Triethylphosphate

Document History
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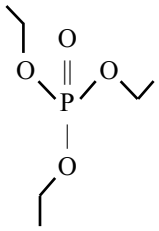
I. IDENTIFICATION

Chemical Name: Triethylphosphate
Synonyms: Phosphoric acid, triethyl ester; TEP
CAS Number: 78-40-0
Molecular Formula: $(C_2H_5O)_3PO$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–5]

Physical State: clear, colorless liquid
Odor Description and Threshold: mild, cider-like
Molecular Weight: 182.16
Conversion Factors: 1 ppm = 7.45 mg/m³; 1 mg/m³ = 0.134 ppm
Boiling Point: 209°C (408°F)
Vapor Pressure: 0.39 mm Hg at 25°C (77°F) (OECD, 2001)
Saturated Vapor Concentration: 513 ppm at 25°C (77°F)
Flammability Limits: Lower: 1.7 Volume% at 139°C (282°F)
Upper: 10 Volume% at 163°C (325°F)
Flash Point: 99°C (210°F); Pensky-Martens Closed Cup
Specific Gravity: 1.067–1.072 at 15.6°C (60°F)
Solubility: miscible with water, soluble in alcohol and ether
pKa: unavailable
Stability Stable
Reactivity and Incompatibilities: reacts with strong oxidizing agents
LogPow: 1.11

III. USES

Used as a catalyst in the manufacture of ketene, as a flame retardant in unsaturated polyester resins, plasticizer and carrier in the plastics industry. Also used in lesser volumes as a solvent and an intermediate in the manufacture of pharmaceuticals, pesticides and lacquers.[2,5]

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. *Oral Toxicity*

Rat (male and female) LD_{50} = 1310 mg/kg. An anesthetic-like, central nervous system depression producing rapid prostration and vasodilatation was observed.[6]

Rat, mouse, guinea pig LD_{50} = 1600 mg/kg; reported as the average for all species tested.[7]

2. *Eye Irritation*

Moderately irritating to rabbit eyes[8]

Undiluted material caused moderate irritation in rabbits; prompt irrigation with water was palliative.[6]

3. *Skin Absorption*

Guinea Pig LD_{50} >20 mL/kg (>21,400 mg/kg)[6]

LD_{50} >20,000 mg/kg (species not specified)[7]

4. *Skin Irritation*

Rabbit: non-irritating in a 4-hour occluded patch application.[8]

Guinea Pig: slight in a 24-hr. occluded patch application; repeated application (10 doses) caused very slight exacerbation of the initial response.[6]

5. *Skin Sensitization*

Guinea Pig: no sensitization was observed in a group of 10 animals. The test method

involved intradermal injection (induction) and topical application (challenge) using Freund's adjuvant.[6]

6. Inhalation Toxicity

Rat LC_{50} >8817 mg/m^3 (4 hour exposure)[9]

Rat LC_{50} >2050 mg/m^3 (6 hour exposure; approximately 28% of aerosol was respirable); unsteadiness of gait and lethargy resolved after 24 hrs. No additional information regarding atmosphere generation and analysis is reported.[6]

All rats died within 48 hours of a 6-hour exposure to either 185 mg/L (185,000 mg/m^3) or 209.1 mg/L (209,100 mg/m^3) triethyl phosphate in two whole-body inhalation studies; exposure concentrations were derived nominally. The exposure atmospheres were generated by passing air through a bubble bottle of the test material, heated to 150°C.[6,10] Clinical signs included gasping and weakness.

7. Other

a. Intraperitoneal

Rat LD_{50} = 950 mg/kg[11]

LD_{50} ~ 800 mg/kg; reported as the average for rats, mice and guinea pigs[7]

b. Intravenous

Mouse LD_{50} = 485 mg/kg[12]

B. Subacute Toxicity

Groups of five rats were exposed via whole-body inhalation to combined vapor and aerosol concentrations of 0, 366, or 1786 mg/m^3 triethyl phosphate 5 hours/day for 12 days over a 16-day period.[6] Approximately 35% of the aerosol atmosphere was respirable; approximate respirable concentrations were 118 mg/m^3 and 625 mg/m^3, respectively. Exposure concentrations were derived analytically. At the high concentration, lethargy, unsteadiness of gait and porphyrin-like nasal discharge occurred daily, but resolved prior to subsequent exposure. Weight gain was normal in all animals. Hematology and clinical chemistry measurements were within normal ranges. No treatment-related changes were noted in organ weights, gross pathology or histopathology. No other details are available. This study established a NOEL of 366 mg/m^3 as a combined vapor and aerosol.

Groups of Wistar rats were administered triethyl phosphate by gavage at 1, 10, 100 or 1000 mg/kg/day for 2 weeks or 0, 10, 100 and 1000 mg/kg/day for 4 weeks.[13,14] The study was conducted under Good Laboratory Practice guidelines and Directive 84/449/EEC "Subacute toxicity (oral)" methods. Following two weeks of treatment, slight decreases in body weight gain and feed consumption were noted at the high dose level as well as an increase in relative and absolute liver weights. There was no effect on histopathology. All other treatment groups were similar to control. Following four weeks of treatment, an increase in metabolic activity in the liver was noted at the high dose; no histopathological correlates were reported. The NOEL in both studies was 100 mg/kg/day and the NOAEL in the 4-week study was 1000 mg/kg/day.

C. Subchronic Toxicity

A group of 6 male JCL-Wistar rats were fed a diet containing 0.5% triethyl phosphate for 9 weeks; a group of 18 rats were utilized as controls receiving 0% test material in the diet.[15] The approximate doses received were not reported. Absolute and relative liver and spleen weights and absolute testes and kidney weights were significantly increased from the control ($P<0.05$). Hematology determinations, including leukocyte and erythrocyte counts, hemoglobin concentration, hematocrit and mean corpuscular volume were similar to the control. Prothrombin time was significantly increased ($P<0.05$). Clinical chemistry analyses including total protein, urea nitrogen, cholesterol, triglycerides, bile acids, potassium, sodium, GOT, GPT and AIP, and ChE activities were similar to the control group. Absolute and relative kidney weights were increased as compared to the control. The results of histological examination were not reported.

Groups of 5 Sprague-Dawley rats of each sex were fed diets containing 0%, 0.1%, 0.5%, 1.0%, 5.0%, or 10.0% of triethyl phosphate for 120 or 150 days in males and females, respectively.[16] The doses received were approximately 67, 335, 670, 3350, and 6700 mg/kg-day, respectively. After 92 days of treatment, a reproductive study was conducted (see Section E.) at the completion of which the males were autopsied at about Day 120 and the females at approximately Day 150. Feed consumption and mean body weights were significantly decreased ($P<0.01$) at the 10% level, with 4/5 females and 1/5 males dying before the end of the treatment period. Mean feed consumption was comparable to the control for all other dose levels. Mean body weights were significantly decreased in males ($P < 0.01$) and females ($P<0.05$) at the 5% level at the compared to the control and/or lower treatment groups. No significant differences in body weight occurred in either sex at a dose levels of 1.0% and

below. Absolute liver weights were significantly increased in a dose-related manner in males at 0.1% and above and in females at 5% only. Hepatocellular hypertrophy, minor bile duct hyperplasia and retention of bile were observed in both sexes at the 5% dose level and in females at the 1% level. The mean erythrocyte count was statistically significantly decreased in males at the 5% dose level at 100 days. No significant hematologic differences were noted in females at any dose level. Blood cholinesterase activity was similar to controls in males at the 5 and 10% dose levels and in females at the 5% dose level while slightly elevated levels were noted in both sexes at the 0.5% and 1.0% dose levels and in females at the 0.1% level at 50 days. At 100 days, enzyme activity in males had decreased in all dose levels; the decrease in the 10% dose group was statistically significant as compared to the controls and other treated groups ($P<0.01$). A decreased activity in blood cholinesterase was also noted in males at autopsy. Brain cholinesterase was lowest in both sexes at 5%, but the difference from controls was statistically significant ($P<0.01$) in males only. The NOAEL was 0.1% (67 mg/kg/day) in males and 0.5% (335 mg/kg/day) in females. The effect seen at this dose level was increased liver weight in the absence of a histopathologic correlate, which is considered an adaptive, non-adverse effect.

D. Chronic Toxicity and Carcinogenicity

Not available

E. Developmental and Reproductive Toxicity

In a one-generation study, groups of 5 Sprague-Dawley female rats were mated to males following a 92-day study in which both sexes were fed diets containing 0%, 0.1%, 0.5%, 1.0%, or 5.0%, of triethyl phosphate.[16] (For details see Section C). The doses received were approximately 67, 335, 670, and 3350 mg/kg/day, respectively. Additional groups of animals were fed a dietary concentration of 10% triethyl phosphate (approximately 6700 mg/kg/day), but mating attempts in this group were unsuccessful due to severely depressed growth and development. No litters were born at the 5.0% dose level. The number of litters was similar to the control at dose levels of 1.0% and below. The mean litter size at birth was statistically significantly decreased at the 1.0% dose level ($P<0.001$). Litter size was similar to the control at both lower concentrations. Mean pup body weights, adjusted to account for the influence of decreased litter size at 5.0%, were slightly decreased at all exposure groups when compared to the control; statistical significance was not reported. The NOEL for reproductive toxicity was 335 mg/kg/day.

In a developmental study, groups of 25 pregnant Wistar rats received daily doses of 25, 125, or 625 mg/kg/day triethyl phosphate by gavage from Gestation Day 6–15.[17] Evidence of maternal toxicity at the high dose level included bloody mouth, staggering gait, ventral posture, and reductions in body weight gain, food intake and feces excretion. No evidence of developmental toxicity was reported at any dose level. The NOAEL for maternal toxicity was 125 mg/kg and for developmental toxicity was 625 mg/kg.

Rats (1 or 2 per dose level) were administered intraperitoneal daily injections of 0, 50, 100, 200, 400, or 800 mg/kg triethyl phosphate in propylene glycol, five days a week for a period of 5 weeks.[6,18] The rat administered 800 mg/kg died on Study Day 9; no mortality occurred at lower dose levels. Surviving rats showed a mainly dose-dependent decrease in body weight (statistical significance not reported). Clinical signs following injection included drowsiness. A few peritoneal adhesions were noted at necropsy.

F. Genotoxicity

Triethyl phosphate was not mutagenic in the Ames *Salmonella typhimurium* assay using strains TA 98, 100, 1535, 1537, and 1538 with and without S-9 metabolic activation.[19,20] Negative results were also obtained in the Ames *Salmonella typhimurium* assay in strains TA102, and TA2638 without activation and in *E. coli* strains Wps and WP2 UVRA without activation.[21] Earlier studies reported positive results in the Ames *Salmonella typhimurium* assay using strain hisC117 without metabolic activation, bacteriophage T4B of *E. coli* and *P. aeruginosa* both without activation.[22,23]

Triethyl phosphate was nongenotoxic in an *in vitro* cell transformation assay with Balb/c 3T3 clone A31-1-13-1.2 cells exposed to dose levels of between 0.3 µL/mL and 4.0 µL/mL for 72 hours in complete medium.[10] Negative results were also obtained in a HGPRT assay with V79 cells with and without metabolic activation.[24]

In a Dominant Lethal Assay, no differences from the control were noted in a group of 10 mice administered 660 mg/kg triethyl phosphate via intraperitoneal injection.[25]

Triethyl phosphate was positive in an eye mosaic assay in *Drosophila*.[26] Triethyl phosphate was positive in the *Drosophila* wing-spot test for small single spots and ambiguous for large single and twin spots.[27]

The frequency of chromosome aberrations did not

increase in male mice administered a single intraperitoneal dose of 1000 mg/kg triethyl phosphate.[28] Chromosome damage was not detected in male Q mice 10–15 days following a single intraperitoneal injection of 300 mg/kg triethyl phosphate.[29]

The weight of evidence suggests that triethyl phosphate is not mutagenic.

G. Metabolism and Pharmacokinetics

Following a single dose of 100 or 1000 mg/kg ^{32}P-triethyl phosphate administered either orally or by intraperitoneal injection, 90% was excreted as diethyl phosphate in the urine within 16 hours.[30] Recovery of the administered dose was nearly complete within 96 hours.

H. Other

Groups of five rats received daily intraperitoneal injections of a 50% solution of triethyl phosphate in propylene glycol at doses ranging from 50 to 800 mg/kg for 37 days.[6,18] No deaths occurred at doses up to and including 400 mg/kg/day. Deaths at the 800 mg/kg dose level occurred on the ninth day of treatment. Control data are not reported.

The apparent *in vitro* anticholinesterase activity of triethyl phosphate reported in pre-1970 studies was found to be due to the presence of the impurity tetraethyl pyrophosphate.[31]

V. HUMAN USE AND EXPERIENCE

One company manufactures triethyl phosphate in the United States. Workroom air concentrations during the manufacture and bottling of triethyl phosphate have been <0.5 mg/m^3.[5] Manufacturing is typically conducted in closed systems.

Negative skin patch test results for triethyl phosphate were reported in a 37-year-old patient found to be allergic to 2,2,2,4-tetrachloroacetophenone while also handling triethyl phosphate.[32]

VI. RATIONALE

Triethyl phosphate is of low to moderate acute toxicity orally and low acute toxicity dermally and by inhalation. It is a moderate eye and slight skin irritant. The available data suggest that it is not a skin sensitizer. The NOEL for signs of central nervous system depression and possible irritation of the upper respiratory tract in rats exposed by inhalation to a combined vapor and aerosol concentration of triethyl phosphate is approximately 366 mg/m^3. When administered orally in repeated-dose studies, triethyl phosphate causes liver effects in rats; the NOAEL is 67 mg/kg/day in males. The available data suggest that triethyl phosphate is not mutagenic nor a developmental toxicant. Reproductive toxicity is only seen at high oral doses that cause frank toxicity and/or lethality in the parental animals.

Occupational exposure to triethyl phosphate would most likely occur by inhalation of vapor and aerosols and by dermal contact. The basis for establishing the OEL is avoidance of the liver effects seen in subchronic animal studies. The irritation threshold data upon which to base a STEL are not available. Triethyl phosphate does not meet the criteria for either a skin or sensitization notation.

VII. RECOMMENDED OEL

7.45 mg/m^3 (1 ppm) as an 8-hour time weighted average

VIII. REFERENCES

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IX. ADDITIONAL REFERENCES

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