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Provisional Peer-Reviewed Toxicity Values for

Diethylene Glycol Monomethyl Ether
(CASRN 111-77-3)

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
FEV_1	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 DIETHYLENE GLYCOL MONOMETHYL ETHER (CASRN 111-77-3)

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 derived values. It is not intended to be a comprehensive treatise on a given chemical or its toxicological nature.

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 a 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 this toxicity 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.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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

Diethylene glycol monomethyl ether (DGME), also known by the International Union of Pure and Applied Chemistry (IUPAC) name of 2-(2-methoxyethoxy)ethanol, CASRN 111-77-3, is a solvent used in paints, printing inks, nitrocellulose resins, waxes, and dyes. DGME is also used as a deicer and added to hydrocarbon fuels, including jet and diesel fuel, and as an antimicrobial agent (HSDB, 2014). The use of DGME as an inert ingredient in pesticides is regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); specifically, this compound is restricted for use as a deactivator or stabilizer for formulations used before crops emerge from soil (40 CFR 180.920; U.S. EPA, 2012b). DGME is approved by the U.S. Food and Drug Administration (FDA) as an indirect food additive when used as a component of adhesives for food packaging (21 CFR 175.105; FDA, 2014). DGME is regulated under section 8(d) of the Toxic Substances Control Act (TSCA) (40 CFR 716.120; U.S. EPA, 2013), requiring all handlers of this material to submit copies and lists of unpublished health and safety studies to EPA. DGME is a liquid at room temperature with a relatively low vapor pressure and is expected to precipitate as a liquid if it is released into the air and will remain as a liquid if released into water (HSDB, 2014). The empirical formula for DGME is $C_5H_{12}O_3$ (see Figure 1). The physicochemical properties for DGME are provided below in Table 1.

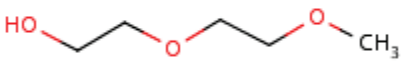

Figure 1. DGME Structure

Table 1. Physicochemical Properties of DGME (CASRN 111-77-3)[a]

Property (unit)	Value
Boiling point (°C)	193
Melting point (°C)	<−84
Density (g/cm^3)	1.035
Vapor pressure (mmHg at 25°C)	0.25
pH (unitless)	ND
Solubility in water (g/L at 25°C)	1,000[b]
Relative vapor density (air = 1)	4.14
Molecular weight (g/mol)	120.15

[a]HSDB (2014).
[b]ChemIDplus (2015).

ND = no data.

A summary of available health-related values for DGME from EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for DGME (CASRN 111-77-3)

Source/Parameter[a]	Value (applicability)	Reference
Noncancer		
ACGIH	NV	ACGIH (2015)
ATSDR	NV	ATSDR (2015)
Cal/EPA	NV	Cal/EPA (2015a); Cal/EPA (2015b); Cal/EPA (2014)
NIOSH	NV	NIOSH (2015)
OSHA	NV	OSHA (2011); OSHA (2006)
IRIS	NV	U.S. EPA (2015)
DWSHA	NV	U.S. EPA (2012a)
HEAST	NV	U.S. EPA (2011a)
CARA (HEEP)	NV	U.S. EPA (1994)
WHO	NV	WHO (2015)
Cancer		
IRIS	NV	U.S. EPA (2015)
HEAST	NV	U.S. EPA (2011a)
IARC	NV	IARC (2015)
NTP	NV	NTP (2014)
DWSHA	NV	U.S. EPA (2012a)
Cal/EPA	NV	Cal/EPA (2015a); Cal/EPA (2015b); Cal/EPA (2011)
ACGIH	NV	ACGIH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygenists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; CARA = Chemical Assessments and Related Activities Database; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profiles; 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.

NV = not available.

Literature searches were originally conducted on sources published from 1900 through March 2015, for studies relevant to the derivation of provisional toxicity values for DGME (CASRN 111-77-3). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA Office of Water, U.S. EPA TSCATS2/TSCATS8e, NIOSH, NTP, and OSHA.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant databases for DGME and include all potentially relevant, repeated, short-term-, subchronic-, and chronic-duration studies. Principal studies are identified in bold. The phrase "statistical significance," used throughout the document, indicates a p-value of < 0.05, unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for DGME (CASRN 111-77-3)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Human								
1. Oral (mg/kg-d)[a]								
ND								
2. Inhalation (mg/m^3)[a]								
ND								
Animal								
1. Oral (mg/kg-d)[a]								
Short-term	6 M/0 F, F344 rat, gavage, 2 d	0, 100, 200, 400, 800 ADD: 0, 100, 200, 400, 800	No suppression of TNP-LPS or TNP-SRBC immune response	800	NDr	NDr	Smialowicz et al. (1992)	PR
	0 M/5 F, Wistar rat, gavage, 11 d	0, 125, 250, 500, 1,000, 2,000, 3,000, 4,000 ADD: 0, 125, 250, 500, 1,000, 2,000, 3,000, 4,000	Decreases in relative thymus and pituitary weights, hematocrit and total protein	2,000	1,074	3,000	Yamano et al. (1993)	PR
	4−8 M/0 F, Wistar rat, gavage, 5 d	0, 2,000	Decreased lymphocyte population in thymus	NDr	NDr	2,000	Kawamoto et al. (1990a)	PR
	4−8 M/0 F, Wistar rat, gavage, 20 d	0, 500, 1,000, 2,000	Decreased relative thymus weight	500	NDr	1,000	Kawamoto et al. (1990a)	PR
	50 M/0 F, S-D rat, gavage, up to 20 d; (5 animals euthanized every 2 d for histopathological evaluation of testes)	0, 5.1 mmol/kg-d ADD: 0, 610	No treatment-related effects on testicular weight or histopathology (no other endpoints examined)	610	NDr	NDr	Cheever et al. (1988)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for DGME (CASRN 111-77-3)

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	10 M/0 F, albino CD rat, gavage, 5 d/wk, 6 wk	0, 900, 1,800, 3,600 ADD: 0, 643, 1,286, 2,571	Decreased absolute and relative testicular weights, testicular atrophy, proteinaceous casts in the kidney and increased BUN	1,286	NDr	2,571	Eastman Kodak (1992)	NPR
Developmental	0 M/50 F, pregnant CD-1 mouse, gavage, GDs 7−14	0, 4,000 ADD: 0, 4,000	Maternal: decreased survival and body weight Fetal: decreased number of viable litters, decreased number and survival of live pups, decreased litter weight	NDr	NDr	Maternal: 4,000 [FEL] Fetal: 4,000 [FEL]	Bioassay Sys (1983a)	NPR
Developmental (dose range-finding study)	0 M/9 F, pregnant S-D rat, gavage, GDs 7−16	0, 1,000, 1,495, 2,235, 3,345, 5,175 ADD: 0, 1,000, 1,495, 2,235, 3,345, 5,175	Maternal: reduced body weight Fetal: decreased body weight, reduced cranial ossification	Maternal: 2,235 Fetal: NDr	NDr 380	Maternal: 3,345 Fetal: 1,000	Hardin et al. (1986)	PR
Developmental	**0 M/25 F, pregnant S-D rat, gavage, GDs 7−16**	**0, 720, 2,165** **ADD: 0, 720, 2,165**	**Maternal: No treatment-related adverse effects** **Fetal: increased rib malformations and renal pelvis dilation, decreased skeletal ossification**	**Maternal: 2,165** **Fetal: NDr**	**NDr** **50**	**Maternal: NDr** **Fetal: 720**	**Hardin et al. (1986)**	**PR, PS**

Table 3A. Summary of Potentially Relevant Noncancer Data for DGME (CASRN 111-77-3)

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 (dose range-finding study)	0 M/4−6 F, pregnant Wistar rat, gavage, GDs 7−17	0, 125, 250, 500, 1,000, 2,000, 3,000, 4,000 ADD: 0, 125, 250, 500, 1,000, 2,000, 3,000, 4,000	Maternal: decreased weight gain Fetal: decreased body weight	Maternal: 1,000 Fetal: 500	NDr NDr	Maternal: 2,000 Fetal: 1,000	Yamano et al. (1993)	PR
Reproductive/ Developmental	0 M/22 F, pregnant Wistar rat, gavage, GDs 7−17	0, 200, 600, 1,800 ADD: 0, 200, 600, 1,800	Maternal: decreased body and thymus weight Fetal: decreased male and female fetal body weight	Maternal: 600 Fetal: NDr	NDr NDr	Maternal: 1,800 Fetal: 200	Yamano et al. (1993)	PR
2. Inhalation (mg/m^3)[a]								
Subchronic	10 M/10 F, F344 rat, 6 h/d, 5 d/wk, 13 wk	0, 31, 102, 216 ppm HEC: 0, 26, 88, 190	No treatment-related effects observed at any concentration	190	NDr	NDr	Miller et al. (1985)	PR

[a]Dosimetry: values are presented as 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. Values from animal developmental studies are not adjusted.

HEC_{EXRESP} for Category 3 gas = (ppm × molecular weight ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × ratio of animal:human blood-gas partition coefficients.

[b]Notes: PS = principal study; PR = peer reviewed; NPR = not peer reviewed.

ADD = adjusted daily dose; BUN = blood urea nitrogen; FEL = frank effect level; GD = gestation day; HEC = human equivalent concentration; ND = no data; NDr = not determined; S-D = Sprague-Dawley

Table 3B. Summary of Potentially Relevant Cancer Data for DGME (CASRN 111-77-3)								
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**
Human								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								
Animal								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								

ND = no data

HUMAN STUDIES

Oral Exposure

No studies have been identified.

Inhalation Exposure

No studies have been identified.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to DGME were evaluated in short-term-duration studies (Yamano et al., 1993; Kawamoto et al., 1990a, b), a 6-week study (Eastman Kodak, 1992), three developmental toxicity studies (Yamano et al., 1993; Hardin et al., 1986; Bioassay Sys, 1983b), and one acute immunotoxicity study (Smialowicz et al., 1992).

Short-Term-Duration Studies

Smialowicz et al. (1992)

Smialowicz et al. (1992) treated groups of six 8−10-week-old male F344 rats with DGME by gavage (in distilled water) for 2 consecutive days following immunization with trinitrophenyl-lipopolysaccharide (TNP-LPS). The doses for DGME were 0, 100, 200, 400 and 800 mg/kg-day. The antibody response was determined 3 days later by the primary plaque-forming cell (PFC) response using previously established methods (Smialowicz et al., 1987). Hemagglutination titers to TNP-haptinated sheep red blood cells (SRBC) were also determined subsequent to treatment.

DGME showed no significant suppression of the antibody response as measured by the PFC assay; SRBC hemagglutination titers were unaffected. Decreased cellularity of the spleen was observed in 400-mg/kg group only, but it was not dose related and was not considered by the study authors to be a treatment-related effect. A no-observed-adverse-effect level (NOAEL) of 800 mg/kg-day for acute immunotoxicity is identified for this study; A lowest-observed-adverse-effect level (LOAEL) is not established.

Yamano et al. (1993)

3-month-old female virgin Wistar rats (5/group) were exposed to doses of 0, 125, 250, 500, 1,000, 2,000, 3,000, or 4,000 mg/kg-day DGME (>99.0% purity) for 11 consecutive days via gavage in water. During the exposure period, body weight, food consumption, and clinical signs of toxicity were monitored daily. Urine was collected for urinalysis on Day 10 within 30 minutes after dosing (commercial reagent strips were used, but the specific tests were not reported). On Day 12, blood was collected for hematology (red blood cell [RBC] count, hemoglobin [Hb], hematocrit [Hct], white blood cell [WBC] count) and clinical chemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], blood urea nitrogen [BUN], total cholesterol, total protein, and glucose). The rats were sacrificed, and weights were recorded for the liver, kidney, heart, spleen, stomach, brain, adrenal gland, thymus, ovary, and pituitary gland. Gross pathology and histopathology evaluation were not performed.

No clinical signs of toxicity were reported. Body-weight gain and food consumption were significantly decreased throughout the exposure period in the 4,000-mg/kg-day group, compared with controls (data presented graphically). Food consumption and body-weight gain

were also decreased relative to controls throughout exposure at 3,000 mg/kg-day, although the decrease in body-weight gain was only statistically significant on Days 2 and 8 at this dose. Urinary pH trended towards acidic in a dose-related fashion from 125 mg/kg-day to 4,000 mg/kg-day (statistics not presented by the study authors). Hematological changes included statistically significant decreases in RBC counts (−9%), WBC counts (−37%), Hb (−13%), and hematocrit (−12%) at 4,000 mg/kg-day, compared with controls (see Table B-1). Hematocrit was also statistically significantly decreased by 8% at 3,000 mg/kg-day (see Table B-1). Clinical chemistry findings included statistically significant increases in BUN (+26%) and triglycerides (+89%) at 4,000 mg/kg-day, compared with controls; no clear dose-related pattern was observed in these measures at lower doses (see Table B-2). Statistically significant decreases were observed in total serum protein levels at 3,000 and 4,000 mg/kg-day (−8 and −10%, respectively) (see Table B-2). Relative thymus weights were decreased dose-dependently by 25, 57, and 69% at 2,000, 3,000, and 4,000 mg/kg-day, respectively, compared with control, but this effect was statistically significant ($p < 0.01$) at 4,000 mg/kg-day only. Similarly, relative pituitary weights were decreased by 20 (not statistically significant), 24 ($p < 0.05$), and 25% ($p < 0.05$) at 2,000, 3,000, and 4,000 mg/kg-day, respectively, compared with control. In addition, relative kidney weight was statistically significantly increased ($p < 0.01$) by 12% at 4,000 mg/kg-day only (see Table B-3). Absolute organ weights were not reported.

A NOAEL of 2,000 mg/kg-day and a LOAEL of 3,000 mg/kg-day are identified in female virgin rats for statistically significant decreases in pituitary weights, hematocrit and total protein, compared with controls.

Kawamoto et al. (1990a); Kawamoto et al. (1990b)

Male Wistar rats were administered DGME (>98% pure) daily via gavage in water at 0, 500, 1,000, and 2,000 mg/kg-day DGME daily for 20 days (4−8/group) or 0 and 2,000 mg/kg-day for 1, 2, or 5 days (4/group) (Kawamoto et al., 1990a, b). Body weight was measured every 5 days in the 20-day study. Organ weights (liver, kidney, spleen, thymus, heart, lung, testis) were measured at 1, 2, 5, and 20 days of exposure (2,000 mg/kg-day only), but only relative organ weights were reported, and only for the control and high-dose groups. Thymus and testes weights were measured in all dose groups following 20 days of exposure; relative organ weights, only, were reported graphically. Histopathology was evaluated in the thymus of rats given 2,000 mg/kg-day DGME for 5 days. Histopathology was not evaluated in the 20-day study.

Statistically significant reductions in body-weight gain were observed in rats given 2,000 mg/kg-day beginning at 10 days of exposure (−8, −8, and −10% compared with controls at 10, 15, and 20 days of exposure, respectively). Exposure to 2,000 mg/kg-day DGME for 5 or 20 days resulted in a decrease in the relative weights of the liver (−9 to −10%), spleen (−26%), thymus (−27 to −40%), and testis (−16 to −19%), compared with controls (see Table B-4). Relative testis weight was similar to controls at 500 and 1,000 mg/kg-day. Relative thymus weight was decreased dose dependently by 15, 27, and 40% at 500, 1,000, and 2,000 mg/kg-day, respectively[1], but statistical significance was not reached until 1,000 mg/kg-day. Absolute organ weights were not reported. Histopathological evaluation of the thymus of rats treated with 2,000 mg/kg-day DGME for 5 days revealed a reduction in lymphocytes in the thymus cortex. A

[1]Relative thymus and testis organ weights for 500 and 1,000 mg/kg-day were reported only in graphical form by the study authors.

LOAEL of 1,000 mg/kg-day and a NOAEL of 500 mg/kg-day in the 20-day study is identified in male rats based on a statistically significant decrease in relative thymus weight, compared with controls.

Cheever et al. (1988)

Cheever et al. (1988) conducted a study of the metabolism and testicular toxicity of diethylene glycol dimethyl ether (DGdME), its principal metabolite (2-methoxyethoxy)acetic acid, and the immediate metabolic precursor 2-(2-methoxyethoxy)acetic acid (i.e., DGME). Each compound (purity 97% to 99.5%) was administered by gavage in distilled water to groups of 50 male Sprague-Dawley (S-D) rats (190−240 g) at doses of 0 or 5.1 mmol/kg-day (610 mg/kg-day) for up to 20 days. The exposure level of 5.1 mmol/kg-day was equivalent to a dose found previously to produce testicular atrophy for DGdME. Five rats from each group were euthanized every 2 days for evaluation of testicular histopathology. Testicular toxicity was not observed in rats treated with DGME or (2-methoxyethoxy)acetic acid at any time point. The study authors concluded that the testicular toxicity previously observed for DGdME was probably due to a minor metabolite, methoxyacetic acid, which is not a metabolite of DGME. A NOAEL for testicular toxicity of 610 mg/kg-day was established in this study; a LOAEL was not identified.

Subchronic-Duration Studies

Eastman Kodak (1992)

In a study that was not peer reviewed, groups of male Albino CD rats (10/group) were exposed to undiluted doses of 0, 900, 1,800, or 3,600 mg/kg DGME (>99.5% purity) via gavage (undiluted) 5 days/week for 6 weeks (adjusted daily doses [ADD] of 0, 643, 1,286, and 2,571 mg/kg-day). Body weights were recorded on Days 0, 3, 6, 13, 20, 27, 34, and 41. All doses were recalculated weekly to adjust for changes in body weights. Control rats were given gavage doses of distilled water equal to the largest volume given a treated animal. Animals were observed 5 days/week for clinical signs of toxicity and mortality. Blood was collected just prior to sacrifice for hematology (Hb, hematocrit, RBC counts, red cell indices, total and relative white cell counts) and clinical chemistry (AST, ALT, ALP, lactate dehydrogenase [LDH], BUN, creatinine, and glucose). At sacrifice, animals were examined for gross pathology, and the following tissues were collected and fixed for histology: lung, heart, thymus, kidneys, liver, spleen, brain, salivary glands, stomach, cecum, colon, duodenum, jejunum, ileum, pancreas, esophagus, adrenal glands, pituitary, thyroid, parathyroid, trachea, mesenteric lymph nodes, testes (control, mid- and high-dose groups only), epididymides (control and high-dose only), prostate, seminal vesicles, coagulating gland, bone marrow, tongue, nasal cavities, and eyes. Prior to fixation, the liver, kidneys, heart, testes, brain, and spleen were weighed. Thymus weights were not reported.

No mortality was observed in rats treated with DGME. One animal in the high-dose group had bloody urine, blood around the nares, and an unkempt coat. No clinical signs of toxicity were observed in animals from the low- and mid-dose groups. Terminal body weights were significantly reduced at 1,286 and 2,571 mg/kg-day by 6 and 11%, respectively, compared with controls. In the 2,571-mg/kg-day group, body weights were significantly reduced ($p \leq 0.05$) on Days 3, 27, and 34 by 7, 8, and 11%, respectively, compared with controls (see Table B-5). These changes were accompanied by significant reductions ($p \leq 0.05$) in food consumption throughout the exposure period in rats exposed to 2,571 mg/kg-day (see Table B-5). No significant changes in hematological parameters were observed. The only exposure-related

clinical chemistry finding was a significant 23% increase ($p \leq 0.05$) in BUN in the 2,571-mg/kg-day group, compared with controls (see Table B-6).

Absolute and relative testes weights were reduced in the high-dose group (27 and 16%, respectively) (see Table B-7). Absolute liver weight was not affected by DGME treatment, although relative liver weight was significantly increased by 11% at 2,571 mg/kg-day ($p \leq 0.05$). Similarly, absolute heart weight was unaffected, while relative heart weight was increased ($p \leq 0.05$) in the mid- and high-dose groups by 13 and 15%, respectively. No statistically significant change was observed in absolute kidney weight. Relative kidney weight was altered in the mid- and high-dose groups; however, these changes were not dose related (+5, −14, and +17% at 643, 1,286, and 2,571 mg/kg-day, respectively). Absolute brain and spleen weights were significantly reduced ($p \leq 0.05$) at the highest administered dose, while relative brain and spleen weights did not differ from controls (see Table B-7). The reported increases in relative organ weights at the highest dose are likely due to the reduction in body weight at the exposure level. However, the decreased relative testes weights in the high-dose group cannot be attributed to a reduction in body weight.

No gross pathology changes were noted in this study. Histopathological changes were found in the testes, epididymides, and kidneys of rats in the high-dose group. No histopathological lesions were reported for the thymus. In the testes, an increase in the incidence of seminiferous tubule atrophy was observed at 2,571 mg/kg-day, compared with controls (see Table B-8). In the epididymides at this dose, there were low incidences of degenerated spermatozoa and hypospermia. In the kidney, hyaline droplet degeneration was seen in all control and treated animals (except one high-dose rat), but there was no indication that this was treatment related (severity was not reported). This lesion may be related to α2u-g accumulation, which is common in male rats, but is not considered relevant to human toxicity (U.S. EPA, 1991a). However, the criteria for establishing alpha 2u-globulin (α2u-g) accumulation, as the etiologic agent for the male rat kidney effects reported in this study have not been met (α2u-g specific antibody staining not performed, sequence of events not observed (U.S. EPA, 1991a). Also in the kidney, there was an increase in the incidence of proteinaceous casts in high-dose rats. Although casts are sometimes seen in association with α2u-g accumulation, they were not observed in control rats or rats from the low- or mid-dose groups in this study, and are therefore considered to be potentially treatment related. A lowest-observed-adverse-effect level adjusted daily dose ($LOAEL_{ADD}$) of 2,571 mg/kg-day and a no-observed-adverse-effect level adjusted daily dose ($NOAEL_{ADD}$) of 1,286 mg/kg-day are identified for decreased absolute and relative testicular weight, testicular atrophy, proteinaceous casts in the kidney, and increased BUN.

Developmental Studies

Bioassay Sys (1983a)

In a non-peer-reviewed study, groups of 50 timed-pregnant CD-1 mice were exposed to 0 or 4,000 mg/kg-day DGME (purity not specified) via gavage in water on Gestation Days (GDs) 7−14. All dams were weighed on GD 7. Females confirmed as pregnant were weighed on GD 14, and dams producing viable litters were weighed on Postnatal Day (PND) 3. Dams were allowed to deliver naturally. The following developmental indices were measured: number of animals producing litters, number of animals with totally resorbed litters, and number of live and dead pups within 12 hours of parturition and on PND 3. Litters were weighed on PNDs 0 (within 12 hours of parturition), 1, and 3. Mated females that failed to deliver a litter by GD 23 were sacrificed and necropsied, and the status of pregnancy was assessed. All uteri not

obviously gravid were treated with sodium sulfide to assess the prior existence of pregnancy. All animals that died during the exposure period were necropsied to determine cause of death. Reproductive postimplantation survival index was calculated as the number of mice producing viable litters divided by the number of mice that were pregnant. For comparisons between treated and untreated groups, the following adjusted values were calculated: mean percent of dead pups/litter, mean percent of litter weight change from PNDs 1−3, and mean percent of pup viability/litter from PNDs 1−3.

Five females from the exposed group died during the exposure period, and none were attributed to gavage error (further necropsy details were not reported). No control animals died. Pregnancies were confirmed in 32/50 and 36/50 females from the control and exposed groups, respectively (see Table B-9). Exposure to 4,000 mg/kg-day resulted in only 14% of confirmed pregnant rats delivering viable litters. The other dams had stillborn litters (25%) or totally resorbed litters (50%). In contrast, 97% of confirmed-pregnant controls delivered viable litters; the other 3% were totally resorbed (see Table B-9). Maternal body weight and body-weight gain on GD 18 were significantly decreased in the exposed group by 19 and 48%, respectively, compared with controls (see Table B-9). Maternal body weight remained significantly decreased by 17% on PND 3 in exposed dams that produced viable litters, compared with controls (see Table B-9). In viable litters, significant exposure-related decreases were observed in the number of live pups per litter (68% decrease), pup survival from PNDs 1−3 (87% decrease), litter weight on PNDs 1 and 3 (71 and 88% decrease, respectively), and litter weight gain from PNDs 1−3 (200% decrease) (see Table B-10). A maternal LOAEL (frank effect level [FEL]) of 4,000 mg/kg-day was identified in mice for decreased survival and decreased maternal body weight. A fetal LOAEL and FEL of 4,000 mg/kg-day was identified for decreased number of viable litters, decreased number and survival of live pups, and decreased litter weight, compared with controls. Because only a single dose level was tested, maternal or fetal NOAELs were not identified.

Hardin et al. (1986); range-finding study

In a dose-range-finding study, groups of time-mated pregnant S-D rats (9/group) were exposed to 0, 1,000, 1,495, 2,235, 3,345, or 5,175 mg/kg-day DGME (purity not specified) on GDs 7−16 via gavage in distilled water. Dams were weighed daily on GDs 6−16 and before sacrifice on GD 21. Food consumption was determined for GDs 7−12, 12−17, and 17−21. At sacrifice, uteri were removed and weighed, and fetuses were counted, weighed, and examined for gross external defects. Fetuses were fixed in alcohol or Bouin's fluid for visceral and skeletal examination. Adjusted maternal body-weight gain was calculated by subtracting gravid uterine weight from weight gain between GDs 6 and 21.

Two females exposed to 5,175 mg/kg-day died during exposure; no other deaths occurred (see Table B-11). Maternal body weight was significantly decreased by 11% at 5,175 mg/kg-day on GD 16 and by 17 and 29% at 3,345 and 5,175 mg/kg-day, respectively, on GD 21 compared with controls (see Table B-11). Adjusted maternal body-weight gain from GDs 6−21 was significantly decreased by 30% at 5,175 mg/kg-day (see Table B-11). Body weight effects were accompanied by significant decreases in food consumption between GD 7 and 12 at 3,345 and 5,175 mg/kg-day (see Table B-11). No viable litters were produced from dams exposed to 5,175 mg/kg-day. The numbers of viable litters and live fetuses/litter in dams exposed to 3,345 mg/kg-day were significantly reduced by 67 and 73%, respectively, compared with controls (see Table B-11). A dose-related trend in the reduction of live fetal body weight

beginning at 1,000 mg/kg-day was evident (see Table B-11). Male fetal body weight was decreased by 5% to 43% over the dose range, becoming statistically significant only at the second highest dose (3,345 mg/kg-day). Female fetal body weight was decreased by 8% to 37% over the dose range, becoming statistically significant only at the second highest dose (3,345 mg/kg-day). However, the 5% to 8% reduction in fetal body weight at 1,000 mg/kg-day is considered to be real and biologically significant. Skeletal examination showed significant increases in malformations at 2,235 mg/kg-day and decreased ossification at ≥1,495 mg/kg-day (see Table B-12). Cardiac malformations and variations were significantly increased at 2,235 mg/kg-day (see Table B-12). No exposure-related effects were observed at 1,000 mg/kg-day. A maternal LOAEL of 3,345 mg/kg-day and NOAEL of 2,235 mg/kg-day are identified for reduced maternal body weight. A fetal LOAEL of 1,000 mg/kg-day is identified for decreased fetal body weight; a NOAEL is not established. The occurrence of fetal effects at doses that did not produce maternal effects indicates that the developing organism is a sensitive target of toxicity for DGME.

Hardin et al. (1987); main study

Hardin et al. (1986) is selected as the principal study for derivation of the subchronic p-RfD value. Based on the results of the dose-range finding study, additional groups of time-mated pregnant S-D rats (25/group) were exposed to doses of 0, 720, or 2,165 mg/kg-day DGME on GDs 7−16 via gavage in distilled water. Body weights, food consumption, and fetal endpoints were assessed as described above for the dose-range finding study. There were no exposure-related effects on survival or number of viable litters. Maternal body weight at GD 21 was statistically significantly decreased in dams exposed to 2,165 mg/kg-day; however, maternal body weights from all exposed groups were within 10% of that from controls throughout the study (see Table B-13) and not considered to be biologically significant. In rats given 2,165 mg/kg-day, the number of live fetuses/litter was significantly decreased by 35%, and male and female fetal body weights were significantly decreased by 24 and 27%, respectively (see Table B-13). There was a significant exposure-related trend for increased gross malformations (see Table B-13). Skeletal examination showed a significant increase in total malformations (primarily rib malformations) and reduced cranial and appendicular skeleton ossification at both doses (see Table B-14). Additional effects that were seen in the high-dose group only included sternebrae, vertebrae, and rib variations (primarily reduced ossification) (see Table B-14). Visceral examination showed an increase in the incidence of dilated renal pelvis at both doses. Cardiovascular malformations were also observed in the high-dose group (see Table B-15). A maternal NOAEL of 2,165 mg/kg-day is identified, and no maternal LOAEL is identified. A fetal LOAEL of 720 mg/kg-day is identified for increased rib malformations and renal pelvis dilation and decreased skeletal ossification, compared with controls. No fetal NOAEL is identified.

Yamano et al. (1993); range-finding study

In a dose-range-finding study, groups of pregnant Wistar rats (4−6/group) were exposed to doses of 0, 125, 250, 500, 1,000, 2,000, 3,000, or 4,000 mg/kg-day DGME (>99.0% purity) on GDs 7−17 via gavage in water. Body weight, food consumption, and clinical signs of toxicity were monitored daily. Dams were sacrificed on GD 20. The position and number of live and dead fetuses, number of resorptions, and number of corpora lutea were recorded. Live fetuses were weighed, sexed, and examined for external malformations.

Body-weight gain was significantly decreased in dams exposed to ≥2,000 mg/kg-day (40−80% of control and about >40 g less at the end of treatment based on visual inspection of data reported graphically). Based on a reference body weight of 156 g for Wistar female rat (U.S. EPA, 1988), this change in absolute body weight at the end of treatment would be more than 10% compared to the control group. Food consumption was also significantly decreased in dams exposed to doses ≥3,000 mg/kg-day (10−40% of control based on visual inspection of data reported graphically). No exposure-related changes were observed in the number of implants or the number of corpora lutea; however, all embryos were resorbed at doses of 3,000 and 4,000 mg/kg-day. In rats given 2,000 mg/kg-day, the incidence of dead or resorbed fetuses was increased (+44% early stage, +21% late stage), the number of live fetuses was decreased (−65%), and the weights of male and female fetuses were decreased by 31 and 27%, respectively (see Table B-16). At 1,000 mg/kg-day, the weights of male and female fetuses were also decreased by 13 and 17%, respectively (see Table B-16); although not statistically significant, these reductions are considered to be real and biologically significant. External malformations (omphalocele[2], anasarca[3], and anury[4]) were observed in one fetus at 1,000 mg/kg-day and three fetuses (two litters) at 2,000 mg/kg-day. External anomalies (dorsum subcutaneous hematomas) were observed in five fetuses (three litters) at 2,000 mg/kg-day (see Table B-16). A maternal LOAEL of 2,000 mg/kg-day and a NOAEL of 1,000 mg/kg-day were identified for decreased maternal weight gain, compared with controls. A fetal LOAEL of 1,000 mg/kg-day and NOAEL of 500 mg/kg-day were identified for decreased male and female fetal body weight, compared with controls.

Yamano et al. (1993); main study

Based on the results of the dose-range-finding study, additional groups of Wistar rats (22/group) were exposed to 0, 200, 600, or 1,800 mg/kg-day DGME (>99.0% purity) on GDs 7−17 via gavage in water. Body weight, food consumption, and clinical signs of toxicity were monitored throughout gestation. On GD 20, 14 dams/group were sacrificed. Maternal thymus weight was measured, and uteri and fetuses were examined as in the dose-range-finding study (described above). Additionally, one-half of the live fetuses in each litter were preserved in Bouin's fixative for visceral examination and the other half were preserved in alcohol for skeletal examination. The remaining eight dams/dose were allowed to deliver naturally. The gestation length, litter size, and number and sex of live and dead pups were noted. Pups were examined for external anomalies. On PND 4, litters were culled to eight pups/litter (approximately four/sex). During the lactation period (PNDs 0−21), the pups were examined for growth and external differentiation (detachment of ears, hair growth, teeth appearance, and opening of eyelids) (the timing and frequency of postnatal observations was not reported). Body weights were recorded on PNDs 7, 14, and 21. On PND 21, pups were sacrificed and x-rayed for skeletal observations. Dams were also sacrificed on PND 21, and the number of implants was recorded.

All dams survived and produced live fetuses. In dams sacrificed on GD 20, food consumption, and thymus weight were significantly decreased at 1,800 mg/kg-day (see Table B-17). Although maternal terminal body weights were also significantly decreased at this dose level, these changes remained within 10% of controls. Also at this dose, the percent of

[2]protrusion of abdominal contents through an opening at the navel.
[3]generalized edema with accumulation of serum in the connective tissue.
[4]absence of tail.

dead or resorbed fetuses was significantly increased, and the number of live fetuses per litter was significantly decreased (−41%), compared with controls. Male and female fetal body weights were decreased in a dose-related pattern beginning at 200 mg/kg-day. Fetal body weight for males was reduced by 12%, 21%, and 36% and for females by 10%, 19%, and 35% at 200, 600, and 1,800 mg/kg-day, respectively, compared with controls (see Table B-17). Although the reduced fetal body weights were not statistically significant below the 600 mg/kg-day exposure, a clear dose-related trend beginning at 200 mg/kg-day is evident. The 10% and 12% decreases in females and males, respectively, are considered to be biologically significant. External malformations and anomalies, visceral malformations and variations, and skeletal malformations and variations were significantly increased in fetuses at 1,800 mg/kg-day, compared with controls (see Tables B-18, B-19, and B-20, respectively). External malformations or anomalies included anasarca, omphalocele, anury, and dorsum subcutaneous hematoma (see Table B-18). Visceral malformations and variations included right aortic arch, ventricular septal defect, thymic remnant in the neck, and dilated renal pelvis (see Table B-19). Skeletal malformations and variations included agenesis of sacrococcygeal vertebrae, splitting of vertebral bodies, and delayed ossification (see Table B-20). Significant increases in visceral variations (thymic remnant in the neck) and skeletal variations (decreased ossification) were also observed at 600 mg/kg-day, compared with controls (see Tables B-19 and B-20, respectively).

In dams allowed to give birth and sacrificed on PND 21, gestation length was significantly increased by ~2 days in dams at 1,800 mg/kg-day, compared with controls (see Table B-21). In the 1,800-mg/kg-day group, the number of live pups/litter was significantly decreased by 63% (see Table B-21), and postnatal survival between PND 0 and 4 was only 5.4% (see Table B-21); survival at PND 4 was reduced to 62.4% at 600 mg/kg-day. However, normal growth and development was observed in pups surviving past PND 4 in all dose groups. No exposure-related changes were observed in the percentage of fetuses with external malformation or anomalies (see Table B-21), and no skeletal observations were reported. A maternal LOAEL of 1,800 mg/kg-day and a NOAEL of 600 mg/kg-day are identified in pregnant rats for decreased thymus weight, compared with controls. A developmental LOAEL of 200 mg/kg-day is identified for decreased male and female fetal body weight; a NOAEL is not established.

Inhalation Exposures

Subchronic-Duration Studies

Miller et al. (1985)

Male and female Fischer 344 rats (10/sex/group) were exposed to DGME (purity >99.5%) as a preheated (60°C) vapor to time-weighted average (TWA)-measured concentrations of 0, 31, 102, or 216 ppm (26, 88, and 190 mg/m^3)[5] by whole-body exposure for 6 hours/day, 5 days/week for 13 weeks. The study authors considered the highest exposure level (190 mg/m^3) to be the maximum attainable concentration due to the relatively low vapor pressure of DGME (it was also >60% of the theoretical maximum vapor concentration for DGME at 25°C and 1 atm pressure). Animals were monitored daily (postexposure) for mortality and clinical signs of toxicity. Body weights were recorded prior to the first exposure, weekly thereafter, and at terminal sacrifice. Hematological parameters were measured after 12 weeks of exposure, including packed cell volume (PCV), Hb concentration, erythrocyte, platelet, and total and differential leukocyte counts, and erythrocyte indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]).

[5]ppm × (molecular weight [120.15] ÷ 24.45) × (hours exposed [6] ÷ 24 hours) × (days exposed [5] ÷ 7 days)

Clinical chemistry analyses were performed after 13 weeks of exposure (BUN, ALT, AST, ALP, glucose, total protein, albumin, and globulin). Urinalysis parameters (including bilirubin, glucose, ketones, blood, pH, protein, urobilinogen, and specific gravity) were examined after 12 weeks of exposure. Rats were sacrificed after 13 weeks of exposure and subjected to gross pathology (48 tissues). Selected organs (liver, kidneys, heart, thymus, and testes) were weighed. Complete histopathological examinations were performed for rats in the control and high-exposure groups only.

No treatment-related mortality or clinical signs of toxicity were observed. The death of one female rat in the 88-mg/m^3 group was attributed to injuries incurred during handling. The body weights of treated male rats did not vary significantly from controls. Female rats exposed at 88 mg/m^3, but not 190 mg/m^3, showed a statistically significant reduction in body weight relative to controls from 4 weeks of exposure until study termination; however, the body weights of rats in this group remained within 10% of controls throughout the study. This effect was not considered to be treatment related by the study authors. No significant effects on hematology, clinical chemistry, or urinalysis parameters were observed in treated rats (limited data shown). No significant effects on absolute or relative organ weights were reported (data were shown for control and high-exposure groups only). No histopathological effects in treated rats were noted (data for gross and microscopic pathology were not shown). A NOAEL of 190 mg/m^3 is established in this study; no LOAEL is determined.

Carcinogenic Studies

No studies could be located regarding the carcinogenic effects of oral or inhalation exposure to DGME in humans or animals.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Acute and Short-Term Tests (Oral, Inhalation, and Dermal)

The acute toxicity of DGME is low. Oral LD_{50} values ranged from about 4,068−14,430 mg/kg in rats and from 7,128−8,188 mg/kg in mice (dose conversion based on a density for DGME of 1,017 g/mL) (Eastman Kodak, 1992; Cook, 1984; Olin Corporation, 1977; Dow Chemical Co, 1947). No toxic effects were reported in rats exposed to DGME via inhalation at a nominal concentration of 200,000 mg/m^3 (200 mg/L) for 1 hour (Olin Corporation, 1977). However, this nominal concentration is several orders of magnitude greater than the maximum attainable concentration of 190 mg/m^3 reported by Miller et al. (1985). Actual measured concentrations were not available for this study, but are likely to have been much lower than nominal; no details were provided regarding the method used to generate the chamber air concentrations (Olin Corporation, 1977). No toxicity was reported in rats exposed to a substantially saturated vapor of DGME for 6 hours (concentration not given) (Cook, 1984).

Dermal toxicity studies in rabbits reported no toxic effects at the highest tested dose (2,000 mg/kg) (Olin Corporation, 1977) or identified LD_{50} values in the range of 9,133−9,404 mg/kg (Eastman Kodak, 1992; Cook, 1984). Primary irritation studies showed no or only slight evidence of skin irritation in rabbits (Eastman Kodak, 1992; Cook, 1984; Olin Corporation, 1977; Dow Chemical Co, 1954) or guinea pigs (Eastman Kodak, 1992); slight and generally transient eye irritation has been noted in rabbits exposed to undiluted DGME (Cook, 1984; Olin Corporation, 1977; Dow Chemical Co, 1954).

Subchronic-Duration and Developmental Studies by Dermal and Subcutaneous Exposure

Karaman et al. (2002) presented a case study of a 5-year-old boy with multisystemic anomalies of the cardiovascular and skeletal systems (ventricular septal defect, a unilateral 12th costal rib, scoliosis of the thoracolumbar spine, L1 hemivertebra), as well as a retrocaval ureter, which is a rare congenital anomaly resulting from abnormal development of the inferior vena cava. The boy's mother worked in the thread-dying section of a weaving company in Turkey for the previous 7 years. Dermal contact with DGME was suspected, but not confirmed. Exposure levels were not estimated in this study.

DGME was shown to induce maternal and developmental toxicity in New Zealand white rabbits by dermal administration during gestation (Scortichini et al., 1986; John et al., 1984; John et al., 1983; Ouellette et al., 1983) (see Table 4). Decreased maternal weight gain and an increase in the percent of resorptions was observed at dermal doses ≥750 mg/kg-day. Developmental effects were observed at dermal doses as low as 250 mg/kg-day (delayed ossification of the skull and cervical spurs) (Scortichini et al., 1986; John et al., 1984). No maternal or developmental toxicity was observed in Wistar rats injected subcutaneously with DGME on GDs 6−20 at doses up to 1,000 mg/kg-day (Doe, 1984) (see Table 4).

Male guinea pigs administered DGME to the skin daily for 13 weeks also showed evidence of systemic toxicity, including decreased spleen weight at 200 mg/kg-day and changes in liver histopathology at 40 mg/kg-day (Hobson et al., 1986) (see Table 4).

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

DGME is used as a deicing agent in jet propulsion fuel-8 (JP-8). Comet assay measurements were performed to evaluate genotoxicity in leukocytes from U.S. Air Force personnel exposed to JP-8 (Krieg et al., 2012). Postshift urinary concentrations of DGME were correlated with the number of leukocytes with highly damaged DNA (measured postshift); however, this association was not statistically significant for creatinine-adjusted urinary concentrations.

DGME was found to be negative for mutagenicity with and without metabolic activation in *Salmonella typhimurium* reverse mutation tests using strains TA1535, TA100, TA1537, and TA98 (BASF, 1989).

Metabolism/Toxicokinetic Studies

In a study (Cheever et al., 1988) of the metabolism and testicular toxicity of diethylene glycol dimethyl ether (DGdME) summarized previously in this document, (2-methoxyethoxy)acetic acid was found to be a major urinary metabolite, accounting for about 70% of the administered dose. A second urinary metabolite, methoxyacetic acid, was a minor metabolite, accounting for only 6% of the administered dose. The study authors stated that DGME is the immediate metabolic precursor to (2-methoxyethoxy)acetic acid and that methoxyacetic acid is not a metabolite of DGME. (2-Methoxyethoxy)acetic acid was not found to be a testicular toxicant and the study authors attributed all the testicular toxicity of DGdME to methoxyacetic acid.

Table 4. Other Studies

Test	Materials and Methods	Results	References
Other route animal studies			
Dermal subchronic	Male guinea pigs (6/treatment group and 7 controls) were dermally exposed to DGME at 0, 40, 200, and 1,000 mg/kg-d, 6 h/d, 5 d/wk, for 13 wk. Gauze patches containing DGME (neat) were applied to the shaved backs and held in place with an occlusive bandage to minimize oral exposure and volatilization. At study termination, hematology (RBC, total and differential WBC counts; Hb, hematocrit, MCV, MCH, and MCHC), clinical chemistry (ALT, AST, AP, creatine kinase, gGT, and LDH activities, BUN, calcium, cholesterol, creatinine, glucose, and total protein), and urinalysis (specific gravity, pH, and activities of AP, ALT, gGT) parameters were evaluated. Animals were subjected to gross and histopathological examinations (23 tissues).	No treatment-related effects on survival or body weight were observed. Decreased absolute and relative spleen weight (14−22%) was observed in guinea pigs exposed to 200 and 1,000 mg/kg-d. A significant increase in urinary calcium excretion was noted in all treatment groups. A 3% decrease in MCHC was observed at 1,000 mg/kg-d. Serum LDH was increased 2.5-fold at the highest dose. No changes in gross pathology were observed. Histopathological changes were observed in the liver (mild, periportal hepatocellular fatty change: 0/6, 2/6, 6/6, and 6/6 at 0, 40, 200, and 1,000 mg/kg-d, respectively).	Hobson et al. (1986)
Dermal developmental	Pregnant New Zealand white rabbits (6/group) were administered 0 or 1,000 mg/kg-d DGME dermally on GDs 6−18. DGME was applied under an occlusive bandage to minimize oral exposure and volatilization. Dosing occurred daily, and bandages were replaced as needed. Animals were monitored daily for clinical signs of toxicity; body weights were also recorded daily (group means on GDs 6, 9, 12, 15, and 19 only). Animals were sacrificed on GD 19. Maternal liver weights were measured and all rabbits were subjected to gross pathology. Numbers of corpora lutea, live and resorbed fetuses, and resorption sites (nonpregnant animals) were recorded.	No treatment-related mortality was observed. Decreased maternal body weight gain was observed in treated rabbits at GDs 6−8. Decreased ingesta at necropsy suggested poor nutritional state of treated does. Dermal treatment produced an 8-fold increase in the number of resorptions/litter.	Ouellette et al. (1983)

Table 4. Other Studies

Test	Materials and Methods	Results	References
Dermal developmental	Pregnant New Zealand white rabbits (25/group) were treated dermally with 0, 50, 250, or 750 mg/kg-d DGME (99.2% pure) on GDs 6−18. DGME was applied under an occlusive bandage to minimize oral exposure and volatilization. Dosing occurred daily, and bandages were replaced as needed. Body weights were statistically analyzed on GDs 6, 9, 12, 15, 19, and 29. Animals were sacrificed on GD 29; hematology parameters (RBC, WBC, and platelet counts, Hb, PCV, MCV, MCH, and MCHC) were evaluated (GD 29); liver weights were recorded. Reproductive endpoints included numbers of resorptions, dead and live fetuses, and resorption sites. Fetuses were weighed, sexed, and examined for external (all animals), and visceral (50% of fetuses) or skeletal (50% of fetuses) malformations.	Maternal effects were seen at 750 mg/kg-d only, including decreased weight gain and 7% reductions in RBC count and PCV. A 22% increase in the percent of implantations resorbed was also observed in the high-dose group. Significant developmental effects occurring at 250 mg/kg-d included delayed ossification of the skull (9/21, 6/22, 19/23, and 16/18 litters at 0, 50, 250, and 750 mg/kg-d, respectively) and cervical spurs (0/21, 3/22, 8/23, and 6/18 litters at 0, 50, 250, and 750 mg/kg-d, respectively). Other developmental effects seen in the high-dose group only included mild forelimb flexure, slight-to-moderate dilation of the renal pelvis, retrocaval ureter, and delayed ossification of the sternebrae.	Scortichini et al. (1986); John et al. (1984)
Dermal developmental	Pregnant New Zealand white rabbits (10/group) were treated dermally with undiluted DGME at doses of 0, 100, 300, and 1,000 mg/kg-d on GDs 6−18. DGME was applied under an occlusive bandage to minimize oral exposure and volatilization. Dosing occurred daily and bandages were replaced as needed. Animals were observed daily for signs of toxicity. Body weights were statistically analyzed on GDs 6, 9, 12, 15, and 19. Animals were sacrificed on GD 19. Gross observations of uterine contents (numbers of resorptions, dead and live fetuses, and resorption sites), skin, and internal organs were performed.	3 rabbits from the high-dose group died or were sacrificed moribund. In the 7 surviving animals given 1,000 mg/kg-d, 5 showed decreased ingesta in the digestive tract, and three showed a decreased amount of fat in the abdominal cavity. Maternal body-weight gain was also significantly decreased at 1,000 mg/kg-d (GDs 6−18). A significantly higher percent of resorbed implantations occurred at 1,000 mg/kg-d (GD 19).	John et al. (1983)

Table 4. Other Studies

Test	Materials and Methods	Results	References
Subcutaneous injection developmental	Pregnant Wistar-derived rats (15/group) were injected subcutaneously with DGME on GDs 6−20 at 0, 250, 500, or 1,000 µL/kg (~0, 254, 509, and 1,017 mg/kg-d). Animals were observed daily for clinical signs of toxicity. Body weights were recorded on GDs 1 and 6−20. Maternal animals were allowed to deliver; numbers of live and dead fetuses were recorded. Offspring were weighed on PNDs 1 and 4. Animals that failed to produce a litter were sacrificed on GD 24.	No maternal or developmental toxicity was observed.	Doe (1984)
Studies of mode of action/mechanism/therapeutic action			
Developmental toxicity in vitro	Chick embryonic limb bud cells were exposed to DGME at concentrations of 0.001−100 µL/mL (8.53×10^{-6} to 0.853M) for 5 d. Effects on cartilage development (chondrogenesis) and cell proliferation were evaluated by staining with alcian green (proteoglycans) and crystal violet, respectively.	After treatment at 100 µL/mL, proteoglycan abundance and cell proliferation were significantly decreased. The effect on proteoglycans was not concentration-related, and the effect on cell proliferation was significant only at the highest tested concentration.	Scofield et al. (2006)
Liver toxicity in vitro	Primary rat hepatocytes were exposed to DGME at 0, 0.001, 0.01, 0.1, 1, and 10 mM for up to 24 h. Toxicity was evaluated by measuring LDH release (cell membrane integrity), tetrazolium dye (MTT) reduction activity (cell viability/mitochondrial function), gSH level (oxidative damage), and rate of protein synthesis (cellular function).	At the highest tested dose (10 mM), DGME exhibited no significant effects on LDH leakage, protein synthesis rates, or gSH levels. DGME induced a small but significant dose-related decrease in MTT dye reduction at ≥0.1 mM.	Geiss and Frazier (2001)
Neurotoxicity in vitro	*Xenopus* oocytes expressing glutamate receptors were exposed to a receptor agonist (kainite [KA] or N-methyl-D-aspartate [NMDA]) and 100 µmol/L DGME for 30 s.	DGME did not significantly affect KA- or NMDA-induced membrane currents.	Musshoff et al. (1999)

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; gGT = γ-glutamyl transferase; Hb = hemoglobin; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell

Absorption studies indicate that diethylene glycol ethers penetrate the human skin at a slower rate than their corresponding monoethylene glycol counterparts (Dugard et al., 1984). Penetration of DGME through the epidermis in vitro is relatively slow (0.21 mg/cm^2-hour), and does not significantly impair barrier function (Dugard et al., 1984). The flux and permeability of DGME from JP-8 was measured in static diffusion cells using excised rat skin (McDougal et al., 2000; McDougal et al., 1999). DGME was measured as a minor component of JP-8 (0.08%) with a flux and permeability coefficient of 0.052 mg/cm^2-hour and 0.81 cm/hour, respectively (from JP-8 vehicle). Significant dermal absorption is suggested, however, by subchronic-duration and developmental studies of dermal toxicity in rabbits (see Table 4). Liver toxicity was observed in guinea pigs following dermal exposure to doses 200 mg/kg-day, or greater, for 13 weeks (Hobson et al., 1986). Developmental effects were observed at dermal doses as low as 250 mg/kg-day (delayed ossification of the skull and cervical spurs) (Scortichini et al., 1986; John et al., 1984).

Rats administered DGME orally or via i.p. injection showed induction of xenobiotic metabolism (including increased microsomal protein content and induction of CYP450 mixed-function oxidase activity), without significant induction of the ethanol-inducible CYP450 isoform (P4502E1), or increased gGT, cytochrome b5 or NADPH-cytochrome c reductase in hepatic microsomes (Ballow, 1992; Kawamoto et al., 1991, 1990b). DGME is a poor substrate for alcohol dehydrogenase (P450J) in vitro (Calhoun, 1982).

Mode-of-Action/Mechanistic Studies

In vitro mechanistic studies are described in Table 4. Scofield et al. (2006) demonstrated DGME-induced inhibition of cell proliferation in chick limb bud cells. DGME altered mitochondrial function in primary rat hepatocytes, but did not affect membrane integrity, gSH levels, or protein synthesis (Geiss and Frazier, 2001). DGME did not impair receptor-meditated ion currents in *Xenopus* oocytes (Musshoff et al., 1999).

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer references values, respectively.

Table 5. Summary of Noncancer Reference Values for DGME (CASRN 111-77-3)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	$POD_{HED/HEC}$	UF_C	Principal Study
Subchronic p-RfD	Rat/females (pregnant)	Thymic remnants, dilation of renal pelvis and reduced ossification in fetal rats	**4×10^{-2} mg/kg-d**	$BMDL_{05}$	12	300	Yamano et al. (1993) Hardin et al. (1986)
Chronic p-RfD	Rat/females (pregnant)	Thymic remnants, dilation of renal pelvis and reduced ossification in fetal rats	**4×10^{-2} mg/kg-d**	$BMDL_{05}$	12	300	Yamano et al. (1993) Hardin et al. (1986)
Subchronic p-RfC	NDr						
Chronic p-RfC	NDr						

NDr = not determined

Table 6. Summary of Cancer Reference Values for DGME (CASRN 111-77-3)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
Provisional oral slope factor (p-OSF) $(mg/kg\text{-}d)^{-1}$	NDr			
Provisional inhalation unit risk (p-IUR) $(mg/m^3)^{-1}$	NDr			

NDr = not determined

DERIVATION OF ORAL REFERENCE DOSES

Derivation of the Subchronic Provisional RfD (Subchronic p-RfD)

There are four short-term-duration studies, one 6-week subchronic-duration study, and three developmental toxicity studies available for consideration for the derivation of the subchronic provisional reference dose (p-RfD). The candidate points of departure (PODs) from these studies are listed in Table 7. Two of the short-term-duration studies (both peer reviewed) evaluated only immunotoxicity (Smialowicz et al., 1992) and testicular toxicity (Cheever et al., 1988); no treatment-related effects were reported in these studies. Two short-term-duration (peer-reviewed) studies (Yamano et al., 1993; Kawamoto et al., 1990a) both reported decreased thymus weights in adult rats after treatment with DGME for 11 and 20 days, respectively. The one subchronic-duration study (Eastman Kodak, 1992) was conducted comprehensively for systemic toxicity, reporting decreased body weight, testicular atrophy, and kidney effects at the highest dose (2,571 mg/kg-day), but was not peer reviewed. Hardin et al. (1986) conducted two developmental toxicity studies using pregnant S-D rats. The first one was a range-finding study with only 9 dams that found fetal effects at a maternal dose of 1,000 mg/kg-day and maternal effects at 3,345 mg/kg-day, establishing DGME as a developmental toxicant. The second, more comprehensive Hardin et al. (1986) study used 25 dams and found similar effects as the range-finding study, also with developmental effects occurring at a lower dose (720 mg/kg-day) than the maternal NOAEL of 2,165 mg/kg-day; a developmental NOAEL was not established. The comprehensive developmental Yamano et al. (1993) study also found developmental effects

at lower doses than those for maternal effects and failed to establish a developmental NOAEL, with a developmental LOAEL of 200 mg/kg-day. Yamano et al. (1993) also conducted a smaller range-finding study, reporting a developmental NOAEL and LOAEL of 500 and 1,000 mg/kg-day, respectively. The Bioassay Sys (1983a) developmental toxicity study in mice tested only one high dose (4,000 mg/kg-day), which was an FEL for maternal and fetal mortality.

Table 7. PODs Considered for the Subchronic p-RfD for DGME

Endpoint	Animal POD[a] (mg/kg-d)	POD_{HED}[b] (mg/kg-d)
Hardin et al. (1986): pregnant S-D rat, GDs 7−16, gavage		
Renal pelvis dilation, fetal	**$BMDL_{05}$[c] = 50**	**12**
Reduced cranial ossification, fetal	$BMDL_{05}$ = 53	13
Total rib malformations, fetal	$BMDL_{05}$ = 131	31
Reduced ossification of appendicular skeleton, fetal	$BMDL_{05}$ = 187	45
Decreased fetal body weight (F)[d]	$BMDL_{RD05}$[e] = 380	91
Decreased fetal body weight (M)[d]	$BMDL_{RD05}$ = 480	115
Yamano et al. (1993): pregnant Wistar rat, GDs 7−17; gavage		
Decreased number of ossification centers; sacral and caudal vertebrae, fetal	$BMDL_{1SD}$ = 142	34
Thymic remnant in the neck, fetal	$BMDL_{05}$ = 55	13
Incidence of dilated renal pelvis, fetal	$BMDL_{05}$ = 90	22
Decreased number of sternebrae ossified, fetal	$BMDL_{1SD}$ = 318	76
Decreased fetal body weight (M)	$BMDL_{RD05}$ = 195	47
Decreased fetal body weight (F)	$BMDL_{RD05}$ = 196	47
Decreased number of ossification centers; thoracic vertebrae, fetal	$BMDL_{1SD}$ = 161	39
Kawamoto et al. (1990a): Wistar rat, 20-d gavage		
Decreased relative thymus weight	NOAEL = 500	120
Yamano et al. (1993): Wistar rat, 11-d gavage		
Decreased relative thymus weight	$BMDL_{1SD}$ = 1,074	258
Eastman Kodak (1992): CD rat, 6-w gavage		
Decreased body and organ weights; testicular atrophy; proteinaceous casts in the kidney, increased BUN	NOAEL = 1,286	309
Bioassay Sys (1983a): pregnant CD-1 mouse, GDs 7−14, gavage		
Decreased maternal and fetal survival	FEL = 4,000	560

[a]BMD modeling results are described in more detail in Appendix C.
[b]HED calculated by multiplying animal POD by a DAF of 0.24 for rats or 0.14 for mice (U.S. EPA, 2011b).
[c]BMR = 5% incidence.
[d]range-finding study.
[e]BMR = 5% relative deviation.

BMDL = benchmark dose lower confidence limit; FEL = frank effect level; NOAEL = no-observed-adverse-effect level

Thus, the two studies of Hardin et al. (1986) and Yamano et al. (1993) establish DGME as a developmental toxicant, finding similar fetal effects at similar maternal exposures. In the Hardin et al. (1986) developmental toxicity study in rats, the most sensitive endpoints (i.e., those at the LOAEL of 720 mg/kg-day) include increased rib malformations, decreased ossification (including reduced cranial and appendicular skeleton ossification), and renal pelvis dilation[6] in fetuses. In the Yamano et al. (1993) study, sensitive developmental endpoints included decreased male and female fetal body weights (at 200 mg/kg-day), decreased ossification (sacral and caudal vertebrae, thoracic vertebrae and sternebrae), and increased incidence of thymic remnant in the neck (at 600 mg/kg-day). These results are supported by the finding of similar developmental effects (dilation of the renal pelvis, retrocaval ureter, and delayed ossification of the sternebrae) in fetuses of pregnant rabbits treated dermally with DGME (Scortichini et al., 1986; John, 1984). Taken together, these findings indicate a concern for the negative impact of DGME on skeletal development, kidney, and urinary tract development, and postnatal immune system development. The thymus appears to be a particularly sensitive target organ, as reduced thymus weight and reduced thymic lymphocytes were reported in adult animals at somewhat higher doses (Yamano et al., 1993; Kawamoto et al., 1990a). Maternal effects were only seen at higher doses in these studies, indicating that DGME is a developmental toxicant. In particular, the fetal thymic remnants suggest a concern for early postnatal development of T cell-mediated immune response mechanisms. The only immunoxicity study is for adult rats and shows no impact of DGME on adult immune function (Smialowicz et al., 1992). There are no early life-stage immunotoxicity studies; the lack of such studies is considered a significant deficiency in the toxicity database for DGME, which is reflected in the selection of the database uncertainty factor for both the subchronic and chronic p-RfDs (see Tables 8 and 10, respectively).

Data sets for sensitive developmental endpoints in Hardin et al. (1986) and Yamano et al. (1993) were considered to derive potential PODs via benchmark dose (BMD) modeling (see Table 7 and Appendices C). Total skeletal malformations from Hardin et al. (1986) were not modeled because the specific endpoints within each of these categories are not considered to be independent. A number of less sensitive endpoints for adult animals were also BMD modeled, with resulting benchmark dose lower confidence limits (BMDLs) also shown in Table 7. All dichotomous models in the EPA BMD software (BMDS Version 2.5) were fit to each of the dichotomous endpoints observed from the Hardin et al. (1986) and Yamano et al. (1993) studies. Similarly, all BMDS continuous models were fit to the continuous endpoints in the Yamano et al. (1993) study. Nested dichotomous models could not be used because individual animal data were not available. Appendix C presents the modeling results for the three endpoints yielding the lowest BMDLs: (1) number of litters with reduced cranial ossification, (2) number of litters with dilated renal pelvis (see Tables C-1 and C-2) (Hardin et al., 1986), and (3) incidence of thymic remnants (see Tables C-3) (Yamano et al., 1993). BMDLs for other endpoints were much higher.

In EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), 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

[6] According to John (1984), dilation of the fetal renal pelvis is indicative of delayed fetal development.

human equivalent oral exposures, 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 DGME is not available for use in extrapolating doses from animals to humans. Therefore, scaling by $BW^{3/4}$ is relevant for deriving human equivalent doses (HEDs) for these effects.

Following U.S. EPA (2011b) guidance, all PODs are converted to HEDs by application of dosimetric adjustment factors (DAFs) as follows:

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

where:

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

Using a BW_a of 0.25 kg for rats and 0.025 kg for mice, and a BW of 70 kg for humans, the resulting DAFs are 0.24 and 0.14 for rats and mice, respectively (U.S. EPA, 1988). Each POD candidate is multiplied by the appropriate species-specific DAF to obtain POD_{HED}s, which are shown in Table 7.

The lowest POD_{HED} in Table 7 is 12 mg/kg-day for fetal renal pelvis dilation reported by Hardin et al. (1986). Two other POD_{HED}s, virtually the same at 13 mg/kg-day, were for reduced cranial ossification (Hardin et al., 1986) and increased incidence of thymic remnants (Yamano et al., 1993) developmental endpoints, and should be considered as co-critical effects.

The subchronic p-RfD for DGME, based on a $BMDL_{05[HED]}$ (for dichotomous developmental endpoints) of 12 mg/kg-day, is derived as follows:

Subchronic p-RfD $= BMDL_{05[HED]} \div UF_C$
$= 12$ mg/kg-day $\div 300$
$=$ **4×10^{-2} mg/kg-day**

Table 8 summarizes the uncertainty factors (UFs) for the subchronic p-RfD for DGME.

Table 8. Uncertainty Factors for the Subchronic p-RfD for DGME (CASRN 111-77-3)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for residual uncertainty in potential toxicokinetic and toxicodynamic differences between laboratory animals and humans. Interspecies toxicokinetic variability has been accounted for by application of a DAF (U.S. EPA, 1988).
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of DGME in humans.
UF_D	10	A UF_D of 10 is applied because, although the database contains two acceptable developmental studies, Hardin et al. (1986) and Yamano et al. (1993), there is no multigeneration reproduction study. In addition, given the concern for developmental immunotoxicity, the lack of an early life-stage immunotoxicity study is a significant weakness.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	NA	Not applicable for subchronic p-RfD derivation
UF_C	300	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L$

NA = not applicable

The confidence in the subchronic p-RfD for DGME is medium as described in Table 9.

Table 9. Confidence Descriptors for the Subchronic p-RfD for DGME (CASRN 111-77-3)

Confidence Categories	Designation	Discussion
Confidence in study	H	Confidence in the co-principal studies (Yamano et al., 1993; Hardin et al., 1986) is high because in each case, preliminary studies were conducted to determine appropriate doses and comprehensive developmental endpoints were examined. Each of the co-principal studies identified sensitive effects at similar dose levels (600 and 720 mg/kg-d) (Yamano et al., 1993; Hardin et al., 1986) (respectively), and Yamano et al. (1993) also identified a NOAEL. Dose-response data are available for both studies. Both studies were well reported.
Confidence in database	L	There is low confidence in the database. Although no peer-reviewed subchronic-duration oral study is available, a 6-wk gavage study in rats (Eastman Kodak, 1992) provided a comprehensive evaluation of systemic toxicity endpoints. Two peer-reviewed, adequately reported developmental toxicity studies with dose-response data in rats are available (Yamano et al., 1993; Hardin et al., 1986). There are no reproductive toxicity studies of DGME. In addition, the lack of information on early life-stage immunotoxicity is a significant weakness.
Confidence in subchronic p-RfD	L	The overall confidence in the subchronic p-RfD is low because the deficiencies in the database, particularly the lack of a full-length peer-reviewed subchronic-duration systemic-toxicity study, outweigh the strength of the principal studies.

H = high; L = low.

Derivation of the Chronic Provisional RfD (Chronic p-RfD)

There are no chronic-duration studies for DGME. The most sensitive endpoints for less-than-chronic-duration exposure are the developmental effects found in two studies (Yamano et al., 1993; Hardin et al., 1986) with POD_{HED}s of 12 mg/kg-day ($BMDL_{05}$), which are the basis for the subchronic p-RfD. However, for the chronic p-RfD, susceptibility to effects arising from longer term-duration exposure must be considered. One concern for long-term-duration exposure is the finding of reduced thymus weight in the two short-term-duration studies (Yamano et al., 1993; Kawamoto et al., 1990a) with a POD_{HED} of 120 mg/kg-day for the Kawamoto et al. (1990a) study. Note that with the application of a 10-fold UF_S, the extrapolated sensitivity of this endpoint would be the same as the developmental effects. However, in the longer 6-week study, which assessed thymus weight and histopathology, no effects on the thymus were reported. In addition, the lack of effects of DGME on antibody response in adult rats at doses up to 800 mg/kg-day (Smialowicz et al., 1992) suggests that adult immunotoxicity may not be an issue. The NOAEL for other systemic effects after a 6-week exposure is 309 mg/kg-day (Eastman Kodak, 1992), which would not constitute a more sensitive POD than the developmental POD_{HED} forming the basis for the subchronic p-RfD.

Therefore, the POD_{HED} ($BMDL_{05[HED]}$) of 12 mg/kg-day for developmental effects in fetal rats is used as the POD for the chronic p-RfD. The chronic p-RfD is derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfD} &= BMDL_{05[HED]} \div UF_C \\ &= 12 \text{ mg/kg-day} \div 300 \\ &= \mathbf{4 \times 10^{-2} \text{ mg/kg-day}} \end{aligned}$$

Table 10 summarizes the UFs for the chronic p-RfD for DGME.

Table 10. Uncertainty Factors for the Chronic p-RfD for DGME (CASRN 111-77-3)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for residual uncertainty in potential toxicokinetic and toxicodynamic differences between laboratory animals and humans. Interspecies toxicokinetic variability has been accounted for by application of a DAF (U.S. EPA, 1988).
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of DGME in humans.
UF_D	10	A UF_D of 10 is applied because the database contains a subchronic study and two acceptable developmental studies (Yamano et al., 1993; Hardin et al., 1986), however, there are no chronic-duration studies, no multigeneration reproduction study, and no early life-stage immunotoxicity study.
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 of 1 was applied to account for subchronic to chronic extrapolation (UF_S) because developmental toxicity resulting from a narrow period of exposure 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, 1991b)
UF_C	300	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

The confidence descriptors for the chronic p-RfD are described in Table 11.

Table 11. Confidence Descriptors for the Chronic p-RfD for DGME (CASRN 111-77-3)

Confidence Categories	Designation	Discussion
Confidence in study	H	Confidence in the co-principal studies (Yamano et al., 1993; Hardin et al., 1986) is high because in each case, preliminary studies were conducted to determine appropriate doses and comprehensive developmental endpoints were examined. Each of the co-principal studies identified sensitive effects at similar dose levels, and Yamano et al. (1993) also identified a NOAEL. Dose-response data are available for both studies. Both studies were well reported.
Confidence in database	L	There is low confidence in the database. Although no peer-reviewed subchronic-duration oral study is available, a 6-wk gavage study in rats (Eastman Kodak, 1992) provided a comprehensive evaluation of systemic toxicity endpoints. Two peer-reviewed, adequately reported developmental toxicity studies with dose-response data in rats are available (Yamano et al., 1993; Hardin et al., 1986). There are no chronic-duration studies and no reproductive toxicity studies of DGME. In addition, the lack of information on early life-stage immunotoxicity is a significant weakness.
Confidence in chronic p-RfD[a]	L	The overall confidence in the chronic p-RfD is low.

H = high; L = low.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

There is a single subchronic-duration inhalation study available for DGME (Miller et al., 1985). This study exposed rats to DGME as a vapor for 13 weeks; however, no toxicity was observed and a LOAEL was not identified. The study authors indicated that the highest exposure concentration used (measured TWA = 190 mg/m^3) was equivalent to a maximally attainable concentration based on the low vapor pressure of DGME. Furthermore, the test article had to be preheated to approximately 60°C in order to generate a vapor. An acute inhalation study reported no toxic effects in rats exposed to a substantially greater DGME concentration in air (nominal concentration of 200,000 mg/m^3) for 1 hour (Olin Corporation, 1977). However, no details were provided regarding the method used to generate the chamber air concentrations and measured concentrations were not reported for this study. Because there were no treatment-related effects in either of these studies at apparent maximally obtainable concentrations using extreme conditions for vapor generation, there is not enough information to assessment human health hazard from environmental inhalation exposure to DGME. Therefore, provisional subchronic and chronic RfCs are not derived.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No studies were located examining possible associations between exposure to DGME and cancer in humans or animals. Studies in animals (one 6-week study and several developmental studies in rodents) are inadequate to assess the carcinogenicity of DGME. Results from a single reverse mutation assay with DGME were negative. Table 12 identifies the cancer weight-of-evidence (WOE) descriptor for DGME.

Table 12. Cancer Weight-Of-Evidence Descriptor for DGME (CASRN 111-77-3)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	There are no human data available.
"Likely to Be Carcinogenic to Humans"	NS	NA	No adequate chronic-duration animal cancer bioassays are available.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	No adequate chronic-duration animal cancer bioassays are available.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No carcinogenicity studies are available that evaluated oral or inhalation exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No adequate chronic-duration animal cancer bioassays are 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 DGME 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 DGME following inhalation exposure precludes the derivation of a quantitative estimate (p-IUR) for inhalation exposure.

APPENDIX A. SCREENING PROVISIONAL VALUES

No provisional screening values are provided for DGME.

APPENDIX B. DATA TABLES

Table B-1. Selected Hematological Parameters of Female Virgin Wistar Rats Exposed to DGME by Gavage for 11 Days[a]

Endpoint[b]	Exposure Group (mg/kg-d)							
	0	**125**	**150**	**500**	**1,000**	**2,000**	**3,000**	**4,000**
Number of animals	5	5	5	5	5	5	5	5
RBCs (× 10^6/mm^3)	8.30 ± 0.12	8.21 ± 0.19 (−1%)	8.25 ± 0.16 (−1%)	8.63 ± 0.14 (+4%)	8.19 ± 0.15 (−1%)	8.11 ± 0.09 (−2%)	8.03 ± 0.17 (−3%)	7.59 ± 0.11* (−9%)
WBCs (× 10^3/mm^3)	5.1 ± 0.4	4.8 ± 0.1 (−6%)	5.2 ± 0.4 (+2%)	4.7 ± 0.4 (−8%)	4.8 ± 0.6 (−6%)	3.9 ± 0.2 (−24%)	3.8 ± 0.2 (−25%)	3.2 ± 0.3* (−37%)
Hb (g/dL)	15.5 ± 0.34	15.3 ± 0.41 (−1%)	15.5 ± 0.40 (0%)	15.2 ± 0.19 (−2%)	15.0 ± 0.47 (−3%)	14.8 ± 0.20 (−5%)	14.5 ± 0.13 (−6%)	13.5 ± 0.19* (−13%)
Hematocrit (%)	44.9 ± 0.34	44.2 ± 0.79 (−2%)	44.6 ± 0.82 (−1%)	43.2 ± 0.44 (−4%)	43.9 ± 0.54 (−2%)	42.7 ± 0.67 (−5%)	41.4 ± 0.43* (−8%)	39.6 ± 0.61* (−12%)

[a]Yamano et al. (1993).
[b]Values expressed as mean ± SE (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from control at $p \leq 0.05$, as reported by the study authors (Dunnett's or Scheffé's multiple comparison test).

Hb = hemoglobin; RBC = red blood cell; WBC = white blood cell

Table B-2. Selected Clinical Chemistry Parameters in Female Virgin Wistar Rats Exposed to DGME by Gavage for 11 Days[a]

Endpoint[b]	Exposure Group (mg/kg-d)							
	0	**125**	**250**	**500**	**1,000**	**2,000**	**3,000**	**4,000**
Number of animals	5	5	5	5	5	5	5	5
BUN (mg/dL)	16.3 ± 0.65	17.0 ± 0.99 (+4%)	17.7 ± 1.40 (+9%)	15.3 ± 0.60 (−6%)	16.4 ± 0.34 (+1%)	14.8 ± 0.77 (−9%)	17.6 ± 1.04 (+8%)	20.6 ± 1.78* (+26%)
Triglycerides (mg/dL)	33.9 ± 2.91	40.6 ± 2.95 (+20%)	47.0 ± 4.60 (+39%)	33.0 ± 1.46 (−3%)	38.4 ± 2.39 (+13%)	49.6 ± 7.65 (+46%)	46.0 ± 5.81 (+36%)	64.1 ± 7.42* (+89%)
Total protein (g/dL)	5.00 ± 0.11	4.90 ± 0.10 (−2%)	4.98 ± 0.06 (0%)	4.80 ± 0.07 (−4%)	4.90 ± 0.06 (−2%)	4.92 ± 0.11 (−2%)	4.62 ± 0.07* (−8%)	4.48 ± 0.07* (−10%)

[a]Yamano et al. (1993).
[b]Values expressed as mean ± SE (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (Dunnett's or Scheffé's multiple comparison test).

BUN = blood urea nitrogen

Table B-3. Selected Relative Organ Weights in Female Virgin Wistar Rats Exposed to DGME by Gavage for 11 Days[a]

Endpoint	Exposure Group (mg/kg-d)							
	0	**125**	**250**	**500**	**1,000**	**2,000**	**3,000**	**4,000**
Number of animals	5	5	5	5	5	5	5	5
Relative organ weight								
Kidney[b]	0.74 ± 0.01	0.77 ± 0.01 (+4%)	0.71 ± 0.01 (−4%)	0.71 ± 0.01 (−4%)	0.71 ± 0.01 (−4%)	0.75 ± 0.02 (+1%)	0.77 ± 0.01 (+4%)	0.83 ± 0.01* (+12%)
Thymus[c]	114.49 ± 3.46	119.44 ± 7.89 (+4%)	115.37 ± 7.85 (+1%)	124.11 ± 6.15 (+8%)	101.26 ± 8.75 (−12%)	85.46 ± 2.24 (−25%)	49.56 ± 2.15 (−57%)	35.62 ± 1.77* (−69%)
Pituitary[c]	6.64 ± 0.47	6.23 ± 0.24 (−6%)	6.14 ± 0.60 (−8%)	5.81 ± 0.52 (−13%)	5.73 ± 0.27 (−14%)	5.34 ± 0.16 (−20%)	5.05 ± 0.24* (−24%)	4.97 ± 0.30* (−25%)

[a]Yamano et al. (1993).
[b]Relative organ weight (organ weight/body weight × 10^2) expressed as mean ± SE (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
[c]Relative organ weight (organ weight/body weight × 10^5) expressed as mean ± standard error mean ± SE (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (Dunnett's or Scheffé's multiple comparison test).

Table B-4. Selected Relative Organ Weights in Male Wistar Rats Exposed to DGME by Gavage for up to 20 Days[a]

	Exposure Duration (d)							
	Control				2,000 mg/kg-d			
Day	**1**	**2**	**5**	**20**	**1**	**2**	**5**	**20**
Number of animals	4	4	4	8	4	4	4	8
Relative organ weight[b]								
Liver	36.92 ± 0.57	38.86 ± 0.63	34.96 ± 2.10	35.34 ± 4.31	37.17 ± 0.58 (+1%)	37.63 ± 1.13 (−3%)	31.88 ± 0.52* (−9%)	31.90 ± 0.85* (−10%)
Kidney	8.81 ± 0.39	8.48 ± 0.19	8.06 ± 0.25	8.22 ± 0.79	8.36 ± 0.39 (−5%)	8.92 ± 0.18* (+5%)	8.59 ± 0.42 (+7%)	8.01 ± 0.72 (−3%)
Spleen	3.31 ± 0.26	3.47 ± 0.19	3.42 ± 0.27	2.28 ± 0.23	3.02 ± 0.33 (−9%)	3.58 ± 0.21 (+3%)	2.54 ± 0.17* (−26%)	2.33 ± 0.17 (+2%)
Thymus	3.15 ± 0.54	2.95 ± 0.54	2.36 ± 0.21	2.08 ± 0.45	2.30 ± 0.14* (−27%)	2.92 ± 0.50 (−1%)	1.49 ± 0.35* (−37%)	1.24 ± 0.24* (−40%)
Testis	10.78 ± 0.91	11.72 ± 1.21	12.54 ± 0.70	11.16 ± 0.69	11.17 ± 0.70 (+4%)	11.58 ± 0.55 (−1%)	10.52 ± 1.09* (−16%)	9.09 ± 2.33* (−19%)

[a]Kawamoto et al. (1990a).
[b]Relative organ weight (organ weight/body weight × 1,000) expressed as mean ± SD (% change compared with control); % change control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (Student's unpaired test).

Table B-5. Average Body Weights and Food Consumption of Male Albino CD Rats Exposed to DGME by Gavage for 6 Weeks[a]

Time Period	Exposure Group, mg/kg-d[b]			
	0 (control)	**643**	**1,286**	**2,571**
Number of animals	10	10	10	10
Body weight (g)[c]				
Day 0	234.6 ± 17.3	239.4 ± 12.2 (+2%)	233.2 ± 8.4 (−1%)	235.9 ± 16.1 (+1%)
Day 3	253.3 ± 19.6	259.1 ± 11.4 (+2%)	252.2 ± 9.0 (0%)	236.6 ± 18.9* (−7%)
Day 6	272.0 ± 18.6	280.2 ± 14.0 (+3%)	274.8 ± 9.1 (+1%)	262.4 ± 18.3 (−4%)
Day 13	311.4 ± 25.1	318.3 ± 12.0 (+2%)	312.7 ± 13.5 (0%)	297.1 ± 16.7 (−5%)
Day 20	328.8 ± 29.1	332.0 ± 17.2 (+1%)	322.9 ± 18.2 (−2%)	309.3 ± 21.0 (−6%)
Day 27	363.3 ± 31.3	367.6 ± 16.3 (+1%)	353.7 ± 16.1 (−3%)	333.9 ± 20.4* (−8%)
Day 34	387.3 ± 36.3	391.1 ± 13.6 (+1%)	369.5 ± 23.4 (−5%)	346.3 ± 26.1* (−11%)
Day 41	405.0 ± 38.5	409.6 ± 14.6 (+1%)	381.6 ± 27.4* (−6%)	359.9 ± 25.9* (−11%)
Food consumption (g/rat/d)[c]				
Day 3	21.93 ± 1.93	25.57 ± 1.75 (+17%)	23.38 ± 1.86 (+7%)	15.07 ± 6.67* (−31%)
Day 6	22.26 ± 2.02	24.58 ± 1.58 (+10%)	23.54 ± 1.62 (+6%)	19.90 ± 4.25* (−11%)
Day 13	22.93 ± 2.73	25.02 ± 1.69 (+9%)	22.84 ± 3.58 (0%)	21.44 ± 1.80* (−6%)
Day 20	22.96 ± 2.36	24.34 ± 1.40 (+6%)	22.78 ± 2.46 (−1%)	20.01 ± 2.35* (−13%)
Day 27	23.43 ± 2.26	24.58 ± 1.37 (+5%)	22.75 ± 1.78 (−3%)	20.47 ± 1.95* (−13%)
Day 34	23.83 ± 2.20	24.81 ± 1.37 (+4%)	22.86 ± 1.68 (−4%)	20.71 ± 1.85* (−13%)
Day 41	24.09 ± 2.14	24.97 ± 1.39 (+4%)	23.12 ± 1.50 (−4%)	20.90 ± 1.65* (−13%)

[a]Eastman Kodak (1992).
[b]ADDs presented here were calculated using the following equation: $Dose_{ADD}$ = dose × (days exposed ÷ 7 days).
[c]Values expressed as mean ± SD (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (statistical test not reported).

Table B-6. Selected Clinical Chemistry Parameters in Male Albino CD Rats Exposed to DGME by Gavage for 6 Weeks[a]

Endpoint	ADD (mg/kg-d)[b]			
	0 (control)	643	1,286	2,571
Number of animals	10	9	10	8
BUN (mg/dL)[c]	11.3 ± 1.6	12.6 ± 2.4 (+12%)	11.5 ± 1.4 (+2%)	13.9 ± 2.6* (+23%)

[a]Eastman Kodak (1992).
[b]ADDs presented here were calculated using the following equation: $Dose_{ADD}$ = dose × (days exposed ÷ 7 days).
[c]Values expressed as mean ± SD (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (statistical test not reported).

BUN = blood urea nitrogen

Table B-7. Selected Absolute and Relative Organ Weights in Male Albino CD Rats Exposed to DGME by Gavage for 6 Weeks[a]

Endpoint	ADD (mg/kg-d)[b]			
	0 (control)	643	1,286	2,571
Number of animals	10	9	10	8
Absolute organ weights (g)[c]				
Liver	10.587 ± 1.392	11.561 ± 1.239 (+9%)	10.552 ± 0.690 (0%)	10.139 ± 0.793 (−4%)
Kidney	2.834 ± 0.418	3.011 ± 0.151 (+6%)	2.954 ± 0.324 (+4%)	2.877 ± 0.342 (+2%)
Heart	1.142 ± 0.152	1.244 ± 0.131 (+9%)	1.204 ± 0.092 (+5%)	1.132 ± 0.101 (−1%)
Testes	3.075 ± 0.167	3.199 ± 0.311 (+4%)	3.208 ± 0.300 (+4%)	2.251 ± 0.240* (−27%)
Brain	2.009 ± 0.099	1.951 ± 0.087 (−3%)	1.915 ± 0.134 (−5%)	1.822 ± 0.195* (−9%)
Spleen	0.673 ± 0.132	0.701 ± 0.062 (+4%)	0.685 ± 0.137 (+2%)	0.559 ± 0.065* (−17%)
Relative organ weights (g/100 g)[c]				
Liver	2.802 ± 0.179	3.031 ± 0.307* (+8%)	3.003 ± 0.124* (+7%)	3.104 ± 0.163* (+11%)
Kidney	0.750 ± 0.063	0.789 ± 0.046 (+5%)	0.642 ± 0.089* (−14%)	0.879 ± 0.075* (+17%)
Heart	0.303 ± 0.019	0.327 ± 0.026 (+8%)	0.343 ± 0.034* (+13%)	0.347 ± 0.033* (+15%)
Testes	0.820 ± 0.064	0.839 ± 0.083 (+2%)	0.915 ± 0.090* (+12%)	0.689 ± 0.066* (−16%)
Brain	0.535 ± 0.040	0.512 ± 0.031 (−4%)	0.547 ± 0.049 (+2%)	0.559 ± 0.056 (+4%)
Spleen	0.179 ± 0.027	0.186 ± 0.017 (+4%)	0.195 ± 0.037 (+9%)	0.171 ± 0.020 (−4%)

[a]Eastman Kodak (1992).
[b]ADDs presented here were calculated using the following equation: $Dose_{ADD}$ = dose × (days exposed ÷ 7 days).
[c]Values expressed as mean ± SD (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (statistical test not reported).

Table B-8. Selected Histopathological Findings from Male Albino CD Rats Exposed to DGME by Gavage for 6 Weeks[a]

Endpoint[c]	ADD (mg/kg-d)[b]			
	0 (control)	643	1,286	2,571
Testes				
Atrophy, seminiferous tubules	0/10	NDr	0/10	6/10*
Epididymides				
Degenerated spermatozoa	0/10	NDr	NDr	3/10
Hypospermia	0/10	NDr	NDr	2/10
Kidneys				
Proximal convoluted tubules, hyaline droplet degeneration	10/10	10/10	10/10	9/10
Proteinaceous casts	0/10	0/10	0/10	9/10*

[a]Eastman Kodak (1992).
[b]ADDs presented here were calculated using the following equation: $Dose_{ADD}$ = dose × (days exposed ÷ 7 days).
[c]Values expressed as number of animals affected/number of animals exposed.
*Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test).

NDr = not determined

Table B-9. Selected Reproductive Parameters of Female CD-1 Mice Exposed to DGME by Gavage on GDs 7−14[a]

Endpoint	Exposure Group (mg/kg-d)	
	0	**4,000**
Number of timed-pregnant animals	50	50
Number of deaths	0	5
Number of confirmed pregnancies	32	36[b]
Number of mice producing viable litters	31	5
Number of stillborn litters	0	9
Number of mated animals with totally resorbed litters	1	18
Number of nonpregnant animals	17[c]	14[d]
Reproductive index[e]	0.97	0.14*
Pre-exposure body weight of time-pregnant animals (GD 7) (g)[f]	28.3 ± 2.5	28.1 ± 3.1 (−1%)
Maternal body weight of dams prior to delivering on GD 18 (g)[f]	48.6 ± 4.6; *n* = 31	39.4 ± 4.1* (−19%); *n* = 14
Maternal body weight gain (GDs 7−18) (g)[f]	19.7 ± 3.7; *n* = 31	10.2 ± 3.5* (−48%); *n* = 14
Maternal body weight of dams producing viable litters on PND 3 (g)[f]	33.9 ± 3.9; *n* = 31	28.2 ± 1.5* (−17%); *n* = 14[g]

[a]Bioassay Sys (1983a).
[b]Includes four dams that died during the dosing period.
[c]One animal in the control group was not accounted for after GD 18.
[d]Includes one dam that died during the dosing period.
[e]Defined as the ratio of the number of animals producing viable litters divided by the number of mice ever pregnant.
[f]Values expressed as mean ± SD (% change compared with control); % change control = [(treatment mean − control mean) ÷ control mean] × 100.
[g]Maternal body weight on PND 3 was not measured for one animal (litter died).
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (reproductive index: χ^2; body-weight data: Model I ANOVA).

Gd = gestation day; PND = postnatal day

Table B-10. Selected Litter Data of Female CD-1 Mice Exposed to DGME by Gavage on GDs 7−14[a]

Endpoint	Exposure Group (mg/kg-d)	
	0	**4,000**
Number of viable litters	31	5
Pup viability		
Live pups/litter[b]	10.1 ± 2.8	3.2 ± 2.2* (−68%)
Dead pups/litter[b]	0.1 ± 0.4	0.6 ± 0.5 (+500%)
Adjusted % dead pups/litter[c]	0.9 ± 0.9	3.4 ± 2.7* (+248%)
Live pups/litter on PND 3[b]	10.1 ± 2.8	1.3 ± 1.3* (−87%); n = 4[d]
Adjusted % pup viability/litter (PNDs 1−3)[e]	10.0 ± 0.1	4.5 ± 3.6* (−55%); n = 4[d]
Litter weight (g)[b]		
PND 1	16.1 ± 3.7	4.6 ± 2.9* (−71%)
PND 3	20.3 ± 4.3	2.5 ± 1.7* (−88%); n = 3[f]
Body weight gain PND 1−3	4.2 ± 1.1	−4.2 ± 2.6* (−200%); n = 3[f]
Adjusted % change in litter weight PNDs 1−3[g]	5.1 ± 0.7	−7.6 ± 2.1* (−249%); n = 3[f]

[a]Bioassay Sys (1983a).
[b]Values expressed as mean ± SD (% change compared with control); % change from control = [(treatment mean − control mean)/control mean] × 100.
[c]Values expressed as mean ± SD, after √(r + 0.5) data transformation, where r = % deaths/litter.
[d]One of the viable litters from the exposed group did not survive until PND 3.
[e]% pup viability = (number of live pups at PND 3 ÷ number of live pups PND 1) × 100. Values expressed as mean ± SD, after √r data transformation, where r = % pup viability.
[f]One available litter was not weighed on PND 3 (no further details provided).
[g]% change in litter weight = (PND 3 weight − PND 1 weight) ÷ PND 1 weight × 100. Values expressed as mean ± SD, after √r data transformation, where r = % change in litter weight.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Model I ANOVA).

PND = postnatal day

Table B-11. Selected Maternal and Litter Data in Female Sprague-Dawley Rats Exposed to DGME by Gavage on GDs 7−16[a]

Endpoint	Exposure Group (mg/kg-d)					
	0	**1,000**	**1,495**	**2,235**	**3,345**	**5,175**
Number of dams	9	9	9	9	9	9
Number of deaths	0	0	0	0	0	2
Number of viable litters per confirmed pregnancy	9/9	8/8	4/4	8/8	3/9*	0/5*
Maternal body weight (g)[b]						
GD 7	207 ± 14	216 ± 12 (+4%)	215 ± 14 (+4%)	211 ± 10 (+2%)	210 ± 15 (+1%)	208 ± 14 (0%)
GD 12	246 ± 17	251 ± 11 (+2%)	254 ± 15 (+3%)	247 ± 16 (0%)	240 ± 22 (−2%)	228 ± 36 (−7%)
GD 16	275 ± 23	276 ± 16 (0%)	282 ± 17 (+3%)	278 ± 16 (1%)	261 ± 23 (−5%)	244 ± 29* (−11%)
GD 21	337 ± 34	327 ± 30 (−3%)	337 ± 30 (0%)	325 ± 19 (−4%)	279 ± 28* (−17%)	239 ± 23* (−29%)
Adjusted maternal body weight gain GDs 6−21 (g)[b,c]	77 ± 18	76 ± 22 (−1%)	77 ± 17 (0%)	72 ± 10 (−6%)	70 ± 18 (−9%)	54 ± 19* (−30%)
Food consumption (g)[b]						
GDs 7−12	123 ± 18	119 ± 11 (−3%)	123 ± 12 (0%)	116 ± 11 (−6%)	96 ± 20* (−22%)	79 ± 21* (−36%)
GDs 12−17	133 ± 21	134 ± 13 (+1%)	134 ± 15 (+1%)	134 ± 13 (+1%)	120 ± 14 (−10%)	109 ± 14 (−18%)
GDs 17−21	107 ± 10	111 ± 14 (+4%)	114 ± 18 (+7%)	116 ± 9 (+8%)	109 ± 14 (+2%)	92 ± 16 (−14%)
Live fetuses/litter[b]						
Number	12.1 ± 3.0	9.5 ± 3.3 (−21%)	11.5 ± 4.4 (−5%)	10.8 ± 1.7 (−11%)	3.3 ± 0.6* (−73%)	0* (−100%)
Percent	91.2 ± 11.9	90.8 ± 7.9	89.7 ± 12.6	87.1 ± 9.8	9.2 ± 13.8*	0*
Fetal weight (g)[b]						
Male	4.0 ± 0.6	3.8 ± 0.8 (−5%)	3.6 ± 0.6 (−10%)	3.5 ± 0.8 (−13%)	2.3 ± 1.3* (−43%)	NA
Female	3.8 ± 0.5	3.5 ± 0.8 (−8%)	3.3 ± 0.7 (−13%)	3.2 ± 0.6* (−16%)	2.4 ± 0.5* (−37%)	NA

[a]Hardin et al. (1986).
[b]Values expressed as mean ± SD (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
[c]Body-weight gain GDs 6−21 minus gravid uterus weight.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (nonparametric m-ranking procedures, with corrections for multiple comparisons to the control).

GD = gestation day; NA = not applicable (100% mortality)

Table B-12. Skeletal and Visceral Malformations and Variation in Litters of Sprague-Dawley Rats Exposed to DGME by Gavage on GDs 7−16[a]

Endpoint	Exposure Group (mg/kg-d)				
	0	**1,000**	**1,495**	**2,235**	**3,345**
Skeletal examination					
Number of litters (fetuses) examined	9 (55)	8 (38)	4 (23)	8 (42)	3 (6)
Number of litters (fetuses) with malformations[b] [% fetuses affected]	1 (1) [3]	1 (2) [5]	2 (4) [13]	6* (13) [34]	1 (1) [17]
Number of litters (fetuses) with variations [% fetuses affected]	6 (11) [18]	5 (12) [13]	4 (18) [80]	8 (32) [76]	3 (6) [100]
Reduced cranial ossifications	2 (2) [3]	3 (8) [23]	4* (13) [60]	6* (15) [36]	3* (5) [83]
Vertebrae					
Misaligned	0	2 (2) [5]	1 (1) [8]	8* (15) [36]	3* (4) [67]
Reduced ossification	2 (2) [3]	1 (1) [4]	2 (5) [31]	6* (15) [36]	3* (6) [100]
Total	2 (2) [3]	3 (3) [9]	2 (5) [31]	8* (20) [48]	3* (6) [100]
Visceral examination					
Number of litters (fetuses) examined	9 (54)	8 (38)	4 (23)	8 (44)	3 (5)
Number of litters (fetuses) with cardiovascular malformations[c] [% fetuses affected]	0	1 (1) [2]	0	4* (7) [17]	2 (3) [50]
Number of litters (fetuses) with cardiovascular variations (missing innominate) [% fetuses affected]	0	0	0	4* (6) [15]	0

[a]Hardin et al. (1986).
[b]Total malformations represents the sum of missing thoracic vertebrae, abnormal cervical arch, rudimentary cervical ribs, missing ribs, wavy/fused ribs (unilateral and bilateral), and cleft sternebrae.
[c]Total cardiovascular malformations represents the sum of double aortic arch, right aortic arch, right ductus arteriosus, and ventricular septal defect.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Fisher's exact test; the litter was the statistical unit of comparison).

Table B-13. Selected Maternal and Litter Data in Female Sprague-Dawley Rats Exposed to DGME by Gavage on GDs 7−16[a]

Endpoint	Exposure Group (mg/kg-d)		
	0	720	2,165
Number of viable litters per confirmed pregnancy	22/22	21/21	21/23
Maternal body weight (g)[b]			
Day 7	213 ± 7	213 ± 9 (0%)	212 ± 11 (0%)
Day 12	248 ± 10	251 ± 13 (+1%)	245 ± 13 (−1%)
Day 16	278 ± 14	279 ± 17 (0%)	273 ± 17 (−2%)
Day 21	332 ± 18	332 ± 24 (0%)	308 ± 29* (−7%)
Food consumption (g)[b]			
Days 7−12	120 ± 13	122 ± 14 (+2%)	111 ± 13* (−8%)
Days 12−17	128 ± 14	127 ± 25 (−1%)	128 ± 12 (0%)
Days 17−21	105 ± 10	109 ± 12 (+4%)	106 ± 23 (+1%)
Live fetuses/litter[b]			
Number	11.4 ± 2.0	10.8 ± 2.8 (−5%)	7.4 ± 3.9* (−35%)
Percent	90.7 ± 8.8	90.5 ± 10.0	60.5 ± 31.5*
Fetal weight (g)[b]			
Male	4.6 ± 0.8	4.5 ± 0.8 (−2%)	3.5 ± 0.8* (−24%)
Female	4.4 ± 0.7	4.2 ± 0.7 (−4.5%)	3.2 ± 0.9* (−27%)
Gross malformations			
Number of litters (fetuses) examined	22 (252)	21 (226)	21 (171)
Number of litters (fetuses) with malformations [% fetuses affected]	1 (1)[c] [0.4]	0	5 (5)[d,e] [3]

[a]Hardin et al. (1986).
[b]Values expressed as mean ± SD (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
[c]Acaudia, imperforate anus.
[d]Acaudia, imperforate anus (four fetuses); gross edema (one fetus).
[e]Litters with gross malformations differed significantly across groups ($\chi^2 = 7.93$, degrees of freedom = 2, $p < 0.05$), but control and 2,165 mg/kg-day groups did not differ significantly by Fischer's exact test ($p < 0.10$), as reported by the study authors.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (nonparametric m-ranking procedures, with corrections for multiple comparisons to the control).

Table B-14. Skeletal Malformations in Litters of Sprague-Dawley Rats Exposed to DGME by Gavage on GDs 7−16[a]

Endpoint	Exposure Group (mg/kg-d)		
	0	**720**	**2,165**
Number of litter (fetuses) examined	22 (123)	21 (111)	20 (89)
Number of litters (fetuses) with malformations[b] [% fetuses affected]	2 (6) [4]	9* (15) [15]	16* (45) [51]
Ribs			
Rudimentary cervical	1 (2) [2]	5 (9) [8]	11* (16) [18]
Wavy/fused: unilateral	0	0	3 (3) [3]
Bilateral	1 (4) [3]	4 (6) [6]	13* (32) [36]
Total	2 (6) [4]	9* (15) [15]	16* (43) [48]
Number of litters (fetuses) with variations [% fetuses affected]	14 (24) [18]	15 (33) [30]	20* (82) [94]
Reduced cranial ossification	4 (6) [4]	10* (17) [16]	16* (51) [56]
Sternebrae			
Reduced ossification	1 (1) [1]	1 (1) [1]	11* (22) [28]
Total[c]	9 (13) [10]	12 (14) [13]	17* (40) [47]
Vertebrae			
Reduced ossification	0	0	15* (44) [58]
Misaligned centra	0	2 (4) [4]	19* (61) [74]
Extra	1 (1) [1]	0	10* (15) [21]
Total	1 (1) [1]	2 (4) [4]	19* (68) [81]
Ribs			
Thoraco-lumbar	8 (10) [7]	3 (3) [4]	15* (35) [42]
Total[d]	8 (10) [7]	3 (3) [4]	16* (38) [45]
Appendicular skeleton			
Reduced ossification	1 (1) [1]	6* (13) [12]	15* (41) [53]

[a]Hardin et al. (1986).
[b]Total malformations represents the sum of abnormal thoracic arch, missing sacrococcygeal vertebrae, rudimentary cervical ribs, and wavy/fused ribs (unilateral and bilateral).
[c]Total sternebrae variations represents the sum of reduced ossification and misaligned sternebrae.
[d]Total rib variations represents the sum of reduced ossification and thoraco-lumbar variations.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Fisher's exact test; the litter was the statistical unit of comparison).

Table B-15. Visceral Malformations in Litters of Sprague-Dawley Rats Exposed to DGME by Gavage on GDs 7−16[a]

Endpoint	Exposure Group (mg/kg-d)		
	0	**720**	**2,165**
Number of litters (fetuses) examined	22 (129)	21 (115)	21 (82)
Number of litters (fetuses) with malformations[b] [% fetuses affected]	3 (3) [3]	4 (4) [3]	16* (37) [50]
Cardiovascular			
Double aortic arch[c]	0	0	7* (9) [12]
Right aortic arch	0	1 (1) [1]	6* (6) [10]
Ventricular septal defect	0	0	14* (27) [39]
Total[d]	0	1 (1) [1]	15* (33) [46]
Number of litters (fetuses) with variations[e] [% fetuses affected]	5 (7) [6]	10 (14) [17]	12* (19) [25]
Urinary			
Dilated renal pelvis	2 (4) [3]	8* (11) [14]	12* (17) [23]
Total[f]	5 (7) [6]	9 (13) [16]	12* (18) [24]

[a]Hardin et al. (1986).
[b]Total malformations represents the sum of cardiovascular (double aortic arch, right aortic arch, right ductus arteriosis, and ventricular septal defect), brain (hydrocephalus), eye (folded retina, anophthalmia, and microphthalmia), and urinary (hydroureter and hydronephrosis) malformations.
[c]Ascending aorta bifurcated to form a vascular ring around the trachea and esophagus, then reformed as a single descending aorta.
[d]Total cardiovascular malformations represents the sum of double aortic arch, right aortic arch, right ductus arteriosis, and ventricular septal defect.
[e]Total variations represents the sum of cardiovascular (missing innominate) and urinary (dilated renal pelvis and dilated ureter) variations.
[f]Total urinary variations represents the sum of dilated renal pelvis and dilated ureter.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Fisher's exact test; the litter was the statistical unit of comparison).

Table B-16. Selected Litter Data of Pregnant Wistar Rats Exposed to DGME by Gavage on GDs 7−17[a]

Endpoint	Exposure Group (mg/kg-d)							
	0	**125**	**250**	**500**	**1,000**	**2,000**	**3,000**	**4,000**
Number of dams	6	5	4	4	5	6	6	5
Number of live fetuses[b]	14.7 ± 0.5	14.0 ± 0.6 (−5%)	14.3 ± 0.9 (−3%)	13.8 ± 0.8 (−6%)	12.8 ± 1.1 (−13%)	5.2 ± 1.3[c] (−65%)	0* (−100%)	0* (−100%)
Incidence of dead or resorbed fetuses (%)								
Early stage	2.2	6.7	3.3	3.5	7.9	44.0	96.7	100.0*
Late stage	0	0	1.7	1.8	8.0	21.1*	3.3	0
Fetal weight (g)[b]								
Male	3.2 ± 0.08	3.1 ± 0.06 (−3%)	3.1 ± 0.06 (−3%)	3.4 ± 0.38 (+6%)	2.7 ± 0.07 (−13%)	2.2 ± 0.04* (−31%)	NDr[c]	NDr
Female	3.0 ± 0.09	2.8 ± 0.10 (−7%)	3.0 ± 0.04 (0%)	3.2 ± 0.39 (+7%)	2.5 ± 0.06 (−17%)	2.2 ± 0.11 (−27%)	NDr	NDr
Number of litters (fetuses) examined	6 (88)	5 (70)	4 (57)	4 (55)	4 (64)	6 (31)	NDr	NDr
Number of litters (fetuses) with external malformations[d] [% fetuses affected]	0	0	0	0	1 (1) [2]	2 (3) [13]	NDr	NDr
Number of litters (fetuses) with external anomalies[e] [% fetuses affected]	0	0	0	0	0	3 (5) [18]	NDr	NDr

[a]Yamano et al. (1993).
[b]Values expressed as litter mean ± SE (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
[c]NDr = not determined; all embryos resorbed at these exposure levels.
[d]Malformations observed included omphalocele, anasarca, and anury.
[e]Anomaly observed was dorsum subcutaneous hematoma.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors (Dunnett's or Scheffé's multiple comparison test; litter was statistical unit of comparison).

Table B-17. Selected Effects on Pregnant Wistar Rats and Their Fetuses after Exposure to DGME by Gavage on GDs 7−17[a]

Endpoint	Exposure Group (mg/kg-d)			
	0	200	600	1,800
Number of dams	14	14	14	14
Body weight (g)[b]	336 ± 4.51	331 ± 6.11 (−1%)	328 ± 6.23 (−2%)	317 ± 4.69* (−6%)
Thymus weight (mg)[b]	228 ± 7.32	208 ± 7.39 (−9%)	218 ± 11.45 (−4%)	181 ± 8.02* (−21%)
Number of live fetuses/litter[b]	13.5 ± 0.9	12.6 ± 1.0 (−7%)	12.9 ± 1.1 (−4%)	7.9 ± 0.9* (−41%)
Percent dead or resorbed fetuses				
Early stage	6.9	7.0	5.1	21.3*
Late stage	0	0	1.7	24.8*
Fetal weight (g)[b]				
Male	3.3 ± 0.17	2.9 ± 0.14 (−12%)	2.6 ± 0.12* (−21%)	2.1 ± 0.06* (−36%)
Female	3.1 ± 0.15	2.8 ± 0.13 (−10%)	2.5 ± 0.13* (−19%)	2.0 ± 0.05* (−35%)

[a]Yamano et al. (1993).
[b]Values expressed as litter mean ± SE (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different at $p < 0.05$), as reported by the study authors (Dunnett's or Scheffé's multiple comparison test; litter was statistical unit of comparison).

Table B-18. External Malformations and Anomalies in Fetuses of Wistar Rats Exposed to DGME by Gavage on GDs 7−17[a]

Endpoint	Exposure Group (mg/kg-d)			
	0	200	600	1,800
Number of litters examined	14	14	14	14
Number of litters (fetuses) examined	14 (189)	14 (176)	14 (181)	14 (111)
Number of litters (fetuses) with malformations[b] [% fetuses affected]	0	0	0	9* (12) [14.1]
Anasarca	0	0	0	7* (7) [8.7]
Anury	0	0	0	7* (8) [9.4]
Number of litters (fetuses) with anomalies[c] [% fetuses affected]	0	0	0	7* (15) [13.5]
Dorsum subcutaneous hematoma	0	0	0	7* (15) [13.5]

[a]Yamano et al. (1993).
[b]Malformations observed included anasarca, anury, and peromelia.
[c]Anomaly observed was dorsum subcutaneous hematoma.
*Statistically significantly different at $p < 0.05$), as reported by the study authors (statistical test not reported; litter was the unit of comparison).

Table B-19. Visceral Observations of Fetuses from Wistar Rat Dams Exposed to DGME by Gavage on GDs 7−17[a]

Endpoint	Exposure Group (mg/kg-d)			
	0	**200**	**600**	**1,800**
Number of litters (fetuses) examined	14 (98)	14 (91)	14 (93)	14 (59)
Number of litters (fetuses) with visceral malformations[b] [% fetuses affected]	0	0	1 (1) [2.4]	9* (18) [28.0]
Right aortic arch	0	0	0	4* (5) [9.6]
Ventricular septal defect	0	0	1 (1) [2.4]	6* (13) [18.4]
% of litters (fetuses) with visceral variations[c] [% fetuses affected]	3 (4) [3.5]	5 (5) [5.0]	13* (32) [35.3]	14* (59) [100.0]
Thymic remnant in the neck				
Unilateral	1 (1) [0.7]	2 (2) [2.0]	11* (20) [20.6]	5 (8) [11.1]
Bilateral	0	0	1 (2) [4.8]	14* (51) [88.9]
Total	1 (1) [0.7]	2 (2) [2.0]	12* (22) [25.4]	14* (59) [100.0]
Dilated renal pelvis				
Unilateral	2 (3) [2.8]	2 (2) [2.1]	6 (10) [11.4]	11* (19) [36.4]
Bilateral	0	0	1 (1) [0.9]	6* (11) [16.4]
Total	2 (3) [2.8]	2 (2) [2.1]	6 (11) [12.3]	13* (30) [52.8]

[a]Yamano et al. (1993).
[b]Malformations observed included double aortic arch, right aortic arch, ventricular septal defect, and agenesis of ductus arteriosus.
[c]Variations observed included thymic remnant in the neck (unilateral and bilateral), dilated renal pelvis (unilateral and bilateral), and kinked ureter.
*Statistically significantly different at $p < 0.05$), as reported by the study authors (statistical test not reported; litter was the unit of comparison).

Table B-20. Skeletal Observations of Fetuses from Wistar Rat Dams Exposed to DGME by Gavage on GDs 7−17[a]

Endpoint	Exposure Group (mg/kg-d)			
	0	**200**	**600**	**1,800**
Number of litters (fetuses) examined	14 (91)	14 (85)	14 (88)	14 (52)
Number of litters (fetuses) with skeletal malformations[b] [% fetuses affected]	0	0	0	5* (5) [13.9]
Agenesis of sacro-coccygeal vertebrae	0	0	0	4* (4) [10.4]
Number of litters (fetuses) with skeletal variations [% fetuses affected][c]	3 (3) [3.2]	1 (1) [1.2]	5 (6) [5.8]	14* (49) [96.2]
Splitting of vertebral bodies				
Thoracic	0	0	0	14* (33) [69.9]
Lumbar	0	1 (1) [1.2]	1 (1) [1.0]	13* (38) [78.4]
Incomplete ossification of occipitale	1 (1) [0.9]	0	2 (3) [2.8]	4* (44) [85.5]
Degree of ossification[d]				
Number of sternebrae ossified	4.2 ± 0.22	3.6 ± 0.19 (−14%)	2.8 ± 0.24* (−33%)	0.3 ± 0.11* (−93%)
Number of proximal and middle phalanges ossified				
Fore limb	3.6 ± 0.34	3.2 ± 0.22 (−11%)	2.9 ± 0.17 (−19%)	1.6 ± 0.12* (−56%)
Hind limb	3.9 ± 0.04	3.8 ± 0.08 (−3%)	3.5 ± 0.11 (−10%)	2.0 ± 0.19* (−49%)
Number of ossification centers of vertebrae				
Thoracic	12.6 ± 0.09	12.2 ± 0.08 (−3%)	11.7 ± 0.15* (−7%)	9.0 ± 0.24* (−29%)
Lumbar	6.0	6.0 (0%)	6.0 (0%)	5.3 ± 0.18* (−12%)
Sacral and caudal	6.7 ± 0.22	5.9 ± 0.19 (−12%)	4.2 ± 0.29* (−37%)	1.1 ± 0.21* (−84%)

[a]Yamano et al. (1993).
[b]Malformations observed included agenesis of digitorum pedis and manus and agenesis of sacro-coccygeal vertebrae.
[c]Variations observed included cervical ribs, rudimentary lumbar ribs, splitting of vertebral bodies (thoracic and lumbar), and incomplete ossification of occipitale.
[d]Values expressed as litter mean ± SE (% change compared with control); % change from control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different compared with controls at $p < 0.05$), as reported by the study authors (dichotomous data statistical test not reported; continuous data: Dunnett's or Scheffé's multiple comparison test; litter was statistical unit of comparison).

Table B-21. Postnatal Observations of Offspring from Wistar Rat Dams Exposed to DGME by Gavage on GDs 7−17[a]

Endpoint	Exposure Group (mg/kg-d)			
	0	**200**	**600**	**1,800**
Number of dams	8	8	8	8
Duration of gestation (days)[b]	22.1 ± 0.13	22.4 ± 0.18 (+1%)	22.5 ± 0.19 (+2%)	23.8 ± 0.25* (+8%)
Number of live pups/litter[b]	12.5 ± 0.96	12.6 ± 0.60 (+1%)	11.6 ± 1.18 (−7%)	4.6 ± 0.82* (−63%)
Viability at PND 4[c]	92	94.1	62.4	5.4*
Viability at PND 21[d]	100	98.4	100	100
Number of litters (fetuses) examined	8 (100)	8 (101)	8 (93)	8 (37)
Number of litters (fetuses) with external malformations[e] [% fetuses affected]	0	1 (1) [0.9]	2 (2) [3.0]	1 (1) [3.1]

[a]Yamano et al. (1993).
[b]Values expressed as litter mean ± SE (% change compared with control); % change control = [(treatment mean − control mean)/control mean] × 100.
[c](Number of offspring on PND 4 ÷ number of offspring on PND 0) × 100.
[d](Number of offspring on PND 21 ÷ number of offspring on PND 4) × 100.
[e]Malformations observed included anury.
*Statistically significantly different from controls at $p < 0.05$), as reported by the study authors (Dunnett's or Scheffé's multiple comparison test; litter was statistical unit of comparison).

PND = postnatal day

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE FOR DICHOTOMOUS DATA

The BMD modeling of dichotomous developmental toxicity data was conducted with the U.S. EPA's BMDS (Version 2.5). For these data, all of the dichotomous models (i.e., Gamma, Multistage, Logistic, Log-logistic, Probit, Log-probit, and Weibull models) available within the software were fit using a BMR of 10% extra risk first. 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. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different models varied greater than three-fold; otherwise, the BMDL from the model with the lowest AIC was selected as a potential POD from which to derive a p-RfD. Once the final model was selected, the same data set was fit with the final model with a BMR of 5% extra risk to estimate $BMDL_{05}$. The tables in Appendix C present the results for the final model with BMR of 5% and results with BMRs of 10% extra risk for comparison purpose.

MODELING PROCEDURE FOR CONTINUOUS DATA

The BMD modeling of continuous data was conducted with the U.S. EPA's BMDS (Version 2.5). For these data, all continuous models available within the software were fit using a default BMR of 1 SD relative risk. For changes in adult body weight, a BMR of 10% change relative to the control mean was also used. However, for changes in fetal body weight, a BMR of 5% change relative to the control mean was used. An adequate fit was judged based on the 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. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was constant. If a constant 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 constant 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 nonconstant variance. If this nonconstant variance model did not adequately fit the variance 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 BMDL was selected if the BMDLs estimated from different models varied greater than three-fold; otherwise, the BMDL from the model with the lowest AIC was selected as a potential POD from which to derive a p-RfD.

Data sets for the most sensitive developmental endpoints observed in the coprincipal studies of rats exposed orally to DGME during gestation (Yamano et al., 1993; Hardin et al., 1986) were selected to determine potential PODs for the p-RfD, using BMD analysis. Data for the endpoints are presented in Table 7. Several models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <two- to three-fold), so the model with the lowest AIC was selected (the AIC for the 1-degree Multistage model was slightly less than the AIC of the LogProbit model, so the former was selected).

Table C-1. Modeling Results for Incidence Data for Number of Litters with Reduced Cranial Ossification from Sprague-Dawley Rats Exposed to DGME by Gavage on GDs 7−16[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residuals[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[d]	0	0	NA	0.00	75.94	184.22	108.00
Logistic	1	0.56	0.46	−0.43	74.50	317.42	227.64
LogLogistic[e]	0	0	NA	0.00	75.94	252.76	58.25
LogProbit[e]	1	0.01	0.92	−0.02	73.952	294.35	191.51
Multistage (1-degree)[f]	**1**	**0.01**	**0.93**	**0.02**	**73.950**	**164.11**	**107.95**
Multistage (2-degree)[f]	0	0	NA	0.00	75.94	173.42	108.00
Probit	1	0.55	0.46	−0.41	74.50	311.58	231.94
Weibull[d]	0	0	NA	0.00	75.94	180.95	108.00
						BMD_{05} (mg/kg-d)	$BMDL_{05}$ (mg/kg-d)
Multistage (1-degree)[e,f]	**1**	**0.01**	**0.93**	**0.02**	**73.95**	**79.89**	**52.55**

[a]Hardin et al. (1986)
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group near BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

NA = not applicable

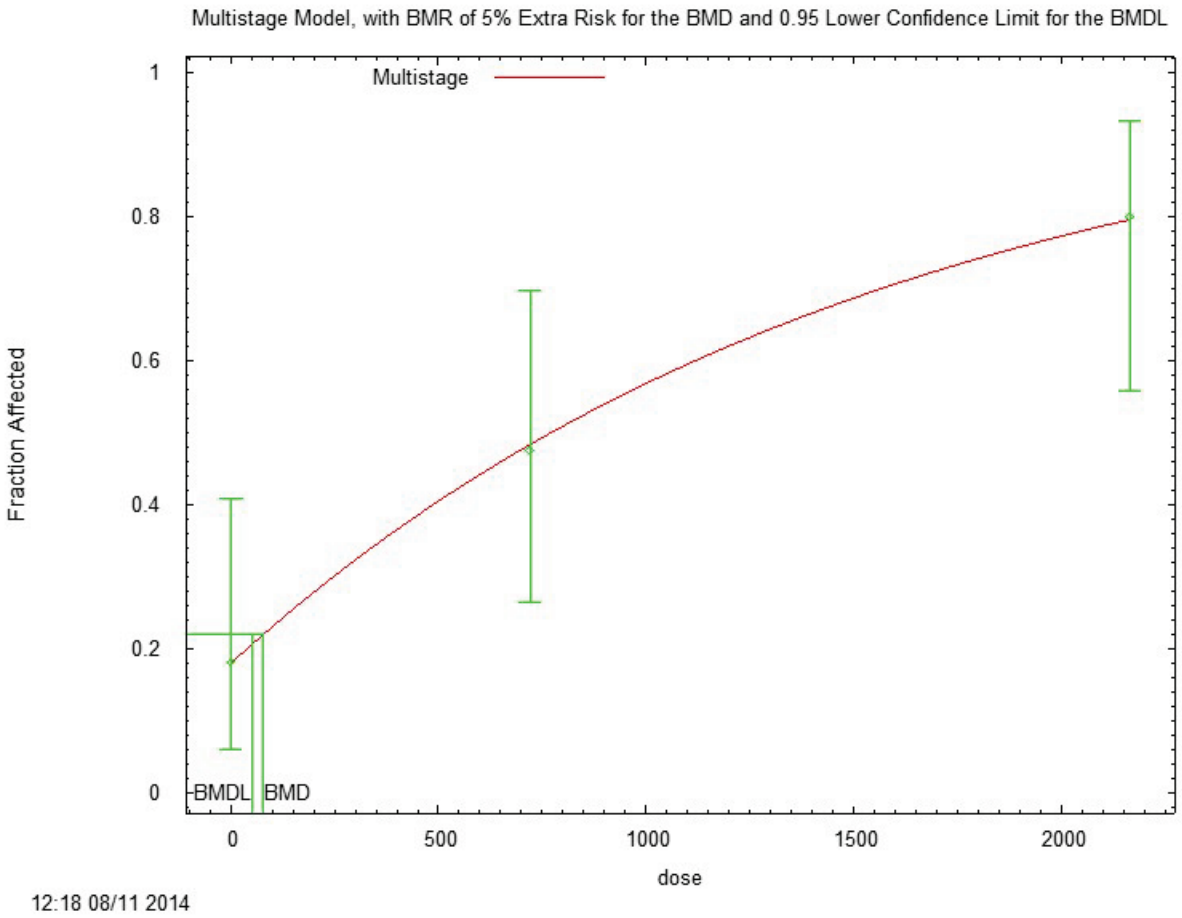

Figure C-1. Incidence of reduced cranial ossification in fetal rats for dams exposed to DGME by gavage on GDs 7−16.

```
=================================================================
          Multistage Model. (Version: 3.4;  Date: 05/02/2014)
          Input Data File:
C:/BMDS250/Data/Diethyleneglycolmonomethylether/Hardin/cranial_oss/mst_cranial_oss_multi1.(d)
          gnuplot Plotting File:
C:/BMDS250/Data/Diethyleneglycolmonomethylether/Hardin/cranial_oss/mst_cranial_oss_multi1.plt
                                                  Mon Aug 11 12:18:17 2014
 =================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive

   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1

 Maximum number of iterations = 500
```

Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0.173867
Beta(1) = 0.000652942

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.58
Beta(1)	-0.58	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.180071	*	*	*
Beta(1)	0.000642014	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.9714	3			
Fitted model	-34.975	2	0.00723248	1	0.9322
Reduced model	-43.5968	1	17.2509	2	0.0001795

AIC: 73.95

goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1801	3.962	4.000	22.000	0.021
720.0000	0.4836	10.155	10.000	21.000	-0.068
2165.0000	0.7958	15.915	16.000	20.000	0.047

Chi^2 = 0.01 d.f. = 1 P-value = 0.9323

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 79.8944

BMDL = 52.5523

BMDU = 140.161

Taken together, (52.5523, 140.161) is a 90% two-sided confidence interval for the BMD

For number of litters with dilated renal pelvis from S-D rats, all models provided adequate fit to the data. BMDLs for models providing adequate fit were judged to be sufficiently close (differed by <three-fold), so the model with the lowest AIC (and also the lowest BMDL) was selected (LogLogistic).

Table C-2. Modeling Results for Incidence Data for Number of Litters with Dilated Renal Pelvis from Sprague-Dawley Rats Exposed to DGME by Gavage on GDs 7−16[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residuals[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[d]	1	0.52	0.47	−0.19	74.51	274.09	175.15
Logistic	1	2.05	0.15	1.09	76.08	546.91	393.28
LogLogistic[e]	**1**	**0.1**	**0.75**	**−0.05**	**74.09**	**196.17**	**105.81**
LogProbit[e]	1	1.47	0.23	0.93	75.42	466.22	304.73
Multistage (1-degree)[e]	1	0.52	0.47	−0.19	74.51	274.08	175.15
Multistage (2-degree)[e]	1	0.52	0.47	−0.19	74.51	274.08	175.15
Probit	1	1.91	0.17	1.08	75.93	517.85	378.99
Weibull[d]	1	0.52	0.47	−0.19	74.51	274.08	175.15
						BMD_{05} (mg/kg-d)	**$BMDL_{05}$ (mg/kg-d)**
LogLogistic[e]	**1**	**0.1**	**0.75**	**−0.05**	**74.09**	**92.92**	**50.12**

[a]Hardin et al. (1986).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group near BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.

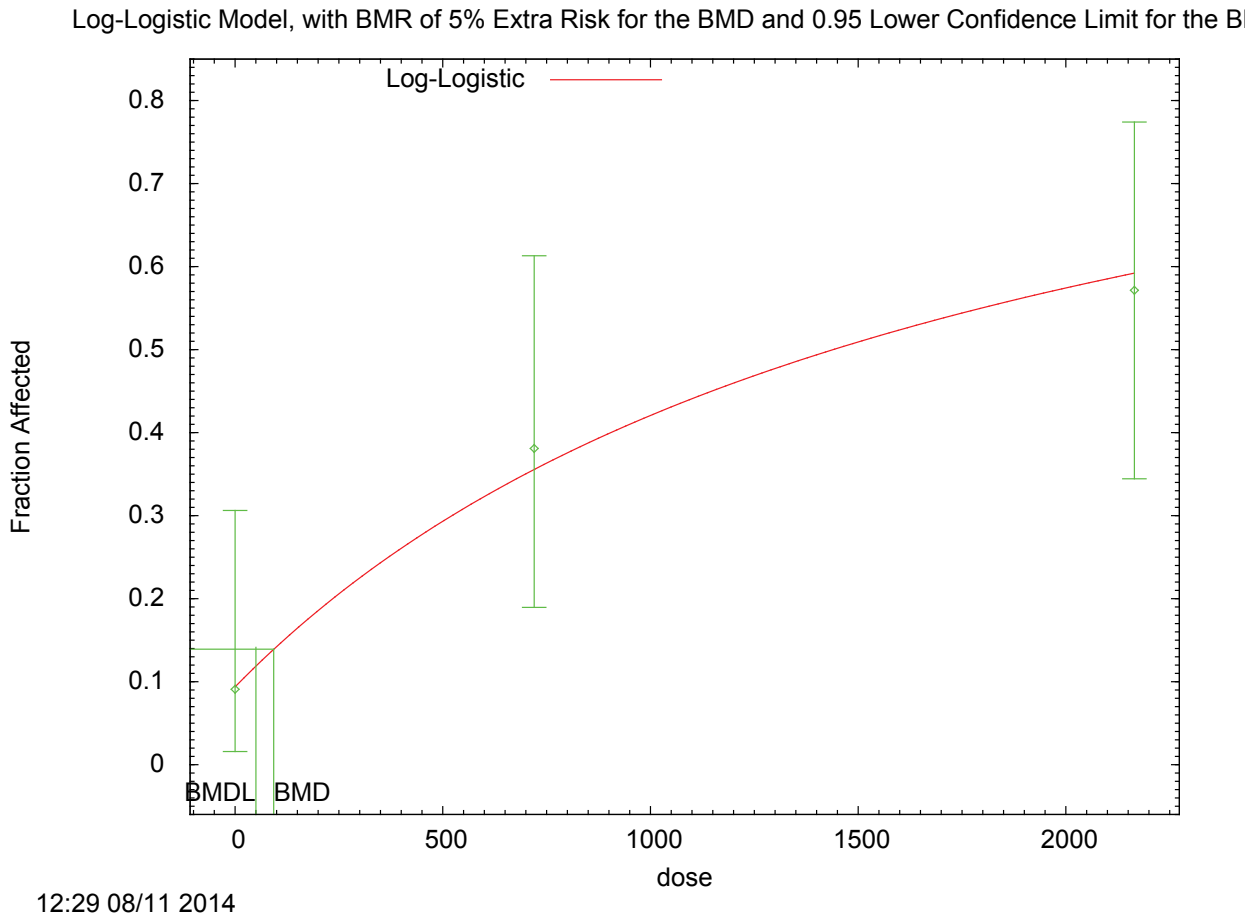

Figure C-2. Incidence of dilated renal pelvis in fetal rats for dams exposed to DGME by gavage on GDs 7−16.

```
 ================================================================
         Logistic Model. (Version: 2.14; Date: 2/28/2013)
         Input Data File:
C:/BMDS250/Data/Diethyleneglycolmonomethylether/Hardin/renal_pelvis_dilation/lnl_renal_pelvis_dil
ation_Lnl-BMR10-Restrict.(d)
         gnuplot Plotting File:
C:/BMDS250/Data/Diethyleneglycolmonomethylether/Hardin/renal_pelvis_dilation/lnl_renal_pelvis_dil
ation_Lnl-BMR10-Restrict.plt
                                                Mon Aug 11 12:29:47 2014
 ================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.0909091
intercept = -7.42199
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	background	intercept
background	1	-0.44
intercept	-0.44	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0938427	*	*	*
intercept	-7.4762	*	*	*
slope	1	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.9982	3			
Fitted model	-35.0468	2	0.097356	1	0.755
Reduced model	-41.1835	1	12.3706	2	0.002059

AIC: 74.0937

goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0938	2.065	2.000	22	-0.047
720.0000	0.3563	7.483	8.000	21	0.236
2165.0000	0.5930	12.452	12.000	21	-0.201

Chi^2 = 0.10 d.f. = 1 P-value = 0.7541

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 92.9219

BMDL = 50.1218

For data on thymus remnants in the neck in fetuses from Wistar rat dams, all models (except for the 1-degree multistage) provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <two- to three-fold), so the model with the lowest AIC was selected (Logistic).

Table C-3. Modeling Results for Incidence Data for Thymic Remnants in the Neck in Fetuses from Wistar Rat Dams Exposed to DGME by Gavage on GDs 7−17[a]

Model	DF	χ^2	χ2 Goodness-of-Fit p-Value[b]	Scaled Residuals[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[d]	1	0.00	1.00	0.00	36.17	215.92	96.47
Logistic	**2**	**0.43**	**0.81**	**−0.40**	**34.57**	**158.66**	**99.32**
LogLogistic[e]	1	0.04	0.85	0.05	36.24	220.57	116.91
LogProbit[f]	1	0.00	0.95	0.01	36.18	214.14	118.78
Multistage (1-degree)[f]	2	4.85	0.09	0.39	39.92	48.24	31.92
Multistage (2-degree)[f]	2	0.62	0.73	−0.67	34.84	149.75	64.77
Multistage (3-degree)[f]	1	0.00	1.00	0.00	36.17	220.57	65.49
Probit	2	0.69	0.71	−0.55	34.82	142.38	92.22
Weibull[d]	1	0.00	1.00	0.00	36.17	220.11	88.43
						BMD_{05} (mg/kg-d)	**$BMDL_{05}$ (mg/kg-d)**
Logistic	**2**	**0.43**	**0.81**	**−0.40**	**34.57**	**99.06**	**55.41**

[a]Yamano et al. (1993).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group near BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

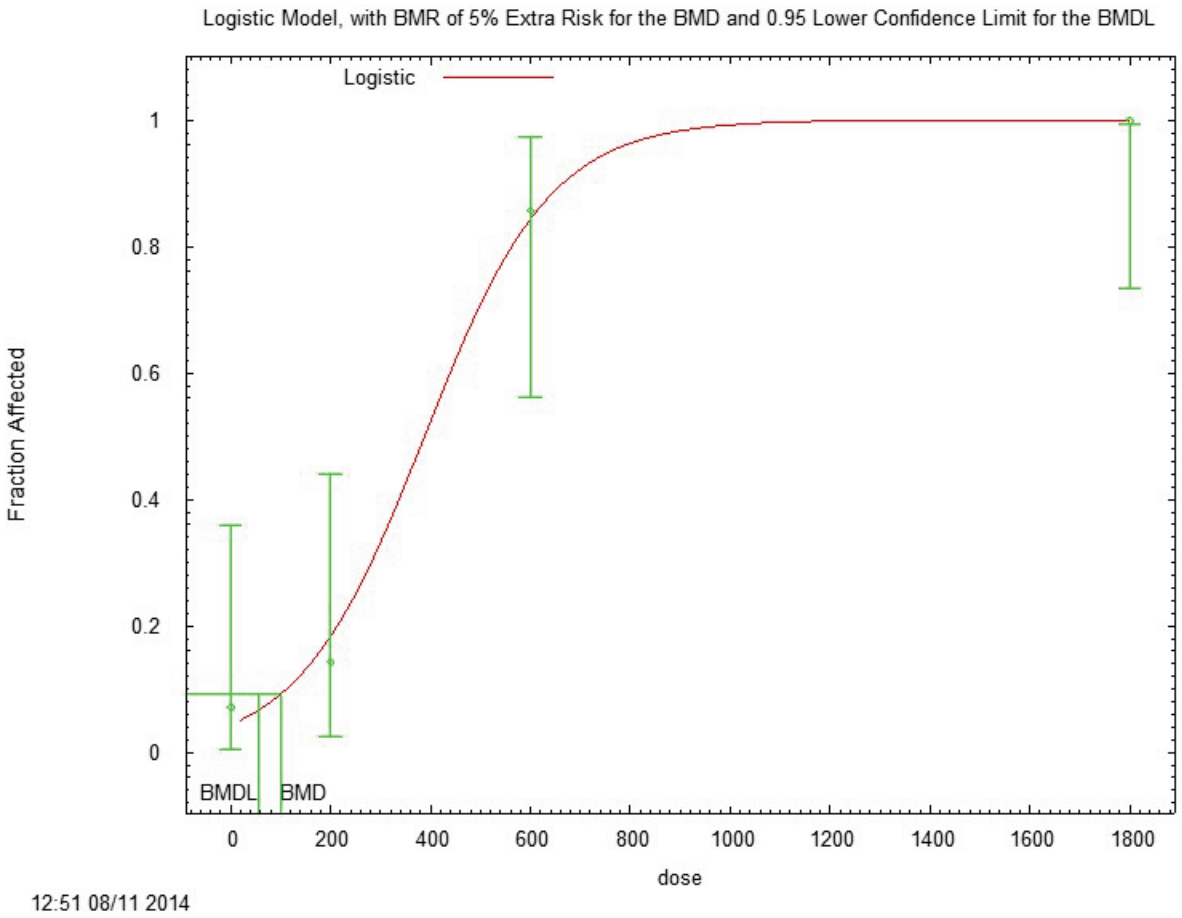

Figure C-3. Incidence of thymic remnant in the neck in fetal rats for dams exposed to DGME by gavage on GDs 7−17.

```
BMDS_Model_Run
=============================================================================
         Logistic Model. (Version: 2.14; Date: 2/28/2013)
         Input Data File:
C:/BMDS250/Data/Diethyleneglycolmonomethylether/Yamano/thymic_remnant_neck/log_thymicremnant_Log-
BMR05.(d)
         gnuplot Plotting File:
C:/BMDS250/Data/Diethyleneglycolmonomethylether/Yamano/thymic_remnant_neck/log_thymicremnant_Log-
BMR05.plt
                                                    Mon Aug 11 12:51:21 2014
=============================================================================
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = 1/[1+EXP(-intercept-slope*dose)]

   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
```

```
                    background =            0   Specified
                     intercept =     -1.68894
                         slope =   0.00304839


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -background
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

             intercept        slope

 intercept            1        -0.83

     slope        -0.83            1

                                Parameter Estimates

                                                                95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     intercept         -3.07755         0.839219           -4.72239            -1.43271
         slope       0.00793681       0.00206455          0.00389037           0.0119833

                          Analysis of Deviance Table

      Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
    Full model         -15.0857         4
   Fitted model        -15.2854         2      0.399343      2           0.819
  Reduced model        -38.7805         1       47.3896      3         <.0001

          AIC:         34.5708

                                goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0440         0.617     1.000          14        0.499
  200.0000     0.1839         2.575     2.000          14       -0.396
  600.0000     0.8435        11.809    12.000          14        0.140
 1800.0000     1.0000        14.000    14.000          14        0.014

 Chi^2 = 0.43      d.f. = 2        P-value = 0.8080

   Benchmark Dose Computation

Specified effect =           0.05

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        99.0554

            BMDL =        55.4101
```

APPENDIX D. REFERENCES

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