United States
Environmental Protection
Agency

EPA/690/R-07/031F
Final
5-01-2007

Provisional Peer Reviewed Toxicity Values for

n-Propyl alcohol
(CASRN 71-23-8)

Superfund Health Risk Technical Support Center
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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR n-PROPYL ALCOHOL (CASRN 71-23-8)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5 year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and

circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

No oral reference dose (RfD) for n-propyl alcohol is available on IRIS (U.S. EPA, 2007) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2004). The HEAST (U.S. EPA, 1997) includes a note that data were inadequate for subchronic or chronic RfD derivation; the source document for this determination was a Health and Environmental Effects Document (HEED) for n-propyl alcohol (U.S. EPA, 1987). In addition to the HEED, the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) includes a Health and Environmental Effects Profile (HEEP) for n-propyl alcohol that also declined to derive toxicity values due to inadequate data (U.S. EPA, 1983). The Agency for Toxic Substances and Disease Registry (ATSDR, 2006) has not assessed the health effects of n-propyl alcohol. An Environmental Health Criteria document that did not derive any oral risk assessment values is available from the World Health Organization (WHO, 1990).

An RfC for n-propyl alcohol is not available on IRIS (U.S. EPA, 2007). The HEAST (U.S. EPA, 1997) indicates that data are inadequate for subchronic or chronic RfC derivation. The World Health Organization (WHO, 1990) did not derive any inhalation risk assessment values for n-propyl alcohol. The American Conference for Governmental Industrial Hygienists (ACGIH, 2006) recommends a TLV-TWA of 200 ppm and TLV-STEL of 400 ppm for n-propyl alcohol based on animal models of sensory irritation and its structure-activity relationship to isopropanol. The National Institute for Occupational Safety and Health (NIOSH, 2006) recommended exposure limit (REL) and Occupational Safety and Health Administration (OSHA, 2006) permissible exposure limit (PEL) for n-propyl alcohol are 200 ppm TWA.

A cancer assessment for n-propyl alcohol is not available on IRIS (U.S. EPA, 2007). The HEED (U.S. EPA, 1987) assigned n-propyl alcohol to U.S. EPA (1986) Cancer Group C (possible human carcinogen), based on increased incidences of total malignant tumors in orally and subcutaneously treated rats and liver sarcomas in subcutaneously treated rats (Gibel et al., 1974, 1975). These findings were also used as a basis for an ACGIH (2006) cancer notation of A3 (confirmed animal carcinogen with unknown relevance to humans) for n-propyl alcohol. The carcinogenicity of n-propyl alcohol has not been assessed by NTP (2006) or IARC (2006).

Literature searches were conducted from the 1960's through August, 2006 for studies relevant to the derivation of provisional toxicity values for n-propyl alcohol. Data bases searched included: TOXLINE/TOXCENTER (including BIOSIS, NTIS and Chemical Abstracts subfiles), MEDLINE (including PubMed cancer subset), TSCATS/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents.

REVIEW OF PERTINENT DATA

Human Studies

Relevant information regarding the toxicity of n-propyl alcohol in humans was not located.

Animal Studies

Oral Exposure. Groups of 5-6 male Wistar rats (4 months old) were exposed to n-propyl alcohol in drinking water at concentrations of 2 M (mol/L) for 2 months or 1 M for 4 months (Hillbom et al., 1974a,b). Unspecified numbers of control rats received tap water. Both groups of exposed rats consumed constant amounts of n-propanol in drinking water throughout the test periods, but consumption data were only reported for the 1 M group (4.8 mmol/100 g-day). Multiplying the mean n-propyl alcohol intake of 4.8 mmol/100 g-day (48 mmol/kg-day) by 60.09 g/mol (molecular weight of n-propyl alcohol) yields a dose of 2884 mg/kg-day for the 1 M group; the dose for the 2 M group can be estimated to be twice as high at 5768 mg/kg-day. Food consumption, total caloric intake and body weight were evaluated at 2884 mg/kg-day, and liver weight and liver histology were evaluated at 2884 and 5768 mg/kg-day; additional end points were not assessed. The rats exposed to 2884 mg/kg-day for 4 months had a reduced ratio of weight gain to caloric intake (not quantified) which, according to the authors, suggested possible interference with food utilization. Slight, non-significant increases in relative liver weight were seen in both treatment groups. Absolute liver weights were not reported. Histological examination of the livers showed no inflammation, cirrhosis, hepatic steatosis, increase in liver fat or other changes in the rats exposed to 2884 mg/kg-day for 4 months or 5768 mg/kg-day for 2 months, although it was noted that Mallory alcoholic hyaline bodies were observed in some of the rats (incidence not reported) at 5768 mg/kg-day. Mallory bodies are characteristic of alcoholic hepatitis, although also seen in other conditions as well; these are fibrillar proteins of intracytoplasmic inclusions within swollen hepatocytes that contain little or no fat (Merck, 2006). The toxicological significance of these bodies is uncertain. The researchers conclude

there was “no clear hepatotoxic effect” in this study. Therefore, the high dose of 5768 mg/kg-day is identified as a NOAEL.

Groups of 10 Wistar rats (sex not reported) were exposed to drinking water containing 0 or 320,000 mg/L of n-propyl alcohol for 5, 9 or 13 weeks (Wakabayashi et al., 1984). Using a conversion factor of 0.15 L/kg-day based on the average of male and female subchronic reference values for water consumption and body weight in Wistar rats (U.S. EPA, 1988), the estimated dose is 48,000 mg/kg-day. The exposed rats gradually became weak, lost their appetites and showed decreased body weight gain. Ultrastructural studies of the liver showed induction of irregularly shaped megamitochondria with few cristae, as well as normally sized but irregularly shaped mitochrondria with reduced numbers of cristae. Biochemical changes included a decreased state 3 respiration using glutamate as a substrate, and decreased specific activities of cytochrome c oxidase and monoamine oxidase. Additional information was not reported in the available summary of this study (WHO, 1990). The lack of other kinds of liver evaluations (e.g., histology or serum enzymes) precludes assessing the toxicological significance of the mitochondrial ultrastructural changes and identification of a NOAEL or LOAEL.

A chronic oral study was conducted in which a group of 18 Wistar rats of both sexes were administered n-propyl alcohol by gavage at a dose level of 0.3 mL/kg (241 mg/kg using a specific gravity of 0.804 g/mL) on 2 days/week from 10 weeks of age for life (Gibel et al., 1974, 1975). A control group of 25 rats was similarly exposed to saline. Average survival time was 570 days in the n-propyl alcohol-exposed rats and >643 days in the controls. This study included parallel experiments in which rats were chronically exposed to n-propyl alcohol by subcutaneous injection and chronically exposed to two other alcohols by gavage and subcutaneous injection. Referring to all three alcohols and both routes, the authors reported that a strong hepatotoxic effect was observed in virtually all treated rats, as shown by histological findings that included steatosis, necrosis and cirrhosis. Changes in the myocardium, such as the appearance of narrow scars resulting from necrosis of the heart muscle, were reported in some rats, as were a few instances of pancreatitis and fibrosis; although the alcohol(s) producing these effects were not specified, similar actions by the three alcohols are inferred. Hematological effects and hyperplasia of the hematopoietic parenchyma of the bone marrow were specifically attributed to n-propyl alcohol. Incidences of non-neoplastic lesions were not reported. Due to the inclusion of a single dose level, episodic exposure regimen (gavage, 2 days/week) and poor reporting of results, this study is of limited utility for non-cancer risk assessment.

n-Propyl alcohol-specific tumorigenicity data were reported by Gibel et al. (1974, 1975). The rats that were orally treated with n-propyl alcohol had a total of 5 malignant and 10 benign tumors. The malignant tumors were identified as two myeloid leukemias, one hepatocellular carcinoma, and two liver sarcomas. No malignant tumors occurred in the control group, although a total of three benign tumors were observed. The benign tumors in the treated and control rats were mostly papillomas of the anterior stomach and mammary fibroadenomas. It is not clear if individual rats had more than one tumor. If each malignant tumor occurred in a different rat, the total incidences of malignant tumors would be 5/18 treated and 0/25 control rats, a difference that is statistically significant ($p=0.009$) by the Fisher Exact test. None of the incidences of individual tumor types are significantly increased.

Inhalation Exposure. Limited information on the short-term inhalation toxicity of n-propyl alcohol is available from an early study in which mice were exposed to concentrations in the range of 0.1-0.2 cm^3 liquid/15 L air (Weese, 1928). Using a liquid density of 0.804 g/cm^3 for n-propyl alcohol and assuming that all of the liquid volatilized, the vapor concentrations ranged from 5330-10,660 mg/m^3 (2185-4370 ppm). The following exposures were conducted using one mouse for each: 2185-4370 ppm for 7.5 hours/day for 8 of 9 days, 3715-4370 ppm for 7.5 hours/day for 14 of 15 days, 2622 ppm for 8.75 hours/day for 14 of 16 days, 2622 ppm for 6.75 hours/day for 24 of 28 days, and 2185-3715 ppm for 8.75 hours/day for 25 of 28 days. Use of controls was not mentioned. Liver, kidneys, heart and lungs were examined histologically. The main effect was fatty degeneration of the liver, which occurred in varying degrees in the mice exposed to 2185-4370 ppm for 14 of 16 days and longer and was considered reversible. The reliability of these data is questionable due to the small number of animals, apparent lack of controls, uncertainty regarding the actual exposure concentrations, variable exposure schedules, reporting insufficiencies and other study limitations.

The developmental toxicity of n-propyl alcohol was evaluated in groups of 15 female Sprague-Dawley rats that were exposed to 0, 3500, 7000 or 10,000 ppm (0, 8602, 17,204 or 24,578 mg/m^3) n-propyl alcohol for 7 hours/day on gestation days 1-19 and sacrificed on gestation day 20 (Nelson et al., 1988). Maternal body weight, food and water consumption and clinical signs were assessed throughout the exposure period. Developmental end points included numbers of pregnancies, corpora lutea, resorptions and live fetuses, and external (all fetuses), skeletal (half of the fetuses) and visceral (remaining fetuses) abnormalities. No maternal or developmental effects were observed at 3500 ppm. Maternal food intake (data not shown in original report) was reduced during the last 2 weeks of gestation at 7000 ppm and throughout gestation at 10,000 ppm, and maternal body weight gain was reduced during the last 2 weeks of gestation at 10,000 ppm (~40% less than controls on gestation day 20). Resorptions were increased at 10,000 ppm; 3/15 litters were totally resorbed, and there were significant ($p \leq 0.05$) changes in resorbed implants/litter (increased, 57% compared to 6% in controls) and live implants/litter (decreased, 43% compared to 94% in controls). Mean fetal body weight was significantly ($p \leq 0.05$) reduced at 7000 and 10,000 ppm in both sexes; at 3500, 7000 and 10,000 ppm, fetal weight was 0.6, 17.7 and 46.2% less than controls in males, and 0.9, 16.8 and 46.2% less than controls in females.

The incidence of fetal total external malformations was significantly ($p \leq 0.05$) increased at 10,000 ppm (9/12 litters and 34/94 fetuses compared to 0/15 and 0/206 in controls), mostly due to short or missing tail ($p > 0.05$) or ectrodactyly (missing fingers or toes) ($p > 0.05$) (Nelson et al., 1988). The incidence of total skeletal malformations was significantly ($p \leq 0.05$) increased at 7000 ppm (9/15 litters and 19/95 fetuses) and 10,000 ppm (12/12 litters and 22/48 fetuses) compared to controls (1/15 litters and 1/100 fetuses), mostly due to rudimentary cervical ribs ($p > 0.05$); incidences of skeletal variants were not increased. The incidence of total visceral malformations was significantly ($p \leq 0.05$) increased at 10,000 ppm (10/10 litters and 26/46 fetuses compared to 4/15 and 4/106 in controls), mainly due to various cardiovascular or urinary system malformations ($p > 0.05$ for specific defects); incidences of visceral variants were not increased. For maternal toxicity, this study identified a NOAEL of 7000 ppm (17,204 mg/m^3) and LOAEL of 10,000 ppm (24,578 mg/m^3) based on reduced body weight gain. For developmental toxicity, a NOAEL of 3500 ppm (8602 mg/m^3) and LOAEL of 7000 ppm (17,204

mg/m^3) were identified, based on decreased fetal weight and increased total skeletal malformations at ≥7000 ppm and increased resorptions and external and visceral malformations at 10,000 ppm. The results of this study suggest that the developing organism may be a sensitive target for propyl alcohol.

A behavioral teratogenicity study of n-propyl alcohol in Sprague-Dawley rats was performed by Nelson et al. (1989). Groups of 18 males were exposed to 0, 3500 or 7000 ppm (0, 8602 or 17,204 mg/m^3) n-propyl alcohol for 7 hours/day, 7 days/week for 6 weeks and, after 2 nonexposure days, mated with unexposed females. Groups of 15 females were mated with unexposed males and exposed to the same concentrations of n-propyl alcohol for 7 hours/day on gestation days 1-19. Litters in both maternally and paternally exposed groups were culled to 4 males and 4 females and fostered by untreated females. Endpoints included mating performance and fertility, maternal food and water intake, maternal body weight, pup body weight through postnatal day 35, and pup behavioral performance and brain neurochemistry. Behavioral tests were conducted on one male and one female pup per litter per dose group during postnatal days 10-60; testing assessed neuromuscular coordination (ascent on wire mesh and rotorod performance), exploratory activity (open field and optically monitored activity), circadian activity (running wheel), aversive learning (avoidance conditioning), and appetitive learning (operant conditioning). Brain neurochemistry (protein, acetylcholine, serotonin, dopamine, norepinephrine, β-endorphin, substance P, and Met-enkephalin) was evaluated in one male and one female pup from 5 litters per dose group on PND 21.

Male fertility was reduced at 7000 ppm, as shown by litter production in 2/16 mated males compared to 18/18 in controls (Nelson et al., 1989). Successful mating by the 16 males was demonstrated by the presence of sperm plugs; of the remaining 2/18 males, one male died as a result of fighting and another did not mate. Six of the 7000 ppm males were remated at biweekly intervals to see if the infertility was reversible; litter production in week 1, 3, 5, 7, 9, 11, 13 and 15 was 1/6, 2/6, 4/6, 4/6, 4/6, 3/6, 6/6 and 6/6, respectively, indicating a reversibility of the effect. Females exposed to 7000 ppm during pregnancy had significantly ($p \leq 0.05$) reduced food intake (20, 16 and 13% less than controls in weeks 1, 2 and 3, respectively), but showed no effect on weight gain. No significant differences were found among any of the groups for number of live pups per litter, gestation length, birth weight, neonatal survival or pup weight gain. External examination of the offspring showed that 2/15 litters from the 7000 ppm maternally exposed group had several pups (2-3/litter) with crooked tails; these defects were noted soon after birth and persisted. The behavioral and neurochemical tests showed no exposure-related effects in the offspring of either exposed males or females. This study identified a NOAEL of 3500 ppm and LOAEL of 7000 ppm for male reproductive toxicity (infertility). While not statistically increased, the external tail malformations observed in the 7000 ppm maternal exposure group are consistent with the results of the earlier teratogenicity study (Nelson et al., 1988). The 7000 ppm level was a NOAEL for postnatal neurotoxicity in offspring of exposed males and females.

Other Studies

Effects of n-propyl alcohol on brain development in neonatal rats were studied by Grant and Samson (1984). Neonatal Long Evans rats (n=28, sex not specified) were reared using an

artificial feeding technique (surgically implanted gastric catheter) from postnatal days (PNDs) 5-18. Half of the pups were gastrically infused with n-propyl alcohol in an artificial milk formula in mean daily doses of 3800, 7500, 3000 and 7800 mg/kg on PND 5, 6, 7 and 8, respectively; these pups subsequently received untreated milk formula until PND 18. The doses were administered in 20-minute feeds every 2 hours with a total of 12 feeds per day. The remaining pups were controls that received untreated milk formula from PNDs 5-18. A total of 21 pups completed the experiment; 7 deaths resulted from surgical complications (4) or apparent overdoses (3). Endpoints assessed during PNDs 5-18 included clinical signs, body weight, and developmental landmarks (emergence of teeth, eye opening and outer ear development). The pups were sacrificed on PND 18 for organ weight measurements (brain, liver, kidneys, heart) and brain biochemical analysis (DNA, cholesterol and protein in forebrain, cerebellum and brainstem). The pups were observed to be intoxicated during the treatment period on PNDs 5-8, frequently showing an impaired righting response, and displayed withdrawal symptoms 8-24 hours after the last exposure. Total absolute brain weight was significantly ($p<0.001$) reduced in the exposed pups (25.5% less than controls) with no changes in weights of the body or other organs. The biochemical analysis showed that the exposed pups had significantly decreased amounts of DNA in the three brain areas, cholesterol in the forebrain and cerebellum, and protein in the forebrain. The results suggested to the authors that exposure to n-propyl alcohol during the brain growth spurt in neonatal rats inhibits brain development in a manner similar to ethanol.

A chronic subcutaneous study was conducted in which a group of 31 Wistar rats of both sexes were injected with n-propyl alcohol at a dose level of 0.06 mL/kg (48.2 mg/kg using a specific gravity of 0.804 g/mL) on 2 days/week from 10 weeks of age for life (Gibel et al., 1974, 1975). A control group of 25 rats was similarly treated with saline. Average survival time was 643 days in the exposed rats and >643 days in the controls. This study also included parallel experiments in which rats were chronically exposed to n-propyl alcohol by gavage and chronically exposed to two other alcohols by gavage and subcutaneous injection. Referring to all three alcohols and both routes, the authors reported that a strong hepatotoxic effect was observed in virtually all treated rats, as shown by histological findings that included steatosis, necrosis and cirrhosis. Although incidences of non-neoplastic liver lesions were not reported, n-propyl alcohol-specific tumorigenicity data were provided. Histological examinations in the n-propyl alcohol subcutaneous study showed a total of 15 malignant and 7 benign tumors in the treated group and 0 malignant and 2 benign tumors in the control group. The malignant tumors in the treated rats were identified as one local sarcoma, four myeloid leukemias, five liver sarcomas, one uterine carcinoma, two splenic sarcomas, one renal pelvic carcinoma and one cystic carcinoma. The benign tumors in treated and control rats were mostly papillomas of the anterior stomach and mammary fibroadenomas. It is not clear if individual rats had more than one tumor. If each malignant tumor occurred in a different rat, the incidences of liver sarcomas (5/31 treated and 0/25 controls) and total malignant tumors (15/31 treated and 0/25 controls) were significantly increased ($p=0.044$ and $p<0.001$, respectively, by Fisher Exact test).

A limited amount of information is available on the genotoxicity of n-propyl alcohol. Negative results were obtained in *in vitro* assays for reverse mutations in *Salmonella typhimurium* TA98 and TA100 (Khudoley et al., 1987; Stolzenberg and Hine, 1979), DNA damage in *Escherichia coli* PQ37 (Mersch-Sundermann et al., 1994), sister-chromatid exchanges

in Chinese hamster ovary and V79 cells (Obe and Ristow, 1977; von der Hude et al., 1987), and micronuclei in Chinese hamster V79 cells (Lasne et al., 1984).

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR n-PROPYL ALCOHOL

Subchronic RfD

Information on the subchronic oral toxicity of n-propyl alcohol is available from two drinking water studies in rats. In one of the studies (Hillbom et al., 1974a,b), rats were exposed to 2884 mg/kg-day for 4 months or 5768 mg/kg-day for 2 months. This study found no significant effects on food consumption, body weight, or liver weight or histology, making the dose of 5768 mg/kg-day a NOAEL. However, it cannot be determined whether the NOAEL is protective of other potential effects of n-propyl alcohol, such as neurotoxicity, because end points other than food consumption, body weight gain and liver histology were not evaluated. The other study (Wakabayashi et al., 1984) was even more limited, with rats evaluated only by an ultrastructural evaluation of the liver that found minor mitochondrial changes (e.g., irregular shape and reduced numbers of cristae) of uncertain toxicological significance. Therefore, the available data are inadequate to support derivation of a subchronic RfD.

Chronic RfD

The data base for chronic oral toxicity of n-propyl alcohol consists of one lifetime study in which 18 rats were exposed to 241 mg/kg by gavage 2 times a week (Gibel et al., 1974, 1975). Due to poor reporting of results, it is unclear what observations pertain specifically to oral exposure to propyl alcohol, as other routes and substances were tested and the results presented only as generalities. However, it does appear that degenerative liver lesions (e.g., steatosis, necrosis and cirrhosis) were observed in exposed animals, and average survival time was reduced. Due to the inclusion of a single dose level, episodic exposure regimen (gavage, 2 days/week) and poor reporting of results, this study is inadequate to support derivation of an RfD.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR n-PROPYL ALCOHOL

Subchronic RfC

Information on the subchronic inhalation toxicity of n-propyl alcohol is available from one systemic toxicity study in mice and two developmental toxicity studies in rats. In the systemic toxicity study (Weese, 1928), a total of 5 mice were exposed to concentrations ranging from 2185-4370 ppm for 6.75-8.75 hours/day for 8-25 days. Liver degeneration was observed in 4 of the 5 mice (i.e., those exposed for $\geq$14 days), but the reliability of the effect level is questionable due to the small number of animals, apparent lack of controls, uncertainty regarding

the actual exposure concentrations, variable exposure schedules, reporting insufficiencies and other study limitations.

Both of the developmental toxicity studies are comprehensive in design and well reported. In one of the studies (Nelson et al., 1988), female rats were exposed to 3500, 7000 or 10,000 ppm for 7 hours/day on gestation days 1-19. This is a conventional teratogenicity study that identified a NOAEL of 7000 ppm and LOAEL of 10,000 ppm for maternal toxicity (reduced body weight gain) and a NOAEL of 3500 ppm and LOAEL of 7000 ppm for prenatal developmental toxicity (decreased fetal weight and increased total skeletal malformations, with additional effects at 10,000 ppm). The other study (Nelson et al., 1989) is a behavioral teratogenicity study that included postnatal evaluations of behavioral performance and brain chemistry in offspring of females that were exposed to 3500 or 7000 ppm for 7 hours/day on gestation days 1-19, and in offspring of untreated females that were mated to males that were exposed to 3500 or 7000 ppm for 7 hours/day, 7 days/week for 6 weeks prior to mating. This study identified a NOAEL of 3500 ppm and LOAEL of 7000 ppm for male reproductive toxicity (infertility), as well as a NOAEL of 7000 ppm for postnatal neurotoxicity in offspring of exposed males and females.

Although 3500 ppm is an apparent NOAEL for male reproductive, maternal and developmental toxicity, including postnatal neurotoxicity (a potential effect of concern for n-propyl alcohol), it is not known if 3500 ppm is a NOAEL for systemic toxicity, because maternal endpoints were limited to clinical signs, body weight, and food and water consumption (Nelson et al., 1988, 1989). Other studies indicate that the liver is a target for n-propyl alcohol. Fatty liver degeneration occurred in the short-term inhalation study of mice exposed to 2185-4370 ppm (Weese, 1928), but study limitations preclude identification of a reliable effect level. Chronic oral exposure induced steatosis, necrosis and cirrhosis in the liver of rats (Gibel et al., 1974). The available information, therefore, suggests that exposures below the 3500 ppm NOAEL for developmental toxicity may be hepatotoxic, but derivation of a subchronic RfC is precluded by the unreliability of the mouse study (Weese, 1928) and the lack of information on liver toxicity and other systemic effects in the developmental toxicity studies in rats (Nelson et al., 1988, 1989).

Chronic RfC

There are no chronic inhalation toxicity studies of n-propyl alcohol available. Derivation of a chronic RfC is precluded by the lack of suitable data.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR n-PROPYL ALCOHOL

Weight-of-evidence Classification

Information on the carcinogenicity of n-propyl alcohol is limited to the results of one gavage and one subcutaneous study in which a single dose level (241 and 48 mg/kg, respectively) was administered to rats on 2 days/week for life (Gibel et al., 1974, 1975).

Findings included low, but statistically significant, increases in incidences of total malignant tumors in the gavage study and total malignant tumors and liver sarcomas in the subcutaneous study, as well as hepatotoxicity (lesions that included steatosis, necrosis and cirrhosis) in most treated rats in both studies and decreased survival time in the gavage study. Although there were apparent increases in total malignant tumors by both routes and liver sarcomas by subcutaneous injection, the studies are inadequate for carcinogenicity assessment due to limitations that include the use of single dose levels, doses that exceeded the maximum tolerated dose (as shown by the liver damage and decreased survival time), low dosing frequency (twice weekly), small numbers of animals (18/route) for a cancer bioassay, and lack of information on the histological type of liver sarcoma.

A limited amount of information is available on the genotoxicity of n-propyl alcohol, which did not induce reverse mutations in *S. typhimurium* (Khudoley et al., 1987; Stolzenberg and Hine, 1979), DNA damage in *E. coli* (Mersch-Sundermann et al., 1994), or sister-chromatid exchanges or micronuclei in Chinese hamster cells (von der Hude et al., 1987; Obe and Ristow, 1977) in *in vitro* assays.

In accordance with current EPA cancer guidelines (U.S. EPA, 2005), the available data are inadequate for an assessment of human carcinogenic potential.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for propyl alcohol is precluded by the lack of suitable data.

REFERENCES

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