Provisional Peer-Reviewed Toxicity Values for

Triacetin
(CASRN 102-76-1)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Jason C. Lambert, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

ICF International
9300 Lee Highway
Fairfax, VA 22031

PRIMARY INTERNAL REVIEWERS

Ghazi Dannan, PhD
National Center for Environmental Assessment, Washington, DC

Zheng (Jenny) Li, PhD, DABT
National Center for Environmental Assessment, Washington, DC

This document was externally peer reviewed under contract to
Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

CONTENTS

COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
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
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
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR
TRIACETIN (CASRN 102-76-1)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

INTRODUCTION

Triacetin, also known as glyceryl triacetate (CAS No. 102-76-1), is a colorless, oily liquid with a slightly fatty odor and a mild, sweet taste that is bitter at concentrations above 0.05% (see Figure 1). Occupational exposure to triacetin can occur through dermal contact and inhalation at production sites during operations such as cleaning, sampling, analysis, and drum filling. Triacetin has the following uses in consumer products: a solvent for celluloid and photographic films; a plasticizer for cigarette filters; a fungicide in cosmetics; a fixative in perfumery; and a general purpose food additive. A table of physicochemical properties is provided below (see Table 1).
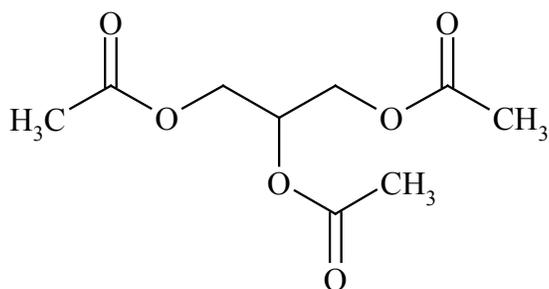
Figure 1. Triacetin Structure

Table 1. Physicochemical Properties of Triacetin (CASRN 102-76-1)[a]	
Property (unit)	**Value**
Boiling point (ºC)	258−259
Melting point (ºC)	3
Density (g/cm^3)	1.1562
Vapor pressure (mm Hg at 25ºC)	0.00248
pH (unitless)	7
Solubility in water (g/100 mL at 25ºC)	5.8−7.0
Relative vapor density (air = 1)	7.52
Molecular weight (g/mol)	218.21

[a]ACGIH (2011), ChemIDPlus (2011), OECD (2002).

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for triacetin is included on the U.S. EPA IRIS database (U.S. EPA, 2010a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). No RfD or RfC values are reported in the HEAST (U.S. EPA, 2010b). The Chemical Assessments and Related Activities (CARA) list does not include a Health and Environmental Effects Profile (HEEP) for triacetin (U.S. EPA,

1994). The toxicity of triacetin has not been reviewed by the ATSDR (2011), and the World Health Organization does not list an Environmental Health monograph for triacetin (WHO, 2011). CalEPA (2008, 2009) has not derived toxicity values for exposure to triacetin. No occupational exposure limits for triacetin have been derived or recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), the National Institute of Occupational Safety and Health (NIOSH, 2010), or the Occupational Safety and Health Administration (OSHA, 2011).

The HEAST (U.S. EPA, 2010b) does not report a cancer weight-of-evidence (WOE) classification or an oral slope factor (OSF) for triacetin. The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of triacetin. Triacetin is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2008) has not derived a quantitative estimate of carcinogenic potential for triacetin.

Triacetin has been reviewed by several committees worldwide and is considered safe under specified exposure scenarios (Ellis and Rodford, 1996). An estimate of the cumulative oral intake in the United Kingdom suggests that an adult might ingest 7.8 mg triacetin/day, and the daily intake was calculated to be 0.111 mg/kg-day (OECD, 2002). The Database of Select Committee on GRAS Substances (SCOGS) Reviews Report No. 30, Glycerin and Glycerides (U.S. FDA, 1975) states that triacetin has been found to be without toxic effects in long-term feeding tests in rats at levels that were several orders of magnitude greater than those to which consumers are exposed. Triacetin was exempted from the requirement of a tolerance when used as a solvent or cosolvent in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals [40 CFR 180.930]. The United States Food and Drug Administration (U.S. FDA) concluded that triacetin is generally recognized as safe (GRAS) when used: as a food additive [21 CFR 184.1901]; in food or food packaging [21 CFR 181.27]; as a general purpose food additive in animal drugs, feeds, and related products [21 CFR 582.1901]; or in certain over the counter drug products [21 CFR 310.545]. The Cosmetic Ingredients Review Expert Panel concluded that triacetin is safe as used in cosmetic formulations (Fiume, 2003). The Joint FAO/WHO Expert Committee on Food Additive (JECFA) considered it unnecessary to assign an acceptable daily intake (ADI), as triacetin is metabolized in the same manner as other dietary triglycerides. In various assessments of triacetin, the JECFA concluded that, based on the available data and anticipated daily intake, triacetin did not represent a hazard to health (JECFA, 1975, 2002). In a separate evaluation, the European Union's Scientific Committee for Food endorsed the JECFA position for triacetin (Commission for the European Communities: Scientific Committee for Food, 1992).

Literature searches were conducted on sources published from 1900 through December 2011 for studies relevant to the derivation of provisional toxicity values for triacetin (CASRN 102-76-1). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases;

SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); WHO; and Worldwide Science. The following databases outside of HERO were searched for health-related values: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA
(CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for triacetin and includes all potentially relevant repeated-dose subchronic- and chronic-duration studies. Principal studies are identified. The phrase "statistical significance" used throughout the document, indicates a *p*-value of <0.05.

HUMAN STUDIES
Oral Exposures
The effects of oral exposure of humans to triacetin have been evaluated in two separate subchronic case studies (Madhavarao et al., 2009; Segel et al., 2011).

Subchronic-Duration Studies
Madhavarao et al. (2009)
In a peer-reviewed study, Madhavarao et al. (2009) administered triacetin in infant formula to a 13-month-old girl and an 8-month-old boy for 6 and 4.5 months, respectively. The initial dose was 25 mg/kg twice daily (50 mg/kg-day) for the first week, followed by a doubling each subsequent week up to a maximum dose of 250 mg/kg twice daily (500 mg/kg-day). These infants were previously diagnosed with Canavan disease, a fatal dysmyelinating genetic disorder characterized by mutations in the enzyme aspartoacylase, resulting in a greatly reduced or absent capacity to hydrolyze the brain metabolite *N*-acetylaspartate to acetate and aspartate. Triacetin was selected for use as a dietary supplement as it is known to be an acetate precursor. The stated aim of this study was to determine the tolerability of low-dose oral triacetin administration in infants having Canavan disease. This study received Institutional Review Board approval and obtained parental consent. The following outcome criteria were evaluated prior to initiation of treatment and reviewed at 4 months of treatment: neurological status, brain magnetic resonance imaging and magnetic resonance spectroscopy, urine *N*-acetylaspartate levels, and ophthalmoscopic examination. Treatment-related effects were screened clinically and by blood work-up of complete blood count, kidney function, electrolytes, liver function, and venous blood gas measurements.

The study authors did not identify a NOAEL or LOAEL; however, they stated that oral administration of triacetin caused no detectable toxicity, and that the infant patients showed no deterioration in their clinical status (Madhavarao et al., 2009). The NOAEL is 500 mg/kg-day; a LOAEL was not determined under the conditions tested.

Table 2. Summary of Potentially Relevant Data for Triacetin								
Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-d)								
Acute[c]	ND							
Short-term[d]	ND							
Subchronic[e]	1/1 infant patients, feeding, 6 mo. exposure (girl) or 4.5 mo. exposure (boy); case study	25 mg/kg twice daily (50 mg/kg-d), doubling weekly to 250 mg/kg twice daily (500 mg/kg-d) (Adjusted)	No effects	500	NDr	NDr	Madhavarao et al. (2009)	PR
Subchronic[e]	1/1 infant patients, feeding, 6 mo. exposure (boy) or 4.5 mo. exposure (girl); case study	500 mg/kg four times daily (2,000 mg/kg-d), doubling every 3 d to 4,500 mg/kg-d	No effects (discomfort reported in both children by parents at 5,000 mg/kg-d; maximum dose titrated back to 4,500 mg/kg-d)	4,500	NDr	NDr	Segel et al. (2011)	PR
Chronic[f]	ND							
2. Inhalation (mg/m³)								
Acute[c]	ND							
Short-term[d]	ND							
Subchronic[e]	ND							
Chronic[f]	ND							

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Table 2. Summary of Potentially Relevant Data for Triacetin								
Animal								
1. Oral (mg/kg-d)								
Short-term[d]	0/8, S-D rat, feeding, 18 d	13,869; 25,670; 25,843 (Adjusted)	No adverse effects	25,843	NDr	NDr	Shapira et al. (1969) (Concentration of triacetin was not the only variable; multiple other dietary factors included in exposure source confounds interpretation; protein levels impacted body-weight gain)	PR
Subchronic[e]	0/8, S-D rat, feeding, 30 d	16,367 (Adjusted)	No adverse effects	16,367	NDr	NDr	Lynch et al. (1994) (Limited scope of endpoints examined for toxicity; multiple other dietary factors included in exposure source confounds interpretation)	PR
Subchronic[e]	0/8, S-D rat, feeding, 30 d	16,367 (Adjusted)	No adverse effects	16,367	NDr	NDr	Lynch and Bailey (1995) (Limited scope of endpoints examined for toxicity; multiple other dietary factors included in exposure source confounds interpretation)	PR
Subchronic[e]	12/12 S-D rat, gavage, 41−48 d from 14 d prior to mating to Postpartum Day (PPD) 3	0, 40, 200, or 1,000 (Adjusted)	No adverse effects	1,000	NDr	NDr	MHW (1998) (This was a combined OECD repeated dose and reproductive/developmental toxicity screening test [OECD TG 422])	NPR

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Subchronic[e]	0/8, S-D rat, feeding, 12−13 wk	17,228; 25,843 (Adjusted)	Decreased body weight, increased liver weight (The toxicological significance of these findings could not be ascertained)	ND	NDr	NDr	Shapira et al. (1975) (Concentration of triacetin was not the only variable; the toxicological significance of these findings could not be ascertained)	PR
Subchronic[e]	Unreported number and sex, rat, feeding and drinking, approximately 110−120 d	4,200 during Postnatal Days (PNDs) 7−14, 5,800 during PNDs 15−22/23, 7099 in food and 7,504 in water, totaling 14,603 for the remaining treatment period (Adjusted)	No adverse effects	14,603 (feed and water doses combined)	NDr	NDr	Madhavarao et al. (2009) (Deficiencies in reporting of study details limits interpretation of results)	PR
Chronic	ND							
Reproductive/ Developmental	**12/12 S-D rat, gavage, 41−48 d from 2 wk prior to mating to PPD 3**	**0, 40, 200, or 1,000 (Adjusted)**	**No adverse effects in dams or offspring**	**F0: 1,000 F1: 1,000**	**NDr**	**NDr**	**MHW (1998)** (Systemic toxicity including reproductive parameters examined in dams; health status of offspring also examined)	**NPR; PS**
Carcinogenicity	ND							
2. Inhalation (mg/m^3)								
Short-term[d]	ND							
Subchronic[e]	3/3 rat, (strain unreported) whole-body vapor inhalation, 6 h/d, 5 d/wk, 103 d	397 for 90 d; 2 additional wk at 117 followed by 13,181 (saturated vapor)	No adverse effects	397	NDr	NDr	Fassett (1955) as summarized in OECD (2002)	NPR; original document could not be obtained

Table 2. Summary of Potentially Relevant Data for Triacetin

Table 2. Summary of Potentially Relevant Data for Triacetin								
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[a]**	**Critical Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (Comments)**	**Notes[b]**
Subchronic[e]	3 rat (sex and strain unreported), 6 h/d, 5 d/wk, 64 d	398; 13,181	No adverse effects	13,181	NDr	NDr	Unichema Chemie B.V. (1994) as summarized by Fiume (2003)	NPR; original document could not be obtained
Subchronic[e]	Unreported number and sex, rat, heated vapor, 6 h/d, 5 d/wk, 13 wk	398	No adverse effects	398	NDr	NDr	Fassett (1963) as summarized by Ellis and Rodford (1996)	PR; original document could not be obtained
Chronic[f]	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure.

  HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood gas partition coefficient.

[b]Notes: IRIS = Utilized by IRIS, date of last update; PS = principal study, PR = peer reviewed, NPR = not peer reviewed.

[c]Acute = Exposure for 24 hr or less (U.S. EPA, 2002).

[d]Short-term = Repeated exposure for >24 hr ≤30 d (U.S. EPA, 2002).

[e]Subchronic = Repeated exposure for >30 d up to approximately 10% of the lifespan in humans (based on 70-yr typical human lifespan; >30–90 days in typically used laboratory animal species) (U.S. EPA, 2002).

[f]Chronic = Repeated exposure for ≥10% lifespan (U.S. EPA, 2002).

DU = data unsuitable, NA = not applicable, NV = not available, ND = no data, NDr = not determinable, NI = not identified, NP = not provided, NR = not reported, NR/Dr = not reported but determined from data, NS = not selected, S-D = Sprague-Dawley.

Segel et al. (2011)

Similar to the Madhavarao et al. (2009) study above, Segel et al. (2011) administered triacetin in infant formula to a 12-month-old boy and an 8-month-old girl for 6 and 4.5 months, respectively. Both of the infants were previously diagnosed with Canavan disease, and as such, triacetin was being evaluated for efficacy as a dietary supplement (as explained under Madhavarao et al. [2009] above). The stated aim of this study was to determine the tolerability and efficacy of high-dose triacetin administration in infants with Canavan disease. The initial dose was 500 mg/kg four times daily (2,000 mg/kg-day) for the first 3 days, followed by a doubling of dose every 3 days up to a maximum dose of 4,500 mg/kg-day (the target maximum dose was 5,000 mg/kg-day, but the parents reported 'discomfort' in each child at this specific dose). The children were evaluated prior to treatment and at 4.5 months after the initiation of treatment for the following outcomes: neurological status, brain magnetic resonance imaging and magnetic resonance spectroscopy, urine *N*-acetylaspartate levels, and ophthalmoscopic examination. Treatment-related effects were screened clinically and by blood work-up of complete blood count, kidney function, electrolytes, liver function, and venous blood gas measurements.

The study authors did not identify a NOAEL or LOAEL; although the study authors did state that administration of triacetin caused no detectable toxicity in either patient at a daily dose of 4,500 mg/kg-day; at the highest dose attempted (5,000 mg/kg-day), the study authors alluded to a potential problem with gastric acidity (Segel et al., 2011). The NOAEL is 4,500 mg/kg-day for lack of effects in human infants; a LOAEL was not determined under the conditions tested.

Chronic-Duration Studies
No studies were identified.

Developmental Studies
No studies were identified.

Reproduction Studies
No studies were identified.

Carcinogenicity Studies
No studies were identified.

Inhalation Exposures
No studies were identified.

ANIMAL STUDIES
Oral Exposures
The effects of oral exposure of animals to triacetin have been evaluated in one short-term (Shapira et al., 1969) and five subchronic studies (MHW, 1998; Madhavarao et al., 2009; Lynch et al., 1994; Lynch and Bailey, 1995; Shapira et al., 1975). Additionally, the MHW study (1998) also evaluated reproductive toxicity.

Short-term Studies

Shapira et al. (1969)

In a peer-reviewed study, Shapira et al. (1969) developed a system capable of serving a regenerative food supply. A mixture of triacetin, glycerol, and *Hydrogenomonas eutropha* (bacteria, rich in protein) was used as a food supplement and a major portion of the diet. Groups of eight male weanling Sprague-Dawley rats were fed one of 12 different diets for 18 days, containing low, medium, or high protein contents (12, 24, and 48% protein, respectively), along with variable carbohydrate sources, including triacetin. The different protein and carbohydrate contents of the 12 diets are shown in Table B-1.

The adjusted doses for triacetin are calculated to be 13,869, 25,670, and 25,843 mg/kg-day for the diets containing triacetin at 16.1, 29.8, and 30% (by weight), respectively. In addition to the dietary components shown above, all diets contained 5% USP XIV salt mixture (plus 16.5 mg $ZnSO_4$/100 g diet), 5% safflower oil, 2% α-cellulose, 1% vitamins, 1% agar, and a total of 2 parts water to each part dry weight. After formulation, the diets were stored at 4°C and fed fresh daily. The animals were caged as pairs and weighed daily. No mortality or clinical signs of toxicity were mentioned; however, the study authors did not report any evaluations other than body weights. It is not apparent from the report that statistical analyses were performed on the body-weight data. This study was performed as part of research into regenerative food systems performed at the Ames Research Center for NASA.

The study authors reported that growth was not adversely affected over 18 days when 29.8% triacetin (by weight in the diet; equivalent to 25,670 mg/kg-day) was included with 29.8% glycerol and 27% protein from *H. eutropha* (minimally affected when protein was casein; see Table B-1). The authors stated that these data show that over 90% of the calories of the diet of growing rats can be composed of a mixture of *H. eutropha*, glycerol, and triacetin without a detrimental effect on the growth of the animal. However, these results also demonstrate that adequate nutritional needs must be met with regards to protein levels. When fed similar amounts of triacetin (29.8−30%), animals fail to achieve the expected body-weight gain when fed the low protein diet, but not when fed the medium protein diet. The study authors did not define a NOAEL or LOAEL; however, the highest dose of 25,843 mg/kg-day showed no adverse effects; therefore, the NOAEL is 25,843 mg/kg-day. A LOAEL for triacetin is not available under the conditions tested. The study authors reported only limited information to assess the toxicity of this compound in this 18-day study, and the dietary exposure to rats included multiple supplements in addition to triacetin; therefore, this study is not considered suitable for derivation of a subchronic p-RfD.

The report by Shapira et al. (1969) also included general findings related to triacetin from a "number of three month feeding studies." However, because detailed methodology and data from these studies were not presented, these generalized findings are unsupported and are not included in this report.

Subchronic-Duration Studies

Lynch et al. (1994)

In a peer-reviewed study, Lynch et al. (1994), administered to eight Sprague-Dawley male rats one of three diets for 30 days: control diet, diet with 30% of the energy as corn oil, or diet with 30% of the energy as mainly short chain triglycerides (95% triacetin and 5% corn oil). All diets contained 20.6% protein (by percentage of calories), and 1.0%, 3.5%, and 5.0% weight

percent vitamins, minerals, and fiber, respectively. The triacetin-diet contained 19.0% triacetin by weight, which is equivalent to an adjusted dose of 16,367 mg/kg-day.

Rats were housed individually in plastic metabolism cages (Lynch et al., 1994). Food intake was measured daily, and body weights were determined at Day 0 and every 5 days thereafter. Animals were euthanized after 30 days, and blood was collected. Nonfasting plasma glucose, triglycerides, total ketone bodies, free fatty acids, lactate, and pyruvate were measured. Jejunal and colon segments were excised and weighed. Intestinal mucosal cells were analyzed for DNA, RNA, and protein content. The protein-DNA ratio for each group was calculated as an index of cell size. Other jejunal and colon segments were fixed in neutral buffered formalin, processed routinely, and analyzed by light microscopy to determine villus height in the jejunum and crypt depth in the colon. Carcasses were eviscerated, frozen, and homogenized with an equivalent weight of water. Aliquots were removed and lyophilized for determination of percent moisture. All data were analyzed by analysis of variance (ANOVA) to determine significant statistical differences among groups caused by diet. When a significant difference was observed, Duncan's Multiple Range Test was used to further analyze the differences. This study did not include relevant evaluation of hematology, clinical chemistry, urinalysis, organ weights, or gross or microscopic pathology.

Lynch et al. (1994) stated that there were no adverse, treatment-related effects observed on mortality, clinical signs, body weights, food consumption, lactate, ketone body, glucose concentrations, mean villus height, intestinal crypt depth, and carcass composition. Compared to the control group, plasma free fatty acids were decreased ($p < 0.05$) by 44%, and plasma triglycerides were increased ($p < 0.05$) by 22%. DNA content was increased ($p < 0.05$) by approximately 68% in the colon mucosa. RNA content was decreased ($p < 0.05$) by approximately 33% in the jejunum. The protein:DNA ratio was decreased ($p < 0.05$) by 38% in the jejunum. The study authors reported no NOAEL or LOAEL; however, the only dose of triacetin tested, 16,367 mg/kg-day, showed no toxic effects; therefore, the NOAEL is 16,367 mg/kg-day. A LOAEL is not available under the conditions tested. The study authors reported only limited information to assess the toxicity of this compound in this study; therefore, this study is not suitable for derivation of a subchronic p-RfD.

Lynch and Bailey (1995)
In a peer-reviewed study by Lynch and Bailey (1995), eight Sprague-Dawley male rats were administered one of three diets for 30 days, with one of the diets containing 19% triacetin by weight (adjusted dose of 16,367 mg/kg-day). The study methodology was the same as described previously in Lynch et al. (1994). In the present study, the adipose cell size and number (as measured by a Coulter counter) for epididymal, perirenal, and inguinal fat depots were reported.

Lynch and Bailey (1995) reported that mean adipose cell size in the triacetin-treated group was less than the control for the epididymal, inguinal, and perirenal fat depots, but cell number was unaffected. A moisture-free sample was used to determine percent lipid with a modified Soxhlet method. Percent protein was determined with the Kjeldahl method, and the percent ash was determined by combustion. The study authors reported no NOAEL or LOAEL; however, the only dose tested, 16,367 mg/kg-day, showed no toxic effects. Therefore, the NOAEL is 16,367 mg/kg-day, and a LOAEL is not available under the conditions tested. The

study authors reported only the limited results detailed above to assess the toxicity of this compound in this study; therefore, this study is not suitable for derivation of a subchronic p-RfD.

Ministry of Health and Welfare, Japan (MHW, 1998)

This study (MHW, 1998) was performed by the Kashima Laboratory of the Mitsubishi Chemical Safety Institute in accordance with the OECD combined repeated dose and reproductive/developmental toxicity screening test guideline (OECD TG 422). Twelve Sprague-Dawley [Crj:CD (SD) IGS] rats/sex (males: 317−375 g; females: 203−240 g; 9 weeks old) were administered triacetin (>98.2% purity) in 3% aqueous gum arabic by gavage once daily at doses of 0, 40, 200, or 1,000 mg/kg-day. Males were dosed for 44 days beginning 2 weeks prior to mating; females were dosed for 41−48 days from 14 days before mating to Postpartum Day (PPD) 3.

In the adults, mortality/morbidity and clinical signs of toxicity were recorded once a day (MHW, 1998). Body weights were measured on Days 0, 3, 7, and 14 of premating in both sexes. Body weights were also measured on Days 21, 28, 35, and 42, and at termination in the males, and on Gestation Days (GD) 0, 7, 14, and 20, PPDs 0 and 4, and at termination in the females. Food consumption (g/rat/day) was recorded for: Days 0−3, 3−7, and 7−14 in both sexes; Days 21−28, 28−35, and 35−42 in the males; and GDs 0−7, 7−14, 14−20, and PPD 0−4 in the females. The following hematological and clinical chemistry parameters were determined in blood collected from males at termination: erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte ratio, thrombocytes, leukocyte differential counts, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, alanine phosphatase, total bilirubin, urea nitrogen, glucose, total cholesterol, triglyceride, total protein, albumin, albumin:globulin ratio, calcium, inorganic phosphorus, sodium, potassium, and chloride. Urinalysis was not performed. It was stated that absolute and relative organ weights were recorded for brain, pituitary, thyroid, heart, liver, kidney, spleen, adrenal gland, thymus, testes, and epididymis; however, data were only presented for thymus, liver, spleen, kidney, adrenal, testes, and epididymis. At necropsy, the following tissues were collected from the controls and 1,000-mg/kg-day group: brain, spinal cord, pituitary, eye, thyroid (with parathyroid), thymus, heart, trachea, lung, liver, kidney, adrenal gland, spleen, stomach, small intestine, large intestine, pancreas, urinary bladder, bone marrow, sciatic nerve, lymph node, testes, epididymis, prostate, seminal vesicle, ovary, uterus, vagina, mammary gland, and any organ that might be expected to have histopathological changes. The following tissues were examined and reported in the histological findings: heart, thymus, spleen, esophagus, stomach, duodenum, liver, kidney, testes, epididymis, ovary, adrenal, brain, and skin. Reproductive data, including reproductive performance indices, delivery data, and litter size, and pup viability indices, pup body weights, and pup body-weight gains were presented. It was stated that the data were analyzed with the Kruskal-Wallis test for noncontinuous data, Dunnett's test, or Scheffe's test for continuous data, and the Chi-square test for quantal data. It was also stated that the study complied with Good Laboratory Practice (GLP) standards.

One 1,000-mg/kg-day male was found dead on Day 32 (MHW, 1998). This animal was observed grossly to have hemorrhage of the thymus and congestion of the lung, liver, and kidney; microscopic examination revealed slight diffuse hemorrhage of the thymus. In the absence of any evidence of systemic toxicity in any other animal at any dose level, this death is considered incidental to treatment. In the animals that survived to scheduled necropsy, triacetin

had no effects on clinical signs of toxicity, body weights, body-weight gains, food consumption, organ weights, or gross or histological pathology findings. Statistically significant decreases were observed in percent of band neutrophils and creatinine in the 40- and 1,000-mg/kg-day males; statistically significant increases in inorganic phosphorus were also noted in the 200-mg/kg-day males. These changes were stated to be within physiological ranges and/or were not dose-dependent. Reproductive and offspring results are discussed under the Reproductive/Developmental Studies section below. In the absence of any reliable finding of toxicity in treated adult rats, the NOAEL was determined to be 1,000 mg/kg-day; a LOAEL was not determined under the conditions tested.

Shapira et al. (1975)

In a peer-reviewed study, Shapira et al. (1975) fed groups of eight male Sprague-Dawley rats diets for 13 weeks containing various carbohydrates in order to investigate the feasibility of replacing starch with alternative carbohydrate sources. The study tested six types of diets: Diet 1 (control, 60% starch), Diet 2 (30% glycerol and 30% propylene glycol), Diet 3 (30% glycerol and 30% triacetin), Diet 4 (30% propylene glycol and 30% triacetin), Diet 5 (40% glycerol and 20% propylene glycol), and Diet 6 (40% glycerol and 20% triacetin). For the diets that included triacetin, the daily adjusted doses of triacetin were 17,228 and 25,843 mg/kg-day for 20 and 30% triacetin diets, respectively. Each diet also contained 27% casein and 5% safflower oil. Identical amounts of cellulose, salts, and vitamins were present in all diets. Rats were kept in pairs in stainless steel cages. For periods of 3−4 and 12−13 weeks, food consumption, body-weight gain, water intake, and liver weight were reported. It is not apparent from the report that statistical analyses were performed.

In this study (Shapira et al., 1975), body weights were decreased by 20% after 12−13 weeks on Diets 3 and 6 (triacetin with glycerol), but body weights were comparable for the control diet and Diet 4 (triacetin with propylene glycol). Water intake varied, and it is not possible to make conclusions without additional test groups where the concentrations of triacetin are varied (while other components remained the same). Body-weight gains as growth percent for periods of 3−4 and 12−13 weeks decreased 29−52% in all triacetin groups compared to the control group. However, due to the other variables in the dietary exposure media (e.g., casein, glycerol, or propylene glycol), it is difficult to attribute changes in body weight to triacetin alone. Alternatively, it is possible that feeding with 30% triacetin may have negatively impacted nutrition over the 13-week period. Regardless, this effect is not considered to be a clear indication of systemic toxicity for triacetin. Relative liver weights were increased by 41−67%. The study authors reported no NOAEL or LOAEL, and the data gaps are such that it is not possible to determine a NOAEL or LOAEL for this study. Insufficient toxicological parameters were examined in this study, and the impact of dietary protein was not sufficiently evaluated; therefore, this study is not considered suitable for derivation of a subchronic p-RfD.

Madhavarao et al. (2009)

In a peer-reviewed study by Madhavarao et al. (2009), wild-type and tremor rat pups (6−12 males or females per group) received triacetin orally twice daily, initially at a dose of 4.2 g/kg during Postnatal Days (PND)s 7−14, then at 5.8 g/kg during PNDs 15−23, and thereafter in both food (7.5%) and water (5%) for a total treatment period of 110−120 days. The calculated doses in food and water are 7,099 mg/kg-day and 7,504 mg/kg-day, respectively, yielding a total oral dose of 14,603 mg/kg-day after PND 23. The tremor rat model of aspartoacylase deficiency is a natural mutant strain that has the entire aspartoacylase gene

deleted. This rat model mimics Canavan disease in humans (described earlier in the Human Studies section [Madhavarao et al., 2009]); thus, this study was conducted to support the efficacy of oral triacetin supplementation for aspartate deficiency. These rats were bred at the Center of Laboratory Animal Medicine at the Uniformed Services University of the Health Sciences, Bethesda, MD, where the studies were conducted. The study authors did not clearly present the number or sex of rats treated. A subset of rats was treated for approximately 110 days, and food intake and body weights were measured on a regular basis throughout the study (schedule not reported). Another subset of rats was treated for approximately 120 days, euthanized, and histopathology and biochemical analyses (29 different blood serum analytes such as lipids, proteins, electrolytes [e.g., Na, Mg]) were conducted. A limited set of tissues were fixed in 10% neutral-buffered formalin. Brain, spinal cord, lung, heart, liver, kidney, stomach, small and large intestine, and spleen were processed routinely, and slides from 2−4 rats per group were examined microscopically. When the data satisfied the assumptions of normality and equal variance, one-way ANOVA was performed followed by the Holm-Sidak post hoc test. When the data failed the assumptions of normality or equal variance or both, Kruskal-Wallis ANOVA of the ranks was applied, and differences in ranks were compared by Dunn's method.

No significant differences in the mean blood chemistry values occurred between treated and untreated groups, and no lesions indicating toxicity were detectable in any of the tissues examined microscopically (Madhavarao et al., 2009). Although triacetin-treated rats displayed slightly decreased food consumption and decreased body weights, the differences in weights between the treated and untreated groups were not statistically significant (data not presented). The study authors reported no NOAEL or LOAEL; the treated rats showed no adverse effects. Therefore, the NOAEL is 14,603 mg/kg-day, and a LOAEL is not available under the conditions tested. The study authors stated that these data support the use of triacetin supplementation for effective treatment of infants diagnosed with aspartoacylase deficiency. However, the following information was not provided: (a) whether the study complied with GLP standards; (b) the purity of the test compound; and (c) rat husbandry conditions. Hematology, urinalysis, organ weights, and necropsy were not performed or were not reported. Histology was limited to 10 tissues, and samples from only 2−4 rats were examined in each group. Due to these data omissions, this study is not considered suitable for derivation of a subchronic p-RfD.

Chronic-Duration Studies
No studies were identified.

Developmental Studies
Please refer to offspring data provided in MHW (1998) below.

Reproductive/Developmental Studies
The study prepared for the Ministry of Health and Welfare, Japan (MHW, 1998) is selected as the principal study and deemed adequate for the derivation of screening level subchronic and chronic p-RfDs. In a combined repeated dose and reproductive toxicity screening study, 12 Sprague-Dawley [Crj:CD (SD) IGS] rats/sex were administered triacetin by gavage once daily at doses of 0, 40, 200, or 1,000 mg/kg-day. Males were dosed for 44 days beginning 2 weeks prior to mating; females were dosed for 41−48 days from 14 days before mating to PPD 3. The methodology of this study (MHW, 1998) was previously described under Subchronic Studies above. The results of the offspring and reproductive parameters are reported here.

No treatment-related effects were observed on copulation, fertility, implantation, number of corpora lutea, gestation length, or delivery in exposed dams (MHW, 1998). No treatment-related effects were noted for the limited number of developmental parameters examined such as viability, offspring born alive, and offspring alive at PND 4. In addition, offspring body weights for triacetin-treated groups were similar to controls at PNDs 0 and 4. Although the study authors reported no NOAEL or LOAEL for reproductive effects, the highest dose of 1,000 mg/kg-day showed no adverse reproductive effects. Furthermore, triacetin exposure before, during, and immediately after pregnancy did not result in overt toxicity in offspring. Therefore, the NOAEL for this study is 1,000 mg/kg-day for both offspring (developmental) and reproductive parameters. A LOAEL is not determined under the conditions tested.

Carcinogenicity Studies
No studies were identified.

Inhalation Exposures
The effects of inhalation exposure of animals to triacetin have been evaluated in 3 subchronic studies in rats: Fassett (1955); Unichema Chemie B.V. (1994); and Fassett (1963). The original citations for these studies cannot be obtained; the information from each study is obtained from the indicated summary articles.

Short-term Studies
No studies were identified.

Subchronic-Duration Studies
Fassett (1955), as summarized in OECD (2002)
Information for the non-peer-reviewed study by Fassett (1955) is reported in the OECD Screening Information Dataset (2002) robust summaries; the original citation cannot be obtained. In this study, three rats/sex (strain not reported) were exposed to triacetin vapor by whole–body vapor inhalation exposure for 6 hours/day, 5 days/week, at a concentration of 249 ppm (HEC is 397 mg/m^3) for 90 days. A concurrent control group was not exposed. It was stated that inhalation was further extended for another week at 73.72 ppm (HEC is 117 mg/m^3), followed by a week at 8,271 ppm (saturated vapor; HEC is 13,181 mg/m^3). Treating the animals at 73.72 ppm for an additional week after no observed effect from 13 weeks of treatment at 249 ppm is without apparent reason; therefore, the summary article may be mistaken. Body weights were recorded prior to the first exposure, every 2−9 days during testing, and prior to termination. Limited hematology (red and white blood cell counts and hemoglobin) and urinalysis (albumin and sugar) parameters were measured. Liver and kidneys were weighed, and microscopic findings for trachea, bronchi, lung, kidney, liver, and bladder were reported.

No symptoms of toxicity were noted during the exposure period (Fassett [1955], as summarized in OECD [2002]). Average daily weight gain was 2.2 g/rat and was considered normal. Hematological evaluation and urinalysis showed no abnormalities in any of the animals. No histopathological changes were observed at the time of necropsy. The study author reported an estimated NOAEL of 249 ppm (HEC is 397 mg/m^3) for the 90-day study. A LOAEL was not observed under the conditions tested. OECD (2002) stated that, although this inhalation study was considered to be useful, it did not fully comply with the current testing protocol. Due to the limited toxicity data, this study is not considered suitable for derivation of a subchronic p-RfC.

Unichema Chemie B.V. (1994), as summarized by Fiume (2003)

Information for the non-peer-reviewed study by Unichema Chemie B.V. (1994) was reported by Fiume (2003); the original citation could not be obtained. Three rats (sex and strain not reported) were exposed to 250 ppm (HEC is 398 mg/m^3) by inhalation for 6 hours per day, 5 days per week, for 64 days. Three rats were also exposed to 8,271 ppm (HEC is 13,181 mg/m^3) for 6 hours per day for 64 days. No adverse effect was observed. The study author reported a NOAEL of 13,181 mg/m^3; a LOAEL was not determined under the conditions tested. Due to the extremely limited toxicity data, this study is not considered suitable for derivation of a subchronic p-RfC.

Fassett (1963), as summarized by Ellis and Rodford (1996)

Information for the peer-reviewed study by Fassett (1963) was reported in a glycerol triacetate safety evaluation by Ellis and Rodford (1996); the original citation could not be obtained. Inhalation concentrations of triacetin averaging 250 ppm (HEC is 398 mg/m^3) for 6 hours per day, 5 days per week, for 13 weeks produced no symptoms or histopathology in rats (sex and strain not reported). No changes were reportedly seen in liver and kidney weights, blood counts, or urine analysis. This concentration is considered the NOAEL; a LOAEL is not determined under the conditions tested. Due to the extremely limited toxicity data, this study is not considered suitable for derivation of a subchronic p-RfC.

Chronic-Duration Studies
No studies were identified.

Developmental Studies
No studies were identified.

Reproduction Studies
No studies were identified.

Carcinogenicity Studies
No studies were identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Other studies that are not appropriate for selection of a point of departure (POD) for triacetin and the determination of p-RfD, p-RfC, p-OSF, or p-IUR values may, however, provide supportive data supplementing a WOE approach to hazard identification and dose-response assessment. These studies may include, but are not limited to, information regarding toxic mode-of-action/mechanistic details, metabolism/toxicokinetics, or potential adverse health outcomes following shorter-term (e.g., <30-days) exposure durations. Although some acute/short-term duration studies exist for triacetin, the experimental designs involved the intravenous route of exposure, which is not necessarily relevant for informing hazard or dose response via the oral or inhalation routes and, thus, are not included.

Genotoxicity

Four genotoxicity studies are available indicating that triacetin has no mutagenic potential (Litton Bionetics, Inc. [1976a,b], Unichema Chemie B.V. [1994], and Efremova [1962]) and are presented in Table 3 and summarized briefly below.

Litton Bionetics, Inc. (1976a) evaluated the mutagenic potential of triacetin in an Ames plate and suspension test using *Salmonella typhimurium* (strains TA1535, TA1537, and TA1538) with and without metabolic activation. Test concentrations were 0.000325%, 0.00065%, and 0.0013% (w/v). Doses were selected based on the results of a preliminary toxicity test. The activation systems included S9 prepared from the liver of male ICR mouse, S-D rat, or Rhesus monkey. A negative control (solvent) and appropriate positive controls were used and gave expected results. Triacetin was not mutagenic with or without metabolic activation.

Table 3. Summary of Triacetin Genotoxicity Studies						
			Results[b]			
Endpoint	**Test System**	**Dose Concentration[a]**	**Without Activation**	**With Activation**	**Comments**	**References**
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium* TA1535, TA1537, and TA1538 in the Ames plate test or suspension test with or without S9	0, 0.000325, 0.00065, and 0.0013%	-	-	Negative and positive controls gave the expected results	Litton Bionetics, Inc. (1976a)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA98, and TA100 in the Ames plate test with or without S9	0, 50−5,000 µg/plate	-	-	The source document could not be obtained. This information is from a review	Unichema Chemie B.V. (1994), as summarized by Fiume (2003)
Gene conversion	*Saccharomyces cerevisiae* strain D4 in a suspension test with or without S9	0, 1.25, 2.5, and 5%	-	-	Negative and positive controls gave the expected results	Litton Bionetics, Inc. (1976b)
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	*Drosophila melanogaster*	0.2−0.3 mg	-	-	The source document could not be obtained. This information is from a review	Efremova (1962), as summarized in Fiume (2003)

[a]Lowest effective dose for positive results, or, highest dose tested for negative results.
[b]- = negative, NA = not applicable, ND = no data.

No evidence of mutagenic potential was obtained in an Ames test using *S. typhimurium* (strains TA1535, TA1537, TA98, and TA100) with and without metabolic activation at concentrations up to 5,000 µg/plate (Unichema Chemie B.V., 1994). The source document could not be obtained; this information was provided in the *Final Report on the Safety Assessment of Triacetin* (Fiume, 2003).

Litton Bionetics, Inc. (1976b) evaluated the mutagenic potential of triacetin in a suspension test using *Saccharomyces cerevisiae* strain D4 with and without metabolic activation. Test concentrations were 1.25%, 2.5%, and 5.0% (w/v). Doses were selected based on the results of a preliminary toxicity test. The activation systems included S9 prepared from the liver of male ICR mouse, S-D rat, or Rhesus monkey. Appropriate negative and positive controls were used and gave expected results. Triacetin did not result in gene conversions in the suspension test with or without metabolic activation.

Efremova (1962) treated adult *Drosophila melanogaster* with a dose of 0.2−0.3 mg triacetin in an in vivo assay and found triacetin not to be mutagenic. The source document could not be obtained; this information was provided in the *Final Report on the Safety Assessment of Triacetin* (Fiume, 2003).

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer reference values. Table 5 presents a summary of cancer values. No cancer values could be derived. IRIS data are indicated in the table, if available.

Table 4. Summary of Noncancer Reference Values for Triacetin							
Toxicity Type (Units)	**Species/ Sex**	**Critical Effect**	**Reference Value**	**POD Method**	**POD$_{HED}$**	**UFc**	**Principal Study**
Screening Subchronic p-RfD (mg/kg-day)	Rat/M/F	No effects observed	8×10^1	NOAEL	240	3	MHW (1998)
Screening Chronic p-RfD (mg/kg-day)	Rat/M/F	No effects observed	8×10^1	NOAEL	240	3	MHW (1998)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

NDr = not determinable.

Table 5. Summary of Cancer Values for Triacetin				
Toxicity Type	**Species/Sex**	**Tumor Type**	**Cancer Value**	**Principal Study**
p-OSF	NDr			
p-IUR	NDr			

NDr = not determinable.

DERIVATION OF ORAL REFERENCE DOSE
Derivation of Subchronic and Chronic Provisional RfD (p-RfD)
Studies identified for the oral route of exposure provided no evidence of triacetin toxicity (i.e., highest doses evaluated were all NOAELs). This was due, in part, to the prevalence of factors that confounded interpretation of hazard (resulting in a lack of hazard) and dose-response (e.g., dietary supplements in the exposure medium that might have conferred cytoprotective properties on target tissues). The combined subchronic/developmental/reproductive study performed for the Ministry of Health and Welfare, Japan (MHW, 1998) was the only study identified that did not suffer from confounding study design conditions, and it is deemed the principal study for the derivation of subchronic and chronic p-RfDs. However, because it cannot be conclusively determined that this study is peer reviewed, and the attendant uncertainty of a hazard database comprised only of NOAELs, screening subchronic and chronic p-RfDs are derived in Appendix A.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS
Derivation of Subchronic and Chronic Provisional RfC (p-RfC)
Three subchronic inhalation studies were located; however, the original documents for these studies could not be obtained. The available data suggest that a saturated triacetin vapor atmosphere of up to 13,181 mg/m^3 can be tolerated without adverse effect for at least 64 days (Unichema Chemie B.V. [1994], as summarized by Fiume [2003]). However, the available summaries for these studies presented only limited experimental details and toxicity data. Due to these limitations, it is not possible to derive subchronic or chronic p-RfCs from these studies.

CANCER WOE DESCRIPTOR
Table 6 identifies the cancer WOE descriptor for triacetin. No data could be located regarding the carcinogenicity of triacetin. Therefore according to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is inadequate information to assess the human carcinogenic potential of triacetin.

Table 6. Cancer WOE Descriptor for Triacetin			
Possible WOE Descriptor	**Designation**	**Route of Entry (oral, inhalation, or both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	NA
"Likely to be Carcinogenic to Humans"	NS	NA	NA
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	NA
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No carcinogenicity studies were identified.**
"Not Likely to be Carcinogenic to Humans"	NS	NA	NA

NA = not applicable; NS = not selected.

MODE OF ACTION DISCUSSION

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) define mode-of-action "…as a sequence of key events and processes starting, with the interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation" (p. 1-10). Examples of possible modes of carcinogenic action for any given chemical include "…mutagenicity, mitogenesis, inhibition of death, cytotoxicity with reparative cell proliferation, and immune suppression" (p. 1-10). No carcinogenicity studies in human or animals were located (see the "Cancer WOE Descriptor" above).

Mutagenic Mode-of-Action

Triacetin was not mutagenic in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, or TA1538 in the Ames plate assay or suspension test, with or without metabolic activation. Triacetin did not result in gene conversion of *Saccharomyces cerevisiae* strain D4 in a suspension test, with or without metabolic activation. Triacetin did not result in mutation in *Drosophila melanogaster*, a eukaryotic organism. There are no available studies to evaluate mutagenic action, and there is no evidence of carcinogenic potential in humans or animals.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES
Derivation of provisional Oral Slope Factor (p-OSF)

No human or animal studies examining the carcinogenicity of triacetin following oral exposure were identified. Therefore, it is not possible to derive a p-OSF.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No human or animal studies examining the carcinogenicity of triacetin following inhalation exposure were identified. Therefore, it is not possible to derive a p-IUR.

APPENDIX A. PROVISIONAL SCREENING VALUES

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional subchronic or chronic p-RfDs for triacetin. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

DERIVATION OF SCREENING LEVEL ORAL REFERENCE DOSES
Derivation of a Screening Level Subchronic Provisional RfD (Screening Subchronic p-RfD)
The two available human studies (Madhavarao et al. [2009] and Segel et al. [2011]) were carefully evaluated in the selection of a principal study and POD. While NOAELs based on a lack of effect in human infants were identified in both of these studies, limitations in study design, questionable exposure compliance during the reported treatment period, and the preexistent disease condition of the infants raises concern over the reliability of the NOAELs. Specifically, only two infants were examined in both the Madhavarao et al. (2009) and Segel et al. (2011) studies. The study authors noted difficulties in maintaining the infants on treatment due to concerns raised by the parents; thus, the difference in exposure period between the male and female infants in each study. In addition, Segel et al. (2011) reported that one of the patients left the country (Israel) two weeks after commencing treatment; follow-up was purportedly monitored by a primary care physician, unrelated to the study, and in the new country of residence (not specified). Lastly, the infants were previously diagnosed with Canavan disease, which results in a significant decrement in acetate levels. Considering that triacetin is an acetate precursor, it is plausible that the triacetin exposures were in part augmenting the deficiency rather than inducing a potential toxicity. Neither human study was considered further for principal study or POD identification.

The study prepared for the Ministry of Health and Welfare, Japan (MHW, 1998) is selected as the principal study and is deemed adequate for the derivation of screening level subchronic and chronic p-RfDs. The MHW (1998) combined subchronic/developmental and reproductive study in rats provides the most complete evaluation of the toxicity of triacetin and identified a NOAEL of 1,000 mg/kg-day for lack of toxicity in either maternal F0 dams or F1 offspring. There are additional subchronic feeding studies (Shapira et al. [1969], Lynch et al. [1994], and Madhavarao et al. [2009]), suggesting that much higher levels of triacetin may be tolerated by rats without adverse effects. For example, the study by Shapira et al. (1969) indicates that triacetin can be tolerated in the diet up to levels that hinder nutrition (e.g., 25,843 mg/kg-day), and the studies by Madhavarao et al. (2009) and Lynch et al. (1994) indicate that rats can tolerate diets containing up to 14,603−16,367 mg/kg-day of triacetin without harm. However, it should be noted that all of these oral repeat-dose studies, except for the MHW (1998) study, employed exposures that included a host of additional dietary supplements (e.g.,

minerals, vitamins, protein, and carbohydrates) that might influence tissue kinetics and dynamics in response to triacetin. Indeed, acute oral exposure to triacetin alone in rats revealed lethal dose (LD_{50}) values ranging from >2,000−12,800 mg/kg (OECD, 2002). Mice appear to be slightly more sensitive, particularly females, to acute oral triacetin exposure with LD_{50}s ranging from 1,100−9,300 mg/kg (OECD, 2002). In addition, many of the repeat-dose studies were severely lacking in the number of toxicological parameters examined, including the studies by Lynch et al. (1994), Lynch and Bailey (1995), Shapira et al. (1969), and Shapira et al. (1975); thus, some caution is warranted in the interpretation of the higher NOAELs identified in these studies compared to MHW (1998).

The principal study (MHW, 1998) was performed by the Kashima Laboratory of the Mitsubishi Chemical Safety Institute in accordance with the OECD combined repeated dose and reproductive/developmental toxicity screening test guideline (OECD TG 422). Because it could not be conclusively determined that this study was peer reviewed and the fact that no effects were observed, screening values are derived below. An adequate number of animals were dosed for a subchronic duration at levels up to 1,000 mg/kg-day and included exposure to progeny during a potentially susceptible lifestage. The parental F0 animals were dosed for 41−48 days from 14 days before mating to PPD3; thus, F1 offspring were exposed throughout gestation and potentially indirectly until PND 4. In the absence of any finding of toxicity in offspring, the NOAEL is considered to be 1,000 mg/kg-day for F1 rats and is selected as the POD to derive both screening subchronic and chronic p-RfDs.

EPA guidance recommends expressing gestational exposures as a daily average during the period of exposure and not to extrapolate to lifetime exposure (U.S. EPA, 1991), so no duration adjustment was needed for each dose in the principal study. However, the POD was extrapolated to a corresponding human equivalent dose using the EPA's guidance document entitled, "Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose" (U.S. EPA, 2011). The Agency endorses a hierarchy of approaches for deriving human equivalent oral exposures (i.e., HEDs) from data in laboratory animals, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches can include using chemical-specific information, in the absence of a complete physiologically-based toxicokinetic model. In lieu of either chemical-specific kinetic models or data to inform the derivation of human equivalent oral exposures, EPA endorses body weight scaling to the ¾ power (i.e., $BW^{3/4}$) as a default approach to extrapolate toxicologically equivalent doses of orally administered agents from adult laboratory animals to adult humans for the purpose of deriving an oral RfD. No physiologically-based toxicokinetic modeling information exists for triacetin. Therefore, consistent with EPA guidance (U.S. EPA, 2011), the POD is converted to a HED employing a standardized dosimetric adjustment factor (DAF) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a BW_a of 0.25 kg for rats and a BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.24. Applying this DAF to the NOAEL identified from the MHW (1998) study yields a $NOAEL_{HED}$ as follows:

$$
\begin{aligned}
NOAEL_{HED} &= 1{,}000 \text{ mg/kg-day} \times DAF \\
&= 1{,}000 \text{ mg/kg-day} \times 0.24 \\
&= 240 \text{ mg/kg-day}
\end{aligned}
$$

The screening subchronic p-RfD for triacetin is derived as follows:

$$
\begin{aligned}
\textbf{Screening Subchronic p-RfD} &= NOAEL_{HED} \div UF_C \\
&= 240 \text{ mg/kg-day} \div 3 \\
&= 8 \times 10^1 \text{ mg/kg-day}
\end{aligned}
$$

Table A-1 summarizes the uncertainty factors (UFs) for the screening subchronic p-RfD for triacetin.

UF	Value	Justification
Table A-1. UFs for Screening Subchronic p-RfD of Triacetin		
UF_A	1	A UF_A of 1 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. Although several limitations in the Segel et al. (2011) human study (e.g., preexistent disease condition, confounded exposures) significantly decreases confidence in making inferences regarding potential differences in the toxicokinetics or toxicodynamics of triacetin between rats and humans, the NOAEL of 4,500 mg/kg-day identified in human infants (Madhavarao et al., 2009) is considerably greater than the NOAEL of 1,000 mg/kg-day identified in neonatal rats (MHW, 1998). Therefore, a UF_A of 1 is applied.
UF_D	3	A UF_D of 3 is selected even though there are no acceptable two-generation reproduction studies, or peer-reviewed developmental studies. However, the MHW (1998) study reported no reproductive or developmental toxicity associated with triacetin exposure. Additionally, the Cosmetic Ingredient Review Expert Panel concluded that triacetin does not present a risk of reproductive or developmental toxicity because it is metabolized to glycerol and acetic acid, which are not reproductive or developmental toxicants (Fiume, 2003). Although triacetin appears to be relatively inert in animals and humans during a potentially sensitive lifestage, acute oral exposure studies using triacetin alone have identified LD_{50}s as low as 2,000 mg/kg in rats. Considering the rat developmental POD of 1,000 mg/kg-day, there is some uncertainty in where a LOAEL for a significant biological effect from a triacetin-only repeat-dose (e.g., subchronic or chronic) study may occur along the dose-response continuum between the POD (NOAEL) of 1,000 mg/kg-day and LD_{50} of approximately 2,000 mg/kg. Therefore, a UF_D of 3 is applied.
UF_H	1	A UF_H of 1 is applied for intra-species differences to account for potentially susceptible individuals in human populations. Segel et al. (2011) demonstrated that infants, a sensitive human population, can tolerate daily doses of up to 4,500 mg/kg-d.
UF_L	1	A UF_L of 1 is applied for using a POD based on a NOAEL.
UF_S	1	A UF_S of 1 is applied because the exposure occurred during a developmental lifestage.
UF_C	3	

Derivation of a Screening Chronic Provisional RfD (Screening Chronic p-RfD)

No chronic toxicity study was located. Therefore, MHW (1998) was also used to derive the screening chronic p-RfD. While the principal study, POD, and resultant screening chronic p-RfD are the same as the screening subchronic p-RfD above, the derivation below is shown for completeness.

$$
\begin{aligned}
\text{Screening Chronic p-RfD} \;&=\; \text{NOAEL}_{HED} \div \text{UF}_C \\
&=\; 240 \text{ mg/kg-day} \div 3 \\
&=\; 8 \times 10^{1} \text{ mg/kg-day}
\end{aligned}
$$

Table A-2 summarizes the UFs for the screening chronic p-RfD for triacetin.

		Table A-2. UFs for Screening Chronic p-RfD of Triacetin
UF	**Value**	**Justification**
UF_A	1	A UF_A of 1 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. Although several limitations in the Segel et al. (2011) human study (e.g., preexistent disease condition, confounded exposures) significantly decreases confidence in making inferences regarding potential differences in the toxicokinetics or toxicodynamics of triacetin between rats and humans, the NOAEL of 4,500 mg/kg-day identified in human infants (Madhavarao et al., 2009) is considerably greater than the NOAEL of 1,000 mg/kg-day identified in neonatal rats (MHW, 1998). Therefore, a UF_A of 1 is applied.
UF_D	3	A UF_D of 3 is selected even though there are no acceptable two-generation reproduction studies, or peer-reviewed developmental studies. However, the MHW (1998) study reported no reproductive or developmental toxicity associated with triacetin exposure. Additionally, the Cosmetic Ingredient Review Expert Panel concluded that triacetin does not present a risk of reproductive or developmental toxicity because it is metabolized to glycerol and acetic acid, which are not reproductive or developmental toxicants (Fiume, 2003). Although triacetin appears to be relatively inert in animals and humans during a potentially sensitive lifestage, acute oral exposure studies using triacetin alone have identified LD_{50}s as low as 2,000 mg/kg in rats. Considering the rat developmental POD of 1,000 mg/kg-day, there is some uncertainty in a LOAEL for a significant biological effect from a triacetin-only repeat-dose (e.g., subchronic or chronic) study may occur along the dose-response continuum between the POD (NOAEL) of 1,000 mg/kg-day and LD_{50} of approximately 2,000 mg/kg. Therefore, a UF_D of 3 is applied.
UF_H	1	A UF_H of 1 is applied for intraspecies differences to account for potentially susceptible individuals in human populations. Segel et al. (2011) demonstrated that infants, a sensitive human population, can tolerate daily doses of up to 4,500 mg/kg-d.
UF_L	1	A UF_L of 1 is applied for using a POD based on a NOAEL.
UF_S	1	A UF_S of 1 is applied because the exposure occurred during a developmental lifestage.
UF_C	3	

APPENDIX B. DATA TABLES

Table B-1. Initial and Terminal Body Weights of Weanling Male S-D Rats Fed Diets Containing Various Levels of Triacetin for 18 Days[a]							
Target Protein Content	**Dietary Components by % Weight**					**Animal weight (g) ± SEM**	
	Protein Source		**Carbohydrate Source**				
	Casein	***H. Eutropha***	**Glycerol**	**Triacetin[b]**	**Starch**	**Original**	**Day 18**
12%	13.7	0	0	0	73.3	79.1 ± 2.9	152.8 ± 4.5
	13.7	0	30	30	13.3	78.0 ± 3.4	117.4 ± 4.3
	0	13.4	0	0	73.6	77.0 ± 5.0	148.6 ± 6.3
	0	13.4	30	30	13.6	77.0 ± 3.9	129.4 ± 6.3
24%	27.4	0	0	0	59.6	76.3 ± 2.9	186.9 ± 4.9
	27.4	0	29.8	29.8	0	84.1 ± 2.6	166.8 ± 6.9
	0	26.8	0	0	60.2	76.5 ± 4.2	182.9 ± 3.1
	0	26.8	29.8	29.8	0.2	74.9 ± 4.0	178.8 ± 3.4
48%	54.8	0	0	0	32.2	79.3 ± 1.7	181.0 ± 3.3
	54.8	0	16.1	16.1	0	78.6 ± 4.1	178.1 ± 5.1
	0	53.6	0	0	33.4	78.4 ± 3.2	204.3 ± 13.1
	0	53.6	16.7	16.1	0	83.3 ± 3.1	191.5 ± 8.3

[a]Source: Shapira et al. (1969).
[b]The three dietary levels of triacetin (16.1, 29.8, and 30%) are equivalent to adjusted doses of 13,869, 25,670, and 25,843 mg/kg-day, respectively.

APPENDIX C. BMD OUTPUTS

No BMD modeling was conducted for this assessment.

Triacetin

APPENDIX D. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2011) Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH. As cited in HSDB (Hazardous Substances Data Bank). Available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB. Accessed on March 31, 2011. 783980

ATSDR (Agency for Toxic Substances and Disease Registry). (2011) Toxicological profile information sheet. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Available online at http://www.atsdr.cdc.gov/toxprofiles/index.asp. Accessed on March 31, 2011. 684152

CalEPA (California Environmental Protection Agency). (2008) All OEHHA acute, 8-hour and chronic reference exposure levels (chRELs) as on December 18, 2008. Office of Environmental Health Hazard Assessment, Sacramento, CA. Available online at http://www.oehha.ca.gov/air/allrels.html. Accessed on March 31, 2011. 595416

CalEPA (California Environmental Protection Agency). (2009) Office of Environmental Health Hazard Assessment. OEHHA Toxicity Criteria Database. Available online at http://www.oehha.ca.gov/risk/\ChemicalDB/index.asp. Accessed on March 31, 2011. 595417

ChemIDplus Advanced. (2011) United States Library of Medicine, Specialized Information Services. Available online at http://chem.sis.nlm.nih.gov/chemidplus/. Accessed on January 6, 2011. 629639

Commission for the European Communities. (1992) Food—science and techniques. Reports of the scientific committee for food (26th series), EUR 13913 EN. Luxembourg: Office for the Official Publications of the European Communities. Available online at http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_26.pdf. 1104562

Efremova, GI. (1962) Mutagenic effect of vanillin and of some of its derivatives. Dokl Akad Nauk SSSR 146:456−459. 699296

Ellis, G; Rodford, R. (1996) Glycerol triacetate: safety evaluation. Report No. D96/050. Gouda, The Netherlands: Uniqema. Available online at http://legacy.library.ucsf.edu/tid/whu60c00. 697254

Fiume, MZ. (2003) Final report on the safety assessment of triacetin. Int J Toxicol 22:1−10. Available online at http://dx.doi.org/10.1177/1091581803022S203. 674886

IARC (International Agency for Research on Cancer). (2011) Monographs on the evaluation of carcinogenic risks to humans. Lyon, France: IARC. Available online at http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php. Accessed on March 31, 2011. 783869

JECFA (Joint Expert Committee on Food Additives). (1975) Toxicological evaluation of certain food colours, thickening agents, and certain other substances. WHO Food Additives Series 8. FAO Nutr. Mtg Rep. Ser. No. 55. 19th Report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: WHO. Available online at http://www.inchem.org/documents/jecfa/jecmono/v08je12.htm. 1323901

JECFA (Joint Expert Committee on Food Additives). (2002) Evaluation of certain food additives and contaminants. Fifty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives WHO Technical Report Series, No. 913. Geneva: WHO. Available online at http://whqlibdoc.who.int/trs/WHO_TRS_913.pdf. 1323902

Litton Bionetics. (1976a,b) Mutagenic evaluation of compound, FDA 75-40, 000102-76-1, triacetin, (Kressco). Report No. FDA-74-2104. Kensington, MD: Litton Bionetics. Available online at http://www.ntis.gov/search/product.aspx?ABBR=PB257871. 699297

Lynch, JW; Bailey, JW. (1995) Dietary intake of the short-chain triglyceride triacetin vs. long-chain triglycerides decreases adipocyte diameter and fat deposition in rats. J Nutr 125(5):1267−1273. 699299

Lynch, J; Miles, J; Bailey, J. (1994) Effects of the short-chain triglyceride triacetin on intestinal mucosa and metabolic substrates in rats. J Parenter Enteral Nutr 18(3):208−213. Available online at http://dx.doi.org/10.1177/0148607194018003208. 697250

Madhavarao, C; Arun, P; Anikster, Y; et al. (2009) Glyceryl triacetate for Canavan disease: A low-dose trial in infants and evaluation of a higher dose for toxicity in the tremor rat model. J Inherit Metab Dis 32(5):640−650. 697238

MHW (Ministry of Health and Welfare, Japan). (1998) Toxicity testing reports of environmental chemical. Tokyo: Ministry of Health & Welfare. 674892

NIOSH (National Institute for Occupational Safety and Health). (2010) NIOSH pocket guide to chemical hazards. Index of chemical abstracts service registry numbers (CAS No.). Center for Disease Control and Prevention, U.S. Department of Health, Education and Welfare, Atlanta, GA. Available online at http://www.cdc.gov/niosh/npg/npgdcas.html. Accessed on March 31, 2011. 625692

NTP (National Toxicology Program). (2011) Report on carcinogens, 12th edition. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. Available online at http://ntp.niehs.nih.gov/?objectid=035E57E7-BDD9-2D9B-AFB9D1CADC8D09C1. Accessed on December 1, 2011. 737606

OECD (Organisation for Economic Co-operation and Development). (2002) SIDS initial assessment report for SIAM 15: Triacetin. United Nations Environment Programme (UNEP) Screening Information Dataset (SIDS) for High Volume Chemicals, Geneva. Available online at http://www.inchem.org/documents/sids/sids/102761.pdf. 674893

OSHA (Occupational Safety and Health Administration). (2011) Air contaminants: occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. U.S. Department of Labor, Washington, DC; OSHA Standard 1915.1000. Available online at
http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286. Accessed on March 31, 2011. 625691

Segel, R; Anikster, Y; Zevin, S; et al. (2011) A safety trial of high dose glyceryl triacetate for Canavan disease. Mol Genet Metab 103(3):203−206. 1137391

Shapira, J; Mandel, AD; Quattrone, PD; et al. (1969) Current research on regenerative systems. In W Vishniac; FG Favorite (Eds.), Proceedings of the Open Meeting of Working Group V at the Eleventh Plenary Meeting of COSPAR, Tokyo, 14−16 May, 1968 and the Symposium on Biological Effects of Radiation in Space, Tokyo, 10 May 1968 (pp. 123−129). Amsterdam, Holland: North-Holland Publishing. 674888

Shapira, J; Vann, L; Furst, A. (1975) Glycerol, propylene glycol and triacetin as dietary starch substitutes: some effects on rats. Proc West Pharmacol Soc 18:339−343. 697251

U.S. EPA (Environmental Protection Agency). (1994) Chemical assessments and related activities (CARA). Office of Health and Environmental Assessment, Washington, DC; EPA/600/R-94/904. Available online at
http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=60001G8L.txt. 596444

U.S. EPA (Environmental Protection Agency). (2002) A review of the reference dose and reference concentration process. Final report. Risk Assessment Forum, Washington, DC; EPA/630/P-02/002F. Available online at http://purl.access.gpo.gov/GPO/LPS44861. 088824

U.S. EPA (U.S. Environmental Protection Agency). (2005) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001F. Federal Register 70(66):17765−17817. Available online at
http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF. 086237

U.S. EPA (Environmental Protection Agency). (2009) 2009 Edition of the drinking water standards and health advisories. Office of Water, Washington, DC; EPA/822/R-09/011. Available online at
http://deq.state.wy.us/wqd/groundwater/downloads/dwstandards2009%5B1%5D.pdf. Accessed on March 31, 2011. 644141

U.S. EPA (Environmental Protection Agency). (2010a) Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris/. Accessed on December 13, 2010. 192196

U.S. EPA (Environmental Protection Agency). (2010b) Health effects assessment summary tables (HEAST). Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. Available online at http://epa-heast.ornl.gov/. Accessed on December 13, 2010. 595422

U.S. EPA (Environmental Protection Agency). (2011) Recommended use of body weight$^{3/4}$ as the default method in derivation of the oral reference dose. Office of the Science Advisor, Risk Assessment Forum, Washington, DC; EPA/1000/R-11/0001. Available online at http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf. 752972

U.S. FDA (Food and Drug Administration). (1975) Database of select committee on GRAS substances (SCOGS) Reviews. Glycerin and glycerides. Report No. 30, Conclusion 1. Available online at http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=142. Accessed March 31, 2011. (Page last updated 10/31/2006) 1323839

WHO (World Health Organization). (2011) Online catalogs for the Environmental Health Criteria series. Available online at http://www.who.int/topics/environmental_health/en/. Accessed on March 31, 2011. 783977