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Provisional Peer-Reviewed Toxicity Values for

Triethylene Glycol
(CASRN 112-27-6)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
$POD_{[ADJ]}$	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR TRIETHYLENE GLYCOL (CASRN 112-27-6)

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 (http://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 U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Triethylene glycol (TEG) is a liquid glycol that has a high boiling point and a very low vapor pressure (HSDB, 2007). It is primarily used as an active ingredient in air sanitizers and hospital disinfectants. Also, it is used as an inert ingredient in agricultural pesticide formulations when a high boiling point and low volatility are important considerations (U.S. EPA, 2005). Its properties are similar to those of diethylene glycol (DEG), but TEG has a higher boiling point, viscosity, and specific gravity. Its uses, as indicated above, were approved by the EPA to be eligible for registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) due to its low toxicity by the oral, dermal, and inhalation routes of exposure (U.S. EPA, 2005). TEG is also approved by the U.S. Food and Drug Administration (FDA) as a preservative for food packaging adhesives (21 CFR 175.105) and as a plasticizer in cellophane (21 CFR 177.1200) (U.S. EPA, 2005). The empirical formula for TEG is $C_6H_{14}O_4$ (see Figure 1). A table of physicochemical properties for TEG is provided below (see Table 1).

Figure 1. Triethylene Glycol Structure

Table 1. Physicochemical Properties of Triethylene Glycol (CASRN 112-27-6)[a]

Property (unit)	Value
Boiling point (°C)	285
Melting point (°C)	−7
Density (g/cm^3)	1.1274 at 15°C/4°C
Vapor pressure (mm Hg at 25°C)	1.32×10^{-3} (estimate)
pH (unitless)	ND
Solubility in water (g/100 mL at 25°C)	Miscible
Relative vapor density (air = 1)	5.2[b]
Molecular weight (g/mol)	150.17

[a]HSDB (2007).
[b]NIOSH (1996).

ND = no data.

A summary of available toxicity values for TEG from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Triethylene Glycol (CASRN 112-27-6)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
Noncancer				
ACGIH	NV	NA	ACGIH (2013)	NA
ATSDR	NV	NA	ATSDR (2013)	NA
Cal/EPA	NV	NA	Cal/EPA (2013)	3-26-2014[b]
NIOSH	NV	Values are available for other countries but not the United States. MAK = 1,000 mg/m^3; Peak limitation category: II(2); Pregnancy risk group: C	NIOSH (2010)	NA
OSHA	NV	NA	OSHA (2011); OSHA (2006)	NA
IRIS	NV	NA	U.S. EPA	3-26-2014
Drinking water	NV	NA	U.S. EPA (2011a)	NA
HEAST	NV	NA	U.S. EPA (2011b)	NA
CARA HEEP	NV	NA	U.S. EPA (1994)	NA
WHO	NV	NA	WHO	3-26-2014
Cancer				
IRIS	NV	NA	U.S. EPA	3-26-2014
HEAST	NV	NA	U.S. EPA (2011b)	NA
IARC	NV	NA	IARC (2013)	NA
NTP	NV	NA	NTP (2011)	NA
Cal/EPA	NV	NA	Cal/EPA (2014a, 2011)	NA

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; CARA = Chemical Assessments and Related Activities; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.
[b]The Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) Toxicity Criteria Database (http://oehha.ca.gov/tcdb/index.asp) was also reviewed and found to contain no information on triethylene glycol.

MAK = maximum allowable concentration; NA = not applicable; NV = not available.

Literature searches were conducted on sources published from 1900 through February 2014 for studies relevant to the derivation of provisional toxicity values for triethylene glycol, CASRN 112-27-6. The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA's Declassified CBI database, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for relevant health information: ACGIH, ATSDR, Cal/EPA, 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 (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant databases for TEG and include all potentially relevant repeat-dose short-term-, subchronic-, and chronic-duration studies. Principal studies are identified. Reference can be made to details provided in Tables 3A and 3B. The phrase "statistical significance," used throughout the document, indicates a *p*-value of <0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Data for Triethylene Glycol (CASRN 112-27-6)								
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-day)[a]								
Acute[c]	ND							
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
2. Inhalation (mg/m^3)[a]								
Acute[c]	ND							
Short-term[d]	Number and sexes of subjects evaluated, as well as exposure duration, are unclear from the study	0, 3−13	No exposure-related effects	13	DUB	NDr	Hamburger et al. (1945)	PR
	Number and sexes of subjects evaluated are unclear from the study, 3.5 weeks	0, 4.4−9.1	No exposure-related effects	9.1	DUB	NDr	Puck et al. (1945)	PR
Long-term[e]	326−336/0, whole-body vapor inhalation, ~2 months	0, Concentrations were greater than or less than 2.5	No exposure-related effects	2.5	DUB	NDr	NMRU (1952)	PR

Table 3A. Summary of Potentially Relevant Data for Triethylene Glycol (CASRN 112-27-6)

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]
Long-term[e]	15−72 male and female infants, whole-body vapor inhalation, 30−41 days	Not reported	No exposure-related effects	NDr	DUB	NDr	Krugman and Ward (1951)	PR
	1,000/0, whole-body vapor inhalation, 6 weeks	0, 1−10	No exposure-related effects	10	DUB	NDr	Bigg et al. (1945)	PR
	16/16, whole-body vapor inhalation, 19 weeks	0, 1.8−3.3	No exposure-related effects	3.3	DUB	NDr	Harris and Stokes (1945)	PR
Chronic[f]	ND							
Animal								
1. Oral (mg/kg-day)[a]								
Short-term	20/20, F344 rat, diet, 7 days/week, 14 days	M: 0, 1,132, 2,311, 5,916[g] F: 0, 1,177, 2,411, 6,209[g]	No treatment-related effects	6,209	DUB	NDr	Van Miller and Ballantyne (2001); BushyRun (1989)	PR
	8/8, CD-1 mouse, drinking water, 7 days/week, 14 days	0, 1,750, 4,375, 8,750, 13,125, 17,500[g]	Mortality, decreased body weight, dehydration, and lethargy at ≥8,750 mg/kg-day	4,375	DUB	8,750 (FEL)	NTP (1984)	NPR
Subchronic	5/group, sex unspecified, mature albino rat, drinking water, 7 days/week, 30 days	0, 8,404, 16,958 (Adjusted)	Mortality at ≥8,404 mg/kg-day	NDr	DUB	8,404 (FEL)	Lauter and Vrla (1940)	PR

Table 3A. Summary of Potentially Relevant Data for Triethylene Glycol (CASRN 112-27-6)

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	5/group, sex unspecified, young albino rat, drinking water, 7 days/week, 30 days	0, 5,103, 8,404 (Adjusted)	Weight loss, behavioral changes, and mortality at ≥8,404 mg/kg-day	5,103	DUB	8,404 (FEL)	Lauter and Vrla (1940)	PR
	5/group, sex unspecified, albino rat, gavage, 7 days/week, 30 days	5.637, 101.47, 11,274, 22,548 (Adjusted)	Overt signs of toxicity (hair loss and diarrhea) at ≥11,274 mg/kg-day	101.47	DUB	11,274	Lauter and Vrla (1940)	PR
	20−30/20−30, F344 rat, diet, 90 days	M: 0, 748, 1,522, 3,849[g] F: 0, 848, 1,699, 4,360[g]	No treatment-related effects	4,360	DUB	NDr	Van Miller and Ballantyne (2001); Union Carbide (1990a)	PR
Chronic	12/0, Osborne-Mendel rat, diet, 7 days/week, 2 years	0, 700, 1,401, 2,802 (Adjusted)	No treatment-related effects	2,802	DUB	NDr	Fitzhugh and Nelson (1946)	PR
	7−24/group, strain, sex unspecified, rat, drinking water, 7 days/week, 13 months	0, 158, 361, 2,999 (Adjusted)	No treatment-related effects	2,999	DUB	NDr	Robertson et al. (1947)	PR
	2−8, sex unspecified, rhesus macaque monkey, diet, 7 days/week, 3−14 months	282, 564 (initial measurements used as control) (Adjusted)	No treatment-related effects	564	DUB	NDr	Robertson et al. (1947)	PR

Table 3A. Summary of Potentially Relevant Data for Triethylene Glycol (CASRN 112-27-6)

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]
Developmental	0/10 pregnant female, CD-SD rat, gavage, GDs 6−15	0, 563, 1,126, 2,815, 5,630, 11,260	Maternal: no treatment-related effects Developmental: decreased fetal body weight at 11,260 mg/kg-day	Maternal: 11,260 Developmental: 5,630	NA	Maternal: NDr Developmental: 11,260	Ballantyne and Snellings (2005) (dose-range-finding study)	PR
	0/25 pregnant female, CD rat, gavage, GDs 6−15	0, 1,126, 5,630, 11,260	Maternal: no treatment-related effects Developmental: decreased fetal body weight per litter and increased incidence of bilobed thoracic centrum; both at 11,260 mg/kg-day	Maternal: 11,260 Developmental: 5,630	DUB	Maternal: NDr Developmental: 11,260	Ballantyne and Snellings (2005); Union Carbide (1991); individual litter data are not available for incidence of bilobed thoracic centrum to run a nested model in BMDS	PR
	0/8 pregnant, CD-1 mouse, gavage, GDs 6−15	0, 563, 1,126, 2,815, 5,630, 11,260	Maternal: no treatment-related effects Developmental: decreased fetal body weight per litter at ≥5,630 mg/kg-day	Maternal: 11,260 Developmental: 2,815	NA	Maternal: NDr Developmental: 5,630	Ballantyne and Snellings (2005) (dose-range-finding); Union Carbide (1990a, b)	PR

Table 3A. Summary of Potentially Relevant Data for Triethylene Glycol (CASRN 112-27-6)

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]
Developmental	**0/30 pregnant, CD-1 mouse, gavage, GDs 6−15**	**0, 563, 5,630, 11,260**	**Maternal: no treatment-related effects** **Developmental: decreased fetal body weight per litter and increased incidence of skeletal variations; both at ≥5,630 mg/kg-day**	**Maternal: 11,260** **Developmental: 563**	**506 for delayed ossification of the supraoccipital bone**	**Maternal: NDr** **Developmental: 5,630**	**Ballantyne and Snellings (2005); Union Carbide (1990a); Union Carbide (1990b)**	**PS, PR**
	0/50 pregnant, CD-1 mouse, gavage, GDs 7−14	0, 11,270	Maternal: none reported Developmental: decreased fetal weight at 11,270 mg/kg-day	Maternal: NDr Developmental: NDr	DUB	Maternal: NDr Developmental: 11,270	Hardin et al. (1987); Schuler et al. (1986); Schuler et al. (1984)	PR
Reproductive	20/20 treated, 40/40 control, CD-1 mouse, drinking water (breeding protocol), 98 days (cohabitation period); final litters and dams received TEG in drinking water for an additional 21 days, 2 generations	0, 590, 3,300, 6,780 (Adjusted)	No treatment-related effects	6,780	DUB	NDr	Lamb (1997); Bossert et al. (1992); Morrissey et al. (1989); NTP (1984)	PR

Table 3A. Summary of Potentially Relevant Data for Triethylene Glycol (CASRN 112-27-6)

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]
2. Inhalation (mg/m^3)[a]								
Short-term	10/10, S-D rat, whole-body aerosol inhalation, 6 hours/day, 9 times over 11 days	0, 101, 411, 987	Clinical chemistry changes indicative of liver toxicity accompanied by an increase in liver weights greater than 10% at 411 mg/m^3; mortality at 987 mg/m^3.	101	DUB	411	Ballantyne et al. (2006)	PR
	10/10, S-D rat, nose-only aerosol inhalation, 6 hours/day, 9 times over 11 days	0, 21, 106, 212	No exposure-related effects	212	DUB	NDr	Ballantyne et al. (2006)	PR
Subchronic	Number unspecified, M/F, strain unspecified, rat, 24 hours/day, 41 days	Supersaturated triethylene glycol vapor (~449 mg/m^3)	No exposure-related effects.	~449	DUB	NDr	Maassen (1953)	PR
Chronic	24/12, strain unspecified, rat, 24 hours/day, 6−13 months	Supersaturated triethylene glycol vapor (0, ~4 mg/m^3)	No exposure-related effects.	~4	DUB	NDr	Robertson et al. (1947)	PR
	17/group, 8/control, sex unspecified, rhesus macaque monkey, 24 hours/day, 13 months	Supersaturated triethylene glycol vapor (0, ~4 mg/m^3)	Decreased body weight; mortality observed in both control and exposed groups	NDr	DUB	NDr	Robertson et al. (1947)	PR

Table 3A. Summary of Potentially Relevant Data for Triethylene Glycol (CASRN 112-27-6)

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]
Chronic	8/group, 8/control, sex unspecified, rhesus macaque monkey, 24 hours/day, 10 months	65−75% saturated triethylene glycol vapor (~2−3 mg/m^3)	No exposure-related effects	~3	DUB	NDr	Robertson et al. (1947)	PR
Developmental	ND							
Reproductive	ND							

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

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

[c]Acute = exposure for ≤24 hours (U.S. EPA, 2002).

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

[e]Long-term = repeated exposure for >30 days ≤10% life span (based on 70-year typical lifespan) (U.S. EPA, 2002).

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

[g]Daily doses as reported by study authors.

DUB = data unamenable to BMDS; FEL = frank effect level; GD = Gestational Day; NA = not applicable; ND = no data; NDr = not determined; S-D = Sprague-Dawley.
HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood gas partition coefficient.

Table 3B. Summary of Potentially Relevant Cancer Data for Triethylene Glycol (CASRN 112-27-6)

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-day)								
Carcinogenicity	ND							
2. Inhalation (mg/m^3)								
Carcinogenicity	ND							
Animal								
1. Oral[a]								
Carcinogenicity	12/0, Osborne-Mendel rat, diet, 7 days/week, 2 years	HED: 0, 205, 410, 820 (Adjusted: 0, 700, 1,401, 2,802)	No carcinogenic effects	NA	DUB	NA	Fitzhugh and Nelson (1946) (small sample size, only one sex studied, limited analysis of tissues and organs)	PR
2. Inhalation[a]								
Carcinogenicity	ND							

[a]Dosimetry: Values are converted to a human equivalent dose (HED in mg/kg-day) for oral carcinogenic effects..
[b]PR = peer reviewed.

DUB = data unamenable to BMDS; NA = not applicable; ND = no data.

HUMAN STUDIES

Oral Exposures

No studies have been identified.

Inhalation Exposures

In six human studies (NMRU, 1952; Krugman and Ward, 1951; Bigg et al., 1945; Hamburger et al., 1945; Harris and Stokes, 1945; Puck et al., 1945), patients in hospital wards and workers in dormitories were continuously exposed to TEG via inhalation. The purpose of these studies was to test the ability of TEG in controlling or reducing bacterial infections and thus, these are not comprehensive toxicity studies. Across the studies, TEG concentrations varied from 1 to 13 mg/m^3 and subjects were continuously exposed for various lengths of time. The studies by Bigg et al. (1945) and Hamburger et al. (1945) reported that no toxicological effects were observed, but the extent and timing of the examinations is not apparent from the studies. The studies by Puck et al. (1945), Naval Medical Research (NMRU, 1952), Harris and Stokes (1945), and Krugman and Ward (1951) did not report any observation of toxicological effects. For most of these studies, it is also unclear if healthy/uninfected people were exposed to TEG. Due to the lack of information for these studies, they are not considered as principal studies to derive a subchronic or chronic p-RfC.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure to TEG in animals have been evaluated in two short-term-duration studies (Van Miller and Ballantyne, 2001; NTP, 1984), four subchronic-duration studies (Van Miller and Ballantyne, 2001; Lauter and Vrla, 1940), three chronic-duration studies (Robertson et al., 1947; Fitzhugh and Nelson, 1946), five developmental toxicity studies (Ballantyne and Snellings, 2005; Schuler et al., 1984), and one reproductive toxicity study (Bossert et al., 1992). Fitzhugh and Nelson (1946) also evaluated TEG for carcinogenicity.

Short-Term-Duration Studies

Van Miller and Ballantyne (2001) and BushyRun (1989)

F344 rats (20/sex/treatment group) were fed 0, 10,000, 20,000, or 50,000 ppm TEG (purity >99%) in the diet for 14 days (Van Miller and Ballantyne, 2001). An unpublished report of this study is also available (BushyRun, 1989). These dietary doses were calculated by the study authors to be equivalent to 1,132, 2,311, and 5,916 mg/kg-day for males and 1,177, 2,411, and 6,209 mg/kg-day for females (values as presented in the abstract, which were slightly different than those presented in the tables from the study report; differences may be due to rounding). Analytical measurements performed by the study authors indicated that TEG was stable in the diet for at least 14 days in open glass feed jars and for at least 21 days in closed polyethylene containers at ambient temperatures. All rats were observed daily for clinical signs of toxicity, pharmacological effects, and mortality. Animals were weighed on Days 0, 7, and 14, and food consumption was measured over Days 0−7 and 7−14. After 14 days, the study authors placed 10 animals/sex/group in metabolism cages, and urine samples were collected over a 24-hour interval. Blood samples were collected from these animals and examined for hematology and serum chemistry. The remaining 10 animals/sex/group were sacrificed, and blood was collected for serum chemistry and complete necropsies were performed. Organ weights for the liver, kidneys, heart, spleen, brain, adrenal glands, testes, and ovaries were recorded. The following organs were examined histopathologically: brain, liver, kidneys, pancreas, testes, ovaries, stomach, duodenum, jejunum, ileum, cecum, colon, urinary bladder,

and sciatic nerve. Any lesions observed were described and recorded. Appropriate statistical evaluations were conducted, including Levene's test for homogeneity of variance, pooled variance *t*-test, analysis of variance (ANOVA), Kruskal-Wallis test, and Fisher's Exact test.

The study authors did not observe any deaths or treatment-related clinical signs in males or females at any dose level. There were no treatment-related findings in body weight, food consumption, hematology, serum chemistry, organ weights, or gross and microscopic pathology. Urinalysis showed a statistically significant increase in urine volume (39−59%) and decrease in urine pH in high-dose males and females. A statistically significant increase in urine volume (22%) was also observed in males in the mid-dose group. Because these urinalysis findings were not associated with any changes in serum chemistry or renal histopathology, the study authors suggested that they were mostly related to the renal excretion of TEG or its metabolites following absorption of large amounts of dietary TEG. Based on the lack of any adverse effects in either sex, the NOAEL is 6,209 mg/kg-day and no LOAEL is determined.

NTP (1984)

NTP (1984) conducted a 14-day dose-range-finding study (unpublished) to aid the dose selection process for a reproductive toxicity study of TEG (Bossert et al., 1992) (included in Table 3 and discussed below). CD-1 mice (8/sex/treatment group) were administered 0, 1.0, 2.5, 5.0, 7.5, or 10.0% TEG (97% pure) in the drinking water for 14 days. The study authors stated that these were approximately equivalent to daily doses of 0, 1,750, 4,375, 8,750, 13,125, and 17,500 mg/kg-day, respectively. Animals were housed four per cage by sex. Clinical signs, morbidity, and mortality were monitored twice daily. Body weight and water consumption were measured weekly. At the end of Week 2, all test animals were sacrificed with no further data collection. Statistical analyses were carried out using two-way ANOVA and the χ^2 test.

Treatment-related deaths occurred at doses ≥8,750 mg/kg-day and included two males at 8,750 mg/kg-day, one female at 13,125 mg/kg-day, and one female at 17,500 mg/kg-day. Clinical signs observed in the animals from these treatment groups included dehydration, lethargy, and piloerection. Mean final body weight and body-weight gain were also reduced by >10% in animals treated with ≥8,750 mg/kg-day. A LOAEL could not be determined because the next highest dose (8,750 mg/kg-day) resulted not only in a reduction in body weight, but also dehydration and death in both sexes. Therefore, 8,750 mg/kg-day is considered a frank effect level (FEL). The NOAEL is 4,375 mg/kg-day.

Subchronic-Duration Studies

Lauter and Vrla (1940): Drinking Water Study

In the first part of this study, the subchronic effects of TEG were investigated in young and mature albino rats. The study authors administered TEG (purity unknown; stated to be commercial grade) at concentrations of 5% or 10% by volume (5.6% or 11.3% by weight) in drinking water to groups of five mature albino rats (sex unspecified) for 30 days. The estimated daily doses are 8,404 and 16,958 mg/kg-day, respectively. Because body weight and water consumption data over the course of the study were not provided, these doses are calculated for this PPRTV assessment using an average body weight (0.2039 kg) and water consumption (0.0306 kg/day) given for male and female rats for all rat strains by U.S. EPA (1988). The control group consisted of 5 rats that were administered regular water; however, the control animals appear to be younger rats based on reported final body weights. Treatment was followed by a 15-day observation period. Additional information regarding experimental design was not

provided by the study authors. All animals in the low-dose group showed signs of severe toxicity, and three of the animals in this group died during the study. The two remaining animals surviving to study completion recovered during the 15-day observation period. All animals in the high-dose group showed signs of toxicity and died by Day 12. Based on mortality observed at both doses tested in the study, an FEL of 8,404 mg/kg-day is established, and no NOAEL or LOAEL is identified for adult rats.

In the second part of this study, the study authors administered TEG at concentrations of 3% or 5% by volume (3.4% or 5.6% by weight) in drinking water to groups of five 3-week-old albino rats (sex unspecified) for 30 days. The study authors used the same control rats as described above. The estimated daily doses are calculated for this PPRTV assessment as 5,103 and 8,404 mg/kg-day, respectively, based on average body weight and drinking water consumption as discussed above (U.S. EPA, 1988). As with the adult rat study, treatment was followed by a 15-day observation period. The study authors provided no further information on the study design or data collected. All animals in the low-dose group survived to study completion without signs of toxicity. The study authors noted that the young rats in the low-dose group drank more than the adult rats. Treatment-related clinical signs were observed in high-dose animals during the first 2 weeks of exposure. Body-weight gains were lagging during the first 2 weeks, but improved afterwards. The study authors also stated that animal behavior improved after the first 2 weeks of exposure. One animal in the high-dose group died on Day 15. Based on the results from both parts of the study, the study authors concluded that exposure to TEG at 5% in drinking water caused higher mortality in adult rats than in young rats. In young rats, the NOAEL is 5,103 mg/kg-day, but no LOAEL can be determined because the next highest dose of 8,404 mg/kg-day is an FEL.

Lauter and Vrla (1940): Gavage Study

Four groups of five albino rats (sex and age unspecified, ranging in weight from 100−210 grams) received daily doses of TEG (stated to be commercial grade) via gavage for 30 consecutive days. No control group was reported. The dosing groups received 0.1 mL TEG/kg body weight (bw)-day as a 5% aqueous solution, 3.0 mL TEG/kg BW-day as a 30% solution, 10.0 mL, or 20.0 mL TEG/kg BW-day of undiluted TEG. The corresponding daily doses are calculated for this PPRTV assessment as 5.637, 101.47, 11,274, and 22,548 mg/kg-day, respectively. Treatment was followed by a 15-day observation period. Body weights were measured during the treatment and posttreatment periods. This is the only experimental design information provided by the study authors; however, the results section indicates that there were more details related to study design that were not provided (such as numbers of litters being delivered). No signs of toxicity or changes in body-weight gain were observed in animals at the two lower doses (5.637 and 101.47 mg/kg-day). Animals exposed to 11,274 mg/kg-day showed signs of toxicity (hair loss and diarrhea) and decreased weight gain during the first week; however, body-weight gain increased during the second week. All five of the high-dose animals died within 3 days. The NOAEL is 101.47 mg/kg-day and the LOAEL is 11,274 mg/kg-day based on the overt signs of toxicity.

Van Miller and Ballantyne (2001) and Union Carbide (1990a)

As presented in an unpublished report by Union Carbide (1990a), F344 rats were fed 0, 10,000, 20,000, or 50,000 ppm TEG (purity >99.45%) mixed in the diet for 90 days. Based on these dietary concentrations, the study authors calculated daily TEG intakes of 0, 748, 1,522, and 3,849 mg/kg-day for males and 0, 848, 1,699, and 4,360 mg/kg-day for females, respectively.

The sample sizes were 20/sex/group for the 10,000- and 20,000-ppm groups and 30/sex/group for the control and 50,000-ppm groups. At the end of treatment, 20 rats/sex/treatment group were sacrificed. Ten control and 10 high-dose rats/sex were retained for a 6-week recovery period. Analytical measurements performed by the study authors indicated that TEG was stable and homogeneous in the diet. The animals were observed daily for signs of toxicity. The study authors performed detailed physical examinations once per week. Ophthalmoscopic examinations were performed before treatment and at the end of the dosing period. Body weight and food consumption were recorded weekly. Blood samples were collected on Day 30, at the end of treatment, and at the end of the recovery period for hematology (hemoglobin concentration, erythrocyte count, hematocrit, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelet count, and total and differential leukocyte counts) and serum chemistry (glucose; urea nitrogen; albumin globulin; total protein creatinine; total, conjugated, and unconjugated bilirubin; phosphorus; sodium; potassium; calcium; chloride; aspartate and alanine aminotransferase; alkaline phosphatase; γ-glutamyl transferase; creatine kinase; lactate; and sorbitol dehydrogenases). Urine samples were collected over a 24-hour period from 10 rats/sex in the control and high-dose groups during Weeks 12−19. Urinalysis parameters included urine volume, pH, specific gravity, color, microscopy, blood, protein, ketones, glucose, bilirubin, and urobilinogen. At sacrifice, the following organs were removed and examined histopathologically: brain, liver, kidneys, pancreas, testes, ovaries, stomach, duodenum, jejunum, ileum, cecum, colon, urinary bladder, and sciatic nerve. Any observed lesions also were examined. The study authors recorded organ weights for the liver, kidneys, heart, spleen, brain, adrenal glands, testes, and ovaries. Appropriate statistical evaluations were conducted and included Levene's test for homogeneity of variance, pooled variance *t*-test, ANOVA, Kruskal-Wallis test, and Fisher's Exact test.

No deaths were observed. There were no treatment-related findings in clinical observations, ophthalmic examination, clinical chemistry, necropsy, or histology. Although some statistically significant decreases in body weights were noted in high-dose males and females, they were not biologically significant (i.e., <10%). There were slight, but statistically significant changes in hematology in high-dose males at the end of the treatment period. The study authors postulated that these effects were probably due to a minor hemodilution following the absorption of large amounts of TEG and its metabolites. Urinalysis showed a dose-related decrease in urine pH in males at all dose levels and in females at the mid and high dose, reaching statistical significance in both sexes at the high dose. A dose-related increase in urine volume was also observed in males at the end of the dosing period, but this increase was statistically significant only at the high dose. An increase in urine volume was observed in high-dose females, but the increase was not statistically significant. Because the urinalysis findings were not associated with any changes in serum chemistry or renal histopathology, the study authors suggested that the findings were mostly related to the renal excretion of TEG or its metabolites following absorption of large amounts of dietary TEG. Although some statistically significant changes in relative organ weights occurred in high-dose males and females, none of the changes are considered biologically significant (i.e., were <10% or not dose related). No gross or microscopic lesions were observed. The study authors considered the NOAEL to be 1,522 mg/kg-day for males and 1,699 mg/kg-day for females; although they stated that there was no specific organ or tissue toxicity in the study. However, the effects observed in the high-dose animals were minimal and are not considered biologically significant. Therefore, the NOAEL is

the highest dose tested (3,849 mg/kg-day for males and 4,360 mg/kg-day for females) with no LOAEL identified.

Chronic-Duration Studies

Fitzhugh and Nelson (1946)

Male Osborne-Mendel rats (12/group) were administered 0, 1, 2, or 4% TEG (purity not reported) in the diet for 2 years. The equivalent daily doses are 0, 700, 1,401, and 2,802 mg/kg-day, respectively. These doses are calculated for this PPRTV assessment using an average body weight (0.514 kg) and food consumption (0.036 kg/day) given for Osborne-Mendel rats by U.S. EPA (1988), because although body weights and food consumption were observed weekly, they were not reported over the course of the study. Eleven organs/tissues (lung, heart, liver, spleen, pancreas, stomach, small intestine, colon, kidney, adrenal, and testis) were routinely examined histologically; others were examined only in some animals. No data was presented for the control group. No treatment-related effects were observed with respect to mortality, food consumption, body-weight gain, and gross or microscopic lesions. As no effects occurred at any dose tested, the NOAEL is 2,802 mg/kg-day, and no LOAEL is identified.

Robertson et al. (1947): Rat Study

Rats of unspecified sex and strain were administered TEG ("purified" material with no further information) in drinking water at daily concentrations of 0 (9 rats), 0.14 (7 rats), 0.32 (8 rats), or 2.66 (24 rats) mL/kg BW-day for 13 months, which are estimated to be equivalent to 158, 361, and 2,999 mg/kg-day, respectively. Blood samples were collected at the end of the exposure period and examined for total and differential leukocyte counts and red blood cell counts. Body weights were measured monthly. Urine samples were examined microscopically (specifics not provided). The study authors performed three sacrifices during the study period (at 3, 8, and 13 months) and the animals were subjected to necropsy. No statistical analysis was performed. No treatment-related effects were observed. Based on these results, the NOAEL is 2,999 mg/kg-day, and no LOAEL is identified.

Robertson et al. (1947): Monkey Study

In this study, the authors administered TEG orally in eggnog at daily concentrations of 0.25 or 0.5 mL/kg body weight-day (approximately 50−100 times the quantity an animal could absorb by breathing air saturated with glycol) to 10 rhesus macaque monkeys (sex unspecified). It appears that there was no specific control group, but measurements taken in these animals prior to treatment were used as the control values. The sample sizes were two animals for the 0.25 mL/kg-day group (treated for 12 months) and eight animals for the 0.5 mL/kg-day group (two monkeys treated for each of the following durations: 3 months, 3.5 months, 12 months, and 14 months). The equivalent daily doses are calculated for this PPRTV assessment as 282 and 564 mg/kg-day, respectively. Body weight was measured weekly. Hematology (white blood cell counts both total and differential, red blood cell counts, and hemoglobin) and urinalysis (specifics not provided) were conducted at study initiation and at the end of treatment. At the end of each treatment period, the animals were necropsied and selected tissues/organs were examined histologically (full details were not provided, but the lungs, liver, kidneys, spleen, bone marrow, stomach, and intestines were specified). No statistical analysis was performed. There were no treatment-related findings in any of the animals. Based on these results, a NOAEL of 564 mg/kg-day is identified and no LOAEL is determined.

Developmental Studies

Ballantyne and Snellings (2005): Rat Developmental Dose-Range-Finding Study

The study authors administered undiluted TEG (purity >99%) at doses of 0, 563, 1,126, 2,815, 5,630, or 11,260 mg/kg-day to groups of 10 pregnant CD Sprague-Dawley female rats by gavage on Gestational Days (GD) 6−15. The study authors examined the animals daily for mortality and signs of toxicity and recorded body weights on GDs 0, 6, 9, 12, 15, 18, and 21. Water consumption was measured over sequential 3-day intervals during gestation. The animals were sacrificed on GD 21 and maternal liver, kidney, and gravid uterine weights were recorded. The study authors also recorded the number of corpora lutea and implants. The maternal kidneys were removed and a histological examination was performed. Fetuses were weighed, sexed, and examined externally for malformations and variations. Appropriate statistical analyses were conducted, including *t*-test, Levene's test, Kruskal-Wallis, ANOVA, Mann-Whitney U-test, and Fisher's Exact test. The intended use of this study was as a dose-range-finding study only, and it is not considered an acceptable developmental toxicity study because visceral and skeletal examinations were not conducted.

There were no deaths in the control or treatment groups. There was a statistically significant decrease in maternal body-weight gain observed in the 11,260 mg/kg-day-dose group on GDs 6−9 (89.4% of controls). A decrease in maternal body-weight gain was also observed on GDs 6−15 (80.3% of controls) and GDs 0−21 (96.9% controls), but these decreases did not reach statistical significance. An increase in water consumption during treatment also was observed in the two highest dose groups. No effects of treatment on maternal liver, kidney, or gravid uterine weights were observed at any dose level. There were also no treatment-related effects on the number of corpora lutea and implants. In the high-dose group, fetal body weights were reduced in males (96.6%) and females (94.5%) compared to the control group (no indication of statistical significance and the quantitative data were not available). Based on these findings, exposure levels of 1,126, 5,630, and 11,260 mg/kg-day were selected for the definitive study. The maternal NOAEL is 11,260 mg/kg-day, and no maternal LOAEL is identified based on the lack of any biologically significant treatment-related effects. Based on decreased fetal body weight, the developmental NOAEL is 5,630 mg/kg-day and the developmental LOAEL is 11,260 mg/kg-day.

Ballantyne and Snellings (2005) and Union Carbide (1991): Rat Developmental Study

Pregnant female CD rats (25/treatment group) were dosed daily by gavage with undiluted TEG (purity >99%) over GDs 6−15 at 0, 1,126, 5,630, or 11,260 mg/kg-day (administered as 1.0, 5.0, and 10.0 mL/kg-day, respectively). Control animals received 10.0 mL/kg-day distilled water. The original report for this study is also available (Union Carbide, 1991). The study authors examined the animals daily for mortality and signs of toxicity. Body weight was recorded on GDs 0, 6, 9, 12, 15, 18, and 21. Water and food consumption were measured over sequential 3-day intervals during gestation. Pregnant rats were sacrificed on GD 21 and necropsied. Examinations of the gravid uterus, ovaries, cervix, vagina, and abdominal and thoracic cavities were performed. The following parameters were evaluated: liver weight, kidney weight, gravid uterine weight, number of ovarian corpora lutea, and status of implantation sites (i.e., resorptions, dead fetuses, and live fetuses). Maternal kidneys were examined histologically. Fetuses were counted, weighed, sexed, and examined for external, soft tissue, visceral (including craniofacial), and skeletal malformations and variations. Appropriate statistical analyses were conducted, including *t*-test, Levene's test, Kruskal-Wallis, ANOVA, Mann-Whitney U-test, and Fisher's Exact test.

There were no treatment-related mortalities or clinical signs of toxicity during the study. However, one pregnant dam in the 5,630 mg/kg-day group died on GD 11 of unknown causes. Pregnancy rates were comparable among all dose groups (92, 96, 80, and 92% for the control, low-, mid-, and high-dose groups, respectively). Statistically significant decreases in body weights were observed in high-dose dams from GDs 9−18 and in the mid-dose dams on GD 18. However, the differences were less than 10% and likely related to decreased food consumption. Statistically significant increases in water consumption were observed in dams in both the mid- (20%) and high-dose (40%) groups during treatment. There were no treatment-related effects on maternal liver or gravid uterine weights. After correcting for the gravid uterine weight, there was a slight (7%), but statistically significant, decrease in maternal body weight that was accompanied by a slight (7.6%), but statistically significant, increase in relative kidney weight; however, neither of the two effects is considered biologically significant (i.e., were <10%). In addition, no treatment-related gross pathology or histopathology was observed in the kidneys. Based on these observations, the study authors stated that the increases in water consumption and relative kidney weight seen in the high-dose group were not associated with nephrotoxicity, and these effects were likely associated with the renal excretion of TEG metabolites.

There were no treatment-related effects observed on the number of corpora lutea, pre- and postimplantation loss, live fetuses/litter, or sex ratio. Fetal body weights per litter were biologically significantly reduced in males and females at 11,260 mg/kg-day compared to the controls (see Table B-1). For all doses tested, there were no treatment-related increases in the incidence of any individual malformations, visceral or skeletal malformations, or total malformations by fetuses or by litter. There were no increases in the incidence of external or visceral variations. However, there was an increase in the incidence of bilobed thoracic centrum that was statistically significant at 11,260 mg/kg-day (see Table B-2). The maternal NOAEL is 11,260 mg/kg-day, and no LOAEL is identified. The developmental NOAEL is 5,630 mg/kg-day with a LOAEL of 11,260 mg/kg-day based on reduced fetal body weight per litter that was accompanied by an increase in the incidence of bilobed thoracic centrum.

Ballantyne and Snellings (2005), Union Carbide (1990a), and Union Carbide (1990b): Mouse Developmental Dose-Ranging-Finding Study

Pregnant CD-1 mice (8/treatment group) were administered undiluted TEG (purity >99%) at doses of 0, 563, 1,126, 2,815, 5,630, or 11,260 mg/kg-day via gavage on GDs 6−15. The study authors examined the animals daily for mortality and signs of toxicity and recorded body weights on GDs 0, 6, 9, 12, 15, and 18. Water consumption was measured over sequential 3-day intervals during gestation. The animals were sacrificed on GD 18, and maternal liver, kidney, and gravid uterine weights were recorded. The study authors also recorded the number of corpora lutea and implants. The maternal kidneys were removed and histological examination was performed. Fetuses were weighed, sexed, and examined externally for malformations and variations. Appropriate statistical analyses were conducted, including *t*-test, Levene's test, Kruskal-Wallis, ANOVA, Mann-Whitney U-test, and Fisher's Exact test. This is not considered an acceptable developmental toxicity study because visceral and skeletal examinations were not conducted. However, its intended use was as a dose-range-finding study only.

No deaths were reported. A significant increase in water consumption was observed at 11,260 mg/kg-day for GDs 6−9, 9−12, 12−15, and 6−15. Results for maternal body weights and gravid uterine weights were not reported. Absolute and relative kidney weights were stated to be

increased in the high-dose group, but the data were not biologically significant. Fetal body weights were biologically significantly reduced at 11,260 mg/kg-day for males (94.8% of controls) and females (93.9% of controls), and at 5,630 mg/kg-day for females (94.5% of controls). Increased incidence of clubbed limbs was observed in six fetuses across the three highest dose groups. Two fetuses from two litters at 2,815 and 5,630 mg/kg-day and a single litter at 11,260 mg/kg-day had clubbed limbs. However, incidence of clubbed limbs was actually decreased compared to controls in the definitive developmental study in mice reported by Ballantyne and Snellings (2005) (see summary below). This observation suggests that the incidence of clubbed limbs in mice from the dose-range-finding study may not be treatment related, and thus was not considered as a potential critical effect and POD for derivation of a subchronic or chronic provisional RfD (p-RfD).

Based on the findings in this study, dosages of 563, 5,630, and 11,260 mg/kg-day were selected for the definitive study. Based on no observed effects, a maternal NOAEL of 11,260 mg/kg-day is identified, but a LOAEL could not be determined. Based on biologically significantly decreased fetal body weight in female fetuses, the developmental NOAEL is 2,815 mg/kg-day and the LOAEL is 5,630 mg/kg-day.

Ballantyne and Snellings (2005), Union Carbide (1990a), and Union Carbide (1990b): Mouse Developmental Study

The definitive mouse study reported in Ballantyne and Snellings (2005) is considered the principal study for derivation of the subchronic and chronic p-RfDs. Timed-pregnant CD-1 mice (30/treatment group) were administered undiluted TEG (purity >99%) at doses of 0, 563, 5,630, or 11,260 mg/kg-day (0.5, 5.0, and 10.0 mL/kg-day) by gavage on GDs 6−15. Control animals received 10.0 mL/kg-day distilled water. The original report for this study is also available (Union Carbide, 1990a, b). The study authors examined the animals daily for mortality and signs of toxicity. Body weight was recorded on GDs 0, 6, 9, 12, 15, and 18. Water and food consumption were measured over sequential 3-day intervals during gestation. Pregnant animals were sacrificed on GD 18 and necropsied. Examinations of the gravid uterus, ovaries, cervix, vagina, and abdominal and thoracic cavities were performed. The following parameters were evaluated: liver weight, kidney weight, gravid uterine weight, number of ovarian corpora lutea, and status of implantation sites (i.e., resorptions, dead fetuses, and live fetuses). Maternal kidneys were examined histologically. Fetuses were counted, weighed, sexed, and examined for external, soft tissue, visceral (including craniofacial), and skeletal malformations and variations. Appropriate statistical analyses were conducted, including *t*-test, Levene's test, Kruskal-Wallis, ANOVA, Mann-Whitney U-test, and Fisher's Exact test. The study authors did not observe any deaths in dams. One dam delivered early. Treatment-related clinical signs (hypoactivity and audible/rapid breathing) were observed in two high-dose dams. There were no treatment-related effects on pregnancy rate: 93.3% (controls), 96.7% (563 mg/kg-day), 93.3% (5,630 mg/kg-day), and 90% (11,260 mg/kg-day). There were no treatment-related effects on maternal body weights, body-weight gains, and food and water consumptions observed at any dose level. In addition, no treatment-related effects were observed on maternal terminal body weight or body weight corrected for gravid uterus weight. However, there was a dose-related decrease in gravid uterine weight that was not statistically significant (see Table B-3). This was likely related to decreased fetal weight. Dams in the high-dose group also exhibited slight (7%), statistically significant but not biologically significant increases in relative kidney weights. There were no treatment-related effects on maternal liver weight (absolute and relative) or absolute kidney weight. The histology of the kidneys was normal.

No treatment-related effects on gestational parameters, including corpora lutea, pre- and postimplantation loss, live fetuses/litter, or sex ratio, were observed at any dose tested. Dose-related, statistically significant decreases in fetal body weights per litter were observed at 5,630 and 11,260 mg/kg-day (see Table B-3). At all doses tested, there were no treatment-related increases in the incidence of visceral or skeletal malformations or in the incidence of total malformations by fetus or by litter. There were no increases in the incidence of external or visceral variations. However, several individual fetal skeletal variations were seen that attained statistical significance (see Table B-4). Mouse fetuses had delayed ossification in the cervical region, and hind-limb proximal phalanges, as well as reduced caudal segments at 11,260 mg/kg-day. Delayed ossification also was observed in the supraoccipital and frontal bones that was statistically significant for both effects at 5,630 mg/kg-day. The study authors considered these patterns of delayed ossification consistent with reduced fetal body weights. The maternal NOAEL is 11,260 mg/kg-day, and no maternal LOAEL is identified. Based on delayed ossification of the supraoccipital and frontal bones and decreased fetal body weight, the developmental NOAEL is 563 mg/kg-day and the developmental LOAEL is 5,630 mg/kg-day.

Schuler et al. (1984) and Hardin et al. (1987)

Pregnant CD-1 mice (50/treatment group) were administered TEG (99% pure) via gavage in distilled water on GDs 7−14 at concentrations of 0 (distilled water; vehicle control) or 10 mL/kg body weight (Schuler et al., 1984). The dose was calculated by the study authors to be equivalent to 11,270 mg/kg-day. The proprietary data for this study also were available (Schuler et al., 1986). Schuler et al. (1986) and Schuler et al. (1984) evaluated TEG as part of a screening assay for 15 glycol ethers; these data also were published by Hardin et al. (1987) as part of an experimental design to test 60 chemicals in an abbreviated test to determine which chemicals needed more conventional testing. All animals were observed twice daily during treatment, once daily on GDs 14−17 (Hardin et al., 1987), and then twice daily for signs of delivery. Maternal body weights were recorded on GDs 7, 17, and18 and on Postnatal Day (PND) 3. Signs of toxicity were recorded daily. Dams were allowed to give birth, and the numbers of live born and stillborn pups were recorded as soon as possible (within 12 hours). Total litter weights were recorded on PNDs 1 and 3. Six reproductive endpoints were evaluated: pup survival in utero (percentage of live litters/pregnant survivors); pup perinatal and postnatal survival (number of live pups/litter, number of dead pups/litter, and pup survival to PND 3); and pup body weight (weight at birth and at PND 3). Females that failed to deliver a litter by the presumed GD 22 were sacrificed and uteri were examined. Statistical evaluations were done using ANOVA and Student's *t*-test. This is not considered an appropriate developmental toxicity study because systematic examinations of pups (living or dead) for malformations were not performed.

Because the above study aimed to screen chemicals for their potential to cause reproductive toxicity in pregnant females, the bioassay was designed to employ doses of the test chemicals that cause 10−20% maternal mortality. The study authors stated that this was necessary to get confidence in the evaluation's findings, indicating that clear maternal toxicity does not mean that reproductive toxicity will follow. For several chemicals including TEG, the LD_{10} could not be determined, and therefore, 10 mL/kg undiluted compound was established as the maximum practicable dose. This 11,270 mg/kg-day dose of TEG produced 4% maternal mortality (2/50), but 100% of the pregnant survivors produced viable litters (36/36; the study report is unclear as to what happened to the other 12 animals). A statistically and biologically significant decrease in mean pup birth weight (94% of controls) was observed at the administered dose of TEG. There were no treatment-related effects on the number of alive or

dead pups per litter or postnatal pup survival. No maternal NOAEL/LOAEL could be determined due to the lack of effects measured and/or reported for the dams. No developmental NOAEL could be determined and the developmental LOAEL is 11,270 mg/kg-day based on decreased fetal body weight.

Reproductive Studies

Lamb (1997), Bossert et al. (1992), Morrissey et al. (1989), and NTP (1984)

Bossert et al. (1992) is the published version of the original study reported by NTP (1984). It does not provide sufficient details on study design, but the study also has been described by Morrissey et al. (1989) and a summary has been provided by Lamb (1997). The Bossert et al. (1992) study was part of a series of studies evaluating glycol ethers and congeners for structure-activity correlations using a reproductive assessment by continuous breeding (RACB) study design.

Male and female CD-1 mice were administered TEG (97% pure) in drinking water at concentrations of 0, 0.3, 1.5, or 3% beginning 1 week prior to mating. Animals were randomly grouped as mating pairs, cohabited, and treated at the same concentration continuously for 98 days (14 weeks). The doses were calculated by the study authors to be equivalent to 0, 590, 3,300, and 6,780 mg/kg-day (Bossert et al., 1992). Doses selected were based upon the results of the 14-day dose-range-finding study described earlier (NTP, 1984). The control group consisted of 40 breeding pairs, and each TEG-treated group consisted of 20 breeding pairs. The F0 females were allowed to deliver during the cohabitation period, and data collected during the F0 cohabitation included the litter interval; number, sex, and weight of pups per litter; number of litters per breeding pair; and the PND 0 dam body weight. Pups produced during the F0 cohabitation period were evaluated (number alive and dead, sexed, and total litter weight) on PND 0 (within 12 hours of birth) and then were euthanized. After the 98-day cohabitation, the breeding pairs were separated. Dams were treated for an additional 21 days while delivering the last litter. These last litters from the control and high-dose groups were used as the second generation and received TEG in drinking water for a 21 day period (Morrissey et al., 1989). Parental F0 body weights and water consumption were measured for Weeks 1, 2, 5, 9, 13, and 18.

The final litters from the F0 control and high-dose TEG dams were allowed to grow until 74 ± 10 days of age while being maintained on the same TEG dietary concentrations to assess the second-generation fertility. These F1 offspring were then mated to nonsiblings from the same treatment group. F1 mice were weighed at birth (Day 0), PND 21, and PND 74 ± 10. They were sacrificed and necropsied after the F2 pups were delivered and evaluated. Endpoints examined for the F1 females included selected organ weights and histology. The endpoints examined for F1 male reproductive function included selected organ weights and histology, percentage motile sperm, epididymal sperm concentration, and percentage abnormal sperm. F2 litters were evaluated for litter size, sex, and pup weight. Appropriate statistical analyses were conducted as described in the RACB protocol. Although this is not a traditional two-generation study design, it is considered an acceptable reproductive study because it examined the reproductive effects of TEG in two generations.

In F0 animals, no treatment-related changes in physical appearance, body weight gain, or fluid consumption were observed. Two F0 animals died in the control group and in each of the mid- and high-dose groups. There were no treatment-related effects on the number of litters

produced per pair, the number of live pups/litter, or proportion of pups born alive. There was a statistically significant decrease in mean live pup weights in the mid- and high-dose groups after adjusting for litter size, but the results are not considered biologically significant because they were less than 5%. There were no treatment-related effects on reproduction in the F1 generation study, including F2 litter size, proportion of F2 pups born alive, sex of the F2 pups born alive, or adjusted F2 pup weight. Necropsy of the F1 animals found no treatment-related effects on body or organ weights. Sperm assessment indicated that exposure of F1 males to 6,780 mg/kg-day of TEG had no significant effects on sperm concentration, motility, and morphology. Based on the lack of any biologically significant findings, the reproductive NOAEL is 6,780 mg/kg-day (the highest dose tested), and no LOAEL is identified.

Carcinogenicity

Fitzhugh and Nelson (1946)

Male Osborne-Mendel rats (12/group) were administered 1, 2, or 4% TEG (purity not reported) in feed for 2 years. The equivalent daily doses calculated for this PPRTV assessment are 0, 700, 1,401, and 2,802 mg/kg-day, respectively, based on an average body weight (0.514 kg) and food consumption (0.036 kg/day) given for Osborne-Mendel rats by U.S. EPA (1988). Human equivalent doses (HEDs) are estimated to be 0, 205, 410, and 820 mg/kg-day. Body weights and food consumption were observed weekly. Eleven organs/tissues (lung, heart, liver, spleen, pancreas, stomach, small intestine, colon, kidney, adrenal, and testis) were routinely examined histologically in all animals with others examined only in some animals. No treatment-related effects were observed for mortality, food consumption, body weight gain, and gross or microscopic lesions.

Inhalation Exposures

The inhalation exposure effects of TEG in animals have been evaluated in two short-term-duration studies (Ballantyne et al., 2006), one subchronic-duration study (Maassen, 1953), and three chronic-duration studies (Robertson et al., 1947). No inhalation studies for the developmental, reproductive, or carcinogenic effects of TEG in animals were identified in the literature.

Short-Term-Duration Studies

Ballantyne et al. (2006)

In the Ballantyne et al. (2006) study, Sprague-Dawley rats (10/sex/exposure group) were administered concentrations of 0, 494, 2,011, or 4,824 mg/m^3 TEG (99.9% pure) aerosols via whole body inhalation for 6 hours/day, 5 days/week, over 11 days. These are equivalent to human equivalent concentrations (HECs) of 0, 101, 411, and 987 mg/m^3 based on extrarespiratory effects adjusting for continuous exposure and a blood-gas partition coefficient of 1. Test concentrations within the chambers were determined by a gravimetric method at 30-minute intervals. The mass median aerodynamic diameter (MMAD) of TEG aerosol particles was obtained using filters and a Sierra 8-stage cascade impactor (values ranged from 1.9–2.9 µm). At the terminus of the exposure period, animals were clinically examined, and body weights, food and water consumption were measured. Samples from necropsied animals were subjected to hematology, serum chemistry, and urine parameter evaluation, organ weights were measured, and histological examination was conducted on what the study authors describe as "multiple tissues and organs."

All rats exposed at the highest inhalation concentration died between Days 2−5; these rats had decreased body weight and body-weight gain and the following clinical signs of toxicity: ataxia, prostration, labored breathing, swollen periocular tissues, ocular discharge, perinasal and periocular encrustation, and blepharospasms (involuntary spasms of the eyelid). There was no mortality in the two lower exposure groups; however, clinical signs of toxicity (periocular swelling and perinasal encrustation) were observed on Days 2−5. On Day 2, body weight was statistically and biologically (>10%) significantly decreased in males and females at 987 mg/m^3. On Day 5, body weight was statistically significantly decreased in males at ≥411 mg/m^3 and biologically significantly decreased at 987 mg/m^3. Body weight was also statistically significantly decreased in males on Days 8−12 at 411 mg/m^3. Body weight gain was statistically significantly decreased in males and females on Days 1−2 at 987 mg/m^3, as well as in males on Days 1−5. Food consumption was statistically significantly increased in females during the entire study period at ≥101 mg/m^3. Water consumption was statistically significantly increased in males at 411 mg/m^3. Water consumption was statistically significantly increased in females at ≥101 mg/m^3. Serum alkaline phosphatase and inorganic phosphorous were significantly increased in females at ≥101 mg/m^3. The following statistically significant clinical chemistry changes were reported in females at 411 mg/m^3: increased erythrocyte count, decreased mean erythrocyte corpuscular volume, decreased serum glucose, decreased serum chloride, increased alanine aminotransferase activity, increased urine volume, decreased urine osmolality, and decreased urine pH. Alanine aminotransferase activity was statistically significantly increased in males at 411 mg/m^3. Urine volume was statistically significantly increased in males at 411 mg/m^3. Urine pH and N-acetyl-β-D-glucosaminidase were both statistically significantly decreased in males at 411 mg/m^3. Absolute liver weight was statistically and biologically (>10%) significantly increased in males at 411 mg/m^3. Absolute kidney weight was biologically (>10%) significantly increased in males at 101 mg/m^3. Absolute kidney weight was statistically significantly increased in males at 411 mg/m^3. Relative liver weight was statistically and biologically (>10%) significantly increased in males and females at 411 mg/m^3. Absolute kidney weight was statistically significantly increased in males at ≥101 mg/m^3 and in females at 411 mg/m^3. The NOAEL is 101 mg/m^3 and the LOAEL is 411 mg/m^3 based on clinical chemistry changes (i.e., increased serum alkaline phosphatase and alanine aminotransferase activities) indicative of liver toxicity and accompanied by an increase in liver weights greater than 10%.

Because whole body administration of TEG also allows for exposure through other routes (e.g., oral exposure through preening), the study was repeated employing nose-only exposure (Ballantyne et al., 2006). Sprague-Dawley rats (10/sex/exposure group) were exposed to TEG aerosol (MMAD range of 1.2−1.4 µm) at measured concentrations of 0, 102, 517, and 1,036 mg/m^3. HECs of 0, 21, 106, and 212 mg/m^3 are estimated based on extrarespiratory effects adjusting for continuous exposure and a blood-gas partition coefficient of 1. Endpoints examined were the same as those examined in the whole-body study described above. Although two mid-dose animals (one male and one female) died, the deaths were not accompanied by any signs of toxicity or any other abnormal findings and were not considered exposure-related. No exposure-related effects were observed at any concentration. The NOAEL is 212 mg/m^3 (the highest concentration tested), and no LOAEL is identified. The study authors concluded that the toxicity noted in the whole-body exposure study was likely due to oral exposure through preening. However, it should be noted that lower concentrations were used for the nose-only study.

Subchronic-Duration Studies

Maassen (1953)

The Maassen (1953) study is reported in a foreign language, and a translation was not available to review at the time of preparing this PPRTV assessment. Very limited information is available in the secondary source (CEC, 2000). No exposure-related effects were observed in rats (sex, strain, number unspecified) exposed continuously to supersaturated TEG vapour (approximately 449 mg/m^3) for 41 days. A NOAEL of 449 mg/m^3 is identified based on lack of effects; identification of a LOAEL is precluded.

Chronic-Duration Studies

Robertson et al. (1947): Rat Study

Robertson et al. (1947) housed 24 male and 12 female rats in a chamber containing supersaturated TEG vapor in air (approximately 4 mg/m^3), maintained by a glycostat device. Four male and two female control rats were kept in a separate chamber containing normal air. Animals remained in the respective chambers for 6 to 13 months. Due to breeding during the test period, the populations increased in the TEG and control chambers to 60 and 14, respectively. The study authors examined the parameters previously detailed in Robertson et al. (1947) with the exception that interval sacrifices were performed at 3,4, 5, and 6 months.

The growth rates of adult and offspring rats exposed to TEG were similar to the growth rates in the control group. The general health of the rats was not affected by the TEG exposure. Hematology was likewise similar between control and treated animals. Necropsies showed no exposure-related lesions. Based on this, a NOAEL of 4 mg/m^3 is identified.

Robertson et al. (1947): Monkey Study

The study authors performed similar tests on rhesus macaque monkeys where 17 monkeys (sex unspecified) were exposed continuously by inhalation to approximately 4 mg/m^3 supersaturated TEG vapor in air from one to 10 months, and 8 monkeys were kept in a separate chamber containing normal air from 5 to 8 months. The study authors reported decreased body weight, browning of the skin of the face, and crusting of the ears in exposed monkeys. Hematology, blood chemistry, and urinalysis were similar between exposed and control animals. There was high mortality or moribund sacrifices in both the exposed (7 of 17 monkeys) and control (5 of 8 monkeys) groups. Due to the lack of quantitative data, it is not possible to identify a LOAEL or NOAEL for monkeys exposed to supersaturated TEG vapor in air.

In a separate study, 8 rhesus macaque monkeys (sex unspecified) were exposed continuously by inhalation to approximately 2−3 mg/m^3 TEG vapor from 2 weeks to 10 months, and 8 monkeys were kept in a separate chamber containing normal air for the same length of time. No adverse reactions or histopathological changes (examined tissues were not specified by the study authors) suggestive of toxicity from prolonged exposure to TEG were seen in the exposed monkeys. Accordingly, a NOAEL of 3 mg/m^3 is identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

TEG has been found to be negative in both genotoxicity and mutagenicity studies with and without metabolic activation, including *Salmonella typhimurium* reverse mutation tests, SOS-chromotest using *Escherichia coli* PQ37, forward mutation studies in Chinese hamster

ovary (CHO) cells, chromosomal aberration tests in CHO cells, and sister chromatid exchange (SCE) assays in CHO cells (Ballantyne and Snellings, 2007; U.S. EPA, 2005; Mersch-Sundermann et al., 1994).

Metabolism/Toxicokinetic Studies

An oral study by Mckennis (1962) that examined rats and rabbits found that TEG was either excreted as unchanged compound or oxidized. TEG was primarily excreted via the urine. Small amounts also were detected in the feces, and trace amounts were measured as exhaled CO_2. A total of 91−98% was excreted through all routes within 5 days of a single oral exposure of 25% (weight/volume) TEG. The proposed metabolic pathway was TEG to hydroxy acid followed by oxidation to ethylenedioxydiacetic acid (Mckennis, 1962).

Mode-of-Action/Mechanistic Studies

No studies have been identified.

Immunotoxicity

No studies have been identified.

Neurotoxicity

No studies have been identified.

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present summaries of noncancer and cancer reference values, respectively.

Table 4. Summary of Noncancer Provisional Reference Values for Triethylene Glycol (CASRN 112-27-6)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD_{HED}	UF_C	Principal Study
Subchronic p-RfD (mg/kg-day)	Mouse/Both	Delayed ossification of the supraoccipital bone in fetal mice	2×10^0	$BMDL_{05}$	70.8	30	Ballantyne and Snellings (2005)
Chronic p-RfD (mg/kg-day)	Mouse/Both	Delayed ossification of the supraoccipital bone in fetal mice	2×10^0	$BMDL_{05}$	70.8	30	Ballantyne and Snellings (2005)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

NDr = not determined.

Table 5. Summary of Provisional Cancer Values for Triethylene Glycol (CASRN 112-27-6)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}day)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The definitive developmental toxicity study in mice by Ballantyne and Snellings (2005) is selected as the principal study for derivation of the subchronic p-RfD. The critical effect is delayed ossification of the supraoccipital bone in fetal mice. This study was presented in a peer-reviewed journal; was performed according to good laboratory practice (GLP) (Union Carbide, 1990a, b); and otherwise meets the standards of study design and performance with regard to numbers of animals, examination of potential toxicity endpoints, and presentation of information. Details of the study are provided in the "Review of Potentially Relevant Data" section.

Justification

There are four subchronic-duration studies available for consideration in the derivation of the subchronic p-RfD (Van Miller and Ballantyne, 2001; Lauter and Vrla, 1940). In addition, there are five developmental toxicity studies (Ballantyne and Snellings, 2005; Schuler et al., 1984) and one reproductive toxicity study (Bossert et al., 1992). Lauter and Vrla (1940) provided information on subchronic-duration exposure via drinking water in young and mature rats and in a rat subchronic-duration gavage study. None of the studies reported in Lauter and Vrla (1940) are considered because the study reports provided insufficient information concerning study design and results, and the numbers of animals used were small. The subchronic-duration study by Van Miller and Ballantyne (2001) is considered to be of acceptable quality; however, because of the lack of any effects observed at any dose tested, the study is not selected as the principal study in light of effects observed in the developmental toxicity studies at lower doses. The Schuler et al. (1984) developmental toxicity study is not considered due to insufficient reporting and because only one high dose was tested. Ballantyne and Snellings (2005) reported on four developmental toxicity studies. Two were dose-range-finding studies in mice and rats and not fully comprehensive developmental toxicity studies. Not all the data were provided in the dose-range-finding studies nor were the fetuses internally examined for malformations. Thus, the dose-range-finding studies are not considered for subchronic p-RfD derivation. Notably, there was a biologically significant increase (i.e., >5%) in the incidence of clubbed limbs per litter in mice in the dose-range-finding study (Ballantyne and Snellings, 2005). However, this effect does not show a clear dose-response and was actually decreased compared to controls in mice from the definitive developmental study. These data suggest that the increased incidence of clubbed limbs in the dose-range-finding study may not be treatment related and was therefore not considered as a potential critical effect and POD. Because the full/definitive developmental toxicity studies in mice and rats reported by Ballantyne and Snellings (2005) tested more animals and are more comprehensive than the dose-range-finding studies (e.g., evaluation of a full suite of developmental effects including visceral and skeletal examinations and the number of live and dead fetuses), they are considered as potential principal studies for derivation of the subchronic p-RfD.

In the Ballantyne and Snellings (2005) developmental toxicity studies in mice and rats, the biological and/or statistically significant effects reported in the fetuses were decreased fetal body weight per litter, as a total and by sex, and increased incidence of skeletal variations. Based on the U.S. EPA's *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991) skeletal variations such as poorly ossified supraoccipital bone, poorly ossified frontal bone, poorly ossified cervical centra, reduced caudal segments, and bilobed thoracic centrum are considered biologically relevant endpoints. As described in Appendix C, all available

continuous models in the U.S. EPA Benchmark Dose Software (BMDS version 2.1.2) are fit to the number of litters with decreased fetal body weight in mice and rats and to the incidence data for delayed ossification of the frontal bone and the supraoccipital bone in fetal mice, following exposure to TEG on GDs 6−15. Although a 10% BMR is standard, a 5% BMR is used in this case because the developmental effects (i.e., decreased fetal body weight and fetal skeletal variations) were observed during a potentially sensitive life stage. For rats, the data for decreased fetal body weight were not amenable to BMD modeling; thus, a NOAEL/LOAEL approach was employed to identify a potential point of departure (POD). For decreased rat fetal body weight in males, females, and males and females combined, the LOAEL is 11,260 mg/kg-day based on a biologically (≥5%) and statistically significant decrease, with a corresponding NOAEL of 5,630 mg/kg-day. For male mice, BMD modeling resulted in a $BMDL_{05}$ of 1,274 mg/kg-day for decreased fetal body weight. The data for decreased fetal body weight in female mice alone and male and female mice combined were not amenable to BMD modeling due to increased variability in the data as indicated by a homogeneity variance *p*-value of less than 0.1. Thus, a LOAEL of 5,630 mg/kg-day for decreased fetal body weight is identified with a corresponding NOAEL of 563 mg/kg-day. The dose-response trend and the extent of change for decreased fetal body weight in mice were almost identical for all categories (i.e., males alone, females alone, and males and females combined; see Table B-3). It is therefore fair to reason that if the data for female mice and male and female mice combined were amenable to BMD modeling, a similar $BMDL_{05}$ as was determined for decreased fetal body weight in male mice ($BMDL_{05}$ = 1,274 mg/kg-day) would likely have been calculated. Taken together, for decreased fetal body weight in rats and mice, the most sensitive potential POD appears to be a NOAEL of 563 mg/kg-day in female mice alone and male and female mice combined.

For increased incidence of delayed ossification of the frontal bone in litters of fetal mice, BMD modeling using nested models resulted in a $BMDL_{05}$ of 847 mg/kg-day. A $BMDL_{05}$ of 506 mg/kg-day was identified for increased incidence of delayed ossification of the supraoccipital bone in litters of fetal mice (see Table C-1). For increased incidence of bilobed thoracic centrum in fetal rats, the individual litter data are not available to perform BMD modeling using nested models; thus, a NOAEL/LOAEL approach was employed to identify a POD. For increased incidence of bilobed thoracic centrum in fetal rats, the LOAEL is 11,260 mg/kg-day with a corresponding NOAEL of 5,630 mg/kg-day.

Increased incidence of fetal skeletal variations is a common developmental effect of TEG toxicity observed in both mice and rats (Ballantyne and Snellings, 2005). Based on the developmental effects from the Ballantyne and Snellings (2005) study, the most sensitive potential POD from all available studies is the $BMDL_{05}$ of 506 mg/kg-day for increased incidence of delayed ossification of the supraoccipital bone in litters of fetal mice. **Thus, delayed ossification of the supraoccipital bone in fetal mice is chosen as the critical effect, with a $BMDL_{05}$ of 506 mg/kg-day as the POD.**

Dosimetric Adjustments:

No dosimetric adjustments for duration are made because developmental toxicity studies are not adjusted for continuous exposure.

In U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011c) the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, U.S. EPA endorses body weight scaling to the 3/4 power (i.e., $BW^{3/4}$) to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite, but not for portal-of-entry effects. A validated human physiologically based toxicokinetic model for TEG is not available for use in extrapolating doses from animals to humans. The selected critical effect of delayed ossification of the supraoccipital bone in fetal mice is associated with the parent compound or a stable metabolite. Furthermore, this fetal skeletal variation is not a portal-of-entry effect. Therefore, scaling by $BW^{3/4}$ is relevant for deriving human equivalent doses (HEDs) for this effect.

Following U.S. EPA (2011c) guidance, the POD for delayed ossification of the supraoccipital bone in fetal mice is converted to a HED through application of a dosimetric adjustment factor (DAF)[1] 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 0.025 kg for mice and a BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.14. Applying this DAF to the $BMDL_{05}$ identified for the critical effect in fetal mice yields a $BMDL_{05HED}$ as follows:

$$\begin{aligned} BMDL_{05HED} &= 506 \text{ mg/kg-day} \times DAF \\ &= 506 \text{ mg/kg-day} \times 0.14 \\ &= 70.8 \text{ mg/kg-day} \end{aligned}$$

The subchronic p-RfD for TEG, based on a $BMDL_{05HED}$ of 70.8 mg/kg-day for delayed ossification of the supraoccipital bone in fetal mice, is derived as follows:

[1]As described in detail in Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose (U.S. EPA, 2011c), rate-related processes scale across species in a manner related to both the direct ($BW^{1/1}$) and allometric scaling ($BW^{3/4}$) aspects such that $BW^{3/4} \div BW^{1/1} = BW^{1/4}$, converted to a $DAF = BW_a^{1/4} \div BW_h^{1/4}$.

Subchronic p-RfD = $BMDL_{05HED} \div UF_C$
= 70.8 mg/kg-day ÷ 30
= **2×10^0 mg/kg-day**

Table 6 summarizes the uncertainty factors for the subchronic p-RfD for TEG.

Table 6. Uncertainty Factors for the Subchronic p-RfD for TEG

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between mice and humans following oral TEG exposure. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) through application of a dosimetric adjustment factor (DAF) as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011c).
UF_D	1	A UF_D of 1 is applied because the database includes one acceptable two-generation reproductive toxicity study in mice (Bossert et al., 1992) and two acceptable developmental toxicity studies in rats and mice (Ballantyne and Snellings, 2005).
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of TEG in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because developmental toxicity resulting from a narrow period of exposure (i.e., delayed ossification of the supraoccipital bone in fetal mice) was used as the critical effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	30	Composite Uncertainty Factor = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

The confidence in the subchronic p-RfD for TEG is high as explained in Table 7 below.

Table 7. Confidence Descriptors for the Subchronic p-RfD for TEG

Confidence Categories	Designation[a]	Discussion
Confidence in study	H	The confidence in the principal study is high because preliminary studies were conducted to determine appropriate doses, and comprehensive developmental endpoints were examined. Rats appeared to be less sensitive than mice, but data in rats also indicate decreased fetal body weight and skeletal variations.
Confidence in database	H	There is high confidence in the database because there were short-term-, subchronic-, and chronic-duration studies, as well as developmental (several) and reproductive toxicity studies.
Confidence in subchronic p-RfD[b]	H	The overall confidence in the subchronic p-RfD is high.

[a]L = low; M = medium; H = high.
[b]The overall confidence cannot be greater than the lowest entry in the table.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

In addition to all the studies considered for the derivation of the subchronic p-RfD (noted above), there were three chronic-duration studies (Robertson et al., 1947; Fitzhugh and Nelson, 1946). Fitzhugh and Nelson (1946) provided insufficient data, including no details on the control group and no reported effects in rats at any dose tested, and Robertson et al. (1947) examined chronic effects in both rats and monkeys. However, neither of these studies is considered sufficient due to the lack of reporting details on study design and results, as well as the small number of animals used throughout. Based on the lack of any sufficient chronic-duration studies, and for the reasons detailed above under the derivation of subchronic p-RfD, the definitive developmental study in mice by Ballantyne and Snellings (2005) is also selected as the principal study for derivation of the chronic p-RfD. The $BMDL_{05HED}$ of 70.8 mg/kg-day for delayed ossification of the supraoccipital bone in fetal mice is again used as the POD, and the chronic p-RfD is derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfD} &= BMDL_{05HED} \div UF_C \\ &= 70.8 \text{ mg/kg-day} \div 30 \\ &= \mathbf{2 \times 10^0 \text{ mg/kg-day}} \end{aligned}$$

Table 8 summarizes the uncertainty factors for the chronic p-RfD for TEG.

Table 8. Uncertainty Factors for the Chronic p-RfD for TEG

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between mice and humans following oral TEG exposure. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) through application of a dosimetric adjustment factor (DAF) as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011c).
UF_D	1	A UF_D of 1 is selected because there is one acceptable two-generation reproduction study in mice (Bossert et al., 1992) and two acceptable developmental studies in rats and mice (Ballantyne and Snellings, 2005).
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of TEG in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because developmental toxicity resulting from a narrow period of exposure (i.e., delayed ossification of the supraoccipital bone in fetal mice) was used as the critical effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	30	Composite Uncertainty Factor = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$

The confidence of the chronic p-RfD for TEG is high as explained in Table 9 below.

Table 9. Confidence Descriptors for the Chronic p-RfD for TEG

Confidence Categories	Designation[a]	Discussion
Confidence in study	H	The confidence in the principal study is high because preliminary studies were conducted to determine appropriate doses, and comprehensive developmental endpoints were examined. Rats appeared to be less sensitive than mice, but data in rats also indicate decreased fetal body weight and skeletal variations.
Confidence in database	H	There is high confidence in the database because there were short-term-, subchronic-, and chronic-duration studies, as well as developmental (several) and reproductive toxicity studies.
Confidence in chronic p-RfD[b]	H	The overall confidence in the subchronic p-RfD is high.

[a]L = low; M = medium; H = high.
[b]The overall confidence cannot be greater than the lowest entry in the table.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

There are no inhalation studies of sufficient quality to derive a subchronic p-RfC. Two short-term-duration studies are available that evaluated whole-body and one nose-only exposure (Ballantyne et al., 2006), but they are of insufficient duration (only 9 days). There is a single subchronic-duration study available (Maassen, 1953). This study is in a foreign language and only evaluated one concentration stated to be a saturated atmosphere. Due to the lack of a sufficient subchronic-duration study, no subchronic p-RfC can be derived.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

Chronic-duration inhalation studies were conducted in rats and monkeys (Robertson et al., 1947). The studies were not conducted according to proper standards, and study details were not sufficiently documented. Small numbers of animals were exposed for various times in chambers containing TEG vapor with no indication that the concentrations were measured or how the vapors were generated. The rats varied in age from 6 weeks to 6 months, but data were not separated by age. Rats were sacrificed throughout the study duration, but it was not clear whether it was due to morbidity or planned interim sacrifice. Control and exposed animals (rats and monkeys), however, were not generally sacrificed during the same time span. In one of the monkey studies, there was high mortality or moribund sacrifices in both the supersaturated exposed (7 of 17 monkeys) and control (5 of 8 monkeys) groups. Few details for each study are provided and only a few endpoints were measured and/or reported. Furthermore, the animals in the studies by Robertson et al. (1947) were exposed to a single concentration of TEG. Based on the lack of information available and the low quality of chronic-duration studies, no chronic p-RfC can be derived.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 10 identifies the cancer weight-of-evidence (WOE) descriptor for TEG.

Table 10. Cancer WOE Descriptor for TEG			
Possible WOE Descriptor	**Designation**	**Route of Entry (oral, inhalation, or both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	There are no human data to support this.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no sufficient animal studies to support this.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There are no sufficient animal studies to support this.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**There is one study that looked for tumors after 2 years of dietary treatment up to a concentration of 4% TEG (2,802 mg/kg-day) in male rats (Fitzhugh and Nelson, 1946) with no tumors reported. However, only 12 animals per treatment group were used, there was no information on any control group, and only a few organs/tissues were routinely examined. No carcinogenicity studies are available that evaluated inhalation exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

NA = not applicable; NS = not selected.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

The lack of sufficient data on the carcinogenicity of TEG following oral exposure precludes the derivation of a quantitative estimate (p-OSF) for oral exposure.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

The lack of data on the carcinogenicity of TEG following inhalation exposure precludes the derivation of a quantitative estimate (p-IUR) for inhalation exposure.

APPENDIX A. SCREENING PROVISIONAL VALUES

No screening values for TEG are identified.

APPENDIX B. DATA TABLES

Table B-1. Developmental Cesarean Section Observations in Rats After Treatment with TEG[a]

Observation	Exposure Group (mg/kg-day)			
	0	1,126	5,630	11,260
Number animals pregnant	25	25	25	25
Total number of litters	22	24	19	23
Mean fetal weight/litter (g)[b]	5.280 ± 0.373	5.333 ± 0.234 (101)	5.304 ± 0.398 (100)	4.990 ± 0.327 (95)*
Male mean fetal weight/litter (g)[b]	5.426 ± 0.368	5.465 ± 0.229 (101)	5.433 ± 0.432 (100)	5.115 ± 0.323 (94)**
Female mean fetal weight/litter (g)[b]	5.126 ± 0.386	5.204 ± 0.260 (102)	5.173 ± 0.400 (101)	4.846 ± 0.332 (95)*

[a]Ballantyne and Snellings (2005).
[b]Mean ± SD (% of controls).
*$p < 0.05$, **$p < 0.01$.

Table B-2. Select Developmental Observations in Rats After Treatment with TEG[a]

Observations	Exposure Group (mg/kg-day)			
	0	1,126	5,630	11,260
Number of fetuses (litters) examined	325 (22)	356 (24)	281 (19)	362 (23)
Number of fetuses (litters) with malformations	22 (8)	22 (10)	22 (10)	49 (14)
Number of fetuses (litters) with variations	324 (22)	353 (24)	281 (19)	362 (23)
Number of fetuses (litters) with thoracic centrum no. 10 bilobed	9 (6)	5 (5)	14 (9)	23 (15)*
Number of fetuses (litters) with poorly ossified thoracic centrum no. 10	5 (5)	9 (6)	9 (3)	16 (12)

[a]Ballantyne and Snellings (2005).
*$p < 0.05$.

Table B-3. Developmental Cesarean Section Observations in Mice After Treatment with TEG[a]

Observation	Exposure Group (mg/kg-day)			
	0	563[b]	5,630	11,260
Number animals pregnant	30	30	30	30
Total number of litters	27	28	26	25
Gravid uterine weight (g)	20.73 ± 6.06	20.30 ± 4.90 (98)	19.63 ± 6.06 (95)	18.56 ± 4.98 (90)
Mean fetal weight/litter (g)[c]	1.429 ± 0.115	1.416 ± 0.097 (99)	1.350 ± 0.066 (94)*	1.303 ± 0.098 (91)**
Male mean fetal weight/litter (g)[c]	1.463 ± 0.114	1.442 ± 0.116 (99)	1.384 ± 0.074 (95)*	1.332 ± 0.106 (91)**
Female mean fetal weight/litter (g)[c]	1.391 ± 0.118	1.395 ± 0.092 (100)	1.321 ± 0.066 (95)*	1.271 ± 0.102 (91)**

[a]Ballantyne and Snellings (2005).
[b]The tables from which information was obtained in the publication had the low dose incorrectly labeled as 1,126; however, because the rest of the document and the proprietary data (Union Carbide, 1990a, b) indicated 563 mg/kg-day is the lowest dose tested in mice, 563 mg/kg-day is used here.
[c]Mean ± SD (% of controls).
*$p < 0.05$, **$p < 0.01$.

Table B-4. Select Developmental Observations in Mice After Treatment with TEG[a]

Observations	Exposure Group (mg/kg-day)			
	0	563	5,630	11,260
Number of fetuses (litters) examined	310 (27)	316 (28)	310 (26)	283 (25)
Number of fetuses (litters) with malformations	13 (12)	10 (7)	6 (5)	15 (6)
Number of fetuses (litters) with variations	310 (27)	315 (28)	310 (26)	283 (25)
Number of fetuses (litters) with frontal bone poorly ossified	36 (13)	48 (20)	60 (21*)	67 (22*)
Number of fetuses (litters) with supraoccipital bone poorly ossified	45 (17)	54 (20)	83 (24*)	85 (23*)
Number of fetuses (litters) with poorly ossified cervical centra—no 1, 2, 3, and/or 4	7 (6)	9 (7)	14 (9)	26 (14*)
Number of fetuses (litters) with reduced caudal segments	11 (5)	22 (8)	24 (12)	46 (14*)
Number of fetuses (litters) with hind limb proximal phalanges, some unossified	17 (11)	32 (14)	31 (13)	63 (19*)
Number of fetuses (litters) with hind limb proximal phalanges, some poorly ossified	18 (11)	23 (9)	35 (18)	47 (18*)

[a]Ballantyne and Snellings (2005).
*$p < 0.05$.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE FOR CONTINUOUS DATA

The benchmark dose (BMD) modeling of continuous data was conducted with U.S. EPA's BMD software (BMDS, version 2.1.2). For decreased fetal body weight data, all continuous models available within the software were fit using a default benchmark response (BMR) of 5% relative risk. An adequate fit was judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. I addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was homogeneous. If a homogeneous variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2), the final BMD results were estimated from a homogeneous variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model did not adequately fit the data (i.e., Test 3; $p < 0.1$), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest benchmark dose lower confidence limit (BMDL) was selected if the BMDLs estimated from different models varied greater than 3-fold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) was selected as a potential POD from which to derive a p-RfD.

MODELING PROCEDURE FOR NESTED DICHOTOMOUS DATA

The BMD modeling of nested dichotomous data was conducted with U.S. EPA's BMDS (version 2.1.2). For delayed ossification of the supraoccipital bone and frontal bone, the nested logistic (NLogistic) dichotomous model was fit using a standard BMR of 5% extra risk for developmental endpoints. For both delayed ossification endpoints, the NLogistic model was fit with and without litter size as a covariate and with and without intralitter correlations. Adequacy of model fit was judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit.

DELAYED OSSIFICATION OF THE SUPRAOCCIPITAL BONE IN FETAL MICE TREATED WITH TEG FROM GESTATIONAL DAYS 6−15 (Ballantyne and Snellings, 2005)

The NLogistic dichotomous model in BMDS (version 2.1.2) was fit to the data for delayed ossification of the supraoccipital bone in fetal mice treated with TEG from GDs 6−15 (Ballantyne and Snellings, 2005) (see Table B-4). For delayed ossification of the supraoccipital bone, a BMR of a 5% change relative to the control mean was used. As assessed by the χ^2 goodness-of-fit statistic, AIC score, and visual inspection, the NLogistic model provided an optimal fit (see Table C-1 and Figure C-1). Including litter size as a covariate and using intralitter correlations had significant effects on the AIC scores. The best fitting NLogistic model as indicated by the lowest AIC was obtained with estimating intralitter correlations and not including litter size as a covariate. The estimated dose associated with 5% extra risk (BMD_{05}) and the 95% lower confidence limit on this dose ($BMDL_{05}$) were 825 and 506 mg/kg-day, respectively.

Table C-1. Model Prediction for Delayed Ossification of the Supraoccipital Bone in Fetal Mice[a]

Model	BMD_{05}	$BMDL_{05}$	χ^2 *p*-Value	AIC	Conclusion
NLogistic	825	506	0.474	721.73	Provided an optimal fit

[a]Ballantyne and Snellings (2005).

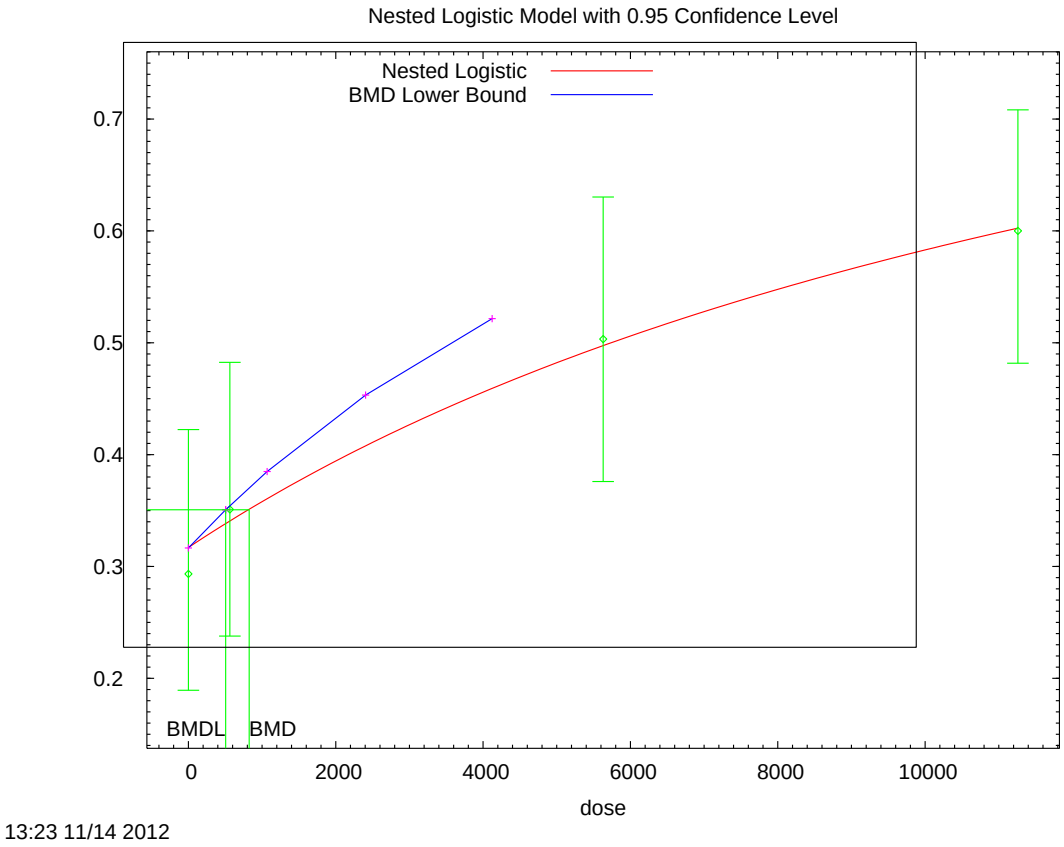

Figure C-1 NLogistic Model Fit for Delayed Ossification of the Supraoccipital Bone in Fetal Mice (Ballantyne and Snellings, 2005).

```
================================================================================
        NLogistic Model. (Version: 2.15; Date: 10/28/2009)
        Input Data File: C:/Documents and Settings/JKaiser/Desktop/modeling
results/nln_nested_supra_teg_Nln-BMR10-Restrict.(d)
                                                  Wed Nov 14 13:23:12 2012
 ================================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

 The probability function is:


 Prob. = alpha + theta1*Rij + [1 - alpha - theta1*Rij]/

                       [1+exp(-beta-theta2*Rij-rho*log(Dose))],

          where Rij is the litter specific covariate.

 Restrict Power rho >= 1.



 Total number of observations = 106
 Total number of records with missing values = 0
```

Total number of specified parameters = 2

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User specifies the following parameters:
theta1 = 0
theta2 = 0

Default Initial Parameter Values

alpha =	0.316508	
beta =	-9.65973	
theta1 =	0	Specified
theta2 =	0	Specified
rho =	1	
phi1 =	0.326483	
phi2 =	0.312191	
phi3 =	0.244159	
phi4 =	0.138021	

Parameter Estimates

Variable	Estimate	Std. Err.
alpha	0.316507	*
beta	-9.65974	*
rho	1	*
phi1	0.326483	*
phi2	0.312191	*
phi3	0.244159	*
phi4	0.138021	*

* - Indicates that this value is not calculated.

Log-likelihood: -354.866 AIC: 721.732

Litter Data

Dose	Lit.-Spec. Cov.	Est._Prob.	Litter Size	Expected	Observed	Scaled Residual
0.0000	2.0000	0.317	1	0.317	0	-0.6805
0.0000	4.0000	0.317	2	0.633	1	0.4844
0.0000	9.0000	0.317	4	1.266	3	1.3249
0.0000	9.0000	0.317	4	1.266	4	2.0890
0.0000	9.0000	0.317	4	1.266	0	-0.9673
0.0000	10.0000	0.317	5	1.583	0	-1.0020
0.0000	10.0000	0.317	5	1.583	5	2.1639
0.0000	11.0000	0.317	5	1.583	0	-1.0020
0.0000	11.0000	0.317	5	1.583	1	-0.3689
0.0000	11.0000	0.317	5	1.583	1	-0.3689
0.0000	11.0000	0.317	5	1.583	0	-1.0020
0.0000	11.0000	0.317	5	1.583	1	-0.3689
0.0000	12.0000	0.317	6	1.899	3	0.5956
0.0000	12.0000	0.317	6	1.899	0	-1.0274
0.0000	12.0000	0.317	6	1.899	0	-1.0274
0.0000	12.0000	0.317	6	1.899	0	-1.0274

0.0000	12.0000	0.317	6	1.899	1	-0.4864
0.0000	12.0000	0.317	6	1.899	4	1.1366
0.0000	12.0000	0.317	6	1.899	3	0.5956
0.0000	13.0000	0.317	6	1.899	4	1.1366
0.0000	14.0000	0.317	7	2.216	2	-0.1018
0.0000	14.0000	0.317	7	2.216	1	-0.5742
0.0000	14.0000	0.317	7	2.216	0	-1.0467
0.0000	15.0000	0.317	7	2.216	3	0.3706
0.0000	16.0000	0.317	8	2.532	0	-1.0619
0.0000	16.0000	0.317	8	2.532	3	0.1962
0.0000	16.0000	0.317	8	2.532	4	0.6156
563.0000	8.0000	0.340	4	1.361	3	1.2431
563.0000	8.0000	0.340	4	1.361	1	-0.2736
563.0000	9.0000	0.340	4	1.361	1	-0.2736
563.0000	9.0000	0.340	4	1.361	1	-0.2736
563.0000	9.0000	0.340	4	1.361	4	2.0015
563.0000	10.0000	0.340	5	1.701	0	-1.0707
563.0000	10.0000	0.340	5	1.701	2	0.1882
563.0000	10.0000	0.340	5	1.701	3	0.8176
563.0000	10.0000	0.340	5	1.701	4	1.4471
563.0000	11.0000	0.340	5	1.701	0	-1.0707
563.0000	11.0000	0.340	5	1.701	5	2.0766
563.0000	11.0000	0.340	5	1.701	1	-0.4413
563.0000	11.0000	0.340	5	1.701	0	-1.0707
563.0000	11.0000	0.340	5	1.701	0	-1.0707
563.0000	11.0000	0.340	5	1.701	0	-1.0707
563.0000	11.0000	0.340	5	1.701	4	1.4471
563.0000	12.0000	0.340	6	2.041	2	-0.0222
563.0000	12.0000	0.340	6	2.041	4	1.0547
563.0000	12.0000	0.340	6	2.041	0	-1.0991
563.0000	12.0000	0.340	6	2.041	2	-0.0222
563.0000	13.0000	0.340	6	2.041	2	-0.0222
563.0000	13.0000	0.340	6	2.041	5	1.5932
563.0000	13.0000	0.340	6	2.041	2	-0.0222
563.0000	13.0000	0.340	6	2.041	3	0.5162
563.0000	14.0000	0.340	7	2.381	0	-1.1208
563.0000	14.0000	0.340	7	2.381	3	0.2911
563.0000	14.0000	0.340	7	2.381	1	-0.6502
563.0000	14.0000	0.340	7	2.381	0	-1.1208
5630.0000	9.0000	0.497	4	1.989	3	0.7685
5630.0000	10.0000	0.497	5	2.486	0	-1.5814
5630.0000	10.0000	0.497	5	2.486	2	-0.3090
5630.0000	10.0000	0.497	5	2.486	0	-1.5814
5630.0000	10.0000	0.497	5	2.486	1	-0.9452
5630.0000	10.0000	0.497	5	2.486	4	0.9634
5630.0000	10.0000	0.497	5	2.486	5	1.5996
5630.0000	10.0000	0.497	5	2.486	1	-0.9452
5630.0000	11.0000	0.497	5	2.486	4	0.9634
5630.0000	11.0000	0.497	5	2.486	1	-0.9452
5630.0000	11.0000	0.497	5	2.486	3	0.3272
5630.0000	12.0000	0.497	6	2.983	4	0.5573
5630.0000	12.0000	0.497	6	2.983	2	-0.5385
5630.0000	12.0000	0.497	6	2.983	0	-1.6343
5630.0000	12.0000	0.497	6	2.983	5	1.1052
5630.0000	12.0000	0.497	6	2.983	4	0.5573
5630.0000	12.0000	0.497	6	2.983	5	1.1052
5630.0000	13.0000	0.497	6	2.983	5	1.1052
5630.0000	13.0000	0.497	6	2.983	5	1.1052
5630.0000	13.0000	0.497	6	2.983	4	0.5573
5630.0000	14.0000	0.497	7	3.480	3	-0.2311
5630.0000	14.0000	0.497	7	3.480	1	-1.1941
5630.0000	14.0000	0.497	7	3.480	2	-0.7126

5630.0000	14.0000	0.497	7	3.480	6	1.2134
5630.0000	15.0000	0.497	7	3.480	5	0.7319
5630.0000	16.0000	0.497	8	3.977	1	-1.2790
11260.0000	6.0000	0.602	3	1.807	0	-1.8867
11260.0000	8.0000	0.602	4	2.409	3	0.5077
11260.0000	9.0000	0.602	4	2.409	3	0.5077
11260.0000	9.0000	0.602	4	2.409	3	0.5077
11260.0000	10.0000	0.602	5	3.011	5	1.4586
11260.0000	10.0000	0.602	5	3.011	4	0.7252
11260.0000	10.0000	0.602	5	3.011	4	0.7252
11260.0000	10.0000	0.602	5	3.011	2	-0.7417
11260.0000	11.0000	0.602	5	3.011	4	0.7252
11260.0000	11.0000	0.602	5	3.011	3	-0.0082
11260.0000	11.0000	0.602	5	3.011	4	0.7252
11260.0000	11.0000	0.602	5	3.011	1	-1.4751
11260.0000	11.0000	0.602	5	3.011	4	0.7252
11260.0000	11.0000	0.602	5	3.011	1	-1.4751
11260.0000	11.0000	0.602	5	3.011	5	1.4586
11260.0000	12.0000	0.602	6	3.613	5	0.8896
11260.0000	12.0000	0.602	6	3.613	4	0.2480
11260.0000	13.0000	0.602	6	3.613	3	-0.3936
11260.0000	13.0000	0.602	6	3.613	3	-0.3936
11260.0000	13.0000	0.602	6	3.613	2	-1.0352
11260.0000	14.0000	0.602	7	4.216	6	1.0191
11260.0000	14.0000	0.602	7	4.216	0	-2.4078
11260.0000	14.0000	0.602	7	4.216	4	-0.1232
11260.0000	14.0000	0.602	7	4.216	3	-0.6944
11260.0000	15.0000	0.602	7	4.216	5	0.4479

Combine litters with adjacent levels of the litter-specific covariate
within dose groups until the expected count exceeds 3.0, to help improve
the fit of the X^2 statistic to chi-square.

Grouped Data

Dose	Mean Lit.-Spec. Cov.	Expected	Observed	Scaled Residual
0.0000	3.0000	0.950	1	0.0568
0.0000	4.0000	1.266	3	1.3249
0.0000	9.0000	4.115	4	-0.0471
0.0000	10.0000	3.165	5	0.8216
0.0000	11.0000	3.165	2	-0.5216
0.0000	11.0000	3.165	1	-0.9694
0.0000	11.0000	1.899	3	0.5956
0.0000	12.0000	3.798	0	-1.4529
0.0000	12.0000	3.798	1	-1.0704
0.0000	12.0000	3.798	7	1.2249
0.0000	12.0000	1.899	4	1.1366
0.0000	13.0000	2.216	2	-0.1018
0.0000	14.0000	4.431	1	-1.1462
0.0000	14.0000	2.216	3	0.3706
0.0000	15.0000	2.532	0	-1.0619
0.0000	16.0000	5.064	7	0.5741
563.0000	16.0000	1.361	3	1.2431
563.0000	8.0000	2.722	2	-0.3870
563.0000	9.0000	4.423	5	0.2357
563.0000	10.0000	3.402	5	0.7112
563.0000	10.0000	3.402	4	0.2661

563.0000	11.0000	3.402	6	1.1563
563.0000	11.0000	3.402	0	-1.5142
563.0000	11.0000	3.402	4	0.2661
563.0000	11.0000	2.041	2	-0.0222
563.0000	12.0000	4.082	4	-0.0314
563.0000	12.0000	4.082	4	-0.0314
563.0000	13.0000	4.082	7	1.1108
563.0000	13.0000	4.423	3	-0.5041
563.0000	14.0000	4.763	4	-0.2539
563.0000	14.0000	2.381	0	-1.1208
5630.0000	14.0000	1.989	3	0.7685
5630.0000	9.0000	2.486	0	-1.5814
5630.0000	10.0000	4.971	2	-1.3367
5630.0000	10.0000	4.971	5	0.0129
5630.0000	10.0000	4.971	6	0.4627
5630.0000	10.0000	2.486	4	0.9634
5630.0000	11.0000	4.971	4	-0.4370
5630.0000	11.0000	2.983	4	0.5573
5630.0000	12.0000	5.966	2	-1.5364
5630.0000	12.0000	5.966	9	1.1756
5630.0000	12.0000	5.966	10	1.5630
5630.0000	13.0000	5.966	9	1.1756
5630.0000	13.0000	3.480	3	-0.2311
5630.0000	14.0000	3.480	1	-1.1941
5630.0000	14.0000	3.480	2	-0.7126
5630.0000	14.0000	3.480	6	1.2134
5630.0000	14.0000	3.480	5	0.7319
5630.0000	15.0000	3.977	1	-1.2790
11260.0000	16.0000	1.807	0	-1.8867
11260.0000	6.0000	2.409	3	0.5077
11260.0000	8.0000	2.409	3	0.5077
11260.0000	9.0000	5.420	8	1.4390
11260.0000	10.0000	3.011	4	0.7252
11260.0000	10.0000	3.011	4	0.7252
11260.0000	10.0000	3.011	2	-0.7417
11260.0000	10.0000	3.011	4	0.7252
11260.0000	11.0000	3.011	3	-0.0082
11260.0000	11.0000	3.011	4	0.7252
11260.0000	11.0000	3.011	1	-1.4751
11260.0000	11.0000	3.011	4	0.7252
11260.0000	11.0000	3.011	1	-1.4751
11260.0000	11.0000	3.011	5	1.4586
11260.0000	11.0000	3.613	5	0.8896
11260.0000	12.0000	3.613	4	0.2480
11260.0000	12.0000	3.613	3	-0.3936
11260.0000	13.0000	3.613	3	-0.3936
11260.0000	13.0000	3.613	2	-1.0352
11260.0000	13.0000	4.216	6	1.0191
11260.0000	14.0000	4.216	0	-2.4078
11260.0000	14.0000	4.216	4	-0.1232
11260.0000	14.0000	4.216	3	-0.6944
11260.0000	14.0000	4.216	5	0.4479

Chi-square = 67.10 DF = 67 P-value = 0.4735

To calculate the BMD and BMDL, the litter specific covariate is fixed
at the mean litter specific covariate of all the data: 11.500000

Benchmark Dose Computation

Specified effect = 0.05

```
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         824.936

            BMDL =        506.316
```

APPENDIX E. REFERENCES

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