphate (TDCPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Single dose						
1 890	Gavage, olive oil	Mouse	10 females	-	No mortality.	(102, 114)
2 250	Gavage, olive oil	Mouse	10 females	-	LD_{50}. Clinical signs included ataxia, hyperactivity and convulsion.	(102, 114)
2 670	Gavage, olive oil	Mouse	10 males	-	LD_{50}. Clinical signs included ataxia, hyperactivity and convulsion.	(102, 114)
Single exposure, aerosol						
5 220 mg/m^3	Inhalation	Rat	5/sex	4 hours	$LC_{50} > 5\ 220$ mg/m^3.	(102) [a]
Multiple doses						
2.5	Subcutaneous, corn oil	Mouse	7-10 females	4 days	No effects when tested 3 days after last exposure. Histological examination revealed no significant lesions in the brain, vagina, uterus, liver, kidney, adrenals, spleen, bone marrow, lung or salivary gland. Normal lympho-proliferative response to mitogens. Same result at 0.25 mg/kg bw.	(137)
5	Oral, in diet	Rat	50/sex	2 years	*Kidney:* Increase of hyperplasia in the convoluted tubules in males (10/49 vs. 2/45 in controls) but not in females (1/48 vs. 0/49). Cortical tumours (benign and/or malignant) in males (3/49 vs. 1/45) and in females (1/48 vs. 0/49). *Liver:* Benign neoplastic nodules in males (7/48 vs. 2/45) and females (1/47 vs. 1/49). Carcinomas in males (2/48 vs. 1/45) and females (2/47 vs. 0/49). *Testis:* Benign interstitial tumours (8/48 vs. 7/43). Seminal vesicle atrophy and decreased secretory products (also seen at 20 and 80 mg/kg bw) *Apparently the same data as Stauffer 1981b, cited in (217) (presented briefly below), and (69).*	(102) [b]

Table VI. Dose-effect and dose-response relationships in animals after exposure to tris(1,3-dichloro-2-propyl) phosphate (TDCPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
5	Oral, in diet	Rat	60/sex	12 and 24 months	*Kidney:* Increase of hyperplasia in the convoluted tubules in males (10/60 vs. 2/60 in controls) but not in females (1/60 vs. 0/60). Cortical tumours (benign and/or malignant) in males (3/60 vs. 1/60) and in females (1/60 vs. 0/60). *Liver:* Carcinomas in males (2/60 vs. 1/60) and females (2/60 vs. 0/60). *Testis:* Interstitial tumours (8/60 vs. 7/57). Significant increase of seminal vesicle atrophy (4/13 vs. 0/56) and significant decrease of secretory product from seminal vesicle (11/13 vs. 1/56).	(217) [c]
15	Oral, in diet	Mouse	12 female	3 months	No increase in relative liver weight.	(102, 114)
20	Gavage	Rabbit	10 male	12 weeks	No changes in mating behaviour. No changes in pituitary gland, liver, kidney, testis or epididymides. No changes in fertility, sperm quantity or quality. Same results at 2 mg/kg bw (presented as an abstract).	(254)
20	Oral, in diet	Rat	50/sex	2 years	*Kidney:* Hyperplasia in the convoluted tubules in males (28/48 vs. 2/45 in controls) and females (3/48 vs. 0/49). Cortical tumours (benign and/or malignant) in males (9/48 vs. 1/45) and females (8/48 vs. 0/49). *Liver:* Benign neoplastic nodules in males (1/48 vs. 2/45) and females (4/46 vs. 1/49). Carcinoma in males (3/48 vs. 1/45) and females (2/46 vs. 0/49). *Testis:* In the seminiferous tubules, a slight increase of germinal epithelium atrophy and oligospermia, eosinophilic material in the tubular lumen, sperm stasis and periarteritis nodosa. Benign interstitial tumours (23/47 vs. 7/43). *Apparently the same data as Stauffer 1981b, cited in (217) (presented briefly below), and (69).*	(102) [b]

Table VI. Dose-effect and dose-response relationships in animals after exposure to tris(1,3-dichloro-2-propyl) phosphate (TDCPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
20	Oral, in diet	Rat	60/sex	12 and 24 months	*Kidney:* Increased kidney weights in both sexes. Hyperplasia in the convoluted tubules in males (29/60 vs. 2/60 in controls) and females (3/57 vs. 0/60). Cortical tumours (benign and/or malignant) in males (9/60 vs. 1/60) and females (8/57 vs. 0/60). *Liver:* Increased liver weight in males. Carcinoma in males (3/60 vs. 1/60) and females (2/55 vs. 0/60). *Testis:* In the seminiferous tubules, a slight increase of germinal epithelium atrophy and oligospermia, eosinophilic material in the tubular lumen, sperm stasis and periarteritis nodosa. Interstitial tumours (26/60 vs. 7/57). Significant increase of seminal vesicle atrophy (6/20 vs. 0/56) and of eosinophilic material in the tubular lumen (12/60 vs. 2/57). Significant decrease of secretory product from seminal vesicle (17/20 vs. 1/56).	(217) [c]
25	Subcutaneous, corn oil	Mouse	7-10 females	4 successive days	Decreased lymphoproliferative responses to conconavalin A and lipopolysacharide and an increased incidence of tumours after tumour cell challenge (55 days observation). Histological examination revealed no significant lesions (for details see 2.5 mg/kg bw).	(137)
25	Gavage, corn oil	Rat	20 females	Gestation days 6-15	No developmental toxicity. No maternal toxicity.	(243) [d]
47	Oral, in diet	Mouse	12 males	3 months	No increase in relative liver weight. Same result at 13 mg/kg bw.	(102, 114)
62	Oral, in diet	Mouse	12 females	3 months	Increased relative liver weight (16 %).	(102, 114)

Table VI. Dose-effect and dose-response relationships in animals after exposure to tris(1,3-dichloro-2-propyl) phosphate (TDCPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
80	Oral, in diet	Rat	50/sex	2 years	Increased mortality in males. Reduced weight gain (20 %) in both sexes. Reduction of erythrocyte values. Slight decrease in plasma cholinesterase activity in females. No effect on erythrocyte acetylcholinesterase activity. Sacculations on the retinal arterioles in 1 male and 4 females. *Kidney*: Increased kidney weight. Increase of hyperplasia in convoluted tubules in males (24/46 vs. 2/45 in controls) and females (22/50 vs. 0/49) and of chronic nephropathy in males (39/46 vs. 25/45) and females (25/50 vs. 7/49) and of cortical tumours (benign and/or malignant) in males (32/46 vs. 1/45) and females (49/50 vs. 0/49). *Liver:* Increased liver weight. Slight increase of local hepatocellular alterations in both sexes. Benign neoplastic nodules in males (13/46 vs. 2/45) and females (8/50 vs. 1/49) and of carcinoma in males (7/46 vs. 1/45) and females (4/50 vs. 0/49). *Testis:* Benign interstitial tumours (36/45 vs. 7/43). Seminiferous tubulus affected as at 20 mg/kg bw and also increase of oligospermia and degene-rated seminal products in epididymides. *Thyroid/parathyroid:* Increased thyroid weight. Parathyroid hyperplasia in males (13/31 vs. 1/21) and females (9/25 vs. 6/26). Thyroid adenomas in females (5/49 vs. 1/42). Parafollicular cell adenomas in males (3/41 vs. 0/40) and females (4/49 vs. 2/42). *Adrenals:* Cortical adenomas in females (19/49 vs. 8/48). *Brain:* Astrocytomas in males (4/46 vs. 0/44). *Bone marrow:* Hyperplasia in males (21/42 vs. 12/40) and females (18/44 vs. 13/41).	(102) [b]
80	Oral, in diet	Rat	60/sex	12 and 24 months	Same effects as above (apparently the same data although group sizes differ). The data are also presented in (69).	(217) [c]

Table VI. Dose-effect and dose-response relationships in animals after exposure to tris(1,3-dichloro-2-propyl) phosphate (TDCPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
100	Gavage, olive oil	Rat	15-24 females	Gestation days 7-15	No maternal toxicity. No increased number of foetal deaths, no abnormal foetal development and no malformations. Same results at 25 and 50 mg/kg bw.	(102, 227)
100	Gavage, corn oil	Rat	20 females	Gestation days 6-15	No developmental toxicity. Maternal toxicity.	(243) [d]
171	Oral, in diet	Mouse	12 males	3 months	Increased relative liver weight (32 %).	(102, 114)
200	Gavage	Rabbit	10 males	12 weeks	Significant increases of liver and kidney weights. No changes in mating behaviour. No changes in pituitary gland, liver, kidney, testis or epididymides. No changes in fertility, sperm quantity or quality (presented as an abstract).	(254)
200	Gavage, olive oil	Rat	15-24 females	Gestation days 7-15	Maternal toxicity. Significant increase in relative kidney weight (15 %) in dams. No foetotoxicity. No evidence of an increased number of foetal deaths, of abnormal foetal development or of malformations.	(102, 227)
214	Oral, in diet	Mouse	12 females	3 months	Significantly increased relative liver weight (29 %) and relative kidney weight (34 %).	(102, 114)
400	Gavage, olive oil	Rat	15-24 females	Gestation days 7-15	Foetotoxicity. Foetal deaths markedly increased. Severe maternal toxicity. Suppressed weight gain and food consumption. 11/15 dams died.	(102, 227)
400	Gavage, corn oil	Rat	20 females	Gestation days 6-15	Developmental toxicity (increased resorptions and foetal mortality). Maternal toxicity.	(243) [d]
420	Oral	Hen	Females	5 days	No signs of neurotoxicity during 21 days of observation (TOCP used as positive control).	(102) [e]
576	Oral, in diet	Mouse	12 males	3 months	Haemoglobin concentrations decreased (13 %). Increased relative liver weight (51 %) and relative kidney weight (39 %).	(102, 114)
598	Oral, in diet	Mouse	12 females	3 months	Haemoglobin concentrations decreased (11 %). Significant increase in relative liver weight (51 %) and in relative kidney weight (40 %). Slight necrosis in the liver of 2 animals.	(102, 114)

Table VI. Dose-effect and dose-response relationships in animals after exposure to tris(1,3-dichloro-2-propyl) phosphate (TDCPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
600	Oral	Chicken	Not given	5 days	No leg and wing weakness.	(102)
1 200	Oral	Chicken	Not given	5 days	Leg and wing weakness. Also seen at 2 400 mg/kg bw.	(102)
1 792	Oral, in diet	Mouse	12 males	3 months	Emaciation, rough hair and tremor. All animals died within 1 month.	(102, 114)
1 973	Oral, in diet	Mouse	12 females	3 months	Emaciation, rough hair and tremor. All animals died within 1 month.	(102, 114)
4 800	Oral	Chicken	Not given	5 days	100 % mortality.	(102, 235)

LC_{50}: lethal concentration for 50 % of the exposed animals at single administration, LD_{50}: lethal dose for 50 % of the exposed animals at single administration.

[a] Anderson 1990b, cited in (102).

[b] Aulette and Hogan 1981, cited in (102).

[c] Stauffer 1981b, cited in (217).

[d] Hazleton 1978, cited in (243).

[e] Bullock and Kamienski 1972, cited in (102).

Table VII. Dose-effect and dose-response relationships in animals after exposure to tris(2-ethylhexyl) phosphate (TEHP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effects	Reference
Single dose						
500	By needle, in crop	Chicken	8 females	-	Chickens appeared normal during 4 weeks of observation. Microscopic examination revealed no effects on nerves.	(140)
1 000	Intramuscular	Chicken	1	-	No signs of intoxication. Same result at 250 and 500 mg/kg bw.	(103) [a]
1 000	Gavage	Hen	1	-	No behavioural abnormalities during 2 months of observation. Same result at 250 and 500 mg/kg bw.	(103) [a]
2 500	By needle, in crop	Chicken	8 females	-	1/8 chicken died during the 4th week due to pericarditis, which was not considered related to exposure. Other chickens appeared normal. Microscopic examination revealed no effects on nerves.	(140)
10 000	Oral	Rat		-	$LD_{50} > 10\,000$ mg/kg bw.	(103) [b]
36 800	Gavage	Rat	6	-	2/6 died. $LD_{50} > 36\,800$ mg/kg bw.	(140)
37 100	Oral	Rat		-	LD_{50}.	(103) [c]
46 000	Gavage	Rabbit	4	-	LD_{50}.	(140)
Single exposure, aerosol						
283 mg/m^3	Inhalation MMD 1.5 µm	Guinea pig	10	3 hours	6/10 died. LC_{50} approximated by authors to 30 000 (mg/m^3 × min).	(140)
447 mg/m^3	As above	Rat	10	3.5 hours	No mortality. $LC_{50} > 447$ mg/m^3.	(140)
448 mg/m^3	As above	Guinea pig	10	1.5 hours	6/10 died. LC_{50} approximated by authors to 30 000 (mg/m^3 × min).	(140)
Multiple doses						
430	Oral	Rat		30 days	No body weight loss.	(103) [c]
500 [d]	Gavage, corn oil	Mouse	10/sex	13 weeks	Inflammatory lesions in the gastric mucosa, with increased severity in the higher dose groups (1 000, 2 000, 4 000 and 8 000 mg/kg bw). No compound-related deaths at any dose.	(172)

Table VII. Dose-effect and dose-response relationships in animals after exposure to tris(2-ethylhexyl) phosphate (TEHP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effects	Reference
500 [d]	Gavage, corn oil	Mouse	50/sex	2 years	Survival of males significantly lower than in the high-dose group (1 000 mg/kg bw). *Liver:* Hepatocellular carcinomas in males (12/50 vs. 9/50 in controls) and females (4/50 vs. 0/48). *Thyroid:* Follicular cell hyperplasia in males (12/48 vs. 0/49) and females (13/47 vs. 1/44).	(117, 172)
750 [d]	Gavage, corn oil	Rat	5/sex	2 weeks	No animals died. No compound-related effects at necropsy. Same result at 375 mg/kg bw.	(172)
926	Gavage	Cat	2	4 weeks	No signs of intoxication. Erythrocyte acetylcholinesterase activity unaffected.	(103) [b]
1 000 [d]	Gavage, corn oil	Rat	10/sex	13 weeks	No compound-related deaths or histopathological effects. Same results at 250 and 500 mg/kg bw.	(172)
1 000 [d]	Gavage, corn oil	Rat	50 females	2 years	No significant difference in survival. *Mammary gland:* Significantly lower incidence of fibroadenomas (2/50 vs. 11/50 in controls).	(117, 172)
1 000 [d]	Gavage, corn oil	Mouse	50/sex	2 years	Survival not different from the controls. *Liver:* Hepatocellular carcinomas in males (12/49 vs. 9/50 in controls; non-significant trend) and in females (7/50 vs. 0/48; significant positive trend). Cytoplasmic vacuolisation in females (18/50 vs. 10/48). *Thyroid:* Follicular cell hyperplasia in males (24/47 vs. 0/49; significant positive trend) and females (12/46 vs. 1/44; non-significant trend).	(117, 172)
1 500 [d]	Gavage, corn oil	Rat	5/sex	2 weeks	Lower final mean body weight in males compared to controls. No animals died. No compound-related effects at necropsy.	(172)
1 550	Oral	Rat		30 days	Body weight loss.	(103) [c]
2 000 [d]	Gavage, corn oil	Rat	10/sex	13 weeks	Mean body weight 10 % lower in females compared to controls. No compound-related deaths or histopathological effects.	(172)

Table VII. Dose-effect and dose-response relationships in animals after exposure to tris(2-ethylhexyl) phosphate (TEHP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effects	Reference
2 000 [d]	Gavage, corn oil	Rat	50/sex	2 years	No significant difference in survival. Decreased body weight in males. *Adrenal:* Significantly higher incidence of phaeochromocytomas in males (9/50 vs. 2/50 in controls).	(117, 172)
2 000 [d]	Gavage, corn oil	Mouse	10/sex	13 weeks	Ulceration in the forestomach in 1/10 males. Other effects as at 500 mg/kg bw.	(172)
3 000 [d]	Gavage, corn oil	Rat	5/sex	2 weeks	Lower final mean body weight in both sexes compared to controls. No animals died. No compound-related effects at necropsy. Same results at 6 000 mg/kg bw.	(172)
3 000 [d]	Gavage, corn oil	Mouse	5/sex	2 weeks	No animals died. No compound-related effects at necropsy. Same results at 375, 750 and 1 500 mg/kg bw.	(172)
4 000 [d]	Gavage, corn oil	Rat	10/sex	13 weeks	Mean body weight 5 % lower for both sexes compared to controls. No compound-related deaths or histopathological effects.	(172)
4 000 [d]	Gavage, corn oil	Rat	50 males	2 years	No significant difference in survival. Decreased body weight in males. *Adrenal:* Significantly higher incidence of pheochromocytomas (12/50 vs. 2/50 in controls; significant positive trend). *Thyroid:* Significant positive trend in the incidence of follicular cell adenomas, cystadenomas or carcinomas (combined) but incidences not significantly different from controls. *Pancreas:* Negative trend for acinar cell adenoma. *Subcutaneous tissue:* Negative trend for lipomas.	(117, 172)
4 000 [d]	Gavage, corn oil	Mouse	10/sex	13 weeks	Mean body weights 5 % lower in females compared to controls. Ulceration in the forestomach in 1/10 females. Other effects as at 500 mg/kg bw.	(172)
6 000 [d]	Gavage, corn oil	Mouse	5/sex	2 weeks	Decreased activity and rough coats. No animals died. No compound-related effects at necropsy.	(172)
8 000 [d]	Gavage, corn oil	Mouse	10/sex	13 weeks	Mean body weight 7 % (males) and 5 % (females) lower compared to controls. Ulcerations in the forestomach in 1/10 males and 3/10 females. No compound-related deaths. Other effects as at 500 mg/kg bw.	(172)

Table VII. Dose-effect and dose-response relationships in animals after exposure to tris(2-ethylhexyl) phosphate (TEHP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effects	Reference
Multiple exposures, aerosol						
1.6 mg/m^3 (SD 0.8)	Inhalation mean particle size 3.8 µm	Guinea pig	20 males	12 weeks	Significantly lower relative kidney weights compared to controls.	(140)
9.6 mg/m^3 (SD 1.5)	As above	Guinea pig	20 males	As above	Significantly higher mean body weight and significantly lower relative kidney weights compared to controls. No effect on plasma or erythrocyte cholinesterase activity. No pathological effects on spinal cord or sciatic nerve.	(140)
10.8 mg/m^3 (SD 6.0)	Inhalation median particle size 4.4 µm	Dog	2/sex	As above	In conditioned avoidance response test, total missed avoidance was 0 vs. 14 in controls. Mild chronic inflammatory changes in pulmonary parenchyma. No animals died. Normal increases of body weight. No effect on plasma or erythrocyte cholinesterase activity.	(140)
26.4 mg/m^3 (SD 16.8)	As above	Dog	2/sex	As above	In conditioned avoidance response test, total missed avoidance was 24 vs. 14 in controls. The number of total missed avoidance was higher compared with the low exposed group, 24 vs. 0 ($p < 0.05$). Otherwise results as at 10.8 mg/m^3.	(140)
85.0 mg/m^3 (SD 33.3)	As above	Dog	2/sex	As above	In conditioned avoidance response test, total missed avoidance was 44 vs. 14 in controls ($p < 0.05$). Otherwise results as at 10.8 mg/m^3.	(140)
85.0 mg/m^3 (SD 33.3)	As above	Monkey	2/sex	As above	No animals died. Normal increases of body weight. No effect on visual discrimination test. No effect on plasma or erythrocyte cholinesterase activity. No histological abnormalities. Same results at 10.8 and 26.4 mg/m^3.	(140)

LC_{50}: lethal concentration for 50 % of the exposed animals at single administration, LD_{50}: lethal dose for 50 % of the exposed animals at single administration, MMD: mass median diameter, SD: standard deviation.

[a] Kimmerle 1958, cited in (103).

[b] Bayer 1958, cited in (103).

[c] Smyth and Carpenter 1948, cited in (103).

[d] 97-99 % TEHP.

Table VIII. Dose-effect and dose-response relationships in animals after exposure to triethyl phosphate (TEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Single dose						
180	Intraperitoneal, corn oil	Rat,	4 females	-	Increase of serum β-glucuronidase activity after 3 hours (× 40).	(221)
333 (308-359)	Intraperitoneal	Rat, adult	67 females	-	ED_{50} for loss of righting reflex. The occurrence and duration of the righting reflex was used to measure narcosis. The righting reflex was considered lost when an animal remained on its back for 30 s or longer.	(21)
412 (396-428)	Intraperitoneal	Rat, adult	32 males	-	ED_{50} for loss of righting reflex.	(21)
437 (401-476)	Intraperitoneal	Rat, weanling	Females	-	ED_{50} for loss of righting reflex.	(21)
495 (476-519)	Intraperitoneal	Rat, weanling	Males	-	ED_{50} for loss of righting reflex.	(21)
500	Intraperitoneal	Rat, adult and weanling		-	Duration of narcosis shorter in weanling than adult rats. Brain cholinesterase activity 85 % of normal in adults 1 hour after dosing.	(21)
500	Intravenous	Rat	Females	-	Deep anaesthesia (4 min), weakness and incoordination (2-3 hours). No cholinergic symptoms.	(247)
600	Intraperitoneal	Mouse	42 males	-	ED_{50} for loss of righting reflex.	(21)
800	Intraperitoneal	Rat		-	LD_{50}.	(66)
1 000	Intravenous	Rat	Females	-	Deep anaesthesia with superficial respiration (about 1 hour); pronounced weakness and dyspnoea (> 12 hours). No cholinergic symptoms.	(247)
1 100-1 600	Oral	Rat		-	LD_{50}.	(237)
Single exposure, airborne						
8 800 mg/m^3	Inhalation	Rat		4 hours	LC_{50} > 8 800 mg/m^3.	(237)

Table VIII. Dose-effect and dose-response relationships in animals after exposure to triethyl phosphate (TEP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Multiple doses						
125		Rat			No maternal toxicity.	(237)
335	Oral	Rat	Both sexes		No effect on litter size (small number of animals).	(237)
500	Oral, in diet	Rat	5-6 males	9 weeks	Increased absolute and relative liver and spleen weights and absolute weight of kidneys and testes. No effect on haematological parameters (leukocyte and erythrocyte counts, haemoglobin concentration, haematocrit, mean corpsular volume), serum components (total protein, urea nitrogen, cholesterol, triglyceride, bile acids, sodium, potassium, prothrombin time, kaolin-partial thromboplastin time) or serum enzyme activities including cholinesterase activity. Slight morphological changes in the liver.	(178)
625		Rat			Maternal toxicity, i.e. reduction of body weight gain, food intake and faeces excretion. No evidence of teratogenic potential.	(237)
670	Oral	Rat	Both sexes		Reduction of litter size. No symptoms of poisoning in parent animals (small number of animals).	(237)
1 000	Oral	Rat		4 weeks	No effect on testicular weight.	(237)
6 700	Oral	Rat	Both sexes		No effect on testicular weight or testicular histological appearance (small number of animals).	(237)

ED_{50}: effective dose for 50 % of the population exposed, LC_{50}: lethal concentration for 50 % of the exposed animals at single administration, LD_{50}: lethal dose for 50 % of the exposed animals at single administration.

Table IX. Dose-effect and dose-response relationships in animals after exposure to isopropylated triphenyl phosphates (TIPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Single dose						
Tri-ortho-isopropylphenyl phosphate						
600	Oral	Hen	Females	-	No neurotoxic response. 88 % brain NTE activity.	(109)
1 000	Oral	Hen	Females	-	LD_{50} > 1 000 mg/kg bw.	(106)
7 900	Dermal	Rabbit	Both sexes	-	LD_{50} > 7 900 mg/kg bw.	(106)
15 800	Oral	Rat		-	LD_{50} > 15 800 mg/kg bw.	(106)
Tri-meta-isopropylphenyl phosphate						
1 000	Oral	Hen	Females	-	No neurotoxic response. 100 % brain NTE activity.	(109)
Tri-para-isopropylphenyl phosphate						
1 000	Oral	Hen	Females	-	No neurotoxic response. 100 % brain NTE activity.	(109)
Di-ortho-isopropylphenyl phenyl phosphate						
600	Oral	Hen	Females	-	No neurotoxic response. 61 % brain NTE activity.	(109)
1 200	Oral	Hen	Females	-	Ambiguous result concerning the brain neurotoxic response. 15 % NTE activity.	(109)
Ortho-isopropylphenyl diphenyl phosphate						
600	Oral	Hen	Females	-	No neurotoxic response. 16 % brain NTE activity.	(109)
1 200	Oral	Hen	Females	-	Neurotoxic response (OPIDN). 10 % brain NTE activity.	(109)
5 000	Dermal	Rabbit		-	LD_{50} > 5 000 mg/kg bw.	(106)
10 000	Oral	Rat		-	LD_{50}.	(106)
Para-isopropylphenyl diphenyl phosphate						
1 000	Oral	Hen	Females	-	No neurotoxic response. 96 % brain NTE activity.	(109)
> 10 000	Oral	Hen	Females	-	LD_{50}.	(106)
Isopropylated triphenyl phosphate (described in Chapter 2)						
12	Oral, corn oil	Hen	4 females	-	No effect on plasma cholinesterase or brain NTE activities. Transient impaired walking behaviour.	(208)

Table IX. Dose-effect and dose-response relationships in animals after exposure to isopropylated triphenyl phosphates (TIPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
180	Oral, corn oil	Hen	4 females	-	50 % inhibition of plasma cholinesterase. No effect on brain NTE.	(208)
370	Oral, corn oil	Hen	4 females	-	70 % inhibition of plasma cholinesterase activity and 50 % inhibition of brain NTE activity. Transient impaired walking behaviour.	(208)
11 700	Oral, corn oil	Hen	4 females	-	Weight loss from day 22. Transient and dose-dependent impaired walking behaviour. Motor incoordination. The inhibition of plasma cholinesterase and NTE was 80-90 %.	(208)
Isopropylated triphenyl phosphate (not specified)						
2 000 (4 products)	Oral	Rat	5 males/ product	-	81-90 % inhibition of serum cholinesterase and 35-60 % inhibition of NTE.	(141)
2 000	Dermal contact for 24 hours	Rat	3/sex	-	No mortality and no irritation. No gross lesions at necropsy. No apparent effect on body weights.	(74) [a]
20 000	Oral	Rat	5/sex	-	No males died but 4/5 females died. No clinical signs reported.	(74) [b]
Kronitex® 300						
8 000	Gavage	Hen	4 females	-	Ataxia in 0/4 (Score 0-8). Same result at 2 000 and 4 000 mg/kg bw.	(251)
16 000	Gavage	Hen	10 females	-	Ataxia in 3/10 (Score 0-8).	(251)
Kronitex® 200						
20 000	Gavage	Hen	10 females	-	Ataxia in 1/10 (Score 0-8).	(251)
Kronitex® 100						
2 000	Gavage	Hen	4 females	-	Ataxia in 0/4 (Score 0-8). Same result at 500 and 1 000 mg/kg bw.	(251)
3 000	Gavage	Hen	10 females	-	Ataxia in 0/10 (Score 0-8). Nervous system lesion in 1/10.	(251)
4 000	Gavage	Hen	10 females	-	Ataxia in 2/10 (Score 0-8). 80 % inhibition of brain NTE activity.	(251)
5 000	Gavage	Hen	10 females	-	Ataxia in 3/10 (Score 0-8). Nervous system lesion in 0/10.	(251)
7 000	Gavage	Hen	10 females	-	Ataxia in 1/10 (Score 0-8). Nervous system lesion in 1/10.	(251)
9 000	Gavage	Hen	10 females	-	Ataxia in 1/10 (Score 0-8). Nervous system lesion in 2/10.	(251)

Table IX. Dose-effect and dose-response relationships in animals after exposure to isopropylated triphenyl phosphates (TIPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Kronitex® 50						
2 000	Gavage	Hen	10 females	-	Ataxia in 1/9 (Score 0-8). Nervous system lesion in 0/10.	(251)
4 000	Gavage	Hen	10 females	-	Ataxia in 4/10 (Score 0-8). Nervous system lesion in 4/10.	(251)
6 000	Gavage	Hen	10 females	-	Ataxia in 6/10 (Score 0-8). Nervous system lesion in 7/10.	(251)
8 000	Gavage	Hen	10 females	-	Ataxia in 3/10 (Score 0-8). Nervous system lesion in 1/10.	(251)
Multiple doses						
Tri-ortho-isopropylphenyl phosphate						
1 000	Oral	Hen	Females	4 days	No neurotoxic response. 100 % brain NTE activity.	(109)
1 000	Gavage	Hen	10 females	Twice/day for 3 days and again for 3 days (day 21-23)	No neurotoxic behavioural effects (0/10) or neurotoxic histological effects (0/10) during 42 days of observation.	(106)
Ortho-isopropylphenyl diphenyl phosphate						
1 000	Gavage	Hen	9 females	As above	Neurotoxic behavioural effects (4/9) and neurotoxic histological effects (5/9) as signs of OPIDN during 42 days observation.	(106)
Para-iso-propylphenyl diphenyl phosphate						
10 000	Gavage	Hen	10 females	As above	No neurotoxic behavioural effects (0/10) or neurotoxic histological effects (0/10) during 42 days of observation.	(106)
Kronitex® 100						
100	Oral, in diet	Rat	10/sex	4 weeks	Increased relative liver weight. No gross lesions at autopsy. Same results at 500 and 1 000 mg/kg bw.	(74) [c]
500	Oral, in diet	Rat	10/sex	4 weeks	Reduction of food consumption in both sexes. Abnormal clinical chemistry measurements.	(74) [c]
1 000	Oral, in diet	Rat	10/sex	4 weeks	Body weights depressed only in females. Reduction of food consumption in both sexes. Abnormal haematological values and clinical chemistry measurements. Kidneys and livers appeared normal on histological examination.	(74) [c]

Table IX. Dose-effect and dose-response relationships in animals after exposure to isopropylated triphenyl phosphates (TIPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Kronitex® 50						
20	Gavage, corn oil	Hen	20 females	13 weeks	Ataxia in 0/20. Nervous system lesion in 0/10 (Grade >2 of 4). Same results at 10 mg/kg bw	(251) [d]
90	Gavage, corn oil	Hen	20 females	13 weeks	Ataxia in 4/20. Nervous system lesion in 5/10 (Grade >2 of 4)	(251) [d]
270	Gavage, corn oil	Hen	20 females	13 weeks	Ataxia in 9/20. Nervous system lesion in 9/10 (Grade >2 of 4)	(251) [d]
Reofos® 65						
5 000	Oral	Hen	5 females	Twice/day, on days 1 and 22	Significantly increased scores regarding peripheral nerve lesions vs. controls (also seen at 10 000 and 15 000 mg/kg bw). No spinal cord lesions (0/5).	(161)
10 000	Oral	Hen	5 females	As above	Spinal cord lesions (2/5).	(161)
15 000	Oral	Hen	6 females	As above	Significantly increased spinal cord lesions (3/6 vs. 0/12 in controls). No clinical neurotoxic effects at this or lower levels.	(161)

LD_{50}: lethal dose for 50 % of the exposed animals at single administration, NTE: neurotoxic or neuropathy target esterase, OPIDN: organophosphorus-induced delayed neuropathy.

[a] FMC 1990a, cited in (74).

[b] Food and Drug Research Laboratories 1975, cited in (74).

[c] Foster 1976, cited in (74).

[d] FMC 1985c, cited in (251).

Table X. Dose-effect and dose-response relationships in animals after exposure to tris(monochloropropyl) phosphate (TMCPP).

Daily dose mg/kg bw	Route of administration	Species	No. of animals	Exposure regimen	Effect	Reference
Single dose						
707-2 500	Oral	Rat	Females	-	LD_{50}. Observed effects included decreased respiratory rate, spasms, lethargy, ataxia and spasmodic jumping, piloerection, hunched posture, tremor, lacrimation, salivation, and convulsions.	(102, 238)
931-4 200	Oral	Rat	Males	-	LD_{50}. Effects as above.	(102, 238)
2 000	Dermal	Rabbit	3/sex	-	No animals died. Observed effects included reversible erythema, oedema, decreased activity and food intake. $LD_{50} > 2\ 000$ mg/kg bw.	(102, 238) [a]
2 000	Dermal	Rat		-	$LD_{50} > 2\ 000$ mg/kg bw.	(102) [b]
Fyrol PCF						
464	Oral	Rat		-	Depression and intermittent muscle spasms.	(102, 238) [c]
1 000	Oral	Rat	Males	-	Depression and tremor at and above 1 000 mg/kg bw.	(102, 238) [d]
1 260	Dermal	Rabbit	Females	-	LD_{50}.	(238) [c]
5 000	Dermal	Rabbit, albino		-	$LD_{50} > 5\ 000$ mg/kg bw (for a mixed population of animals). Mild erythema was the only local effect.	(238) [e]
13 200	Oral	Hen	Females	-	No significant decrease of plasma cholinesterase or brain NTE activity.	(209)
Single exposure, aerosol						
4 600 mg/m^3 (Fyrol PCF)	Inhalation	Rat		4 hours	Mild lethargy and matted fur. $LC_{50} > 4\ 600$ mg/m^3.	(102, 238) [e]
5 050 mg/m^3 (Antiblaze 80)	Inhalation	Rat	5/sex	4 hours	3/5 females and 0/5 males died. Salivation, decreased activity, closed or semi-closed eyes. Lethargy, reddish lacrimation, body weight depression, brownish oral discharge, convulsions and dyspnoea. All effects had disappeared in the survivors by 14 days post-treatment.	(102, 238) [f]
7 900 mg/m^3	Inhalation	Rat	5/sex	4 hours	$LC_{50} > 7\ 900$ mg/m^3.	(102) [g]
17 800 mg/m^3	Inhalation	Rat	5/sex	1 hour	No animals died. Decreased activity, partially closed eyes, swollen eyelids, lacrimation in all animals. Excessive salivation in some rats.	(102, 238) [f]

Table X. Dose-effect and dose-response relationships in animals after exposure to tris(monochloropropyl) phosphate (TMCPP).

Daily dose mg/kg bw	Route of administration	Species	No. of animals	Exposure regimen	Effect	Reference
Multiple doses						
Tris(chloropropyl) phosphate (and 2 other components)						
6	Oral, in diet	Rat	11-14 females	Gestation days 0-20	*In dams:* No effect on body weight, no clinical signs, no effect on implantation or resorption. *In foetus:* No effect on mortality, body weight or sex ratio. No significant increase of external, visceral or skeletal malformations. However, dose-related (6-625 mg/kg bw) increase in cervical ribs and missing 13th rib. At weaning, no effect on survival or body weight. Same results at 70 and 625 mg/kg bw.	(216) [h]
8	Gavage	Rat	5 females	7 days	No effect on mortality, clinical signs or body weight.	(216) [h]
40	Gavage	Rat	5 females	7 days	Relative kidney weights increased. No effect on mortality, clinical signs or body weight. Same results at 200 mg/kg bw.	(216) [h]
1 000	Gavage	Rat	5 females	7 days	1/5 died. Relative liver and kidney weights increased. No effect on clinical signs or body weight.	(216) [h]
Tris(1-chloro-2-propyl) phosphate (97.85 %) plus unspecified isomer						
10	Gavage	Rat	5/sex	7 days	No effect on mortality, clinical signs, body weight, food intake. Same results at 1 mg/kg bw.	(216) [i]
100	Gavage	Rat	5/sex	7 days	No effect on mortality, clinical signs, body weight, food intake, gross pathology or weight of testis (but decreased size and weight of testes in 1/5).	(216) [i]
1 000	Gavage	Rat	5/sex	7 days	Water intake increased. No effect on mortality, clinical signs, body weight or food intake. No effect on gross pathology or weight of testis.	(216) [i]
Fyrol PCF						
13 200	Oral	Hen	18 females	2 doses 3 weeks apart	1/18 died. Decreased body weight and severe feather loss. No behavioural effects. Histological changes in brain, spinal cord and sciatic nerve similar to controls.	(209)

Table X. Dose-effect and dose-response relationships in animals after exposure to tris(monochloropropyl) phosphate (TMCPP).

Daily dose mg/kg bw	Route of administration	Species	No. of animals	Exposure regimen	Effect	Reference
Fyrol PCF (70 % tri(1-chloro-2-propyl) phosphate and 22 % 2-chloropropanol phosphate)						
40	Oral in diet	Rat	20/sex	13 weeks	Significantly increased absolute and relative liver weights in males (also seen at 125, 375 and 1 000 mg/kg bw). Increased absolute and relative liver weights without concomitant histopathological changes (regarded as a non-adverse effect by the authors). No effect on body weight.	(238) [j]
375	Oral in diet	Rat	20/sex	13 weeks	Significantly increased absolute and relative liver weights in both sexes (regarded as a non-adverse effect, see 40 mg/kg bw). In males, significantly increased kidney weights and very mild cortical tubular degenerative changes. No effect on body weight.	(238) [j]
1 000	Oral, in diet	Rat	20/sex	13 weeks	Reduced body weights. Significantly increased absolute and relative liver weights in both sexes. Mild swelling of cells in the hepatic periportal region. Significantly increased kidney weights in males. Very mild cortical tubular degenerative changes in both sexes. Mildly hypoplastic sternal bone marrow in 3 rats. Mild thyroid follicular hyperplasia in all rats. No treatment-related effects in haematology, clinical chemistry or in brain, plasma and erythrocyte cholinesterase activities at this or lower levels.	(238) [j]
1 060	Oral, in diet	Rat	10/sex	2 weeks	No effect on body weight, clinical signs or food consumption. No effect on cholinesterase activities. Same results at lower doses (420 and 660 mg/kg bw).	(238) [k]
1 660	Oral, in diet	Rat	10/sex	2 weeks	Significant reduction of body weight gain and reduced food consumption in males. No effect on cholinesterase activities. Increased absolute and relative liver weights without concomitant histopathological changes (regarded as a non-adverse effect).	(238) [k]

LC_{50}: lethal concentration for 50 % of the exposed animals at single administration, LD_{50}: lethal dose for 50 % of the exposed animals at single administration, NTE: neurotoxic or neuropathy target esterase.

[a] Gordon 1980, Smithey 1981c, cited in (102, 238), [b] Cuthbert 1989a, cited in (102), [c] Stauffer 1970, cited in (102, 238), [d] Stauffer 1972, cited in (102, 238), [e] Stauffer 1979, cited in (238), [f] Mehlman and Singer 1981, cited in (102, 238), [g] Anderson 1990a, cited in (102), [h] Kawasaki *et al* 1982, cited in (216), [i] Bayer 1993, cited in (216), [j] Stauffer 1981a, cited in (238), [k] Stauffer 1980a, cited in (238).

Table XI. Dose-effect and dose-response relationships in animals after exposure to triphenyl phosphate (TPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Single dose						
10	Oral	Mouse	5 males	-	13 % decrease of whole blood cholinesterase activity.	(218)
50	Oral or intraperitoneal	Mouse	5 males	-	11 or 14 % decrease of whole blood cholinesterase activity.	(218)
75 [a]	Intraperitoneal	Rat	5	-	No significant decrease of plasma cholinesterase. Induction of liver microsomal CYPs with a concomitant increase in the activities of mixed function monooxygenases (unclear if the effect appears at this level, see 150 and 300 mg/kg bw).	(244)
100	Oral or intraperitoneal	Mouse	5 males	-	39 or 50 % decrease of whole blood cholinesterase activity.	(218)
100	Intraperitoneal	Cat	1 female	-	No neuromuscular signs at 30 days.	(218)
150 [a]	Intraperitoneal	Rat	5	-	Significant decrease of plasma cholinesterase. Induction of liver microsomal CYPs with a concomitant increase in the activities of mixed function monooxygenases.	(244)
200	Oral	Mouse	5 males	-	46 % decrease of whole blood cholinesterase activity.	(218)
200	Intraperitoneal	Cat	2 females	-	One cat had first neuromuscular signs at 18 days and died at 50 days. The other cat had no neuromuscular signs at 28 days.	(218)
300	Intraperitoneal	Cat	2 females	-	One cat had no neuromuscular signs at 30 days. The other cat died after 3 days due to a perforated ulcus of the stomach.	(218)
300 [a]	Intraperitoneal	Rat	5	-	Significant decrease of plasma cholinesterase by 38 % and 26 %, respectively. Significant induction of CYPs (as at 150 mg/kg bw). Inhibition of brain 2´,3´-cyclic nucleotide 3´-phosphohydrolase and demyelination in peripheral nerves.	(244)
400	Intraperitoneal	Cat	1 female	-	First neuromuscular signs at 16 days.	(218)

Table XI. Dose-effect and dose-response relationships in animals after exposure to triphenyl phosphate (TPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
400	Subcutaneous	Cat	2	-	One cat lost weight (about 30 %), regained weight within 3 months. The other cat did not lose weight. No evidence of delayed neurotoxic effects.	(256)
500	Oral or intraperitoneal	Mouse	5 males	-	70 or 49 % decrease of whole blood cholinesterase activity.	(218)
500	Subcutaneous	Leghorn cockerel	2	-	No paralysis.	(84)
700	Subcutaneous	Cat	2	-	Both cats became anorectic. One cat became prostrated within 3 days (on necropsy day 5, two bleeding ulcers in the stomach) and the other by day 7. Histological examination of the cats revealed generalised vascular damage with perivascular oedema in many tissues. No signs of axon degeneration, demyelination or other pathologic change in the nervous system. No effect on plasma and erythrocyte cholinesterase activities.	(256)
1 000	Oral	Leghorn cockerel	2	-	No paralysis. Decrease of plasma cholinesterase (35 %) and acetyl-cholinesterase activity in brain (2 %) and spinal cord (24 %).	(84)
1 000	Subcutaneous	Cat	1	-	Anorectic after 1 week. After 3 weeks, unable to rise from the floor and some days later moribund. No signs of axon degeneration or demyelination in the brain stem and spinal cord.	(256)
1 320->5 000	Oral	Mouse		-	LD_{50}.	(100) [b]
3 500->5 000	Oral	Rat		-	LD_{50}.	(100) [b, c]
3 000	Oral or subcutaneous	Mouse, rat	10-11 males	-	LD_{50} > 3 000 mg/kg bw.	(218)
4 000	Oral	Guinea pig	5 males	-	LD_{50} > 4 000 mg/kg bw.	(218)
5 000	Oral	Hen		-	LD_{50} > 5 000 mg/kg bw.	(106)

Table XI. Dose-effect and dose-response relationships in animals after exposure to triphenyl phosphate (TPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
Single exposure, vapour						
363 mg/m^3	Inhalation	Mouse	5 males	6 hours	Slight decrease (17 %) in whole blood cholinesterase activity.	(218)
757 mg/m^3	Inhalation	Mouse	7 males	2 hours	Significant decrease (24 %) in whole blood cholinesterase activity.	(218)
757 mg/m^3	Inhalation	Mouse	7 males	4 hours	Slight decrease (16 %) in whole blood cholinesterase activity.	(218)
Multiple doses						
100	Oral, in diet	Rat	5 males	5 weeks	No effect on body weight or relative liver and kidney weights. No haematological effects (haemoglobin content, cell volume, erythrocyte and leukocyte count and differential).	(218)
161	Oral, in diet	Rat	10	4 months	No effect on body weight gain. No effect on behavioural test.	(203)
166	Oral, in diet	Rat	38	91 days through mating and gestation	Significantly increased average number of foetuses having at least two soft-tissue variations and significantly more foetuses with moderate hydroureter than in controls. No effect on fertility. Same results at 341 and 516 mg/kg bw. Unclear dose-response relationships but also small spacing of doses.	(252)
345	Oral, in diet	Rat	10	4 months	Reduced body weight gain. No effect on behavioural test. Same results at 517 and 711 mg/kg bw.	(203)
375	Oral, in diet	Rat	10/sex	4 months	Reduction in the growth rate of males. No significant pathological lesions in investigated lymphoid tissues. Same results at 125 and 250 mg/kg bw.	(85)
500	Oral, in diet	Rat	10/sex	4 months	Reduction in the growth rate of males. Trend towards increasing total serum protein with increasing TPP concentrations.	(85)
500	Oral, in diet	Rat	5 males	5 weeks	Increased relative liver weight and slightly depressed growth rate. No effect on relative kidney weight. No haematological effects (haemoglobin content, cell volume, erythrocyte and leukocyte count and differential).	(218)
690	Oral, in diet	Rat	34	91 days through mating and gestation	Reduced body weight gain. Average number of foetuses having at least two soft-tissue variations not significantly higher than in controls. Significantly more foetuses with moderate hydroureter than in controls.	(252)

Table XI. Dose-effect and dose-response relationships in animals after exposure to triphenyl phosphate (TPP).

Daily dose mg/kg bw	Route of administration	Species	No. and sex of animals	Exposure regimen	Effect	Reference
2 × 5 000	Oral, in diet	Hen	9 females	Twice a day for 3 days and again for 3 days (day 21-23)	No neurotoxic response regarding behaviour or histology.	(106)

CYP: cytochrome P450, LD_{50}: lethal dose for 50 % of the exposed animals at single administration.

[a] Exposure to commercial cresyl diphenyl phosphate containing approximately 35 % TPP, 45 % cresyl diphenyl phosphate, 18 % dicresyl phenyl phosphate and 2 % TCP.

[b] Antonyuk 1974, cited in (100).

[c] Hierholzer 1957, cited in (100).

Appendix 2. Occupational exposure limit values

Occupational exposure limit values for the phosphate triesters in different countries [a] as 8-hour TWAs (numbers in brackets are short-term exposure limits).

Country	TOCP		TBP		TPP		Ref.
	ppm	mg/m^3	ppm	mg/m^3	ppm	mg/m^3	
Denmark	-	0.1 (0.2)	0.2 (0.4)	2.5 (5)	-	3 (6)	(1)
Finland	-	0.1 (0.3)	0.2 (0.4)	2.5 (5)	-	3 (6)	(2)
Germany (MAK)	-	-	1	11 (44)	-	-	(3)
Norway	-	0.1 (0.3)	0.2	2.5	-	3 (6)	(4)
United Kingdom	-	0.1 (0.3)	-	5	-	3	(5)
US (ACGIH)	-	0.1	0.2	-	-	3	(6)
US (NIOSH)	-	0.1	0.2	2.5 (5)	-	3	(7)

[a] Sweden, the Netherlands and the European Union do not have occupational exposure limits for the phosphate triesters.
TWA: time-weighted average.

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Appendix 3. Previous NEG criteria documents

NEG criteria documents published in the scientific serial Arbete och Hälsa (Work and Health):

Substance/Agent	*Arbete och Hälsa issue*
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
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Allyl alcohol	1986:8
Aluminium	1992:45, 1993:1*
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Antimony	1998:11*
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Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8
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White spirit	1986:1
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D = collaboration with the Dutch Expert Committee on Occupational Safety (DECOS).
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