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TRIS- (2-BUTOXYETHYL)-PHOSPHATE

CAS : 78-51-3

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Joint Assessment of Commodity Chemicals

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ECETOC (European Chemical Industry Ecology and Toxicology Centre), 4 avenue Van Nieuwenhuyse, Bte. 6, 1160 - Brussels, Belgium.

THE ECETOC SCHEME FOR THE

"JOINT ASSESSMENT OF COMMODITY CHEMICALS" (JACC)

This report has been produced as part of the ECETOC programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

In the programme, commodity chemicals, that is those produced in large tonnage by several companies and having widespread and multiple uses, are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as an impurity are not normally taken into account.

ECETOC is not alone in producing such reviews. There are a number of organisations that have produced and are continuing to write reviews with the aim of ensuring that toxicological knowledge and other information are evaluated. Thus a Producer, Government Official or Consumer can be informed on the up-to-date position with regard to safety, information and standards. Within ECETOC we do not aim to duplicate the activities of others. When it is considered that a review is needed every effort is made to discover whether an adequate review exists already; if this is the case the review is checked, its conclusions summarised and the literature published subsequent to the review assessed. To assist ourselves and others working in this field we publish annually a summary of international activities incorporating work planned, in hand, or completed on the review of safety data for commodity chemicals. Interested readers should refer to our Technical Report N°30 entitled "Existing Chemicals: Literature Reviews and Evaluations".

This document presents a critical assessment of the toxicology and ecotoxicology of tris-(2-butoxyethyl)-phosphate (CAS N° 78-51-3).

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1. SUMMARY AND CONCLUSION

Tris-(2-butoxyethyl)-phosphate (TBEP) is used as a plasticizer or flame retardant in rubber and plastics and as a component of lacquers and floor finishes. Worldwide production volumes are not high relative to other phosphate esters. In Europe the production is estimated to be less than 1000t/a.

TBEP occurs in the environment only as a result of human activity. Its distribution in the environment has been investigated in certain industrialised countries. In the few situations in which it was found in water, the concentration never exceeded 300 ng/l. None of 167 analyses detected TBEP in fish. TBEP is not a common air pollutant but it has been detected associated with fine particulates indoors and, in an isolated study, outdoors.

Sewage treatment plants and semi-continuous sludge laboratory tests indicated substantial elimination of TBEP (>80%). In river and coastal water TBEP was completely degraded. The half-life in estuarine water was about 50 days and there was little degradation in clean seawater.

There are no quantitative estimates of human exposure but there is one report that TBEP has been detected at ppb levels in human adipose tissue.

Toxicity to aquatic organisms is moderate. The 48-hour LC_{50} in Daphnia magna was 75 mg/l and the 96-hour LC_{50} in Pimephales promelas was 16 mg/l.

The acute toxicity and skin and eye irritation potential are low. In hens, TBEP caused no clinical or histopathological neurotoxic effects in single doses of up to 10,000 mg/kg and while brain acetylcholinesterase and plasma butyrylcholinesterase activities were slightly inhibited there was no inhibition of neurotoxicity target esterase. Neurotoxic effects in rats are inconsistent; reversible neurotoxicity has been described in animals repeatedly administered high-doses by gavage. Other effects of subchronic dosing in rats

included mild changes in the liver and possibly an acceleration of the focal myocarditis to which Sprague-Dawley rats are subject. Chronic toxicity and carcinogenicity have not been studied but bacterial and mammalian cell tests for mutagenicity were negative. Teratogenicity was not observed in two studies both of which included maternally toxic doses.

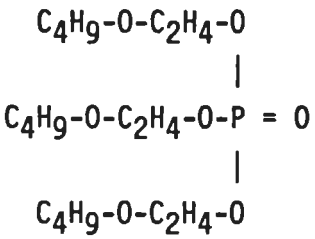
A Repeat Human Insult Patch Test indicated no sensitisation and minimal skin irritation.

Toxicity data, structural considerations and human experience do not indicate a significant hazard to man. Since the toxicity to aquatic organisms is no more than moderate and persistence (based on degradation rate in natural water) is not expected to occur, TBEP is unlikely to be harmful to the environment.

2. IDENTITY, PHYSICAL CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1. Identity

Chemical Structure :



Chemical Formula : $C_{18}H_{39}O_7P$

Common Name : Tris-(2-butoxyethyl)-phosphate

Synonyms : Phosphoric acid, tris-(2-butoxyethyl)-ester;
Tri-(2-butoxyethanol) phosphate;
Tris (2-n-butoxyethyl) phosphate;
Tributoxyethylphosphate;
TBEP;
TBXP (only in Japanese literature).

Other names (RTECS,1989) : TBOP; 2-Butoxyethanol phosphate;
Tri-(2-butylethylether) phosphate;
Tris (butylglycol) phosphate;
Tributyl cellosolve phosphate.

CAS Registry No. : 78-51-3

EINECS-No. : 2011229

RTECS-No. : KJ 9800000

CAS-name : Ethanol, 2 - butoxy-, phosphate (3:1).

TBEP is a technical product which contains as impurities tributylphosphate (about 3%) and traces of 2-butoxyethanol and phosphoric acid. In addition, traces of arsenic (up to 1 ppm) may be present (FMC, 1990). There is no information on the concentration of mono- or diesters or other impurities in the technical product.

2.2. Physical and Chemical Properties

TBEP is a nearly colourless, high-boiling, non-flammable liquid under normal conditions. It is more soluble in non-polar than in polar solvents. Additional physical and chemical properties of TBEP are given in Table 1.

2.3. Conversion Factors at 20°C

1 ppm = 16.53 mg/m^3

1 mg/l = 60.5 ppm

2.4. Analytical Methods

TBEP is usually analysed by gas chromatography (GC) coupled with either mass spectrometry (MS), infrared spectroscopy or nuclear magnetic resonance spectrometry. The detection limit is about 1 ng using any of these methods or a nitrogen/phosphorus-selective detector. (LeBel et al, 1981; Benoit and LeBel, 1986; Rivera et al, 1987).

2.4.1. Air

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

2.4.2 Water

TBEP has been extracted either with dichloromethane after acidification to pH 2 or by passage through a column filled with Amberlite XAD-2 resin which was subsequently extracted with acetone and hexane. After dehydration and concentration, extracts are analysed as described above (section 2.4). (LeBel et al, 1981; Benoit and LeBel, 1986; Watts and Moore, 1988).

2.4.3. Sediments

After decanting the supernatant water the sediment samples were mixed with an equal volume of pre-extracted anhydrous sodium sulphate and transferred to a Soxhlet thimble. Soxhlet extraction was carried out overnight using dichloromethane (300 ml). The solvent extract was concentrated to a volume of 5 ml using a Kuderna-Danish apparatus with a macro-Snyder column and further concentrated to 1 ml using a micro-Snyder column and a concentrator tube (Watts and Moore, 1988).

2.4.4. Soils and Foodstuffs

There are no reports of extraction or clean up methods for soils and food.

2.4.5. Biological Media

LeBel and Williams (1983) analysed human adipose tissue for TBEP by extraction with a mixture of acetone and hexane in presence of anhydrous sodium sulphate. The solution was centrifuged and the supernatant filtered and evaporated. The resulting extract was dissolved in solvent (5% methylene chloride in cyclohexane) for gel permeation chromatography (GPC) to separate residual lipids from phosphate esters.

In investigating artifacts in the measurement of plasma drug concentrations, Devine (1984) analysed blood which had been in contact with rubber stoppers for TBEP by extracting the serum with

dichloromethane, dehydrating and evaporating to dryness and dissolving in ethyl acetate (See Section 7).

3. PRODUCTION, STORAGE, TRANSPORT AND USE

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

Production capacities and tonnages used have not been reported. Annual European production is likely to be less than 1000 tonnes. The product is normally transported in drums. TBEP is used as a plasticizer or flame retardant in rubber, plastic materials and lacquers and as a component in floor-finishes.

4. ENVIRONMENTAL DISTRIBUTION, TRANSFORMATION AND FATE

4.1. Environmental Distribution

TBEP has not been found to occur naturally in the environment. All environmental TBEP derives from human activities but the input rate to the environment cannot be estimated from available data. The input is expected to be mainly to soil, sediments and surface waters from leachates from plastics on landfills from spillages and from effluents.

The low vapour pressure, the high soil sorption coefficent KOC and water solubility of approx. 1 g/l suggests that TBEP in the environment will be found mainly in water and sediment. In actual fact, TBEP has been detected in surface water and sediments but only at low concentrations (ppb level).

In Canada, TBEP was found in sewage effluent and in river water downstream but not upstream of its point of discharge (LeBel *et al*, 1987). Inputs

to indoor air may derive from volatilisation or dusts from plasticized rubber and plastics and from floor coatings (Weschler, 1984).

4.2. Transformation

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

4.3. Fate

4.3.1. Water

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

In a sewage treatment plant in Osaka, 81% TBEP was found to be eliminated. In 1 of 3 river water samples, TBEP concentrations decreased to zero between 10 and 20 days, in the other two there was no significant decrease in 30 days (Fukushima and Kawai, 1986).

Hattori et al (1981) studied the degradation of TBEP in environmental water. Using the molybdenum blue colorimetric method the increase of phosphate ions was analysed in river water and seawater from Osaka-Bay to which 1 ppm TBEP had been added. The degradation depended on the source of water, as follows:

	Degradation %			
Test time (days)	Oh-river	Neya-river	Osaka Bay Off Tomagashima (clean seawater)	Osaka Bay Off Senboku (coastal water)
7	29.1	0	1.9 [b]	0
14	100 [a]	100	17.6	100

a) 15 days b) 8 days

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

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

TBEP was considered to behave similarly to other phosphate esters in drinking water purification plants. Chlorine water treatment lead to formation of chlorinated compounds while treatment with chlorine oxides, peroxides or ozone resulted in oxidation products. (Huck et al, 1987).

4.3.2. Air

No data have been reported on the fate of TBEP in air and soil.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1. Environmental levels

5.1.1. Air

Weschler (1984) studied air pollutants inside and on the roof of air-conditioned office buildings in USA cities. TBEP was not detectable outdoors or in the vapour phase indoors but it was detectable indoors associated with small (<2.5 µm) but not larger (2.5 - 15 µm) particulates.

The mean concentrations measured in representative samples of dust from 7 offices was reported to be 15 ng/m^3 (Weschler and Shields, 1986). The significance of floor finishes - which may contain 1% TBEP - as a source

of these particulates is suggested by the fact that the highest concentration measured (25 ng/m^3) was found immediately following floor polishing work.

Yasuda (1980) reported the results of a study of pesticides in 19 air samples from 7 locations in 1976. Three samples were reported to contain TBEP. Two samples from Kawauchi Town contained 149.1 and 176.8 ng/m^3 and one from Ehime University 9.6 ng/m^3. It is not clear whether TBEP was unmeasured or not detectable in the other 16 samples, nor whether the samples were indoor or outdoor.

TBEP was also detectable (quantities not specified) in cigarette smoke (Schumacher et al, 1977).

5.1.2. Drinking Water and Surface Water

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

TBEP was detected at a wide range of concentrations :

Surface water	:	0.2	-	125 ng/l
Drinking water	:	8	-	272 ng/l
Effluents	:	12	-	34,900 ng/l

Details are given in Table 2.

The Japanese Environmental Agency (EAJ) summarised the results of environmental monitoring programmes which included measurements of TBEP. The EAJ 1975 report summarised analyses of 100 samples of surface water from various locations throughout Japan: TBEP was identified in none (detection limits ranged from 20 to 500 ng/l). The EAJ 1978 report summarised analyses of a further 114 samples: TBEP was again not identified (detection limits ranged from 5 to 1,500 ng/l).

5.1.3. Sediment and Fish

Sediment:
TBEP was detected in 7 out of 80 samples of sediment; concentrations ranged from 0.22 - 0.54 mg/kg and the detection limits were 0.002 - 0.1 mg/kg (EAJ, 1975). The 1978 review reported that none of 114 sediment samples contained TBEP; detection limits were 0.0005 - 0.12 mg/kg sediment (EAJ, 1978). These samples were not taken systematically so that the results from the two reports can not be compared.

Watts and Moore (1988) did not detect TBEP in suspended particles or bottom sediments in a UK river even though TBEP was found in corresponding water columns.

Fish:
No TBEP could be detected in 74 samples of fish from numerous locations throughout Japan, (detection limits ranged from 0.005 to 0.1 mg/kg) (EAJ, 1975). Another report (EAJ, 1978) states that TBEP was not detected in 93 fish samples (detection limits ranged from 0.0005 to 0.15 mg/kg).

5.2. Human Exposure

No data are available. The range of environmental data available is insufficient for an estimate of total exposure to man.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1. Invertebrate Aquatic Species Toxicity

The LC_{50} values in Daphnia magna were 84 mg/l (24 hours) and 75 mg/l (48 hours) (Monsanto, 1984a).

6.2. Fish Toxicity

The 96-hour LC_{50} in fathead minnow (Pimephales promelas) was 16 mg/l (95 % confidence interval 13 - 22 mg/l) (Monsanto, 1984b).

The 48-hour LC_{50} in killifish (Oryzias latipes) at 10°C, 20°C and 30°C was 44 mg/l, 27 mg/l and 6.8 mg/l respectively (Tsuji et al, 1986).

7. KINETICS AND METABOLISM

7.1 Human Data

LeBel and Williams (1986) reported the results of analysis of 115 human adipose tissue samples for TBEP. Samples were obtained from the greater omentum of cadavers at autopsy from two eastern Ontario (Canada) cities. TBEP was detectable in 21 of 68 male and 20 of 47 female samples. Although the frequency of detection was similar in the two cities, average concentrations in Ottawa were about 2.5 times those in Kingston. In both cities the concentrations in women (F) were 2-3 times greater than in men (M). The arithmetic mean concentration of TBEP in 41 detectable samples was 11.3 ng/g in extracted fat (M = 6.3, F = 16.6). The mean concentration overall was 4.2 ng/g in extracted fat. It is surprising that the higher mean concentration in Ottawa was not accompanied by a higher frequency of detection. Regrettably data relating concentrations and age at death are not available.

Anderson et al (1984) measured peaks of TBEP determined by High Performance Liquid Chromatography in spiked samples of serum during the development of an analytical refinement. There was a marked inter-individual variation in peak height which correlated with serum lipoprotein concentration. This finding, combined with the effects of TBEP in blood (depression of plasma drug concentration) (Devine, 1984; Young and Nysewander, 1986), indicates that TBEP has a high but variable affinity for plasma proteins.

7.2 Animal Studies

No data are reported.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

8.1. Acute Toxicity

The acute toxicity of TBEP following a single administration is low: the lethal dose determined by various routes of administration and in various species is shown below.

Route	Species	LD_{50} (mg/kg body wt.)	Reference
Oral	rat	3,000	Sax and Lewis, 1988
Oral	rat	4,700	Monsanto, 1984c
Oral	rat	9,490	FMC, 1976a
Oral	guinea pig	3,000	Sax and Lewis, 1988
Oral	chicken	>5,000	Carrington et al, 1990
Intravenous	mouse	180	Sax and Lewis, 1988
Dermal	rabbit	>5,000	Monsanto, 1984c
Dermal	rabbit	>10,000	FMC, 1976a

The lethal concentration in air has also been studied in a 4-hour aerosol inhalation test (Hoechst, 1989). Groups of 5 male and 5 female SPF-Wistar rats were exposed to measured concentrations of 3.3, 3.4 and 6.4 mg/l TBEP. No animal died but at all concentrations the animals exhibited depressed and irregular respiration, increased salivation and sneezing and unsteadiness and tremor but these symptoms had cleared in most animals 9 days later. There were no body weight changes and gross necropsy revealed no abnormality. The 4hr - LC_{50} was thus greater than 6.4 mg/l. A 1-hour LC_{50} in rats was reported as 30 mg/l (nominal) (FMC, 1976b).

Experiments to determine any neurotoxic effects from acute exposure in hens are described in Section 8.7.

8.2. Repeated Exposure Toxicity

In a four-week study, diet containing 0, 500, 2,000, 7,500 or 15,000 ppm TBEP was fed to male and female Sprague-Dawley rats. No signs of toxicity were found in male rats of any group whereas there was a slight decrease in body weight and food consumption in females receiving diets containing 7,500 and 15,000 ppm. No compound related changes were observed at necropsy (Monsanto, 1985a).

In a sub-chronic gavage study (Laham et al, 1985a) groups of 12 male and 12 female Sprague-Dawley (SD) rats received 0, 0.25 or 0.5 mg/kg body weight undiluted TBEP on 5 days per week for 18 weeks. During the first week, two high-dose female groups showed muscular weakness and ataxia which had disappeared by the end of the fourth week. After about 7 weeks, nearly all animals exhibited some signs which seemed to be treatment related. All treated animals appeared less active, and one female died during week 13. Breathing difficulties and ataxia were present in several males and females in both treatment groups, though the low dose group was affected to a lesser extent. Tremors, piloerection, lacrimation and increased urination were observed in both males and females in the high-dose group. After the last dose, the clinical signs observed in the high-dose group decreased in intensity. Biochemical analysis of blood obtained from animals at the end of dosing showed in male rats the minor changes tabulated below. Female

rats did not show these changes, but high-dose females had significantly elevated levels of γ-glutamyltranspeptidase.

Dose	Bilirubin	BUN	URATE	Red Cell AChE	SGPT
0.5 mg/kg	-	+	-	-	-
0.25 mg/kg	0	0	-	-	0

\+ = significant increase (compared
\- = significant decrease with
0 = no significant change controls)

AChE = Acetylcholinesterase
SGPT = Serum glutamic - pyruvate - transaminase
BUN = Blood urea nitrogen

There were no haematological changes. Animals were necropsied one week after the last dose. Liver weight was significantly increased (about 20%) in both high- and low-dose groups. Kidney weight was increased by about 20% in both groups and the increase was statistically significant in high-dose groups. Histopathological changes were confined to the hearts of male rats of both dose groups. Three of 6 high-dose and 2 of 6 low-dose animals had multiple foci of mononuclear cell infiltration, haemorrhage and/or myocardial fibre degeneration. Two of 6 high-dose, 3 of 6 low-dose and 1 of 6 control rats demonstrated multifocal interstitial fibrosis with or without macrophages containing haemosiderin pigment. The authors concluded that TBEP may have accelerated the development of focal myocarditis which is a normal feature of older male SD-rats. A No-Adverse-Effect-Level was not ascertained in this study. This study is very similar (perhaps identical) to that reported by Laham et al (1984b) which is discussed in 8.7.1.

In an eighteen-week study 4 groups of 20 male and 20 female SD-rats were fed diet containing 0, 300, 3,000 and 10,000 ppm TBEP. One high-dose female died during the study but the death was not attributed to test material. Body weights, food uptake and clinical observations were similar in treated and control animals. Haematological and clinical chemistry evaluations were normal except for increased platlet counts in the 10,000

ppm groups and increased γ-glutamyltranspeptidase and a depressed plasma cholinesterase activity in the 3,000 and 10,000 ppm groups. Absolute and relative liver weights were increased in 10,000 ppm groups. Microscopic examination showed mild periportal hepatocellular hypertrophy and periportal vacuolization in males receiving 3,000 or 10,000 ppm diet. The NOEL was 300 ppm (Monsanto, 1987a).

In a 21 day dermal toxicity study in 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/day, 5 days per week for three weeks. No animal died and no adverse clinical signs were observed. Findings were limited to the treated skin. There was no indication that dermal exposure to 1,000 mg/kg/day TBEP resulted in any adverse systemic effect but local skin irritation occurred at all dose levels (see 8.3.1.) (Monsanto, 1985b).

8.3. Skin, Eye and Respiratory Irritation

8.3.1. Primary Skin Irritation

Undiluted TBEP was held in contact with two intact sites (0.5 g/site) on each of six New Zealand albino rabbits for either 4 hours or 24 hours. All animals were observed for dermal irritation for 14 days. Irritation was generally mild to moderate and transient. No tissue destruction was seen and all animals were free of all dermal irritation within 3 to 10 days after application (Monsanto, 1984c). FMC (1990) reported a study which indicated that TBEP was non-irritating to rabbit skin but no experimental details were given.

In the 21-Day Dermal Toxicity Study in New Zealand White rabbits slight to moderate erythema was noted (Monsanto, 1985b). Histopathological changes associated with subacute skin irritation included squamous epithelium hyperplasia and erosions/ulceration (See section 8.2.).

8.3.2. Primary Eye Irritation

Details were available of four independent tests of the eye irritancy of TBEP (FMC, 1976a; Monsanto, 1984c; Hoechst, 1988; and FMC, 1991). All studies involved instillation of 0.1 ml undiluted TBEP. All except the FMC (1976a) study were undertaken to GLP standards. In addition one safety data sheet (Akzo, 1989) reports that TBEP is a slight irritant to rabbit eyes.

Of 21 rabbits used in the four independent studies TBEP produced mild transient eye irritation only in 20 animals. One animal had an unremarkable initial conjunctival reaction but developed extensive corneal changes involving between half and three quarters of the cornea and iritis which persisted throughout the observation period of 21 days. There was a delayed exacerbation of the conjunctival response which had almost completely resolved by 48 hours after the instillation.

In those experiments in which eyes were washed 4 seconds after the instillation, there were no adverse effects.

Though on the basis of one experiment, application of the rules for classification applicable in the European Community would lead to TBEP being considered a severe eye irritant requiring labelling with R41 - 'Risk of serious damage to the eyes', the weight of the evidence from all the experiments is that TBEP is minimally irritant to the eyes and should not require classification for this hazard. It is likely that a complication such as secondary infection was responsible for the aberrant results in one animal.

8.3.3. Respiratory Irritation

In a 4-hour inhalational study there were indications of respiratory irritation (see section 8.1.)

8.3.4. Dermal Sensitisation

No data available. For human data, see chapter 9.

8.4. Mutagenicity

TBEP was tested at concentrations of 0, 50, 100, 500, 1,000, 5,000 and 10,000 µg/plate without and with 1, 5, or 20% S-9 mix in an AMES TEST using Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537 strains with the plate incorporation method. TBEP did not cause any positive response either without or with any level of metabolic activation. TBEP was toxic to the bacteria at the two highest concentrations tested (Monsanto, 1984d).

Monsanto (1985c) carried out a CHO/HGPRT mammalian cell forward gene mutation assay with TBEP. The tests were conducted with 5% of S-9 mix at 50, 100, 150, 225 and 300 µg/ml and in the absence of metabolic activation at dosages of 5, 50, 75, 100 and 130 µg/ml. Under the condition of this study, cytotoxicity was noted at the highest dose level with a dose-related trend in toxicity both with and without metabolic activation, TBEP was not considered to be mutagenic.

8.5. Chronic Toxicity and Carcinogenicity

No reports of chronic toxicity and carcinogenicity studies on TBEP have been found.

8.6. Reproduction, Embryotoxicity and Teratogenicity

Monsanto (1985d) undertook a range-finding teratology study in rats with TBEP (purity 98.7%). This was administered in corn oil to groups of five mated Charles River CD female rats at dosage levels of 0, 25, 250, 500, 1,000 and 2,000 mg/kg/day as a single 5 ml/kg oral daily dose by gavage, on days 6 to 15 of gestation, inclusive. At doses up to 1,000 mg/kg/day all

rats survived while in the high-dosed group 2 animals died or were sacrificed. Maternal toxicity (reduced righting reflex, hypoactivity, lethargy, ataxia and stained anogenital haircoat) was observed in the animals receiving 500 to 2,000 mg/kg/day. Maternal weight gain was normal in animals receiving 1,000 mg/kg/day and less. TBEP had no effect, at any dosage level, on fetal resorption, fetal viability, postimplantation loss and total implantations.

In another study (Monsanto, 1985e), TBEP was administered by gavage in corn oil to three groups of 25 mated Charles River CD female rats at dose levels of 250, 500 and 1,500 mg/kg/day on days 6 to 15 of gestation. A fourth group served as a vehicle control. Maternal weight gain was depressed only in the high-dose group. The treatment had no effect at any dosage level on fetal resorption and fetal viability, postimplantation loss, total implantations or the incidence of fetal malformations.

8.7. Neurotoxicity and Esterase Inhibition

These aspects of the toxicity of TBEP have been studied by two groups of workers and are subsequently described. Laham and his coworkers have used non-standard protocols and have reported both neurophysiological changes and neurohistological changes which they have ascribed to TBEP. Monsanto's studies attempted to address the issues raised by the Laham studies using more conventional protocols and routes of administration which they considered more relevant to human exposure conditions.

The situation is therefore complicated, with similar (but not completely comparable) studies yielding results which were not always consistent within one experiment and sometimes in conflict with another experiment.

Some of the repeated dose studies which have provided information on sub-chronic toxicity have been described in section 8.2.

8.7.1. Studies of Neurotoxicity on Acute Administration

Monsanto commissioned a classical hen delayed neurotoxicity study (Monsanto, 1986) which was subsequently reported by Carrington et al (1990). Twenty adult hens were given 5,000 mg/kg body weight TBEP in gelatin capsules and 21 days later the dose was repeated. A positive control group received 750 mg/kg body weight of tri-o-cresyl phosphate in gelatin capsules and a negative control group received empty capsules. No cholinergic effects or other signs of toxicity were noted in TBEP animals, whereas the positive control hens all developed ataxia with paralysis. No treatment-related changes were observed on neuropathological examination of peripheral nerves of TBEP-treated animals. TBEP did not reduce levels of Neuropathy Target Esterase (NTE).

A further study of similar design but with dermal application of 5,000 mg/kg body weight both on day 0 and on day 21 showed no clinical signs of toxicity (Monsanto, 1986).

Laham et al (1985b) reported the results of the administration by gavage to Sprague-Dawley rats of single high doses of TBEP. Different dose ranges were used in males and females, but some of these were combined (differently in males and females) to constitute 'high', 'medium' and 'low' dose groups (Table 3). Dose-related changes were seen in neurophysicological and neuropathological indicators, but doses were in the region of or greater than the LD_{50}. There was a high mortality and survivors were ill and had marked weight loss. High-dose animals had diarrhoea.

8.7.2 Studies of Neurotoxicity on Repeated Dosing

The first repeated dose study (Laham et al, 1984a) involved dosing on days 1-14 and making measurements on days 15 and 28. The second (Laham et al, 1984b) involved dosing on 5 days per week for 18 weeks with observations at 6, 12 and 18 weeks. The doses administered and the neuro-physicological results are summarised in Table 4.

Apart from a significant (p=0.001) decrease in the body weight of low-dose females at 7 days, there were no clinical signs or significant differences between dosed groups and controls in the 14 day study. No morphological changes were found on light- or electronmicroscopy.

In the 18-week study, there were no significant body weight differences between exposed groups and their controls at any stage. For 4 weeks during the first half of the study 2 of 12 high-dose female rats showed transient weakness and ataxia. In the second half of the study almost all treated animals exhibited ataxia and breathing difficulty and high-dose animals exhibited tremors, pilo-erection, lacrimation and increased urination. Males were less affected than females. Three animals of each sex at each dose level were examined for neurohistological abnormalities by light- and electronmicroscopy. Five of 6 high-dose animals and 3 of 6 low-dose animals exhibited myelin degeneration and axonal swelling in myelinated fibres and lamellated electron dense inclusions and axonal swelling in unmyelinated fibres.

In the 14-day study, males show a prolongation of refractory periods occurring early in the observation period and in females a prolongation of refractory period occurring late in the observation period. The change in conduction velocity in females is dissociated from changes in refractory period. In the repeated-dose study of 18 weeks, the increased refractory period and the decreased conduction velocity were dose-related in females but in males the maximum effect appears to have been reached by the low dose, suggesting that the magnitude of the maximum attainable neurophysiological changes is modest. The inconsistency of these observations calls into question their clinical significance.

In similar or identical 18-week study (Laham et al, 1985a) discussed in chapter 8.2, clinical signs were similar. In this study, serum magnesium was significantly increased in low- and high-dose and magnesium levels in males. These changes in ionic concentrations could be relevant to changes in neurophysiological function.

In the 18-week studies of Monsanto (1987a) (described in chapter 8.2) and Monsanto (1987b), neurophysiological and neuropathological observations were also reported. No clinical signs of neurotoxicity were observed. The only neurophysiological alteration observed was a reduced caudal nerve conduction velocity in high-dose females and there were no treatment-related changes in peripheral nerve or spinal cord histopathology.

Calculated daily doses of TBEP from analytical food concentrations and measured average food intake were:

low-dose: 20-12 mg/kg body weight per day for males and 24-16 mg/kg body weight per day for females over the whole study period.
high-dose: 608-433 mg/kg body weight per day for males and 717-548 mg/kg body weight per day for females.

These doses thus encompass the range of doses administered by Laham et al (1985a) and were administered seven rather than five days per week. As a rule, absorption from dietary administration is more effective than from bolus administration. The total exposures in these experiments were therefore similar but the peak and time course of the concentrations of TBEP may have been different and therefore the experiments are not completely comparable.

8.7.3. Effects on Esterase Activity

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

A study was made of the effect of TBEP on neurotoxicity target esterase (NTE), brain acetylcholinesterase (AChE) and plasma butyrylcholinesterase (BuChE) in 3 groups of 5 hens. Each was administered a single oral dose of 5,000 mg/kg/bw TBEP. All animals were sacrificed 24 hours after treatment. The NTE activity was unchanged but plasma BuChE and

brain AChE-levels were depressed to 5% and 13% respectively of control levels Monsanto (1986).

Cholinergic symptoms were more marked in female rats (Laham et al, 1985a) while changes in AChE levels were more marked in male rats (Laham et al, 1984b). Not only is this inconsistent but the observed decrease in AChE activity (5-7%) is not sufficient to account for cholinergic symptoms. In addition, the reductions in plasma BuChE and brain AChE levels in hens (Monsanto, 1986) would be regarded as clinically significant.

8.7.4. Conclusions regarding Neurotoxicity and Esterase Inhibition

TBEP has a weak anticholinesterase activity and produces electrophysiological disturbance at nearly-lethal dosage levels but gave clearly negative results in tests in adult hens (the most sensitive species) for organo-phosphorus induced delayed neurotoxicity. The reports, of ultrastructural changes in large and small fibres in the sciatic nerve of rats administered TBEP by gavage is of interest but warrant further investigation since dietary studies failed to confirm the findings. Of particular relevance would be a study on the effects of substances (different from organophosphate cholinesterase inhibitors) administered in doses producing high mortality or gross metabolic disturbance, on the neurohistology and electronmicroscopy of nervous tissue.

Any neurotoxic activity in TBEP is not the type characteristically associated with organophosphates and occurs only with massive doses which are of no relevance to human exposure.

9. EFFECTS ON MAN

A Repeat Human Insult Patch Test on a panel of 209 volunteers was undertaken by Monsanto (1984e). In the 3 week induction period, 4 applications per week of 0.2 ml were applied for 24 hours to the skin using Parke-Davis Readi-Bandages. During the fourth week, four similar applications were made to previously untreated sites. During induction, minimal irritation was observed on one or two occasions in 9 of the subjects. There was no dermal reaction to challenge applications. The results indicate minimal skin irritation potential and do not indicate any sensitising potential.

10. FIRST AID AND SAFE HANDLING ADVICE

10.1. Exposure Regulations:

1.0 mg/m^3 (vapour and aerosol) is specified as a ceiling value for occupational exposure in the Soviet Union.

Neither a TLV^R value (USA) nor a German MAK value has been set.

In the USA TBEP may be used as a component of adhesives in articles intended for use in packaging, transporting or holding food (UNEP, 1989).

10.2. First Aid and Medical Treatment

10.2.1. First Aid

- In case of contact with eyes, immediately flush eyes with copious amounts of water; obtain medical advice if there is persistent irritation.
- In case of contact with skin, wash with soap and water.
- If inhaled, remove to fresh air.
- If breathing is difficult, give oxygen.

- If not breathing, give artificial respiration, preferably using a ventilator; call a physician.
- If swallowed, send to a hospital for treatment.
- Remove contaminated clothing and launder before re-use.

10.2.2. Medical Treatment

Ingestion
Consider administration of atropine and oximes only if there are cholinergic symptoms.
Inhalation
Exposure sufficient to cause severe symptoms is extremely unlikely. Keep under observation for 24-48 hours and treat symptomatically.
Eyes: Examine for corneal damage (unlikely). Treat symptomatically.

Note: In case of fire, harmful fumes can be generated, containing carbon monoxide, carbon dioxide, phosphorus oxides and/or phosphines.

10.3. Safe Handling, Storage and Transport Regulations

Care should be taken when handling TBEP to avoid the generation of vapours and aerosols.

Where TBEP is used at high temperatures, enclosure or local exhaust ventilation is recommended. Avoid inhalation, contact with eyes, skin or clothing. As a precaution, when handling the product wear chemical safety goggles and rubber gloves. Wash thoroughly after handling. In case of fire, respirators should be worn.

Keep in tightly closed containers and store in a cool, dry place.

In Europe, transportation and storage of TBEP are not regulated. The product is not included in Annex I of EC Directive 67/458/EEC and its adaptations. According to the US D.O.T. regulation the following must be considered:

D.O.T. Shipping Name	:	Hazardous Substance, Liquid, N.O.S.
D.O.T. Identification Number	:	NA9188
D.O.T. Hazard Classification	:	ORM-E
Other Shipping Regulations	:	None, no limits with passenger or cargo.

10.4. Management of Spillage and Waste

Spillages should be collected by absorbing on sand or organic absorbant materials, which then can be incinerated.
Large quantities should be incinerated in a suitable incinerator equipped with a scrubber for phosphorus oxides.

Contaminated water should be collected and oxidised with hydrogen peroxide or ozone or dosed slowly into a biological treatment plant.

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TABLE 1 Physical and Chemical Properties of TBEP

				Reference
Molecular weight	:	398.5		
Physical form	:	liquid		
Colour	:	colourless to yellowish		
Odour	:	mild		
Boiling range °C at 5.0 - 5.3hPa	:	200-230		1,2,3)
Freezing point °C	:	- 70		2)
Density g/ml at 20°C	:	1.02		2,3)
Viscosity mPa.s at 20°C	:	11-15		4)
Vapour pressure hPa at 25°C	:	2.8×10^{-7}		9)
hPa at 150°C	:	0.33		4)
Solubility in water g/l at 20°C	:	1.1		4)
		1.3		7)
Solubility in petroleum at 20°C	:	miscible		4)
Acidity/alkalinity 1 g/l in water at 20°C	:	neutral		4)
Flashpoint °C	:	210 (approx.)		3)
		223		4)
		224		8)
Ignition point °C	:	251		4)
Autoignition temp °C	:	261		8)
Refractive index at 20°C	:	1.4359		1)
25°C	:	1.434		3)
log Koc	:	4.38	calculated	5)
log Pow	:	4.78	calculated	5)
		3.65		6)
		4.1		11)

(1) = Lenga (1985)
(2) = Sax and Lewis (1988)
(3) = Keith and Walters (1985)
(4) = HOECHST (1987)
(5) = Watts and Moore (1988)
(6) = Fukishima and Kawai (1986)
(7) = Eldefrawi et al (1977)
(8) = FMC (1990)
(9) = Hinckley et al (1990)
(10) = Leo (1989)

Table 2. Concentrations of TBEP in water bodies (ng/l)

Country	Surface Waters	Drinking Water	Sewage Effluents	Reference
CANADA	0.2 - 73.8	7.7 - 271.6 0.9 - 74.5		LeBel et al (1987) Williams et al (1982) LeBel et al (1981)
UK	10 - 100		100 - 200	Watts and Moore (1988)
SPAIN	detected (no figures given)			Rivera et al (1987)
FRG	5 - 70 max. 125		12 - 34,900	Ernst (1988) Bohlen et al (1989)
USA	0.3 - 3			Sheldon and Hites (1978)
JAPAN	not detected 50 - 6000 (mean 400)	0 - 0.0585		Adachi et al (1984) EAJ (1975 & 1978) Fukushima and Kawai (1986)

Table 3. Observations following acute dosing with TBEP in SD rats (Laham et al, 1985b)

	MALES				FEMALES			
Dose Group	Control	Low	Medium	High	Control	Low	Medium	High
Dose (g/kg) (a)	0	1.0	6.8	8.0	0	1.0	1.75	3.2
Dose (g/kg) (a)		3.2		9.0		1.5	2.0	
WEIGHT								
Weight change	increase	=	- 10 %	- 15 %	increase	=	- 10 %	- 15 %
DURATION OF SYMPTOMS								
Tremors	0	0	3 days	7 - 14 days	0	0	3 days	7 - 14 days
Piloerection	0	0	3 days	7 - 17 days	0	0	3 days	7 - 14 days
Abnormal gait	0	0	0	7 - 14 days	0	0	0	7 - 14 days
Diarrhoea	0	0	0	7 - 14 days	0	0	0	7 - 14 days
Increased urination	0	0	0	7 - 14 days	0	0	0	7 - 14 days
Mortality (b)	< 6/10	< 6/10	< 6/10	< 6/10	< 6/10	?	7/10	9/10
		< 6/10		8/10		?	8/10	
NEUROPHYSIOLOGY								
Nerve Conduction								
Velocity m/sec (b)	32.80	?	27.60*	28.10*	34.5	?	28.73*	27.40*
		31.38*		26.75*		?	27.7*	
Relative Refractory								
Period ms (b)	1.73	?	2.25	2.5*	1.65	?	2.13	2.6
		1.95		3.1*		?	2.70	
Absolute Refractory								
Period ms (b)	0.85	?	1.23	1.4*	0.9	?	1.17	1.70
		1.08		2.2*		?	1.60	
NEUROPATHOLOGY								
Sciatic nerve								
pathology (b)	0	0	+	+	0	0	0	++
		+		+		0	++	

a) Five dose levels in addition to a control were administered to each sex and grouped as 'high' 'mid' or 'low' as indicated

b) Two figures in any column correspond to the individual dose levels.

Electrophysiological measurements were made 3 weeks after dosing; where there were more than 4 survivors per sex per dose, 4 symptomatic animals were examined.

* $p < 0.05$ = no change + present ++ marked ? not known or not reported

Table 4. A selection of results of electro-physiological measurements in the studies by Laham et al (1984a,b)

14 DAY STUDY (Rats)

		Control (water)		Low dose TBEP		High dose TBEP (4)	
		10 M	10 F	10 M	10 F	10 M	10 F
DAY	DOSE (ml/kg/day)	2.24	1.12	0.8	0.8	2.24	1.12
15	Cond. Vel.(1) (m/s)	30.61	34.00	20.24	32.78	30.41	30.34
15	Abs. Ref. Per.(2) (ms)	0.83	0.98	1.0	1.13	0.98*	1.18
15	Rel. Ref. Per.(3) (ms)	1.68	1.97	2.0 **	2.1	2.10*	2.23
28	Cond. Vel. (m/s)	31.81	33.36			31.12	32.04
28	Abs. Ref. Per. (ms)	0.83	0.78			0.88	0.90
28	Rel. Ref. Per. (ms)	1.75	1.65			1.88	1.85

18 WEEK STUDY (Rats)

WEEK	DOSE (ml/kg/day)	0.5	0.5	0.25	0.25	0.5	0.5
18	Cond. Vel. (m/s)	36.3	36.3	30.7**	32**	30.1**	30.8**
18	Abs. Ref. Per. (ms)	1.02	0.95	1.24**	1.26**	1.24*	1.34*
18	Rel. Ref. Per. (ms)	2.06	1.93	2.39***	2.33***	2.32***	2.43***

Results shown in brackets were insignificantly different from controls. In the 18 week study, results at 6 and 12 weeks were quantitatively similar to those at 18 weeks. Males were less severely affected than females.

* $0.01 < p < 0.05$; ** $0.001 < p < 0.01$; *** $p < 0.001$

(1) Conduction velocity (2) Absolute refractory period (3) Relative refractory period (4) Male rats were more tolerant of TBEP treatment than female rats.

APPENDIX I

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APPENDIX II

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