MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Tris (2-butoxyethyl) Phosphate (CAS # 78-51-3)

FROM: Brian J. Hughes, Toxics Unit, Air Quality Division

DATE: August 17, 2023

SUBJECT: Screening Level for Tris (2-butoxyethyl) Phosphate

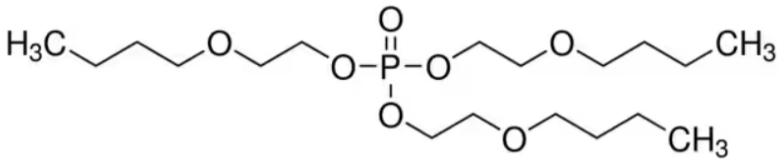
SUMMARY

The initial threshold screening level (ITSL) for tris(2-butoxyethyl) phosphate is 8 µg/m^3 (annual averaging time).

USES AND PHYSICAL CHEMICAL PROPERTIES

Tris (2-butoxyethyl) phosphate (TBOEP) is produced by chemical synthesis via condensation of phosphorus oxychloride and butoxyethanol (ATSDR 2012). It is used as a flame retardant, plasticizers, solvent, and anti-foam agent. It is found in floor polishes, lacquers, paints and glues. As a flame retardant, TBOEP functions by suppressing flammability of pyrolysis products (vapor-phase mechanism) or by chemical interaction through changing the nature of the decomposition products.

Table 1. Physical/Chemical Properties of TBOEP [1]

Structure	
Synonyms	Tri(2-butoxyethyl) phosphate, tributoxyethyl phosphate, 2-butoxyethanol, phosphate, phosphoric acid, tributoxyethyl ester
Appearance/Odor	Slightly yellow oily liquid with a sweet butyl-like odor
Molecular Weight	398.48 g/mol
Melting Point	-70° C
Boiling Point	215-228° C at 4 mm Hg
Solubility: Water	1.1 g/L @ 25° C
Vapor Pressure	0.03 mm Hg @150° C

[1] ATSDR (2012)

LITERATURE SEARCH

The literature was searched to find relevant data to assess the toxicity of TBOEP. The following references or databases were searched: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Levels (RELs), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) SciFinder (searched August 1, 2023), U.S. EPA ChemView, California Office of Environmental Health Hazard Assessment (OEHHA), the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR), European Chemical Agency (ECHA), and the U.S. National Toxicology Program (NTP).

CURRENT LEVELS IN THE ENVIRONMENT

Levels of TBOEP have been evaluated in the ambient air (Weschler 1984). TBOEP was not detected in the vapor phase in the outside or inside environment. Detections of TBOEP were observed indoors associated with particulates < 2.5 µm but not larger (2.5 to 15 µm). In another study, the mean concentrations measured in dust samples from seven offices was 15 ng/m^3 (Weschler and Shields, 1986). In a study by Gbadamosi (et al. 2020), the overall contributor to TBOEP exposures in children is through the dust, dermal and inhalation. In adults, exposure is greatest through inhalation followed by dermal absorption.

TOXICOKINETICS

There is limited information on the absorption, metabolism, distribution, and excretion of TBOEP in humans. Volkel et al. (2018) examined the toxicokinetics of TBOEP in human volunteers. Three men and three women were administered 20 µg/kg bw of TBOEP (95% purity) orally as a single dose in olive oil. Urine was collected hourly for 39 hours post-dose; no blood sampling occurred. Besides bis(2-butoxyethyl) phosphate (BBOEP), two hydroxylated metabolites tris(2-(3-hydroxy) butoxyethyl) phosphate (OH-TBOEP) and bis(2-butoxyethyl)-(2-hydroxyethyl) phosphate (BBOEHEP) were detected in urine samples of all volunteers within the first hour. The maximum concentrations (C max) of BBOEHEP and OH-TBOEP were observed between 1 and 3 h for all volunteers. For a single subject, the corresponding t 1/2 values were between 2.4 and 5.3 h for BBOEHEP and 1.5 and 6.1 h for OH-TBOEP. In vitro studies using human liver microsomes and serum enzymes indicate that the major metabolite of TBOEP is bis(2-butoxyethyl) hydroxyethyl phosphate followed by 3-HO-TBOEP and 1- and 2-HO-TBOEP. The metabolic transformation pathway is described in Figure 1.

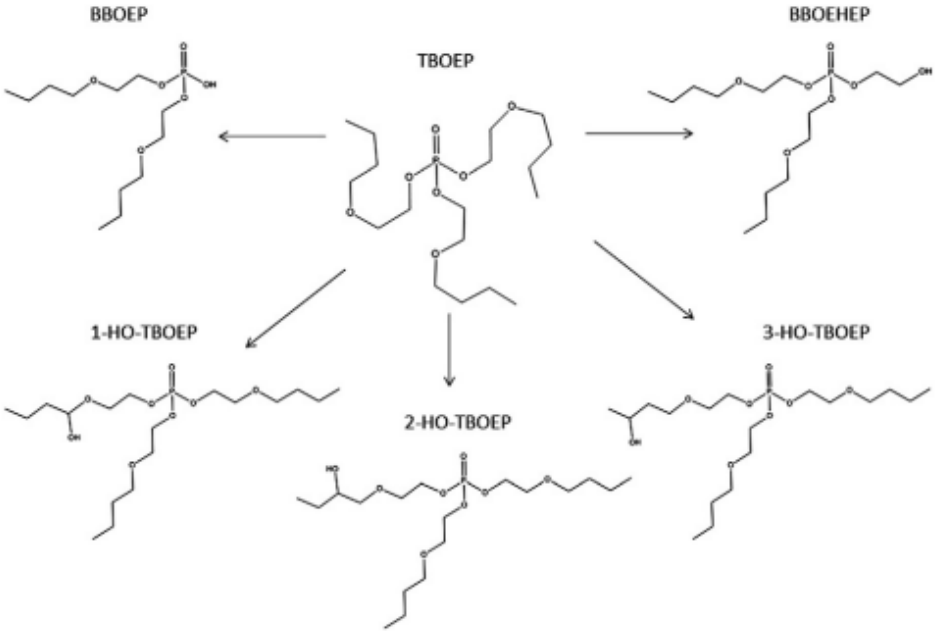


Figure 1. Metabolic Transformation Pathway for TBOEP (Van den Eede et al. 2015)

The concentration of TBOEP in the human population was investigated by LeBel and Williams (1986). An analysis of 115 human adipose samples were obtained from the greater omentum area of cadavers from two different eastern Canadian cities. TBOEP was detectable in 21 of 68 male and 20 of 47 female samples. The arithmetic mean of the 41 samples, where TBOEP was detected, is 11 ng/g (female = 16.6 ng/g vs. male = 6.3 ng/g). Concentrations in females were 2-3 times greater than males regardless of location.

Blood serum concentrations are correlated with serum lipoprotein concentrations (Anderson et al. 1984).

Distribution studies were limited to one human study, which demonstrated that TBOEP was found in the breast milk from mothers in Asian countries (Kim et al. 2014). The daily intake of TBOEP estimated in 1.38 µg/kg bw/day.

ACUTE DATA

Acute studies were not used in the calculation of the screening level. Studies of longer duration that evaluated multiple toxicological endpoints are more appropriate to determine the point of departure and deriving the ITSL. Thus, the acute data are presented for informational purposes.

Skin Irritation

In an OECD guideline 404 (Acute Dermal Irritation/Corrosion) study, TBOEP was administered to the shaved skin of three rabbits with 0.5 mls of undiluted compounds on the shaved skin for four hours covered with a semi-occlusive bandage (ECHA 2023 study report dated 2000). After the exposure period, the residual TBOEP was removed and the site was observed for 30-60 minutes, and 24, 48, and 72 hours, and scored according to the Draize method. Erythema was apparent at 30-60 minutes (3 of 3 animals) and at 72 hours two of three animals showed well-defined to

severe erythema. All effects were reversible 14 days after exposure. TBOEP was considered irritating to the skin. Several older non-guideline studies, available through ECHA (2023) indicated that TBOEP would be a mild to moderate skin irritant.

Eye Irritation

In an OECD guideline 405 (Acute/Eye Irritation/Corrosion) study, three New Zealand White rabbits were administered 0.1 mg of undiluted TBOEP in the left eye with the right eye serving as the control (ECHA 2023 study report dated 2000). The study revealed that from one to 72 hours the eyes exhibited vascular swelling, reddening of the iris, and diffused translucent areas of the cornea. All signs of irritation resolved after 7 days. TBOEP was noted by the authors to be slightly irritating to the eyes, but not requiring classification. A review of older studies confirms that TBOEP is slightly irritating to the eyes (ECETOX 1992).

Skin Sensitization

There are two conflicting studies regarding the potential for skin sensitization in animals. The first a modified Buehler method (OECD Guideline 406) in guinea pigs in which no signs of irritation or sensitization were observed when 0.5 mls of undiluted TBOEP was applied according to the guideline (ECHA 2023 study report dated 1980). A guideline Local Lymph Node assay (Banks 2010) was conducted in CBA mice at concentrations of 10, 25, and 50% of TBOEP in olive oil. The stimulation index of 3 was measured at a concentration of 25%, indicating that TBOEP has sensitization potential. A human repeat insult patch test (HRIPT) was conducted on a panel of 209 volunteers. After a three-week induction period with four applications per week of undiluted TBOEP of 0.2 mls to the skin, there were no reactions to challenge indicating a lack of sensitization potential in humans.

Lethality

In a guideline study (OECD 401: Acute Oral Toxicity, Sprague-Dawley rats (5 animals/sex/group)) were administered 2000 mg/kg bw of TBOEP in water and observed for 14 days (ECHA 2023 study report dated 2000). The LD_{50} was greater than 2000 mg/kg bw. The clinical signs noted were spontaneous activity, irregular respiration, stilted and uncoordinated gait in males and females. In females, stupor, panting, bristled coat, sunken flanks, ataxic gait, forward crawling, lateral/prone position, no righting reaction, twitching, squatting posture and dilated pupils were reported.

In an older study similar to an OECD 401 Acute Oral study, groups of five Sprague-Dawley rats were administered TBOEP in water at doses of 500, 4000, 5000, 7500 and 10000 mg/kg bw in females; and 500, 5000, 10000, 12500, and 50000 mg/kg bw in males (ECHA 2023 study dated 1979). The NOAEL was 500 mg/kg. Doses of 4000-10000 mg/kg in females and 10000 and 15000 mg/kg bw induced depression, prostration, labored respiration, ataxia, red staining of nose or ears, rough coat, soft feces, urine stains, tremors at 4 hours. Mortality for females was 500 mg/kg: 0/5; 4000 mg/kg: 1/5; 5000 mg/kg: 2/5; 7,500 mg/kg: 4/5; 10,000 mg/kg: 5/5. Mortality for males was 500 mg/kg: 0/5; 5000 mg/kg: 0/5; 10,000 mg/kg: 1/5; 12,500 mg/kg: 1/5; 15,000 mg/kg: 4/5. Gross pathology on dead rats showed reddened intestines and/or stomach linings and some had dark livers. The oral LD_{50} was calculated to be 13,278 mg/kg bw for male rats and 5383 mg/kg bw for female rats. Based on these results there is a sex-related difference in sensitivity to the test article.

In a study similar to an OECD Acute Oral toxicity 401 study, Sprague-Dawley rats (5/sex/dose) were administered 5000 mg/kg bw of TBOEP (ECHA 2023 study dated 1981). The oral LD_{50} was > 5000 mg/kg for both males and < 5000 for females. Clinical signs of female decedents were lethargy, salivation, unresponsiveness, and diarrhea.

In a non-guideline study, Sprague-Dawley rats (6/sex/dose) were administered 500 and 5000 mg/kg bw of TBOEP (ECHA 2023 study dated 1991). The LD_{50} was between 500 and 5000 mg/kg bw.

In another non-guideline study (ECHA 2023 study dated 1980), Sherman-Wistar rats (5/sex/dose) were administered 5000 mg/kg bw of TBOEP. The LD_{50} was > 5000 mg/kg bw. One female and two males died at the high dose with the clinical signs of ruffled coat, gasping, and eventually comatose.

Inhalation

In a guideline compliant OECD Guideline 403 (Acute inhalation Toxicity) study, Wistar rats (5/sex/dose) were exposed to nose only concentrations of 3.3, 3.4, and 6.4 mg/L TBOEP for four hours (ECHA 2023 study dated 1990). The mass median diameter (MMD) was determined to be 0.8 to 1.3 microns and the geometric standard deviation (GSD) was 1.8 to 2.0 microns. There were no deaths during the study. All rats exhibited depressed and irregular breathing, increased salivation, sneezing, unsteadiness and tremor; all clinical signs of toxicity and symptoms had resolved in the majority of animals by day 9 of the observation period. There was no effect on bodyweight gain and no macroscopic changes were noted at necropsy. The median lethal inhalation concentration of TBOEP in Wistar rats was greater than 6.4 mg/l following nose-only exposure for 4 hours.

In another OECD guideline compliant study, Sprague-Dawley rats (5/sex/dose) were exposed to 5.03 mg/L (mean calculated concentrations) of TBOEP (ECHA 2023 study report dated 1981). Rats were exposed 4-hour whole body. The MMD was determined graphically as 3.7 microns and the GSD was 2.3 microns. During the first 4-hours post exposure 2/5 female rats died. All males were lethargic with signs of brown discharge around the oral cavities and the surviving females were prostrate with shallow breathing and lethargy. All 8 rats had wet hair coats. During the subsequent 14-day observation period 4/5 males and all female rats died. There were no gross abnormalities found in rats which died during the post-exposure 14-days except for a female with corneal opacity. The LC_{50}/4 h was determined to be > 5.03 mg/l.

In a study conducted under EPA OPPT guidelines (Acute Inhalation Toxicity), Sprague-Dawley rats (5/sex/group) were exposed to 0.52 mg/L of TBOEP via whole body inhalation for 4 hours (ECHA 2023 study report dated 1981). The mass median aerodynamic diameter (MMAD) was 2.8 µm; the GSD was 3.0 µm. During the post-dosing 14-day period rats exhibited signs of excessive salivation, slight alopecia, lethargy and rough coat, and death occurred in 1/5 females on day 8. The LD_{50} was > 0.52 mg/L.

In another study, equivalent to an OECD 403 (Acute Inhalation Toxicity) study, Sprague-Dawley rats (3/sex/group) were exposed to 4.43 mg/L of TBOEP for 4 hours via whole body exposure (ECHA 2023 study report dated 1991). There were no deaths. Clinical signs included abdominal/urogenital staining, chromorhinorrhea, lachrymation, oral-nasal discharge, rales, squinting eyes and unkempt appearance. These signs resolved by day 8 post-exposure. All rats lost weight through day 2 except for a single female. The LD_{50} was > 4.42 mg/L.

Table 1: Acute Oral and Inhalation Studies for TBOEP

Study	Species	Sex/group	Dose (mg/kg bw)	Duration	NOAEL (mg/kg bw)	LOAEL (mg/kg/d)	Critical Effect	Reference
Acute (oral)	Rat (Sprague-Dawley)	M/F (5/sex/group)	2,000	Single	LD_{50} > 2000		↓Spontaneous activity, irregular respiration, stilted and uncoordinated gait.	ECHA 2023 study report dated 2000
Acute (oral)	Rat (Sprague-Dawley)	M/F (5/sex/group)	500, 5000, 10000, 12500, 15000	Single	LD_{50} = 13278 (M) LD_{50} = 5383 (F)		NOAEL @ 500. Mortality (1/5 F) at	ECHA 2023 study report dated 1979
Acute (oral)	Rat (Sprague-Dawley)	M/F (5/sex/group)	5000	Single	LD_{50} > 5000 (M) LD_{50} < 5000 (F) LD_{50} > 5000 (M/F)			
Acute (oral)	Rat	F & M (10/sex/group)	F: 1000 to 3200 M:1000 to 9000	Single		F: 2000 M: 6800	Degenerative nerve changes	Laham et al. 1985
Acute (inhalation)	Rat (Sprague-Dawley)	F & M (5/sex/group)	5.03 mg/L	4 hours	No LC50 <5.03 mg/L		9 died during study	Mobile Oil 1981
Acute (inhalation)	Rat (Wistar)	F & M (5/sex/group) (Nose only)	3.3, 3.4, 6.4 mg/L	4 hours	No LC50 >6.4 mg/L		Depressed/ irregular breathing, ↑ salivation, sneezing, unsteadiness, and tremor	ECHA 2023 Study report dated 1990

REPEAT DOSE

During an oral study in Sprague-Dawley rats (10/sex/dose), 0, 1, 10, 100 mg/kg/day of TBOEP was administered in a corn oil vehicle for 14 consecutive days (Kosta et al. 1989). All animals were examined daily for clinical signs and body weight. Blood was taken and analyzed for biochemical and hematological evaluation. Liver samples were taken for microsomal evaluation of aniline hydroxylase, aminopyrine demethylase and ethoxyresorufin deethylase activities. Tissues taken for histological examination included: brain, pituitary, liver, kidneys, spleen, heart, thyroid, parathyroid, thymus, lungs, skeletal muscle, adrenals, pancreas, small and large intestines, salivary gland, esophagus, and gastric fundus and cardi, testis, ovary, and bone marrow. Toxicological evaluation of all end points indicated a lack of effects at all dose levels.

Two 90-day oral studies have been conducted with TBOEP. In the first study, Sprague-Dawley rats (12/sex/dose) were administered 0.25 and 0.5 mL/kg of undiluted TBOEP (or 255 and 509 mg/kg/day, respectively) via gavage for 18 weeks, one dose/day for five days/week (Laham et al. 1985a). Daily clinical observations and weekly body weights were conducted throughout the experiment. At the end of the experiment, the various hematological parameters included: red and white blood cell counts, hematocrit, mean corpuscular volume, hemoglobin, and leukocyte differential count as well as calculated mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. The biochemical parameters included: acetylcholinesterase activity, bilirubin, blood urea nitrogen, cholesterol, glucose, inorganic phosphorus, total protein, triglycerides, uric acid, calcium, chloride, magnesium, potassium, sodium, amylase, cholinesterase, creatine phosphokinase, gamma-glutamyl transferase (GGT), glutamate-oxaloacetate transaminase (GOT), glutamate-pyruvate transaminase, alpha-hydroxybutyrate dehydrogenase, lactate dehydrogenase, alkaline phosphatase, glucose, blood urea nitrogen (BUN), total protein calcium, chloride, sodium, and potassium. At necropsy, a gross pathological examination was conducted on all surviving rats. Histopathology was conducted on the following tissues: adrenals, brain, heart, kidneys, liver, lungs, small and large intestines, stomach, testes/ovaries, and spleen.

Clinical observations included two female rats in the high-dose group with muscular weakness and ataxia which ended in four weeks. After seven weeks of exposure, rats from the other groups exhibited similar symptoms. The high-dose group also exhibited tremors, piloerection, lacrimation, and increased urination. In females, magnesium was increased in the low and high-dose groups. In the high-dose group only there were increases in amylase, GGT and GOT. In males, acetylcholinesterase (AChE) and uric acid decreased in the low and high-dose groups. In the high-dose male rat, bilirubin, and glutamate-pyruvate transaminase decreased, and BUN increased, in the low-dose male rat, glucose decreased.

In females, kidney weights, absolute and relative, increased in the high-dose group. Liver weights, absolute and relative, increased in both the low and high-dose groups. In males only, an increase in relative liver weight was observed. There was no histopathological correlate for either the liver or kidney. The only histopathological finding was in the heart of male test animals. Focal or multifocal areas of mononuclear cell infiltration, hemorrhage and/or myocardial fiber degeneration were found in three of six high-dose rats and two of six low-dose rats. No such damage was found in control animals. Another lesion consisting of focal or multifocal interstitial

fibrosis with or without macrophages containing hemosiderin pigment was found in two of the six high-dose and three of the six low-dose rats and in only one of the controls.

In another 90-day study (Tsuda et al. 1994), Wistar rats (15/sex/dose) were administered 0.0, 0.03, 0.3, or 3.0%) TBOEP in the diet. The doses were equivalent to 20, 200 and 2000 mg/kg/day in the male rat and 22, 220, and 2200 mg/kg/day in the female rat. In the high-dose group, a decrease in body weight gain was observed in males only. Serum acetylcholinesterase was decreased in both males and females at 0.3 and 3.0 %. Serum amylase levels were also increased in males in the 0.3 and 3.0% groups and in the 3.0% group in females. GGT was increased in the high-dose males and females. Both absolute and relative liver weights were increased in the high-dose males and females. However, only males showed a moderate periportal swelling upon histological examination. The authors concluded that the NOEAL was 0.03% based on decreased acetylcholinesterase activity and increased amylase activity.

In an eighteen-week subchronic dietary study Reyna et al. (1987) administered to Sprague-Dawley rats (20/sex/dose) 0, 300, 3000, and 10000 ppm for 18 weeks corresponding to 0, 17.3, 176, or 578 mg/kg/day for males and 0, 21, 209, pr 698 mkd for females. An interim and terminal sacrifice occurred at 9 and 18 weeks. Measurements included: body weight, feed consumption, clinical observations, hematology, clinical chemistry, absolute and relative organ weights, and gross and histopathology.

Results showed that no treatment related effects occurred on body weight and clinical observations. Feed consumption was lower in the exposure groups during the initial phase of the experiment but similar to controls at terminal sacrifice. Only a few hematological effects were treatment related. There was a decrease in white and red blood cells in the high-dose group at 8 weeks. Elevated platelets counts were observed in the high-dose group at both sampling periods and in the mid-dose group at the interim sampling period.

The biochemical parameters affected were an increase in cholesterol in the high-dose males at the terminal sacrifice and in the mid- and high dose females at the interim sacrifice. There was an increase in GGT in the high-dose group in both males and females at the interim and terminal sacrifice. A decrease in plasma cholinesterase was observed in males and females in high-dose groups at interim and terminal sacrifice and a decrease in RBC cholinesterase in females at the mid- and high-dose groups at terminal sacrifice.

The only change in organ weight was an increase in absolute and relative liver weights in the males and females in the high-dose group. This was accompanied by a periportal hepatocellular hypertrophy and vacuolization in mid- and high dose males.

Table 1: Repeat Dose Studies for TBOEP

Study	Species	Number of animals	Route	Duration	Dose	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical Effect	Reference
Repeat Dose	Sprague-Dawley	10/sex/dose	Oral	14 day	1, 10, and 100 mg/kg/day	100 (highest dose tested)		None	Komsta et al. 1986
Repeat Dose	Sprague-Dawley	12/sex/dose	Oral	90 day	225 and 509 mg/kg/day		225	Histologic lesions in the heart	Laham et al. 1985
Repeat Dose	Wistar	15/sex/dose	Oral (Dietary)	90 day	0.03, 0.3, 3.0% in feed (or 20, 200, and 2000 mg/kg/day in males)	20	200	Based on ↓ AChE and ↑ GGT	Tsuda 1994
Repeat dose	Sprague-Dawley	20/sex/dose	Oral (Dietary)	18 weeks	0, 3000, 3,000, and 30,000 ppm in the diet (or 16.4, 163, or 537 mg/kg/day in males)	17.3	173 mg/kg/day	Liver Histopathology periportal hepatocellular hypertrophy/ Periportal vacuolization.	Reyna and Thake, 1987
Developmental	Sprague-Dawley (CD®)	25 females/dose	Oral	GD 6-15	0, 250, 500, and 1500 mg/kg/day	Maternal 500 Teratogenic >1500	500	Reduced grooming, ataxia, reduced body weight gain and lethargy, and death	IRDC 1985
Reproductive	Sprague-Dawley	15/group	Oral	PND* 42 - 105	0, 20, and 200 mg/kg/day		20	Sperm morphology and histopathology	Pan et al. 2022

*PND: Post Natal Day

DEVELOPMENTAL

In a study equivalent to a guideline (OCED 414) prenatal developmental toxicity study, 25 mated female rats received TBOEP at 0, 250, 500, or 1500 mg/kg/day via gavage (vehicle: corn oil) on gestational day (GD) 6-15 (IRDC 1985). The rats were observed twice daily for mortality and overt changes in appearance and behavior prior to test article administration. Observations were made twice daily for mortality and once daily for clinical signs of toxicity after Day 6 of gestation. Body weights were recorded on gestations Days 0, 6, 9, 12, 16 and 20. uterine examinations were performed on all surviving females on gestation Day 20; fetuses were examined externally and processed for further teratologic evaluations.

TBOEP apparently had no effect, at any dose level, on uterine examinations including fetal resorptions and fetal viability, post-implantation losses and total implantations, and in the incidence of fetal malformations and developmental variations. According to the authors of the study, the NOAEL for teratological effects was greater than 1500 mg/kg/day and the NOEAL for maternal toxicity was 500 mg/kg/day based on reduced grooming, ataxia, reduced body weight gain and lethargy, and one recorded death at 1500 mg/kg/day. However, an earlier pilot study, with five rats per group exposed to 0, 25, 250, 500, 1000, or 2,000 mg/kg/day on GD 6-15, did note similar effects in the 500 mg/kg/day dose group.

Reproductive Studies

A non-guideline study was conducted to determine the effects of TBOEP on morphology of sperm and testicular histopathology in rats (Pan et al. 2022). In this study male Sprague-Dawley rats (15/group) were administered 0, 20 and 200 mg/kg/day of TBOEP in corn oil via gavage from postnatal day 42 to 105. The following measurements were conducted on sperm: count, motility, morphology, chromatin structure, membrane potential, and hydrogen peroxide levels as well as reproductive hormones and testicular histopathology.

Results indicate no statistically significant changes in body weight, absolute weight of testis, epididymis, cauda epididymis, and seminal vesicles. There was no difference in the average sperm count and motility between control and treated groups. However, the ratio of normal heads was lower in the high-dose group while flattened heads and bent tails were higher the high-dose group. There was no effect on reproductive hormones and no effect on membrane potential. Hydrogen peroxide levels were greater than controls in both dose groups and O_2 generation higher in the high-dose group. Histopathology revealed a widening of the lumen diameter and vacuolar degeneration occurred in the 20 mg/kg/day group increasing in severity in the high-dose group. An evaluation of seminiferous tubular structure indicated that the ratio of seminiferous tubular area and the ratio of seminiferous tubular diameter ($P<0.001$) was higher in the high-dose exposed groups. The ratio of seminiferous epithelial height and sum of epithelium seminiferous height ($P < 0.001$) were lower in the high-dose groups. The LOAEL was 20 mg/kg/day.

Mechanism of Action:

TBOEP is a neurotoxic compound. There are few studies involving a mechanism of action. Acute administration of TBOEP led to clinical signs including paralysis, increased secretions, ataxia, muscular flaccidity, and decreased reflexes. Laham et al. (1984, 1985b) noted a histopathological change in nerve structure and a decrease in nerve conduction velocity which has been

considered to be, in humans, an indicator of neurological deficits induced by organophosphate compounds. TBOEP was shown to be a weak inhibitor of carboxylesterase as demonstrated by Tsugoshi et al. (2020).

For chronic administration, the target organ is the liver. In a study by Kodama et al. (2021), TBOEP is a strong inducer of the pregnane X nuclear receptor. Inducers of PXR have been associated with liver hypertrophy and centrilobular hepatocellular hypertrophy. PXR plays a pivotal role in drug metabolism and protection of the body from environmental compounds by up-regulating drug-metabolizing enzymes and drug transporters.

TBOEP is neurotoxic at high doses; however, the mechanism underlying the reproductive effects has yet to be fully elucidated.

Critical Study and Effect:

The 18-week repeat dose oral study by Reyna and Thake (1987) served as the critical study from which to derive a point of departure. The critical effect was hepatocellular vacuolization. A benchmark dose (BMD) analysis was conducted on this endpoint and the $BMDL_{10}$ was determined to be 8.33 mg/kg/day (EPA 2020) (Appendix A). The next viable endpoint of liver toxicity was periportal hepatocyte hypertrophy. The BMD analysis calculated a higher $BMDL_{10}$ for hepatocyte hypertrophy The $BMDL_{10}$ for hepatocellular vacuolization was identified as the most sensitive critical effect; therefore, this $BMDL_{10}$ was used for the point of departure.

The average rat body weight during the study was 0.5 kg. Therefore, the human equivalent dose (HED) was calculated using the recommended dosimetric adjustment factor (DAF), which is derived from the ratio of the rat to human body weight to the ¼ power.

Where:

$DAF = (\text{animal body weight/human body weight})^{0.25}$

$DAF = (0.5\ \text{kg}/70\ \text{kg})^{0.25}$

$DAF = 0.29$

The HED is calculated as:

$BMDL_{10HED} = BMDL_{10} \times DAF$

$BMDL_{10HED} = 8.33\ \text{mg/kg} \times 0.29 = 2.42\ \text{mg/kg}.$

The duration of the study (i.e., 18 weeks) was of sufficient duration to designate the study as a subchronic study.

A Reference Dose (RfD) was calculated as follows:

$$RfD = POD/(UF1 \times UF2 \times UF3 \times UF4)$$

Where,

POD is point of departure (e.g., $BMDL_{10HED}$)
UF1 is 3 for interspecies extrapolation since a human equivalent dose was calculated for the toxicokinetic portion (1x) and the remaining toxicodynamic portion is 3x.
UF2 is 10 for Intraspecies due to lack of information lack of data to identify human sensitivity in a population.
UF3 is 10 for extrapolation for Subchronic to Chronic duration.
UF4 is 3 for database deficiency for possible effects in male rat reproductive system.

The RfD is calculated as:

RfD = (2.42 mg/kg/day)/(3 × 10 × 10 × 3)
RfD = 0.00242 mg/kg

Pursuant to rule 232(1)(b), the ITSL is calculated from an RfD as follows:

ITSL = RfD × 70 kg/20 m^3 × unit conversion
ITSL = 0.00242 mg/kg × 3.5 kg/m^3 × 1000µg/1mg
ITSL = 8.47 µg/m^3; rounded to 1 significant figure is 8 µg/m^3.

Pursuant to Rule 229, the averaging time is annual.

The ITSL for Tris (2-butoxyethyl) phosphate is 8 µg/m^3, with annual averaging time.

References:

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BH/lb

Appendix A: BMD for Hepatocellular Vacuolization in Rats (Reyna and Thake 1987)

Dichotomous Results

BMDS 3.2

Return to Summary

Scroll right to see BMD Cumulative Distribution Function (CDF) table →
Scroll down to see Dose Response Plot ↓

User Input

Info	
Model	frequentist Log-Logistic v1.1
Dataset Name	DataSet Name1
User notes	[Add user notes here]
Dose-Response Model	P[dose] = g+(1-g)/[1+exp(-a-b*Log(dose))]

Model Options	
Risk Type	Extra Risk
BMR	0.1
Confidence Level	0.95
Background	Estimated

Model Data	
Dependent Variable	[Custom]
Independent Variable	[Custom]
Total # of Observations	4

Model Results

Benchmark Dose	
BMD	20.59671398
BMDL	8.332928668
BMDU	104.9401669
AIC	46.70794418
P-value	0.764339323
D.O.F.	2
Chi^2	0.537486897

Model Parameters	
# of Parameters	3
Variable	Estimate
g	0.113554031
a	-5.222356125
b	Bounded

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.113554031	1.135540314	1	10	-0.1350956
16.4	0.185604798	1.856047981	2	10	0.1170862
163	0.528315682	5.283156822	6	10	0.4541002
537	0.772525479	7.725254789	7	10	-0.5471014

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-21.09361366	4	-	-	NA
Fitted Model	-21.35397209	2	0.52071686	2	0.7707753
Reduced Model	-26.92046668	1	11.653706	3	0.0086686