CPSC Staff Statement on University of Cincinnati Report "Toxicity Review for 2,2,4-trimethyl-1,3-pentanediol-diisobutyrate (TPIB)"[1]

October 2018

The U.S. Consumer Product Safety Commission (CPSC) contracted with the University of Cincinnati to conduct toxicology assessments for six dialkyl o-phthalate (o-DAP) substitutes: acetyl tri-n-butyl citrate (ATBC); bis(2-ethylhexyl) adipate (DEHA); di-2-ethylhexyl terephthalate (DEHT); 1,2-cyclohexanedicarboxylic acid, dinonyl ester, branched and linear (DINX); trioctyltrimellitate (TOTM); and 2,2,4-trimethyl-1,3-pentanediol-diisobutyrate (TPIB). The reports will be used to inform staff's assessment of products that may contain these compounds and is the first step in the risk assessment process.

CPSC staff assesses a product's potential health effects to consumers under the Federal Hazardous Substances Act (FHSA). The FHSA is risk-based. To be considered a "hazardous substance" under the FHSA, a consumer product must satisfy a two-part definition. First, it must be "toxic" under the FHSA, or present one of the other hazards enumerated in the statute. Second, it must have the potential to cause "substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use." Therefore, exposure and risk must be considered in addition to toxicity when assessing potential hazards of products under the FHSA.

The first step in the risk assessment process is hazard identification, which consists of a review of the available toxicity data for the chemical. If it is concluded that a substance may be "toxic", then a quantitative assessment of exposure and risk is performed to evaluate whether a specified product may be considered a "hazardous substance".

The toxicity review for TPIB follows.

[1] This statement was prepared by the CPSC staff, and the attached report was produced by the University of Cincinnati for CPSC staff. The statement and report have not been reviewed or approved by, and do not necessarily represent the views of, the Commission.

TOXICITY REVIEW FOR 2,2,4-TRIMETHYL-1,3-PENTANEDIOL-DIISOBUTYRATE (TPIB)

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Contents

1 Introduction

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with 2,2,4-trimethyl-1,3-pentanediol-diisobutyrate (TXIB®, TPIB[1]). It is an update of a previous CPSC report (Patton, 2010).

Literature searches for physico-chemical, toxicological, exposure, and risk information were performed in November 2017 using the CAS number and synonyms (see Appendix 1 for the full list of search terms), and using the following databases:

- EPA SRS
- PUBMED
- RTECS
- TSCATS (included in TOXLINE)
- TOXNET databases, including
    - TOXLINE
    - CCRIS
    - DART/ETIC
    - GENE-TOX
    - HSDB

Searches of the PubMed and Toxline databases covered from all dates to the date of the search (November, 2017). However, studies dated up to 2007 were screened out of the library during the screening process using the Endnote files, as the current report supplements and updates a staff report prepared in 2010 (Patton, 2010). Other databases and websites were also used to identify additional key information, particularly authoritative reviews. Searches for authoritative reviews addressing general toxicity and physicochemical information were conducted with the following databases using the CAS number for TPIB and synonyms. These sites included:

- ANSES Information on Chemicals (https://www.anses.fr/en)
- ChemIDPlus (https://chem.nlm.nih.gov/chemidplus/)
- ECHA Information on Chemicals (https://echa.europa.eu/information-on-chemicals)
- EFSA (https://www.efsa.europa.eu/)
- EPA (https://www.epa.gov/)
- EPA chemistry dashboard (https://comptox.epa.gov/dashboard)
- EPA IRIS (https://www.epa.gov/iris)
- FDA (https://www.fda.gov/)

[1] TXIB® is a registered trademark of Eastman Chemical Co. Although TXIB® is the commonly used abbreviation, the alternate abbreviation TPIB is used here to represent the generic chemical, even in studies that used the term TXIB.

- Google
- Health Canada (https://www.canada.ca/en/health-canada.html)
- IARC (https://www.iarc.fr/)
- INCHEM (http://www.inchem.org/)
- JEFCA (http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/)
- NICNAS (https://www.nicnas.gov.au/)
- NTP (https://ntp.niehs.nih.gov/)
- OECD (http://www.oecd.org/)
- WHO (http://www.who.int/en/)

Two new TPIB toxicology studies, a subchronic feeding study in rats (Anonymous, 2005, as cited by ECHA, 2011a and Eastman Chemical, 2007), and a developmental toxicity study in rats (Eastman Chemical, 2014; ECHA, 2011a) were identified by literature searches. New studies that were found also included studies in toxicokinetics and exposure, as well as several reviews. Several of the key toxicity studies were unpublished and not available as the primary studies. Therefore, these studies were evaluated based on authoritative reviews and data compilations, including JMHLW (1993), OECD (1995), Eastman Chemical (2007), and EFSA (2006).

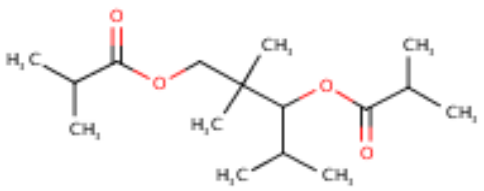
Several additional review publications have been published since the previous CPSC assessment (Patton, 2010). Reviews and posted data from ECHA (2011a, 2011b) provided useful new information.

2 Physico-Chemical Characteristics

Some physical and chemical properties of TPIB are summarized below in Table 1.

Table 1: Physicochemical Properties and Identification Information for 2,2,4-Trimethyl-1,3-pentanediol-Diisobutyrate

Chemical Name	2,2,4-Trimethyl-1,3-pentanediol-diisobutyrate
Synonyms	2,2,4-Trimethylpentanediol-1,3-diisobutyrate; TMPD-DIB; Isobutyric acid, 1-isopropyl-2,2-dimethyltrimethylene ester; Kodaflex TPIB; TPIB; 1,3-Pentanediol, 2,2,4-trimethyl-, diisobutyrate (ester); 1-Isopropyl-2,2-dimethyltrimethylene diisobutyrate; Propanoic acid, 2-methyl-, 1,1'-(2,2- dimethyl-1-(1-methylethyl)-1,3-propanediyl) ester; Propanoic acid, 2-methyl-, 2,2-dimethyl-1-(1-methylethyl)- 1,3-propanediyl ester; TXIB; 2,2,4 – trimethyl-1,3-pentanediol monoisobutyrate (Texanol)
CAS Number	6846-50-0

Structure	 (Pubchem: CID 23284)
Chemical Formula	$C_{16}H_{30}O_4$
Molecular Weight	286.42 g/mol
Physical State	Liquid
Color	Colorless
Melting Point	-70°C
Boiling Point	280°C
Vapor Pressure	0.0009 @ 20°C
Water Solubility	1-2 mg/L @ 20.5°C
Log Kow	>4.1 (DEPA, 2010)
Flashpoint	128°C
Source	IUCLID, 2000 (unless otherwise stated)

K_{ow} is the octanol-water partition coefficient. See Appendix 2 for more detail.

3 Manufacture, Supply, and Use

Manufacture

TPIB is a non-phthalate, low-viscosity plasticizer, intended for use as a secondary plasticizer[2] (DEPA, 2010). TPIB has higher hardness than phthalates, higher volatility (though lower than dibutyl phthalate), and higher water extractability. TPIB is commonly used in polyurethane elastomer mixtures to lower the viscosity (Eastman Chemical, 2006b). TPIB is compatible with polyvinyl chloride (PVC) and with common primary and secondary plasticizers such as dioctyl phthalate and dioctyl terephthalate (Eastman Chemical Company, 2006a, 2009). TPIB can be used with fillers without compromising the viscosity of the plastisol.

Supply

The production volume of TPIB in Japan was estimated to be 1,200 tons/year in 1990–1993 (OECD, 1995). Bui et al. (2016) reported the production in the European Union to be 1000 – 10,000 tons/year. TPIB is not considered a high production volume chemical by the U.S. EPA, but estimates of U.S. production volume are unknown.

Use

[2] A secondary plasticizer has limited compatibility with a polymer, but instead acts on a primary plasticizer to increase its effectiveness.

TPIB can be found in apparel, weather stripper, furniture, wallpaper, nail care, plastisols, sheet vinyl flooring, toys/sporting goods, traffic cones, vinyl compounding, vinyl gloves, and as a diluent for methyl ethyl ketone peroxide formulations (Eastman Chemical 2002, 2010). The use of TPIB in vinyl flooring declined in the 1990s, due to high emissions from end products (DEPA, 2010). TPIB is also used in inks, coatings, urethane elastomers, and water-based paints (DEPA, 2010, Kim et al., 2007). In the Netherlands, 14% of toys and child care articles surveyed in 2007 contained TPIB; in Germany, Austria, and Switzerland, 11% of such products contained TPIB (DEPA, 2010).

4 Toxicokinetics

No data on the toxicokinetics of TPIB in humans were located.

Toxicokinetic studies of TPIB in laboratory animals are limited to two related studies. In these studies, radiolabeled TPIB was administered by gavage to Holtzman albino rats at a variety of doses (Astill et al., 1972; also reported in Eastman, 2007). These studies determined that TPIB is readily absorbed, rapidly metabolized, and primarily excreted in the urine. There is no indication that TPIB accumulates with repeated exposures.

Absorption

Blood levels of TPIB or its metabolites were not measured in these studies, but the finding of radiolabel in the urine within 24 hours of dosing is consistent with relatively rapid oral absorption. In addition, absorption was relatively efficient, based on the finding of 47-72% of the total dose in the urine (see text on Elimination, below).

Distribution

Within 8 days after dosing with 283 mg/kg bw, the carcass and organs combined accounted for 2.9% of the original dose, and by 15 days after dosing with 895 mg/kg, tissue levels were comparable to controls.

Metabolism

Characterization of the radioactivity in the urine found that a small percentage was unchanged TPIB. Most of the radioactivity in both the feces and urine was found in the form of 2,2,4-trimethyl-1,2-pentanediol (TMPD, the parent glycol) and its glucuronide and sulfate conjugates. The other major metabolite was the oxidation product 2,2,4-trimethyl-3-hydroxyvaleric acid and its conjugates. These data indicate that TPIB is metabolized by successive esterase hydrolysis of the two isobutyrates, followed by oxidation.

Elimination

In rats administered 236-283 mg/kg bw (one rat per dose), urinary excretion accounted for 47-72% of the total doses. Most of the urinary excretion occurred within the first 3 days, with additional slow excretion until the end of monitoring at day 10. Fecal excretion accounted for 14-31% of the dose, with most of the excretion occurring within the first 2 days; fecal excretion was essentially complete by 7 days post-dosing. The study authors attributed slower elimination of the last few percent of the dose to possible enterohepatic circulation. No radiolabel was detected in expired air. Urine and feces accounted for 95-99% of the administered dose, with the remaining radioactivity in the carcass.

5 Hazard Information[3]

No single or repeat-dose empirical TPIB hazard data exists for humans. Human toxicity and hazard incident data exists, however, for people exposed to TPIB, other plasticizers, and volatile organic compounds during an episode of sick building syndrome. These data are discussed in Section 6, Exposure.

5.1 Acute Single Dose Toxicity

5.1.1 Acute Oral Toxicity

The acute oral LD_{50} of TPIB was reported to be >2000 mg/kg bw or >3200 mg/kg bw in rats, and >6400 mg/kg bw in mice (Astill et al. 1972; Eastman Chemical, 2007).

5.1.2 Acute Dermal Toxicity

The dermal LD_{50} for TPIB in guinea pigs (Eastman Chemical, 1962a) and rabbits (Eastman Chemical, 2007) was greater than 20,000 mg/kg bw and 2000 mg/kg bw, respectively. In the guinea pig study, toxicity was evidenced by decreased body weight, slight-to-moderate edema and erythema with some desquamation. No toxicity or signs of irritation were seen in the rabbit study.

5.1.3 Acute Inhalation Toxicity

No mortality was observed in rats (3/concentration) exposed via inhalation to 120 or 5300 mg/m^3 TPIB for six hours, followed by a two-week observation period (Eastman Chemical, 1962, 2007). The LC_{50} value for TPIB, therefore, was determined to be greater than 5300 mg/m^3. In this study, it is unclear if the inhaled test dose is a vapor or aerosol, but the author of this review notes that this concentration is 100x the saturated vapor concentration.

[3] Where available, this report provides significance level p values in all sections. However, secondary references used as data sources often reported only that a change was significant without reporting the p level, or just reported an effect without noting if it was statistically significant. If no p level is reported in this text, the p level was not available in the cited secondary reference, but the significance is presumed to be statistical.

5.1.4 Irritation/Sensitization

TPIB was slightly irritating to the skin of guinea pigs when the skin was exposed uncovered to 20,000 mg/kg bw, and more irritating when covered (Eastman Chemical 1962). The EC classification for skin response in this test was "not irritating." There was no evidence that TPIB was absorbed into the skin, but small skin flakes, desquamation, and little hair were visible after one week. After two weeks, desquamation and sparse hair persisted. No evidence of irritation was observed after a 24-hour occlusive patch exposure in rabbits at 2000 mg/kg performed under OECD test guideline 404 (Eastman Chemical, 2007).

In an OECD test guideline 405 study, TPIB was considered "slightly irritating" to rabbits (Eastman Chemical, 2007). Conjunctival redness (score of 1) was seen in one of three rabbits with unwashed eyes at 1 hour, and in 3/3 rabbits that had their eyes washed after instillation of 0.1 mL TPIB. All animals of both groups were normal by 24 hours.

Guinea pigs receiving TPIB injections in the footpad, followed by a topical challenge, showed no signs of sensitization after 24 or 48 hours (Eastman Chemical, 1961). However, repeated daily inhalation exposure to 9 $\mu g/m^3$ TPIB (5 hours/day) increased the allergic immune response in ovalbumin-sensitized mice (Bonisch et al., 2012), when the mice were exposed during antigen sensitization but not in already sensitized mice. A somewhat higher concentration of 32 $\mu g/m^3$ TPIB was required to enhance the allergic immune response during the antigen challenge. The authors noted that both of the tested concentrations were relevant to concentrations that could result in indoor air from new polyvinylchloride (PVC) flooring.

In a human repeat insult patch test, based on an adaptation of the Draize Patch Test, 201 volunteers received dermal applications of 1 percent (v/v) TPIB under a semi-occlusive patch three times per week for three weeks (David et al., 2003). Following a two-week rest period, reactions to a dermal challenge exposure were observed. Slight erythema was noted in two subjects exposed to 1% TPIB following at least five of the nine induction exposures. None of these subjects reacted following the challenge. Reactions on challenge (slight or patchy erythema) were observed in 3/201 other subjects. There were no sensitization scores of 1.0 or greater in those that reacted. The study authors and ECHA (2011a) concluded that TPIB did not demonstrate evidence for skin irritation or sensitization.

5.2 Repeated Dose Toxicity

No publications were found on repeat dose systemic toxicity in humans.

Two guideline or equivalent repeat-exposure laboratory animal toxicity studies and three older non-guideline studies were, however, available for TPIB.

In a USFDA (2004) guideline-compliant subchronic toxicity study (Anonymous, 2005, as cited by Eastman Chemical, 2007; ECHA, 2011a[4]), TPIB was fed to groups of CD[Crl:CD(SD)] rats

[4] ECHA (2011a) provided extensive details on statistically significant changes but did not report the level of significance. Presumably significance was defined as $p<0.05$.

(20/sex/dose) at dietary doses of approximately 0, 30, 150 or 750 mg/kg-day. Concentrations in the diet were adjusted to maintain a constant dose level. Actual doses were calculated to be 0, 30.28, 151.34, and 751.59 mg/kg-day for males, and 0, 30.84, 153.03, and 754.81 mg/kg-day for females. Special investigational emphasis was placed on kidney histopathology, including the accumulation of alpha-2-u-globulin, as well as histopathology of the male reproductive tract.

No test substance-related mortalities, or clinical signs of toxicity were observed, and no adverse effects were seen in a functional observational battery (FOB). Body weight gains in high-dose males and females were reduced by 5 to 7% beginning in weeks 8 to 10, and was accompanied by sporadic slight decreases in food consumption. Mean body weight of males was significantly reduced at week 9 (no further details provided), but other body weights were comparable to controls throughout the study. Hematology and urinalysis revealed no adverse chemical-related changes. Statistically significant differences in clinical chemistry were noted only at 750 mg/kg-day compared to controls. Statistically significant differences noted included: 1.29- to 1.42-fold increase in cholesterol levels on days 15, 45 and at termination in males and 1.30- to 1.37-fold in females on day 45 and at termination; a 1.24- fold increase in total bilirubin at termination in males; and a 1.24-fold increase in creatinine at termination in males. Gamma glutamyltransferase (GGT) was "slightly increased" on Day 45 and at termination in males. It is not clear from the available information whether the change was statistically significant, but even if it was, the small magnitude of the change (3.2 U/L vs. 3.0 U/L in controls) means that this change was not biologically significant.[5] Other statistically significant changes in clinical chemistry were sporadic and/or not dose-related, and were not considered toxicologically significant by the study authors. The study authors noted that the data were consistent with an "alteration of lipid chemistry" at the high dose.

Increases in liver weights in both males and females were considered treatment related. At 750 mg/kg-day, absolute and relative (to body weight) liver weights increased 17% and 25%, respectively, in males, and 16% and 20%, respectively in females. An increase in liver weight of less than 150% of control is considered by some to not be adverse in the absence of degenerative or necrotic liver changes (Hall et al., 2012). U.S. EPA (2002) also states that "a dose with only hepatocellular hypertrophy and or liver size/weight should be considered the study NOAEL unless there is a known mode of action for toxicity and/or the other study data (e.g., clinical chemistry and histopathology) are not equivocal." Relative brain weight also increased by 10% in males at 750 mg/kg-day. No test substance-related macroscopic liver changes were observed in either sex. A 14% increase in relative kidney weights was noted in males at 750 mg/kg-day. This increase was not considered adverse by the study authors because the changes correlated to an increase in hyaline droplets (which can be a marker for male rat-specific toxicity).

Histopathological examination revealed test article-related changes in the kidneys of male rats. Increases in hyaline droplets, characterized as minimal to mild, were observed in 4/20, 11/20,

[5] U.S. EPA (2002) suggests that a doubling of GGT may be indicative of toxicity. The language in that document is not precise, and is consistent with an interpretation that the threshold for an adverse effect may be lower than a doubling, but in this case the change is less than 10%, which is substantially below a doubling, and thus unlikely to be toxicologically meaningful.

and 19/20 males in the 30, 150, and 750 mg/kg-day groups, respectively. Although the methods noted that particular attention was paid to assessing the accumulation of alpha-2u-globulin, there was no mention of specific staining for this protein, or otherwise identifying the hyaline droplets as containing this protein. The study authors suggested that the increase in hyaline droplets was treatment-related at 750 mg/kg-day, given the significant increase at this dose compared to that seen in the control group. Male rats also exhibited chronic progressive nephropathy (CPN) of minimal severity at the incidence of 9/20, 9/20, 12/20, and 17/20 in the 0, 30, 150, and 750 mg/kg-day dose groups, respectively. The incidence was statistically significant only at the high dose. Further details were not provided on the gradation or dose-related changes in hyaline droplets or CPN. Kidney effects were not noted in female groups at any dose level. No adverse histopathology was observed in any of the male reproductive organs.

The study authors identified a LOEL of 750 mg/kg-day in males, based on the increased incidence, but not severity, of progressive nephropathy. The NOAEL in males was identified as 150 mg/kg-day, because this dose caused only minimal increases in hyaline droplet formation without augmenting neuropathy. For females, the highest dose of 750 mg/kg-day was identified as the NOAEL based on limited to slight decreases in body weight, increased liver weights, and increased cholesterol levels that were considered minor in nature. Although any of these effects could be adverse, the degree of change was below that considered adverse. EFSA (2006) agreed with the study authors in identifying a NOAEL of 150 mg/kg-day, based on statistically significant increases in relative liver weights at 750 mg/kg-day. EFSA did not appear to consider the kidney effects relevant in identifying effect levels. ECHA (2011a) also considered 150 mg/kg-day to be a NOAEL in males, based on increased hyaline droplets and increased incidence of progressive nephropathy at the LOAEL of 750 mg/kg-day; 750 mg/kg-day was considered a NOAEL in females.

In evaluating the implications of the male rat kidney effects, it is important to distinguish between judgements of adversity and judgments of human relevance. Effects may be adverse in the rat, but not relevant to humans. US EPA (1991) nephropathy related to alpha 2u-globulin accumulation in male rats is not relevant to humans, and should not be used as the basis for a noncancer assessment. That document further states that hyaline droplet accumulation is a nonspecific response, and so to exclude human relevance it is important to show that alpha 2u-globulin accounts for the hyaline droplet accumulation. This condition was not met in the current study. However, Hard et al. (2009) also argue that rat chronic progressive nephropathy (CPN) is not relevant to humans, based on differences in histology and etiology. Although this assessment agrees that there are many strong aspects to that argument, no mode of action was proposed for the rat CPN, and so it must be considered relevant to humans, according to the International Programme on Chemical Safety (IPCS) MOA/human relevance framework (Meek et al., 2003; Boobis et al., 2006). Furthermore, in light of the relatively high incidence of hyaline droplet formation at 150 mg/kg-day (11/20, compared with 0 in the controls), even in the absence of a significant increase in nephropathy, this assessment considers 150 mg/kg-day to be a LOAEL for adverse kidney effects in males, with a corresponding NOAEL of 30 mg/kg-day. This judgement is based on the data as a whole, considering similar kidney effects reported by JMHLW (1993) at 150 mg/kg-day.

The high dose of 750 mg/kg-day is identified as the NOAEL for females for all endpoints, since the magnitude of the changes in cholesterol are considered to be of minimal toxicological significance.

A combined repeated dose and reproductive/developmental toxicity screening test (OECD Guideline 422) using TPIB was performed male and female Sprague-Dawley rats (JMHLW, 1993; OECD, 1995; Eastman Chemical, 2007; ECHA, 2011a). Rats (12/sex/dose) were administered gavage doses of 0, 30, 150 or 750 mg/kg-day TPIB (purity: 99.7%) in corn oil. Females were dosed from 14 days before mating through day 3 of lactation; males were exposed for 44 days. JMHLW (1993) did not specify the timing of the male exposure, but based on the test guideline, the males would have been exposed for at least two weeks prior to mating, approximately 2 weeks of mating and 2 weeks after the completion of the mating period. At the high-dose, depressed body weight gain (males) and increased food consumption (females) were observed, but these changes were not described as statistically significant. Rats receiving 150 or 750 mg/kg-day had significantly higher levels of creatinine and total bilirubin, and high-dose males had significantly higher total protein content in the blood, suggesting liver and kidney effects. Eastman Chemical (2007) also reported that rats treated with 150 or 750 mg/kg-day had significantly increased albumin and albumin:globulin ratio, but that levels of aspartate aminotransferase (AST[6]), alanine aminotransferase (ALT[7]) and GGT were reduced. Increases (not decreases) in these serum enzymes are generally indicative of liver damage. The available sources did not state the degree of change, or any of the other clinical chemistry measurements, making it difficult to independently interpret the adversity of these findings.

Relative liver weights were significantly higher for male rats receiving the two higher doses of TPIB, and absolute liver weights were significantly increased in high-dose males. In females, absolute and relative liver weights were increased at the high dose. Discoloration, decreased fatty change, and centrilobular hypertrophy were also seen in males at 750 mg/kg-day, but not in females. Absolute and relative kidney weights were significantly elevated in high-dose males, and were accompanied by dilation of the lumens of the distal tubules, and fibrosis. Although the incidence of basophilic changes in the renal tubular epithelium and hyaline droplet formation was not affected, a dose-related increase in severity was observed in male rats receiving 150 or 750 mg/kg-day. Eastman Chemical (2007) reported an accumulation of alpha 2u-globulin in 5/11 mid-dose males and 10/11 high-dose males. However, since the methods did not note protein-specific staining, and other sources (e.g., JMHLW, 1993; ECHA, 2011a) described this endpoint only as hyaline droplet accumulation (with no information on the severity), it is unclear whether alpha 2u-globulin was definitively identified in the droplets. At the lowest dose only, there was a decrease in absolute but not relative thymus weight, which was not considered treatment-related, since there was no dose-response.

Eastman Chemical (2007) determined a NOEL for systemic toxicity of 30 mg/kg-day for males, and considered the effects at 150 mg/kg-day to be adaptive or a result of alpha 2u-globulin accumulation, making that dose a NOAEL. In females, 150 mg/kg-day was also considered a NOAEL. ECHA (2011a) considered 30 mg/kg-day to be a NOEL in males and 150 mg/kg-day to be a NOEL in females, based on increased liver weight. This assessment agrees with the

[6] Previously known as serum glutamic oxaloacetic transaminase (SGOT)
[7] Previously known as serum glutamic pyruvic transaminase (SGPT)

study authors that the changes in liver weight, centrilobular hypertrophy, discoloration were adaptive and non-adverse in nature, in light of the absence of supporting histopathology or clinical chemistry changes (U.S. EPA, 2002). The fatty change was not considered adverse, since an increase in liver fattiness is considered adverse. Based on the kidney effects, 30 mg/kg-day is a NOAEL in males, and 150 mg/kg-day is a LOAEL; 750 mg/kg-day is a LOAEL in females.

There were three non-guideline studies. Astill et al. (1972) reported on two repeat-dose studies on TPIB performed by Eastman Kodak Company. In the first, four beagle dogs/sex/dose received dietary doses of 0, 0.1, 0.35, or 1.0% TPIB by weight, 6 days/week for 13 weeks (approximately equivalent to 0, 22, 77, and 221 mg/kg-day for males and 0, 26, 92, and 264 mg/kg-day for females)[8]. Clinical chemistry parameters were evaluated prior to study initiation, and at 6 and 12 weeks, and included hematology, blood urea nitrogen (BUN), AST, and urinalysis. At the end of the study, animals were sacrificed and extensive gross, microscopic, and histopathological analyses were conducted. There was no mortality or evidence of neurological stimulation, depression, or reflex abnormality. There were also no effects on growth or food consumption, and no changes were observed in the hematology, clinical chemistry, histopathology, or urinalyses. Relative organ weights were similar to control animals, except for the liver and pituitary gland in the two higher dose groups. These organ weights were increased slightly compared to controls. However, elevated pituitary gland weights were still within normal historical ranges, and the absence of microscopic pathological findings in both of these organs suggested that the observed weight changes were not adverse. Astill et al. (1972) interpreted these findings as having no toxicological significance. The NOEL for this study was 0.1% in feed, or 22–26 mg/kg-day, and the NOAEL was 1% in feed, corresponding to 221 and 264 mg/kg-day for male and female dogs, respectively (CPSC, 2014; ECHA, 2011b).

The second study reported by Astill et al. (1972) was a feeding study in rats. Albino Holtzman rats (10/sex/dose) received TPIB for 103 days in the diet at levels of 0, 0.1 or 1.0% by weight (average doses equivalent to 0, 75.5 and 772 mg/kg-day for males and 0, 83.5 and 858.5 mg/kg-day for females).[9] At the end of the dosing period, rats were necropsied and tissues (esophagus, small and large intestine, liver, trachea, lung, thyroid, parathyroid, spleen, brain, heart, kidney, bladder, adrenal, gonad, and bone) were removed for histological examination. There were no significant differences between feed consumption and weight gain or growth between controls and treated rats, or on hematology. Kidney weights in females were statistically significantly decreased ($p<0.05$) compared to controls, but the decrease was not dose related, and was only ~12%. Relative liver weights in both sexes[10] and absolute liver weights in male rats were significantly higher in high-dose rats compared with controls (Table 2). No other effects in organ weights or histology were noted. Astill et al. (1972) considered the liver weight changes to be adaptive because they were within normal historical ranges, were reversible, and were

[8] Assuming a food intake of 0.4 kg food/day and a body weight of 15.5 kg (males) and 13 kg (females) for beagle dogs (U.S. EPA 1988). Example calculation: 0.4 kg food/15.5 kg bw/day * 6 days/7days * 1% TPIB = 221 mg TPIB/kg bw/day.

[9] Doses reported in Eastman Chemical 2007.

[10] Astill et al. (1972) reported that relative liver weights in females were significantly higher in the high-dose group. Eastman Chemical (2007) stated that this reported change was probably an error, because the laboratory report did not report this result as significant.

paralleled by increases in microsomal enzymes (as further reported by Krasavage et al., 1972). Several incidental findings reflected poor animal husbandry that might have affected TPIB toxicity, including intestinal roundworms in four control animals, bronchopneumonia in all dose groups, and scattered tracheitis and bronchitis. The study authors derived a NOAEL of 1.0 percent, or 772–858.5 mg/kg-day.

The current assessment agrees with the study authors that the high dose was a NOAEL, based on the absence of histopathology and the magnitude of the change in liver weight. CPSC (2010, 2014) reported only the authors' assessment of the NOAEL, although ECHA (2011b) reported the NOAEL to be 0.1%, apparently based on a slight, significant increase in the relative liver weights in both sexes and in the absolute liver weight in males.

Table 2. Mean Organ Weights of Rats Fed TPIB for 100 Days (Astill et al., 1972)

Concentration in Diet	Liver		Kidney	
	Absolute (g)	Relative (% bw)	Absolute (g)	Relative (% bw)
Control – M	14.27 (1.82)[a]	3.51 (0.32)	2.85 (0.29)	0.70 (0.05)
0.1% - M	15.23 (1.47)*	3.68 (0.21)	2.86 (0.15)	0.69 (0.03)
1.0% - M	17.03 (1.85)*	4.23 (0.43)*	2.93 (0.29	0.73 (0.05)
Control – F	7.83 (0.63)	3.40 (0.26)	1.77 (0.16)	0.77 (0.06)
0.1% - F	7.23 (0.84)	3.16 (0.31)	1.56 (0.16)*	0.68 (0.06)*
1.0% - F	8.24 (1.11)	3.71 (0.33)*	1.59 (0.17)	0.72 (0.06)

[a]Mean (SE)
*Significantly different from controls (p=0.05)

The third non-guideline study was conducted by Krasavage et al. (1972) to investigate the reversibility of liver effects. Krasavage et al. (1972) carried out three concurrent experiments to determine whether the effects on liver weights reported by Astill et al. (1972) were reversible, and whether they were associated with changes in microsomal enzymes. Sprague-Dawley rats (10/sex/dose) were fed 0, 0.1, or 1.0 percent TPIB by weight (approximately equivalent to 0, 147.5, and 1475 mg/kg-day).[11] Rats were fed this diet continuously for 52 days (in experiment I) or 99 days (in experiment II). For experiment III (evaluating reversibility), rats either received the TPIB diet for 52 days followed by the control diet for 47 days, or they received control diet for 52 days followed by TPIB diet for 47 days. SGOT/AST and alkaline phosphatase were evaluated after each phase. Following sacrifice, livers were collected and weighed, and analyzed for the activity of four microsomal enzymes: glucose-6-phosphatase (G-6-Pase), *p*-nitroanisole

[11] Assuming an average food factor of 0.1475 kg food/ kg bw/day for Sprague-Dawley rats weighing 64–77 grams (U.S. EPA 1988).

demethylase (*p*-NDase), UDP-*p*-aminophenol-beta-D-glucuronyl transferase (*p*-AG-Tase), and UDP-bilirubin-beta-D-glucuronyl transferase (BG-Tase). In addition, groups of five to eight male rats received seven daily ip doses of 0, 25 or 100 mg/kg-day TPIB or its metabolite 2,2,4-trimethyl-1,3-pentanediol (TMPD), followed by sacrifice one day after the last injection. Livers from these animals were collected for analysis of *p*-NDase and BG-Tase activity.

There was no significant treatment-related effect on mean body weight gain, group feed consumption (based on 5 rats/cage), hematological parameters, alkaline phosphatase activity, liver tissue histology, or absolute organ weight in any group compared to controls (Krasavage et al. 1972). SGOT/AST levels were elevated in all high-dose animals relative to controls, except for females in experiment I, but the magnitude of the increase was relatively small (less than a doubling), and the elevated levels were still within normal ranges. The relative liver weights of male and female rats fed 1% TPIB were significantly greater than controls in all three experiments, except for experiment III rats fed TPIB first and control diet second. Differences in other relative organ weights were not determined to be treatment-related. Likewise, the only consistent finding with respect to microsomal enzymes was a significant ($P<0.05$) increase in activity at the high-dose level, but only when the animal was consuming TPIB at the time of sacrifice (i.e., not in the experiment III rats that ate a control diet in the second part of the experiment. Thus, the effects on both liver weight and microsomal enzymes levels were reversible. In the ip injection study, enzyme induction by TMPD was somewhat lower than that by TPIB, suggesting that TPIB is the active inducer, and not its metabolic product. Overall, the results of this study were consistent with the conclusion that the increased liver weight resulting from TPIB exposure is adaptive and reversible, and at least partially related to enzyme induction.

5.3 Chronic Toxicity/Carcinogenicity

No data on potential TPIB chronic toxicity or carcinogenicity were identified in the literature.

5.4 Reproductive Toxicity

A combined repeated dose and reproductive/developmental toxicity screening test (OECD Guideline 422) described the effects of TPIB on male and female Sprague-Dawley rats after administering gavage doses of 0, 30, 150, or 750 mg/kg-day TPIB from 14 days before mating until 30 days after (males) or through postnatal day (PND) 3 (females) (JMHLW 1993; OECD 1995; Eastman Chemical 2007; ECHA, 2011a). Systemic toxicity for rats in this study has been described in Section 5.2. Estrous cycle length was significantly shorter in high-dose females (4.1 days versus 4.6 days in the control), but values were within the historical control range for the testing laboratory. In addition, Goldman et al. (2007) described a “regular” rat cycle as 4-5 days. TPIB had no significant effect on any reproductive endpoint, including fertility index, gestation duration, pre- or post-implantation loss, live pups, or viability on PND 4. There was also no effect on reproductive organ weight at any dose. Parameters evaluating developmental toxicity were limited to litter weights at PND 0 and 4, and necropsy findings at PND 4; these

examinations revealed no TPIB-related effects at any dose. The reproductive and developmental NOAEL, therefore, is 750 mg/kg-day. Therefore, this assessment agrees with the conclusions of ECHA (2011a, 2011b) and Eastman Chemical (2007) that the high dose of 750 mg/kg-day was a reproductive and developmental NOAEL. However, it is noted that the males were not exposed for the entirety of the spermatogenic cycle, and so some effects on male reproduction could have been missed.

A reproductive/developmental toxicity screening test was performed by Eastman Chemical Company (OECD Guideline 421; Eastman Chemical, 2001; ECHA, 2011a). Sprague-Dawley rats (12/sex/dose) received diets containing 0, 1.5, 4.5, or 15.0 ppm TPIB, corresponding to doses of 0, 120, 359, or 1135 mg/kg-day (females) or 0, 91, 276, or 905 mg/kg-day (males). Dosing began 14 days before mating, and continued through mating, for a total of 51 days (males) or through PND 4-5 (females). Sporadic statistically significant ($p \leq 0.05$) reductions in mean body weight, body weight gain, and feed consumption/utilization were observed in both sexes of the parent generation at the high-dose level. Because the decreased body weight and body weight gain were seen only at initial time points, and the decrease in feed consumption was greater than that in body weight (or in body weight gain after the first time point) these changes were not considered adverse.

The study included a number of sperm measurements beyond those that are part of the OECD 421 protocol. There was no effect on mean sperm motility. Absolute and relative (to testis weight) testicular sperm counts were lower ($p \leq 0.05$) in the high- and low-dose groups, and mean absolute epididymal sperm counts were lower ($p \leq 0.05$) in all treated groups. There was, however, no effect on fertility or testicular histopathology. Eastman Chemical (2007) included an expert review of the sperm effects that stated that the apparent effect on testicular and epididymal sperm counts could not be chemical-related, because the sperm collected from the testes and epididymides resulted from cell divisions that occurred prior to the start of exposure. The current assessment agrees that the changes were not dose-related and could not have resulted from TPIB exposure. The expert review noted that definitive reproductive toxicity studies include exposure for 70 days prior to mating, to ensure that the entire spermatogenic cycle is covered. Consistent with that concern, the OECD 421 test guideline notes the limited pre-mating dosing period, which may be why sperm analysis is not a standard part of the study design.

The mean number of implantation sites was significantly reduced at the high dose (~15%), but there was no corresponding effect on pre- or post-implantation loss. There was no statistically significant effect on litter size on PND 0, but there was an apparent dose-related trend, and at PND 4, the litter size was significantly smaller than controls. There was also a dose-related decrease in litter weight on PND 0 and PND 4, which was statistically significant at the high dose. There was no effect on other measures, including reproductive organ weights, gross or microscopic lesions, fertility, sex ratio, or mean pup weight. Eastman Chemical (2007) and ECHA (2011a) concluded that the NOAEL for reproductive or developmental toxicity was the mid dose, 276 mg/kg-day for males and 359 mg/kg-day for females, based on decreased total litter weight and litter size on PND 0 and PND 4, and decreased number of implants and number

of corpora lutea. This assessment agrees that the mid dose was a reproductive and developmental NOAEL, and the high dose was a reproductive and developmental LOAEL.

In the USFDA subchronic toxicity study described above, administration of TPIB to male and female rats up to 750 mg/kg-day in the diet for 13 weeks did not result in any test-substance-related effects in the reproductive organs of either sex (Anonymous, 2005, as cited by Eastman Chemical, 2007; ECHA, 2011a).

5.5 Prenatal, Perinatal, and Post-natal Toxicity

In a prenatal developmental toxicity study (OECD Guideline 414), TPIB was administered in the diet to groups of female Crl:CD(SD) rats (25/dose) at 0, 1.5, 4.5, or 15 mg per gram of food from gestation day (GD) 6 to day 20. ECHA (2011a) reported the corresponding doses as 0, 118, 343 and 1077 mg/kg-day. This was an unpublished study, for which a company summary is available (Eastman Chemical, 2014), with additional details reported by ECHA (2011a), but primary data were not available. No mortality was observed up to the scheduled necropsy on day 20, and there were no treatment-related clinical findings. At the high dose, mean body weight gain was significantly ($p<0.01$) lower than that of controls during GDs 6-9, with a corresponding significant ($p<0.01$) decrease in mean food consumption. Mean body weight gain was significantly increased ($p<0.01$) in the following interval, GDs 9-12. Mean body weight gains were similar to controls for the remainder of the treatment period (GDs 12-15 and 15-20), but the overall mean body weight gain and body weight was significantly ($p<0.01$) lower than controls when the entire exposure period (GD 6-20) was evaluated. Mean food consumption was also lower during GDs 15-20 and over the entire exposure period (GDs 6-20). ECHA (2011a) further noted that due to the initial mean body weight loss in the high-dose group, mean body weights were lower by 6.9% to 11.4% (reported only as 6.9% by Eastman Chemical (2014). ECHA (2011a) considered the changes in mean body weight, net body weight, and net body weight gain attributable to TPIB. In the mid-dose group, a significantly ($p<0.01$) lower mean body weight gain was reported on GDs 7-8, and corresponded to a significantly ($p<0.01$) lower mean food consumption on GDs 6-9. There was no effect on gravid uterine weight at any dose.

The effects on body weight were chemical-related, but this assessment concludes that it is likely that they were secondary to decreased food consumption due to poor palatability. In the high-dose group, food consumption was initially decreased, rebounded during the next measurement period, and decreased again later in the study. Similarly, the only period in which the mid-dose group had decreased food consumption was at study initiation. This pattern suggests that the decrease is due to poor palatability, rather than a toxic effect of the chemical. However, because quantitative information by exposure period is not available for the decreases in body weight gain and food consumption, and so it is not possible to directly compare the magnitude of the decreases in body weight and food consumption, the high dose of 1077 mg/kg-day is considered a maternal LOAEL, based on decreased body weight, and the mid dose of 343 mg/kg-day is a NOAEL.

Maternal macroscopic examination revealed no test substance-related findings in any treatment group.

Statistically significant (p value not reported) treatment-related reductions in mean fetal body weights in males, females and combined were noted in the high-dose group compared to the control group. However, all of these measurements differed from the control group by a minimal amount (only 0.1 g). In addition, the body weights were within the range of historical controls, supporting this consideration that the changes were of minimal significance. Eastman Chemical (2014) noted that skeletal malformations (stemoschisis (i.e., cleft in the sternum), bent scapula) were observed at the high dose, but ECHA (2011a) described the bent scapula as a variation. In addition, the malformations were seen in 1, 0, 1, and 1 fetus/litter in the control, low-, mid-, and high-dose groups, respectively, so the malformations were not dose-related or statistically significant. Other variations were noted only at the high dose, and included bent ribs (significance not reported), and sternebra(e) nos. 5 and/or 6 unossified ($p<0.05$). According to ECHA (2011a), the bent scapula and bent ribs are substance related, but they are transient alterations that resolve postnatally. ECHA (2011a) found no statistically significant differences between animals in the high dose and control groups when the total malformations and variations were evaluated on a per litter basis.

The study authors (Eastman Chemical, 2014) considered the mid-dose, equivalent to 343 mg/kg body weight, to be a NOAEL for maternal toxicity based on the lower mean body weight and reduced food consumption in high-dose group. ECHA (2011a) agreed with the designated maternal NOAEL but noted the basis to be the significantly lower body weight gain and/or body weight loss observed at the high dose. In light of the immediate decrease in food consumption, followed by rebounded food consumption and body weight gains (even though without a full return to control, it is reasonable to suggest that the body weight changes were secondary to decreased food consumption due to poor palatability. However, in the absence of quantitative data on food consumption and body weight, this assessment also considered the middle dose of 343 mg/kg-day to be the maternal NOAEL (a health protective approach).

The existing assessments considered the embryo/fetal development NOAEL to be 343 mg/kg-day, based on the significantly lower fetal body weights (Eastman Chemical, 2014 and ECHA, 2011a) and fetal variations (Eastman Chemical, 2014) at the high dose. This assessment considers the developmental effects to be of minimal adversity, based on the small magnitude of the fetal body weight decreases, which may be due to the decreased maternal body weights. Similarly, there is considerable debate over the adversity of delayed ossification and other variations that rapidly resolve postnatally.

5.6 Genotoxicity

Eastman Chemical (2007) reported briefly on three genotoxicity assays performed on TPIB under GLP conditions. TPIB (purity 99.7%) was not mutagenic in *Salmonella typhimurium* strains TA100, TA98, TA1535, TA1537, or *Escherichia coli* strain WP2 uvrA at concentrations of 0, 312.5, 625, 1250, 2500, or 5000 µg/plate with or without exogenous metabolic activation. Similarly, no significant increase in forward mutations at the hypoxanthine-guanine

phosphoribosyltransferase (HGPRT) locus was observed in Chinese Hamster Ovary (CHO) cells in the presence or absence of metabolic activation. TPIB also did not induce chromosomal aberrations in CHO cells with or without metabolic activation. No further details of these studies were available.

The genotoxicity of TPIB was examined in another reverse mutation assay, in *S. typhimurium* strains TA100, TA98, TA1535, TA1537, or *Escherichia coli* strain WP2 uvrA, with or without S9 metabolic activation from rats induced with induced with phenobarbital and 5,6-benzoflavone (JMHLW, 1993). There was no evidence of cytotoxicity or mutagenicity up to the highest concentration tested, 5000 µg/plate. JMHLW (1993) also reported on a chromosomal aberration test in cultured Chinese Hamster Lung (CHL/IU) cells, also with or without S9 from rats induced with induced with phenobarbital and 5,6-benzoflavone. TPIB did not induce structural or numerical chromosomal aberrations in these cells under short-term treatment with metabolic activation at 0–1.3 mg/mL and without activation at 0–0.018 mg/mL. Cells under continuous treatment without metabolic activation also showed no increase in chromosomal aberrations at concentrations of 0–0.04 mg/mL. Based on these studies, TPIB does not appear to cause point mutations or chromosome aberrations.

No *in vivo* gene mutation or clastogenicity studies were located for TPIB. ECHA (2011a) noted that no *in vitro* or *in vivo* germ cell mutagenicity/genotoxicity studies were available for TPIB. They also stated that the "weight of evidence indicates that TPIB is not expected to induce heritable mutations in the germ cells of humans."

5.7 Mechanistic Studies

The only TPIB mechanistic study reviewed involved endocrine receptor activation. Satoh et al. (2008) used stably transfected reporter gene cell lines expressing the androgen receptor (AR) or the estrogen receptor (ER) to examine the potential for TPIB to be an endocrine disruptor. No AR or ER agonist or antagonist activity was observed, and no significant AR or ER binding was observed.

5.8 Mode of Action

No information was located on the mode of action of the liver effects of TPIB. Experimental data suggests, however, that the increased liver weights and hypertrophy are reversible and associated with enzyme induction.

The observation of hyaline droplets and kidney chronic progressive nephropathy in male rats treated with TPIB is suggestive of an association with renal toxicity due to alpha-2u-globulin accumulation. However, a definitive conclusion regarding this MOA is not possible in the absence of any studies that reported staining specific for alpha 2u globulin. According to U.S EPA (1991), the observation of hyaline droplets alone is insufficient to support the alpha-2u-globulin MOA.

CPN was observed following high dose exposures in a subchronic rat study. Hard et al. (2009) argued that rat CPN is not relevant to humans, based on differences in histology and etiology, but this argument is insufficient to meet the criteria of the IPCS MOA/human relevance framework (Meek et al., 2003; Boobis et al., 2006), because key events in the MOA have not been identified.

5.9 Lowest Hazard Endpoints by Organ System and Exposure Duration

The available toxicity studies consistently show that the primary targets of TPIB toxicity are the liver, kidney and possibly the male reproductive tract. Decreased fertility and developmental effects of minimal adversity have also been reported.

Decreased body weight was seen at doses above approximately 1000 mg/kg-day in reproductive (screening) (Eastman Chemical, 2001, 2007; ECHA, 2011a) and developmental toxicity studies (Eastman Chemical, 2014; ECHA, 2011a). However, these changes were considered either not adverse or potentially adverse as a health-protective measure, because they were transient, and possibly related to poor palatability of the chemical in the diet.

Effects in the liver appear to be due to microsomal induction, leading to centrilobular hypertrophy and increased liver weight (Krasavage et al., 1972). Increased liver weight, sometimes accompanied by hypertrophy has been reported at doses of approximately 750–800 mg/kg-day in several rat studies of approximately subchronic duration (Anonymous, 2005, as cited by Eastman Chemical, 2007 and ECHA, 2011a; Astill et al. 1972; JMHLW, 1993, and as cited by Eastman Chemical, 2007 and ECHA, 2011a; Krasavage et al., 1972), and in one study at 150 mg/kg-day in males (JMHLW, 1993; Eastman Chemical, 2007; ECHA, 2011a). Increased liver weight was also reported in dogs exposed to about 200 mg/kg-day for 13 weeks (Anstill et al., 1972). The only other effect on the liver was increased bilirubin in male rats, but not female rats, at 150 and 750 mg/kg-day in a combined repeated dose/reproductive toxicity screening test (JMHLW, 1993; Eastman Chemical, 2007; ECHA, 2011a). However, the significance of this change is unclear, since no data were provided on the degree of change, or whether the changes were statistically significant.

Kidney effects were also seen following subchronic exposure. Increased kidney weight, CPN and hyaline droplet accumulation clearly occurred in male rats, but not female rats, at 750 mg/kg-day (Anonymous, 2005, as cited by Eastman Chemical, 2007 and ECHA, 2011a; JMHLW, 1993, and as cited by Eastman Chemical, 2007 and ECHA, 2011a). Increased incidences of hyaline droplet accumulation were also noted in both studies at 150 mg/kg-day, although secondary sources interpreted the change at 150 mg/kg-day as a NOAEL in one study and a LOAEL in the other study. Although there are suggestions that the kidney effects are associated with alpha 2u-globulin, this association has not been histologically confirmed. JMHLW (1993, and as cited by Eastman Chemical, 2007 and ECHA, 2011a) also reported other kidney histopathology in males: basophilic changes in renal tubular epithelium, proximal tubule

necrosis, fibrosis, and distal tubule dilatation. Of these other histopathology findings, only the epithelial changes occurred at 150 mg/kg-day.

No histopathological changes have been seen in male or female reproductive organs. There were also no reproductive effects in a repeated dose/reproductive toxicity screening assay (Eastman Chemical 2001; ECHA, 2011a). Changes reported in in sperm counts were considered non-treatment related, because careful analysis of the data revealed that the observed decreases occurred prior to the start of exposure. Decreased implantation sites and decreased corpora lutea were seen in a reproductive/developmental screening study at 15 ppm in the diet (1135 mg/kg-day for females and 905 mg/kg-day for males (Eastman Chemical, 2001, 2007; ECHA, 2011a). It is not known whether these effects reflect male or female reproductive toxicity, since no cross-over study was conducted.

Developmental effects were limited to decreased fetal body weight and skeletal variations (increased incidence of unossified sternebrae and bent ribs) at a maternal dose of more than 1000 mg/kg-day. The decreased fetal body weight is likely secondary to maternal decreased food consumption due to poor palatability. The observed variations resolve postnatally and are of minimal severity.

5.10 Uncertainties and Data Gaps

Several uncertainties of varying importance were identified in this assessment.

Database:

The overall database on TPIB is fairly complete, including many of the key studies. For most study types, only one study is available (i.e., one subchronic study, one developmental toxicity study, etc.). Most of the studies (including published studies) were performed by a manufacturer of TPIB. High-quality studies are available only in rats, although there is one non-guideline 13-week dog study. Rather than a standard reproductive toxicity study, a screening-level reproductive toxicity study and a screening-level reproductive/developmental toxicity study are available. Data were available primarily for the oral route. The only inhalation study was an acute lethality study. The dermal database included an acute lethality study, as well as irritation and sensitization studies. Sensitization has been evaluated in both humans and guinea pigs.

The key data gaps are a repeated dose systemic toxicity study in a second species, repeated exposure inhalation studies, and a standard reproductive toxicity study that included an evaluation of sperm quality. The lack of inhalation studies is of particular interest, since most adult exposure is expected to occur via the inhalation route. In addition, several of the key studies are available only from reviews or robust summaries, rather than from the publications or primary reports. This limits the amount of primary data available, and thus limits the potential for independent evaluation of the data.

Hazard:

Body weight: There is some uncertainty in the conclusion regarding whether the decreased body weight is related to poor palatability of the chemical in the diet.

Liver: Effects on the liver were limited to increased liver weight, with one study (JMHLW, 1993**;** Eastman Chemical, 2007; ECHA, 2011a) and increased bilirubin in males. In the absence of the primary data, it is unclear whether the bilirubin change reflects an adverse effect.

Kidney: The clearest effect was chronic progressive nephropathy (CPN) with hyaline droplet accumulation in male rats; a key uncertainty is whether these effects are related to alpha 2u-globulin, and whether the CPN is relevant to humans. In addition, there is uncertainty regarding the effect level (i.e., whether 150 mg/kg-day is a NOAEL or a LOAEL), particularly in the absence of the primary data. Other kidney effects (increased creatinine, changes in renal tubular epithelium, increased kidney weight, proximal tubule necrosis, fibrosis, and distal tubule dilatation) were also limited to male rats, but seem to be more clearly relevant to humans.

Reproductive: There is uncertainty whether the decreased fertility and delayed estrous cycle reflects reproductive effects.

Developmental: There is some uncertainty regarding the adversity of the observed variations, and whether the decreased fetal weight is secondary to decreased maternal food consumption.

Table 3. Summary of NOAELs/LOAELs Identified for TPIB by Organ System

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[12]	Toxicological Basis	Comments
CD[Crl:CD(SD)] rats (M&F) US FDA guideline compliant Anonymous, 2005, as cited by ECHA (2011a), Eastman Chemical, (2007)	90 day Diet Target doses: 0, 30, 150 or 750 mg/kg-day Actual doses: 0, 30.28, 151.34, 751.59 mg/kg-day (M); 0, 30.84, 153.03, 754.81 mg/kg-day (F) (20/sex/dose)	Liver	NOAEL = 750 (M, F)	At 750 mg/kg-day, absolute and relative liver weights increased 17% and 25%, respectively, in males, with corresponding values being 20% and 16% in females.	Concentrations in diet were adjusted to maintain a constant dose level. EFSA (2006) considered 150 mg/kg-day to be a NOAEL in males, based on increased liver weight at 750 mg/kg-day.
		Kidney	NOAEL = 30 (M), 750 (F) LOAEL = 150 (M)	Chronic progressive nephropathy with hyaline droplet accumulation	Eastman Chemical (2007) argued that the CPN is not relevant to humans, but insufficient information is available on the mode of action to reach this conclusion rigorously. ECHA (2011b) considered 150 mg/kg-day to be a NOAEL in males, based on increased hyaline droplets and progressive nephropathy at 750 mg/kg-day.
Beagle dog (M&F) Not guideline compliant Astill et al. 1972	6 day/week for 13 weeks Diet 0, 0.1, 0.35, or 1.0% (equivalent to ~0, 22, 77, 221 mg/kg-day (M);	Liver	NOEL= 22-26 NOAEL = 221-264	Increased liver weight	Relative liver and pituitary gland weights elevated but still within historically normal range. CPSC (2010, 2014) identified the same NOEL and NOAEL.
		Pituitary	NOEL= 22-26 NOAEL = 221-264	Increased pituitary weight	

[12] All effect levels as identified by the authors of this assessment. Effect levels identified by previous assessments are in the comments column

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[12]	Toxicological Basis	Comments
	~0, 26, 92, 264 mg/kg-day (F) (4/sex/dose)				
Holtzman rats (M&F) Not guideline compliant Astill et al. 1972	103 days Diet 0, 0.1 or 1.0% 0, 75.5, 772 mg/kg-day (M); 0, 83.5, 858.5 mg/kg-day (F) (10/sex/dose)	Liver	NOAEL = 772-858.5	Relative liver weight elevated but within historically normal range	Only two doses tested. Other findings suggested poor animal husbandry, including intestinal roundworms in four control animals, bronchopneumonia in all dose groups, and scattered tracheitis and bronchitis. CPSC (2010, 2014) identified the same NOAEL.
Sprague-Dawley rats (M&F) OECD test guideline 422. Combined repeat dose/ reproductive screening JMHLW 1993; Eastman Chemical	14 days pre-mating + during mating and an additional 2 weeks (M) or through PND 3 (F) Gavage in corn oil 0, 30, 150, 750 mg/kg-day (12/sex/dose)	Systemic	NOAEL = 750 (M, F)	Decreased body weight gain (M); increased food consumption (F)	The degree of change was not reported; no secondary review considered the body weight changes to be the basis for designation of a LOAEL.
		Liver	NOAEL = 750 (M, F)	At 750, increased total bilirubin (M); increased liver weights (M, F) and centrilobular hypertrophy (M) At 150, increased total bilirubin and liver weights (M)	No data provided on degree of change for the clinical chemistry and organ weight changes, or whether the changes were statistically significant. The increased liver weight is likely adaptive. Clinical chemistry results were inconsistent, and ALT and AST levels were *decreased*, while increases are associated with adverse liver changes. Eastman Chemical (2007) considered the liver changes adaptive. In contrast, ECHA (2011a) based the NOAEL in both sexes on the liver weight changes in males

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[12]	Toxicological Basis	Comments
2007; ECHA, 2011a					at 150 mg/kg-day and in females at 750 mg/kg-day.
		Kidney	NOAEL = 30 (M); 750 (F) LOAEL = 150 (M)	At 750, increased creatinine and blood protein (M); changes in renal tubular epithelium (M); increased kidney weight (M); proximal tubule necrosis, fibrosis (M); distal tubule dilatation (M). At 150, increased creatinine (M); basophilic changes in renal tubular epithelium (M).	Eastman Chemical (2007) considered the male kidney effects to be related to alpha 2u-globulin accumulation and thus not adverse. However, it is not clear if the hyaline droplets were shown to contain alpha 2u-globulin, and so the kidney effects should be considered adverse and relevant to humans.
		Reproductive	NOAEL = 750	No effects	Estrous cycle was significantly shorter at the high dose, but was within the normal range.
		Developmental	NOAEL = 750	No effects	
Sprague-Dawley rats (M&F) OECD test guideline 421 (reproductive/ developmental screening study)	14 days pre-mating through PND 4-5 (F) or for a total of 51 days (M) Diet 0, 1.5, 4.5, or 15.0 ppm	Systemic	NOAEL = 905 (M); 1135 (F)	Sporadic significant decrease in mean body weight, body weight gain, and feed consumption at the high dose (M and F). Transient changes in body weight or weight gain were not considered adverse	Eastman Chemical (2007) and ECHA (2011a) reached the same conclusions regarding the effect levels.
		Reproductive	NOAEL = 276 (M); 359 (F) LOAEL = 905 (M), 1135 (F)	Decreased implantation sites and decreased corpora lutea	

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[12]	Toxicological Basis	Comments
Eastman Chemical 2001, 2007; ECHA, 2011a	0, 91, 276, 905 mg/kg-day (M);0, 120, 359, 1135 mg/kg-day (F) (12/sex/dose)	Developmental	NOAEL = 359 LOAEL = 905 (M), 1135 (F)	Decreased total mean litter weight and litter size on PND 4 and decreased total mean litter weight on PND 0.	
Sprague Dawley rats (F) OECD test guideline 414 (prenatal developmental toxicity) Eastman Chemical, 2014; ECHA, 2011a	GD 6-20 Diet 0, 1.5, 4.5, or 15 mg per **gram** of food 0, 118, 343 and 1077 mg/kg-day	Maternal body weight	NOAEL = 343 LOAEL = 1077	Changes in body weight gain correlated with decreased food consumption	Decreased food consumption is likely due to poor palatability, since it started immediately, and then the animals rebounded in food consumption. However, high dose considered a LOAEL as a health-protective approach, in the absence of quantitative information on food consumption and body weight.
		Developmental - Fetal body weight	NOEL = 343	Fetal body weight significantly reduced at high dose (p value not reported), but weights differed from control by only 0.1 g	Biological significance unclear. May have been secondary to decreased maternal weight gain (which likely was secondary to decreased food consumption due to poor palatability)
		Developmental - variations	NOEL = 343	Significantly ($p<0.05$) increased incidence of unossified sternebrae and bent ribs	The effects are of minimal adversity, since they resolve postnatally. No increases in malformations or in total malformations and variations per litter.

6 Exposure

The use of TPIB in consumer products has been described in Section 3 of this report.

Oral exposure to TPIB can occur when infants and children interact with child care articles and children's toys. CPSC (2014) estimated the mean oral TPIB exposure from mouthing soft plastic objects (except pacifiers) to be 0.92, 0.60, and 0.55 µg/kg-day in babies aged 3 to <12 months, 12 to <24 months, and 24 to <36 months, respectively. In a similar analysis, ANSES (2016) estimated that the median daily exposure dose of TPIB from mouthing toys was 0.37 µg/kg-day for children 0-12 months, and 0.1 µg/kg-day for children 13-24 months and for children 25-36 months. The 95th percentile daily dose for the youngest group was estimated to be 9.42 µg/kg-day.

The general population may be exposed to TPIB via inhalation in the presence of building materials containing this compound. Due to its high vapor pressure, TPIB is expected to partition >60% to the air indoors (Bui et al., 2016). Levels of TPIB and other volatile organic compounds were significantly higher in freshly painted or newly constructed buildings compared with unpainted or existing buildings (Wieslander et al. 1997; Kim et al. 2007). Emissions of TPIB also come from PVC materials and adhesives associated with flooring; the specific emission rate was found to be higher in the finished products than in the individual materials themselves (Järnström et al. 2008). TPIB-specific emission rates from PVC materials measured in the laboratory ranged from <1 to 13 µg/m^2/hour, while emission rates from PVC-covered floor structures ranged from <1 to 53 µg/m^2/hour. Concentrations of 10-73 µg/m^3 have been reported in painted bedrooms and living rooms (Bui et al., 2016). Using a high-end air concentration, Bui et al. (2016) estimated a daily intake of 8.5 µg/kg-day.

TPIB has been implicated in "sick building syndrome" based on sampling levels exceeding 10-100 µg/m^3 in the air of office buildings, other public buildings, and temporary housing (Rosell 1990; Norback et al. 1995; Maddalena et al. 2009). An average indoor air concentration of 1.64 µg/m^3 TPIB was reported in schools in Sweden and, along with other plasticizer compounds and microbial volatile organic compounds, was associated significantly with incidence of asthma, respiratory symptoms, and allergies in children ($p < 0.05$) (Kim et al., 2007). However, a study finding the threshold for sensory irritation to be about 500 ppb (v/v) (Cain et al., 2005) suggests that reports of irritation at low levels may be better attributed to simultaneous exposure to multiple chemicals in indoor air.

Occupational exposure to the monoisobutyrate of 2,2,4-trimethyl-1,3-pentanediol has been noted in painters using water-based paints and was associated with self-reported asthma and other respiratory issues (Wieslander et al., 1994).

Biomonitoring

Currently, very little biomonitoring information exists for TPIB.

7 Discussion

7.1 Toxicity Under FHSA

It is not clear whether TPIB fits the designation of "acutely toxic" under the Federal Hazardous Substances Act (FHSA) (16 CFR§1500.3(c)(2)(i)(A)) following single oral exposures. Acute LD_{50} values for TPIB in rats were described as >2000 mg/kg, but it is not clear how high the LD_{50} is (Astill et al. 1972; Eastman Chemical). TPIB does not fit the designation of "acutely toxic" under the Federal Hazardous Substances Act (FHSA) (16 CFR§1500.3(c)(2)(i)(A)) following single dermal exposures, based on a rabbit dermal LD_{50} >2000 mg/kg (Eastman Chemical, 2007). The inhalation LC_{50} value for TPIB was greater than 5300 mg/m^3, a concentration that is 100x the saturated vapor concentration (Eastman Chemical, 1962, 2007), but it is not known whether the LC50 is >200,000 mg/m^3.

Slight dermal irritation has been noted in human subjects (David et al., 2003), and guinea pigs (Eastman Chemical 1962), but not in rabbits (Eastman Chemical, 2007) following TPIB exposures. The degree of irritation was sufficiently slight that TPIB is classified as "not irritating." In an eye instillation study, TPIB was considered "slightly irritating (Eastman Chemical, 2007). Dermal exposure to TPIB was not sensitizing to humans at 1% (David et al., 2003), or to guinea pigs receiving a footpad injection of TPIB followed by topical challenge (Eastman Chemical, 1961). However, low concentrations of TPIB in the air increased the allergic immune response in OVA-sensitized mice (Bonisch et al., 2012), suggesting that TPIB may be sensitizing when inhaled.

Sufficient animal data exist to support the conclusion that TPIB can be considered "toxic" under the FHSA due to its toxicity following short-term and subchronic exposures. TPIB caused kidney toxicity in rats at durations ranging from 28 days to 90 days. Observed effects included increased kidney weight, CPN and hyaline droplet accumulation in male rats, but not female rats, at 750 mg/kg-day (Anonymous, 2005, as cited by Eastman Chemical, 2007 and ECHA, 2011a; JMHLW, 1993, and as cited by Eastman Chemical, 2007 and ECHA, 2011a).

No standard 2-generation reproductive toxicity study was available for TPIB. No effects were seen on male or female reproductive organs in a subchronic toxicity study (Anonymous, 2005, as cited by Eastman Chemical, 2007; ECHA, 2011a). Decreased total litter weight and litter size, and decreased number of implants and number of corpora lutea were reported in a reproductive/developmental toxicity screening assay (Eastman Chemical 2001; ECHA, 2011a); the NOAEL for reproductive or developmental toxicity was the mid dose, 276 mg/kg-day for males and 359 mg/kg-day for females. Decreased sperm counts were reported, but were not chemical-related, because the sperm collected from the testes and epididymides resulted from cell divisions that occurred prior to the start of exposure. However, it is noted that because the males were not exposed for the entirety of the spermatogenic cycle some effects on male

reproduction could have been missed. No effects on male or female reproduction were seen in a combined repeated dose and reproductive/developmental toxicity screening test (JMHLW 1993; OECD 1995; Eastman Chemical 2007; ECHA, 2011a), but that study also did not include the entirety of the spermatogenic cycle.

Developmental effects were limited to decreased fetal body weight and skeletal variations (increased incidence of unossified sternebrae and bent ribs) at a maternal dose of more than 1000 mg/kg-day. The decreased fetal body weight is likely secondary to maternal decreased food consumption due to poor palatability, and the variations resolve postnatally and are of minimal severity.

There is sufficient evidence to support the conclusion that TPIB is not a direct acting genotoxicant (Eastman Chemical, 2007; JMHLW, 1993).

No data on the potential carcinogenicity of TPIB via any route were located.

8 References

Astill BD, Terhaar CJ, Fassett DW. 1972. The toxicology and fate of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. Toxicology and applied pharmacology. 22(3):387–99

Bönisch U, Böhme A, Kohajda T, Mögel I, Schütze N, et al. 2012. Volatile Organic Compounds Enhance Allergic Airway Inflammation in an Experimental Mouse Model. *PLoS ONE*. 7(7):e39817

Bui TT, Giovanoulis G, Cousins AP, Magnér J, Cousins IT, deWit CA 2016. Human exposure, hazard and risk of alternative plasticizers to phthalate esters. Sci Total Environ. 541:451-467.

Cain WS, Wijk RA, Jalowayski AA, Pilla Caminha G, Schmidt R. 2005. Odor and chemesthesis from brief exposures to TXIB. Indoor Air. 15(6):445–57

CPSC. 2014. Chronic Hazard Advisory Panel of Phthalates and Phthalate Alternatives. Consumer Product Safety Commission (CPSC), Bethesda, MD

David R., Lockhart L., Ruble K. 2003. Lack of sensitization for trimellitate, phthalate, terephthalate and isobutyrate plasticizers in a human repeated insult patch test. Food and Chemical Toxicology. 41(4):589–93

Danish Environmental Protection Agency (DEPA). 2010. Identification and assessment of alternatives to selected phthalates. Environmental Project No. 1341 2010. Available: http://www2.mst.dk/udgiv/publications/2010/978-87-92708-00-7/pdf/978-87-92708-01-4.pdf . [Cited in Patton, 2010].

Eastman Chemical. 2001. Reproduction/developmental toxicity screening test in the rat with 2,2,4-trimethyl-1,3-pentanediol diiosbutyrate - final report w/cover letter dated 082401. U.S. EPA/OPTS Public Files; Fiche #: OTS0560045-1; Doc#: 89010000299. TSCATS.

Eastman Chemical. 2002. Eastman Plasticizers Selector Chart. Publication L-174L, June 2002. [Cited in Patton, 2010].

Eastman Chemical. 2006a. Eastman TXIB formulation additive for vinyl plastisols. Available: http://www.eastman.com/Literature_Center/L/L231.pdf. [Cited in Patton, 2010].

Eastman Chemical. 2006b. Eastman TXIB Formulation Additive technical tip. TT-78A. [Cited in Patton, 2010].

Eastman Chemical. 2007. Toxicity summary for Eastman ® TXIB Formulation Additive. Available: http://www.cpsc.gov/about/cpsia/docs/EastmanTXIB11282007.pdf.

Eastman Chemical. 2009. Eastman product data sheet for TXIB. Available: http://www.eastman.com/ProductCatalogApps/PageControllers/ProdDatasheet_PC.aspx?Product=71066420&sCategoryName=Generic. [Cited in Patton, 2010].

Eastman Chemical. 2010. Eastman TXIB Formulation Additive. Product overview. Available: http://www.eastman.com/Brands/Eastman_TXIB/Pages/Overview.aspx. [Cited in Patton, 2010]

Eastman Chemical. 2014. TSCA 8(e) submission for 2,2,4-trimethyl-1-3-pentanediol diisobutyrate. (CASRN 6846-50-0). Letter from Prakash Surana, July 10, 2014. CBIC Control Number 360936.

ECHA. 2011. *1-Isopropyl-2,2-dimethyltrimethylene diisobutyrate.* European Chemicals Agency (ECHA). https://echa.europa.eu/registration-dossier/-/registered-dossier/13895/7/6/2.

ECHA. 2011. Annex XV Restriction Report. Proposal for a Restriction. European Chemical Agency (ECHA). Available at: https://echa.europa.eu/documents/10162/c6781e1e-1128-45c2-bf48-8890876fa719

EFSA. 2006. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request related to a 12th list of substances for food contact materials. Question N° EFSA-Q-2004-073, EFSA-Q-2006-024, EFSA-Q-2005-238a, EFSA-Q-2005-238b, EFSA-Q-2005-238c, EFSA-Q-2006-012, EFSA-Q-2006-027. *EFSA Journal*. 395–401:1–21

Hard GC, Johnson KJ, Cohen SM. 2009. A comparison of rat chronic progressive nephropathy with human renal disease—implications for human risk assessment. *Critical Reviews in Toxicology*. 39(4):332–46

HSDB. 2010. *2,2,4-trimethyl-1,3-pentanediol-diisobutyrate.* Hazardous Substance Data Bank (HSDB), U.S. National Library of Medicine (NLM), National Institutes of Health, Health & Human Services, Bethesda MD. http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+8097

IUCLID. 2000. IUCLID Dataset for 2,2,4-Trimethyl-1,3-pentanediol-diisobutyrate. International Uniform Chemical Information Database (IUCLID).
Available: http://ecb.jrc.ec.europa.eu/iuclid-datasheet/6846500.pdf .

IUCLID. 2011. IUCLID Dataset for 2,2,4-Trimethyl-1,3-pentanediol-diisobutyrate. International Uniform Chemical Information Database (IUCLID). Available:
http://ecb.jrc.ec.europa.eu/iucliddatasheet/6846500.pdf.

Järnström H, Saarela K, Kalliokoski P, Pasanen A-L. 2008. Comparison of VOC and ammonia emissions from individual PVC materials, adhesives and from complete structures. *Environ Int*. 34(3):420–27

JMHLW. 1993. Japan Existing Chemical Data Base(JECDB). Test report on 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (6846-50-0). Abstract only. Japanese Ministry of Health, Labor, and Welfare (JMHLW). Available: http://dra4.nihs.go.jp/mhlw_data/home/file/file6846-50-0.html

Kim JL, Elfman L, Mi Y, Wieslander G, Smedje G, Norbäck D. 2007. Indoor molds, bacteria, microbial volatile organic compounds and plasticizers in schools -- associations with asthma and respiratory symptoms in pupils. *Indoor Air*. 17(2):153-163. [Cited in Patton, 2010].

Krasavage WJ, Tischer KS, Roudabush RL. 1972. The reversibility of increased rat liver weights and microsomal processing enzymes after feeding high levels of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. *Toxicology and Applied Pharmacology*. 22(3):400–408

Maddalena R, Russell M, Sullivan DP, Apte MG. 2009. Formaldehyde and other volatile organic chemical emissions in four FEMA temporary housing units. *Environ. Sci. Technol.* 43(15):5626–32

Norbäck D, Wieslander G, Edling C. 1995. Occupational exposure to volatile organic compounds (VOCs), and other air pollutants from the indoor application of water-based paints. *The Annals of Occupational Hygiene*. 39(6):783–94

OECD. 1995. Screening Information Dataset (SIDS) initial assessment report for 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate. Organisation for Economic Co-operation and Development (OECD). Available: http://www.inchem.org/documents/sids/sids/6846500.pdf. [Cited in Patton, 2010].

Patton LE. 2010. Memorandum: CPSC Staff Toxicity Review of Two Phthalates and One Phthalate Alternative for Consideration by the Chronic Hazard Advisory Panel. Consumer Product Safety Commission (CPSC), Bethesda, MD

Rosell L. 1990. High Levels of a Semi-VOC in Indoor Air due to Emission from Vinyl Floorings. Indoor Air ’90, The 5th International Conference on Indoor Air Quality and Climate, Toronto, July 29 August 3, 1990, Volume 3, pages 707–712. Abstract only.

U.S. EPA. 1988. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. EPA/600/6-87/008. U.S. Environmental Protection (EPA), Washington DC

U.S. EPA. 1991. Alpha2µ-Globulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Male Rat. EPA/625/3-91-019F. U.S. Environmental Protection (EPA), Risk Assessment Forum, Washington, DC.

U.S. EPA. 2002. Hepatocellular hypertrophy. HED guidance document #G0201. Prepared by the HED Toxicology Science Advisory Council (ToxSAC). October 21, 2002.

U.S. FDA. 2004. IV.C.4.a: Subchronic Toxicity Studies with Rodents. In *Redbook 2000: Toxicological Principles for the Safety Assessment of Food Ingredients*. U.S. Food and Drug Administration (FDA)

Wieslander G, Janson C, Norbäck D, Björnsson E, Stålenheim G, Edling C. 1994. Occupational exposure to water-based paints and self-reported asthma, lower airway symptoms, bronchial hyperresponsiveness, and lung function. *Int Arch Occup Environ Health*. 66(4):261–67

Wieslander G, Norback D, Bjornsson E, Janson C, Boman G. 1997. Asthma and the indoor environment: the significance of emission of formaldehyde and volatile organic compounds from newly painted indoor surfaces. *International archives of occupational and environmental health*. 69(2):115–24

APPENDIX 1

Search Terms Used

“2,2,4-Trimethyl-1,3-pentanediol diisobutyrate” OR “Isobutyric acid, 1-isopropyl-2,2-dimethyltrimethylene ester” OR “Kodaflex TXIB” OR “TXIB” OR “1,3-Pentanediol, 2,2,4-trimethyl-, diisobutyrate (ester)” OR “1-Isopropyl-2,2-dimethyltrimethylene diisobutyrate” OR “Propanoic acid, 2-methyl-, 1,1'-(2,2-dimethyl-1-(1-methylethyl)-1,3-propanediyl) ester” OR “Propanoic acid, 2-methyl-, 2,2-dimethyl-1-(1-methylethyl)-1,3-propanediyl ester” OR “2,2,4-Trimethyl-1,3-pentanediol ester” OR (6846-50-0) OR "2,2,4-trimethyl-1,3-pentanediol monoisobutyrate" OR "Texanol"

APPENDIX 2

Explanation of Physico-chemical Parameters

The organic carbon normalized solid-water partition coefficient (K_{oc}), also known as the organic carbon adsorption coefficient, is defined as the ratio of the chemical's concentration in a state of sorption (i.e. adhered to soil particles) and the solution phase (i.e. dissolved in the soil water). K_{oc} is crucial for estimating a chemical compound's mobility in soil and the prevalence of its leaching from soil. For a given amount of chemical, the smaller the K_{oc} value, the greater the concentration of the chemical in solution. Thus, chemicals with a small K_{oc} value are more likely to leach into groundwater than those with a large K_{oc} value (http://www.acdlabs.com/products/phys_chem_lab/logd/koc.html).

Henry's law, one of the gas laws formulated by William Henry, states that "at a constant temperature, the amount of a given gas dissolved in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid (http://en.wikipedia.org/wiki/Henry's_law)." Henry's Law Constants characterize the equilibrium distribution of dilute concentrations of volatile, soluble chemicals between gas and liquid phases (http://www.epa.gov/athens/learn2model/part-two/onsite/esthenry.htm).

The octanol/water partition coefficient (K_{ow}) is defined as the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system. In recent years, this coefficient has become a key parameter in studies of the environmental fate of organic chemicals. It has been found to be related to water solubility, soil/sediment adsorption coefficients, and bioconcentration factors for aquatic life. Because of its increasing use in the estimation of these other properties, K_{ow} is considered a required property in studies of new or problematic chemicals (http://www.pirika.com/chem/TCPEE/LOGKOW/ourlogKow.htm).

The bioconcentration factor (BCF) is the concentration of a particular chemical in a tissue per concentration of chemical in water (reported as L/kg). This property characterizes the accumulation of pollutants through chemical partitioning from the aqueous phase into an organic phase, such as the gill of a fish. The scale used to determine if a BCF value is high, moderate or low will depend on the organism under investigation. The U.S. EPA generally defines a high potential BCF as being greater than 5,000; a BCF of moderate potential as between 5,000 and 100; a low potential BCF as less than 100 (http://en.wikipedia.org/wiki/Bioconcentration_factor; http://sitem.herts.ac.uk/aeru/footprint/en/Quest/ecotox.htm).