MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Triisobutyl Phosphate [CAS# 126-71-6]

FROM: Doreen Lehner

SUBJECT: Screening Level Determination for Triisobutyl phosphate [CAS# 126-71-6]

DATE: January 3, 2014

The initial threshold screening level (ITSL) for triisobutyl phosphate [CAS# 126-71-6] is 22 $\mu g/m^3$ based on an 8-hour averaging time. This memo describes the basis and derivation of the ITSL.

Triisobutyl phosphate (TiBP) [CAS# 126-71-6] (also known as phosphoric acid tri-iso-butyl ester) is a clear, colorless liquid with a characteristic odor. It is a very strong, polar solvent and is used: as an antifoam in various aqueous systems to destroy and inhibit foam; in the production of solutions of synthetic resins and natural rubber; in cellulose based plastics; as a pasting agent for pigment pastes; in the manufacture of aircraft hydraulic fluids; as a wetting agent; and in adhesives.

The following references or databases were searched to identify data to determine the screening level: 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), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) - Online (searched 12/19/2013), National Library of Medicine, and the EPA Aggregated Computational Toxicology Resource (ACToR) Database. The EPA has not established a reference concentration or a reference dose for TiBP. TiBP and tributyl phosphate are structural isomers, both having a molecular weight of 266.32. ACGIH has not established a TLV for TiBP, but has a TLV for tributyl phosphate (TBP). Figures 1 and 2 below show the comparison of the structures of TiBP and TBP.

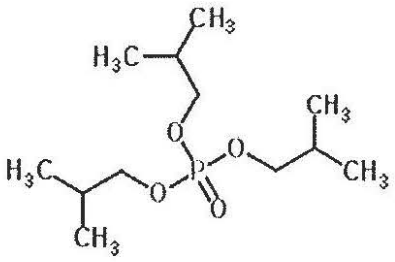


Figure 1. Structure of TiBP.

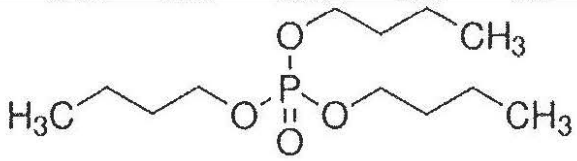
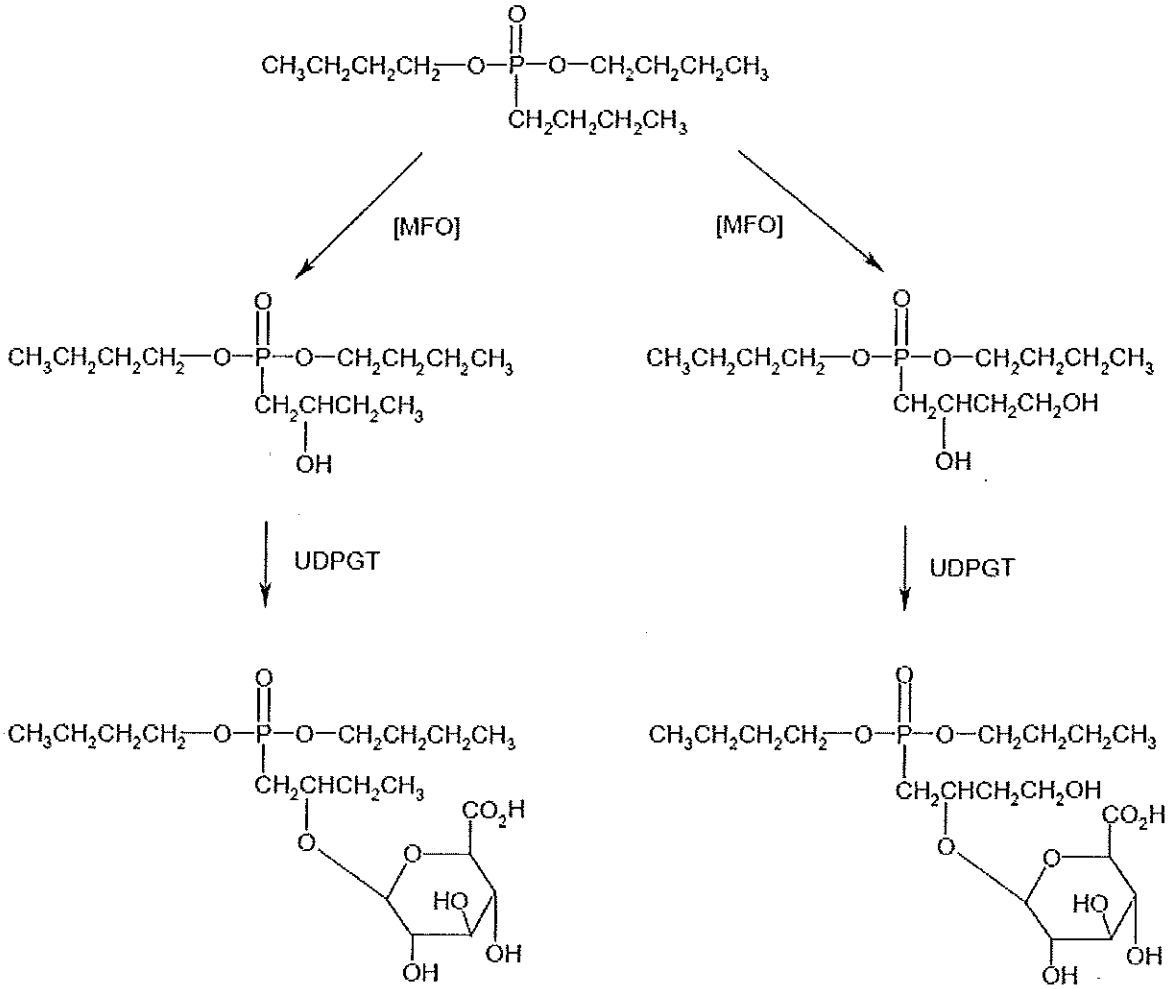


Figure 2. Structure of TBP.

Both TiBP and TBP are alkyl esters of phosphoric acid and are slightly soluble in water with greater solubility in organic solvents (EPA, 2009). In general phosphoric acid esters are metabolized via dealkylation. The metabolism of TBP occurs in the liver firstly through mixed function oxidase, producing dibutyl hydrogen phosphate, butyl dihydrogen phosphate, and butyl bis(3-hydroxybutyl) phosphate (see figure 3). These TBP metabolites then interact with uridine diphosphate glucuronyl transferases (UDPGT) and the resulting conjugates are eliminated in the urine. As TBP and TiBP are structural isomers it may be assumed that TiBP would undergo similar metabolism in the liver. The metabolic pathways below are for Yucatan® Minipigs; pig liver metabolism is much more similar to human metabolism than is the rat or mouse. Therefore, this is the most likely metabolic pathway for TiBP in humans.

Figure 3. Proposed Metabolic Pathway of TBP in Yucatan® Minipigs.



MFO = mixed function oxidase; TnBP = tributyl phosphate; UDPGT = uridine diphosphate glucuronyl transferases

Source: SOCMA 1994.

There are fewer studies available for TiBP. One of the studies found that a rat LD_{50} study via gavage was 3,200 mg/kg for TiBP. This study also found that the rats exhibited ataxia, jerking, and white foam visible around the mouth. A rat LC_{50} of 122 ppm (1,328 mg/m^3 using the ppm to mg/m^3 conversion equation in Appendix A) for TiBP was also determined (Eastman Kodak Co., 1990).

In a 13-week oral feeding study on male and female Sprague-Dawley rats performed by Naylor and Ribelin (1990), 30 rats/sex for the control and highest TiBP dose group and 10 rats/sex for the remaining TiBP dosage levels were used. Overall averages for consumption of TiBP converted to mg/kg body weight/day were approximately 0, 13.9, 68.4, and 346.1 in males and 0, 16.8, 84.3, and 403.9 in females for the control, T-1, T-2, and T-3 levels respectively. The study authors determined the no-observed-effect-level (NOEL) to be 68.4 mg/kg/day in male rats and 84.3 in female rats. "Decreased neutrophil count and increased MCH and MCHC were reported in males rats treated with dietary doses of 346 mg TiBP/kg day for 13 weeks...clinical chemistry tests at termination showed a significant increase in serum cholesterol in males dosed with 346 mg/kg/day. The NOAEL was 68 mg/kg/day" (ATSDR, 2012). This was the only longer term study performed on TiBP. The Naylor and Ribelin (1990) documents are barely legible, and ATSDR (2012) raised several issues regarding the study protocols and reporting. For example, only 10 of the 30 rats in the control and high dose groups examined at necropsy, and the only tissue taken from these groups was the urinary bladder. It was unclear how the rats that were necropsied in these groups were chosen. The study lists all the tissues taken from the other groups. These questions may have been answered in the Naylor and Ribelin (1990) study, but due to the poor quality of the documents, this reviewer found the tables nearly impossible to read.

TiBP and TBP are structural isomers and the proposed metabolic pathways would most likely be similar as well. There is much more reliable data available on TBP. TBP has an LD_{50} of 3,000 mg/kg in the rat and a 6-hour LC_{50} in rats of 123 ppm (ACGIH, 2001) which is similar to what is reported for TiBP.

Subchronic oral bioassays suggest similarities between TBP and TiBP dose-response relationships, although it is unclear if there was concordance of the target organ and critical effects, due to inadequate reporting and legibility of Naylor and Ribelin (1990). "In [an] 18-week study, Laham et al., (1985) administered TBP by gavage once a day, 5 days/week to Sprague-Dawley rats. Low-dose animals received 200 mg/kg/day throughout the study, high-dose animals received 300 mg/kg/day for the first 6 weeks and 350 mg/kg/day for the remaining 12 weeks. Histopathological examination revealed that all treated animals developed diffuse hyperplasia of the urinary bladder epithelium" (ACGIH, 2001). It is interesting that in the 90-day feeding study, Naylor and Ribelin (1990) also collected the urinary bladder for histological examination; however, findings were not legibly reported.

The similarities in the LD_{50}, LC_{50}, and subchronic study allows for greater confidence in using the same ITSL basis for TBP and TiBP. TBP has an ITSL of 22 $\mu g/m^3$ based on an 8-hour averaging time based on the ACGIH TLV-TWA of 2.2 mg/m^3 (ACGIH, 2001), and an uncertainty factor of 100 as per Rule 232(1)(c). An ITSL of 22 $\mu g/m^3$ would be health protective for TiBP and is chosen as the most appropriate approach from among the options shown below.

The calculation of potential ITSLs based on the information available for TiBP (see Appendix A for details).

Available benchmark type	Value	Candidate ITSL ($\mu g/m^3$)	Candidate ITSL Averaging Time
TiBP 90-Day Rat NOAEL	68 mg/kg/day	170	24-Hour
TiBP Rat oral LD_{50}	3,200 mg/kg/day	10	Annual
TiBP Rat LC_{50}	122 ppm (1,328 mg/m^3)	27	Annual
TBP ACGIH TLV-TWA	2.2 mg/m^3	22	8-Hour

References:

ACGIH. 2001. Tributyl Phosphate. TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices. ACGIH Worldwide Signature Publications.

ATSDR. September 2012. Toxicological Profile for Phosphate Ester Flame Retardants. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Available online at: http://www.atsdr.cdc.gov/toxprofiles/tp202.pdf

Eastman Kodak Co. 1990. Letter from Eastman Kodak Company to US EPA submitting enclosed health and safety studies on triisobutyl phosphate with attachments. Eastman Kodak Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0528335. EPA86-910000041.

EPA. 1988. Recommendation for and documentation of biological values for use in risk assessment. PB 88-179874.

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Laham S., Long G., Broxup B. 1985. Induction of Urinary Bladder Hyperplasia in Sprague-Dawley Rats Orally Administered Tri-n-butyl Phosphate. Arch. Environ. Health 40:301-306.

Naylor and Ribelin. 1990. 90-Day study of triisobutyl phosphate (TiBP) administered in feed to albino rats. Monsanto Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0534406. EPA86-920000201.

Reference Dose (RfD): Description and Use in Health Risk Assessments. Last updated September 26, 2012. Available online at: http://www.epa.gov/ncea/iris/rfd.htm

SOCMA. 1994. Metabolism of tributyl phosphate in Yucatan minipigs following intravenous and dermal exposure (part II), with cover letter dated 05/16/1994. Synthetic Organic Chemical Manufacturers Association, Inc. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA 86-940000966. OTS0557376.

DL:lh

Appendix A:

Candidate ITSL calculation based on the TiBP 90-Day Rat Feeding Study by Naylor and Ribelin (1990).

90-Day feeding study in Sprague-Dawley rats, male rat NOAEL of 68mg/kg/day based on hematological effects. According to Rule 232(1)(b), an ITSL can be calculated using an RfD using the equation below:

$$ITSL = oral\ RfD \times \frac{70\ kg}{20\ m^3}$$

A 13-week study is the minimum study length needed to develop an RfD. The EPA uses the following equation to determine an RfD from a NOAEL.

$$RfD = \frac{NOAEL}{(UF \times MF)} = \frac{NOAEL}{(UF_H \times UF_A \times UF_S \times MF)}$$

UF: the uncertainty factor used to account for differences between the available data and the possible effects in the human population, usually expressed as factors of 10.

UF_H = uncertainty factor used to account for the variation in sensitivity among individuals of the human population.

UF_A = uncertainty factor used to account for the extrapolation from animal data to humans.

UF_S = uncertainty factor used to account for the extrapolation from less than chronic NOAELs to chronic NOAELs.

MF: the modifying factor which is an additional scientific uncertainty of the study not accounted for in the uncertainty factor, usually expressed as a value greater than 0 and less than or equal to 10.

Before using the above equation, we need to calculate an adjusted average daily dose using the equation below:

$$NOAEL_{adj} = NOAEL \times \frac{dosage\ days}{7\ days}$$

$$NOAEL_{adj} = 68\ {}^{mg}/_{kg/day} \times \frac{5\ days}{7\ days} = 48.5714\ {}^{mg}/_{kg/day}$$

Using the adjusted average daily dose ($NOAEL_{adj}$) and using 10 for the above uncertainty factors in EPAs RfD equation above:

$$RfD = \frac{NOAEL_{adj}}{(UF_H \times UF_A \times UF_S \times MF)} = \frac{48.5714\ {}^{mg}/_{kg/day}}{(10 \times 10 \times 10 \times 1)} = 0.04857\ {}^{mg}/_{kg/day}$$

Inserting the RfD above into the ITSL equation gives:

$$Candidate\ ITSL = Oral\ RfD \times \frac{70\ kg}{20\ m^3} = 0.04857\ {}^{mg}/_{kg/day} \times \frac{70\ kg}{20\ m^3} = 0.1700\ {}^{mg}/_{m^3}$$

$$Candidate\ ITSL = 170\ {}^{\mu g}/_{m^3}$$

Candidate ITSL calculation based on the rat oral LD_{50} for TiBP (Eastman Kodak Co., 1990).

Rat oral LD_{50} of 3,200 mg/kg/day via gavage.

Using Rule 232(1)(h) equation below:

$$ITSL = \frac{1}{500} \times \frac{1}{40} \times \frac{1}{100} \times \frac{LD_{50}\left({}^{mg}/_{kg}\right) \times W_A}{0.167 \times I_A}$$

Where W_A = the body weight of the experimental animal in kilograms (kg).
I_A = the daily inhalation rate of the experimental animal in m^3/day.

W_A for an unknown species and unknown gender rat is 0.395 kg.
The daily inhalation rate (I_A) of a laboratory rat is determined by an equation from the EPA (1988) below:

$$I_A = 0.80 \times W^{0.8206} = 0.80 \times 0.395\ kg^{0.8206} = 0.3733\ {}^{m^3}/_{day}$$

Using the values for W_A and I_A, the ITSL can be calculated using the above equation:

$$Candidate\ ITSL = \frac{1}{500} \times \frac{1}{40} \times \frac{1}{100} \times \frac{3{,}200\ {}^{mg}/_{kg} \times 0.395\ kg}{0.167 \times 0.3733\ {}^{m^3}/_{day}} = 0.01014\ {}^{mg}/_{m^3}$$

$$Candidate\ ITSL = 10\ {}^{\mu g}/_{m^3}$$

Candidate ITSL calculation based on the rat oral LC_{50} for TiBP (Eastman Kodak Co., 1990).

A 6 hour rat LC_{50} of 122 ppm.

Using Rule 232(1)(f) an ITSL can be calculated from an LC_{50} of 6 hours or more duration using the following equation:

$$ITSL = \frac{LC_{50}}{500 \times 100}$$

Before an ITSL can be calculated from this LC_{50}, the LC_{50} must be converted from ppm to mg/m^3. This can be accomplished using the following equation:

$${}^{mg}/_{m^3} = \frac{ppm \times MW\ ({}^{g}/_{mol})}{24.45}$$

The molecular weight of TiBP is 266.32 g/mol. Inserting this value and the rat LC_{50} in ppm into the above equation gives:

$$^{mg}/_{m^3} = \frac{122\ ppm\ \times 266.32\ ^{g}/_{mol}}{24.45} = 1{,}328.8769\ ^{mg}/_{m^3}$$

Using ITSL equation with the converted LC_{50} above gives:

$$Candidate\ ITSL = \frac{1{,}328.8769\ ^{mg}/_{m^3}}{500\ \times 100} = 0.02658\ ^{mg}/_{m^3}$$
$$Candidate\ ITSL = 27\ ^{\mu g}/_{m^3}$$