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Provisional Peer-Reviewed Toxicity Values for

Diethylene Glycol Monoethyl Ether (DGEE)
(CASRN 111-90-0)

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

Commonly Used Abbreviations

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR DIETHYLENE GLYCOL MONOETHYL ETHER (CASRN 111-90-0)

Background

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

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

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

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

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment,

Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

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

INTRODUCTION

Diethylene glycol monoethyl ether (DGEE; see Fig. 1) is a colorless liquid with a molecular weight of 137.17 g/mol and a density of 0.989 g/mL. It is miscible in water (at 25°C) and organic solvents. It is used mainly as a solvent in the manufacture of cellulose esters, lacquers and paint thinners, protective coatings, textile and printing dyes, hydraulic brake fluids, and cosmetics and toiletries. It is also an inert ingredient in many pesticide formulations (HSDB, 2008).

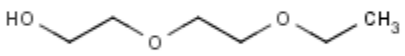

Figure 1. Chemical Structure of DGEE

There is no RfD for DGEE on IRIS (U.S. EPA, 2008). Subchronic and chronic oral RfD values of 5E+0 and 2E+0 mg/kg-day, respectively, are listed for DGEE in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997). The subchronic RfD was derived by applying an uncertainty factor (UF) of 100 to a NOAEL of 500 mg/kg-day[1] (with an associated LOAEL of 2500 mg/kg-day) for kidney and testicular effects from a 90-day dietary study in rats (Hall et al., 1966). The chronic RfD based on a 3-generation reproduction study was derived by applying a UF of 100 to a NOAEL of 200 mg/kg-day (with an associated LOAEL of 950 mg/kg-day) for kidney effects from a 2-year drinking water study in rats (Smyth et al., 1964). The source for both of these RfDs is a Health Effects Assessment (HEA) on glycol ethers (U.S. EPA, 1984), which is the only document including DGEE in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a). Subchronic and chronic oral RfD values of 2E+0 and 2E-1 mg/kg-day, respectively, were derived for DGEE in an unpublished draft (SRC, 1992) Health and Environmental Effects Document (HEED) on glycol ethers based on a subchronic NOAEL of 167 mg/kg-day in pigs (Gaunt et al., 1968) and a UF of 100 (subchronic RfD) or 1000 (chronic RfD). No RfD is available for DGEE on the Drinking Water

[1] Doses of 125, 500, and 2500 mg/kg-day, based on a food factor of 0.05 kg food/kg body weight, were estimated in the HEA (U.S. EPA, 1984) that was used as the source of the subchronic RfD for DGEE listed in the HEAST (U.S. EPA, 1997).

Standards and Health Advisories list (U.S. EPA, 2006), and no Agency for Toxic Substances Disease Registry (ATSDR) toxicological profile (ATSDR, 2008) or an Environmental Health Criteria document (WHO, 2008) is available for DGEE. The Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives evaluated DGEE due to its use as a carrier solvent for flavoring; no acceptable daily intake (ADI) was derived due to the lack of an adequate chronic carcinogenicity study in rats or mice (WHO 1976, 1993, 1995).

There are no RfC values for DGEE available on IRIS (U.S. EPA, 2008), listed in the HEAST (U.S. EPA, 1997) or derived in the HEA or HEED on glycol ethers (U.S. EPA, 1984; SRC 1992). No occupational exposure limits have been recommended or promulgated by the American Conference for Governmental Industrial Hygienists (ACGIH, 2007), National Institute of Occupational Safety and Health (NIOSH, 2005), or Occupational Safety and Health Administration (OSHA, 2008).

There is no carcinogenicity assessment for DGEE available on IRIS (U.S. EPA, 2008). DGEE is not listed in the HEAST cancer table (U.S. EPA, 1997) or indicated in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The carcinogenicity of DGEE has not been assessed by the International Agency for Research on Cancer (IARC, 2008) or World Health Organization (WHO, 2008), or tested by the National Toxicology Program (NTP, 2005, 2008).

Literature searches were conducted from 1960s through October 2008 in the following databases for studies relevant to the derivation of provisional toxicity values for DGEE: TOXLINE, MEDLINE, TSCATS1/2, RTECS, CCRIS, DART, HSDB, GENETOX, CCRIS, CHEMABS, BIOSIS, and Current Contents (May–October 2008). An OECD SIDS Initial Assessment Report (OECD, 2005) was also consulted for relevant information. An updated literature seach was conducted through June 2009.

REVIEW OF PERTINENT DATA

Human Studies

No pertinent data were located regarding health effects of DGEE in humans following oral or inhalation exposure.

Animal Studies

Oral Exposure

Subchronic Studies—Groups of five male and five female Sherman rats were exposed to DGEE (purity not reported) in drinking water at reported doses of 0, 210, 490, 870, 1770, or 3880 mg/kg-day for 30 days in a briefly summarized range-finding study (Smyth and Carpenter, 1948). Endpoints included mortality, water consumption, body weight, and histology of the liver, kidney, spleen, and testis. Water consumption was reduced at ≥870 mg/kg-day (magnitude unspecified), and reduced growth (no details given) and histopathological changes (unspecified) occurred at ≥1770 mg/kg-day. No effects were observed at ≤490 mg/kg-day. The limited scope and inadequate reporting of this study preclude identification of a NOAEL or LOAEL.

Groups of 10 male albino rats were exposed to DGEE (purity >99.5%) by gavage at doses of 0, 1340, 2680, or 5360 mg/kg-day (equivalent to 0, 1/8, 1/4, or 1/2 of the acute oral

LD_{50}), 5 days/week for 6 weeks (Kodak, 1982). Endpoints evaluated included mortality, clinical signs, body weight, organ weights (liver, kidneys, heart, testes, brain, and spleen), hematology (red blood cell count [RBC], hematocrit [Hct], hemoglobin [Hgb], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], and total and differential white blood cell count [WBC]), clinical chemistry (aspartate aminotransferase [AST, also called SGOT], alanine aminotransferase [ALT, also called SGPT], alkaline phosphatase [ALP], lactate dehydrogenase [LDH], blood urea nitrogen [BUN], creatinine, glucose), and gross and histological examination of 30 tissues. Significant mortality (7/10 rats died within 24 days) and clinical signs of toxicity (including bloody urine, lethargy, prostration, piloerection, unkempt hair coat, and blood near the mouth and nose) were observed in the high-dose group. One death each also occurred in the low- and mid-dose groups, but these were not considered chemical-related by the researchers. Body weights were lower than controls throughout the study in the high-dose group, although the differences were not statistically significant; at necropsy, the deficit in high-dose rats was approximately 14%. Table 1 shows the selected changes in hematology, clinical chemistry, organ weights, and pathology. Hematological changes reported in the study included reduced mean RBC counts, with corresponding increases in MCV and MCH, and reduced MCHC in the high-dose group. The only significant serum chemistry change was an increase in ALP in the high-dose group. Small, but statistically significant increases in relative, but not absolute, liver and kidney weights in the high- and mid-dose groups were considered by the researchers to reflect changes in body weight. Histological examinations showed hyperkeratosis of the stomach, hepatic anisokaryosis, and loss of cytoplasmic basophilia, splenic congestion, and proteinaceous casts with hemosiderin in the kidneys. Lesions occurred primarily in the high-dose animals. The high-dose of 5360 mg/kg-day is a FEL for mortality. The mid-dose of 2680 mg/kg-day appears to be a NOAEL.

Groups of 12 male and 12 female Wistar rats were fed diets containing 0, 0.25, 1.0, or 5.0% DGEE (purity not specified except to note that it contained $\leq$0.4% ethylene glycol) for 90 days (Hall et al., 1966). Doses of 195, 750, or 3750 mg/kg-day in the males and 205, 810, or 4000 mg/kg-day in the females were estimated for this assessment[2]. Endpoints evaluated in the study included body weight, food consumption, hematology (total RBC counts, total and differential WBC counts, hemoglobin, and hematocrit), BUN, urinalysis (pH, AST activity, reducing substances, and protein concentration), organ weights (liver, kidneys, brain, spleen, heart, adrenals and gonads), and gross and histological observations of the organs weighed and 18 other organs. Table 2 shows the dose-related changes. Lower body weight, without an associated reduction in food consumption, was observed in high-dose rats of both sexes at week 12 (17% lower than controls in males, and 10% lower in females). Urinary protein concentration was increased in the male, but not female rats; levels in the males were 0-, 3-, and 8-fold higher than controls in the low-, mid-, and high-dose groups, respectively. Oxalate crystals were observed in urinary sediment of mid- and high-dose males (incidence not reported). Increased urinary AST activity (approximately 46% higher than controls in males and 75% higher in females) was observed at the high dose. Other effects observed in high-dose rats included increased relative (but not absolute) kidney weight in both sexes and increased relative brain and testes weight in males. Increases in organ weights may have been related to the reduced body weight. However, evidence of pathology was observed in the testes, kidney, and liver. Testicular edema was noted in high-dose males (5/12, incidence in controls not reported).

[2] These values are based on mean food consumption and body-weight values reported in the study. Doses of 125, 500, and 2500 mg/kg-day, based on a food factor of 0.05 kg food/kg body weight, were estimated in the HEA (U.S. EPA, 1984) that was used as the source of the subchronic RfD for DGEE listed in the HEAST (U.S. EPA, 1997).

In the kidneys of high-dose animals, hydropic degeneration of renal tubules (2/12 males and 1/12 females; incidence in controls not reported), tubular dilation, inflammatory cell infiltration, and protein in the tubules (incidences not reported but stated to be higher in high- dose group) were noted. Slight-to-moderate fatty changes in the liver reportedly occurred in most high-dose animals (incidences not given). Notably, a male rat in the 3750 mg/kg-day (5% in diet) group died on day 23 after a period of weight loss, and the histological examination following the autopsy showed hydropic degeneration of the kidney tubules and of the liver. The study authors identified 750 mg/kg-day (1% in diet) as a NOEL. Because kidneys are considered as the most sensitive target for DGEE in this study, with effects progressing from an effect level of 750 mg/kg-day (1% in diet) for proteinuria in males to a higher effect level of 3750–4000 mg/kg-day (5% in diet) for oxalate crystal formation, increased urinary AST, increased kidney weight, and kidney lesions in both males and females.. As a result, a LOAEL of 750 mg/kg-day (1% diet) and a NOAEL of 195 mg/kg-day (0.25% in diet) are identified.

Table 1. Selected Findings in Male Albino Rats Treated with DGEE via Gavage 5 Days/Week for 6 Weeks[a]

	Dose in mg/kg-day			
	Control	**1340**	**2680**	**5360**
Hematology, Serum Chemistry, and Terminal Body and Organ Weights (mean ± 1 std. dev.)				
No. Animals Evaluated (survivors at study termination)	10	9	9	3
RBC (10^6 cells)	8.771 ± 0.497	8.729 ± 0.246	8.933 ± 0.469	7.89 ± 0.574 [b]
MCV (Hct/RBC)	53.60 ± 2.98	53.62 ± 2.13	54.06 ± 2.32	62.57 ± 2.66 [b]
MCH (Hgb/RBC)	16.97 ± 0.70	17.16 ± 0.52	16.90 ± 0.61	18.77 ± 0.57 [b]
MCHC (Hgb/Hct)	31.68 ± 0.68	32.02 ± 0.56	31.29 ± 0.53	30.20 ± 0.53 [b]
ALP (U/L)	177.3 ± 43.3	161.9 ± 20.8	152.7 ± 29.3	247 ± 106.1 [b]
Terminal Body Wt (g)	377 ± 34.3	357.9 ± 38.1	348.3 ± 25.3	325.3 ± 5.5
Absolute Liver Wt (g)	10.59 ± 1.39	10.44 ± 1.11	11.12 ± 1.04	11.38 ± 0.14
Relative Liver Wt (% body wt)	2.80 ± 0.18	2.92 ± 0.11	3.19 ± 0.15 [b]	3.50 ± 0.09 [b]
Absolute Kidney Wt (g)	2.83 ± 0.18	2.81 ± 0.30	2.91 ± 0.31	3.20 ± 0.10
Relative Kidney Wt (% body wt)	0.75 ± 0.06	0.79 ± 0.07	0.84 ± 0.06 [b]	0.98 ± 0.02 [b]
Gross and Histologic Pathology (includes early deaths)				
Blood in urinary bladder	0/10	0/10	0/10	4/8[c, d]
Hyperkeratosis of the stomach	0/10	0/10	2/10	7/10[c]
Liver anisokaryosis	0/10	0/10	0/10	7/10[c]
Lack of hepatic cytoplasmic basophilia	0/10	0/10	0/10	4/10
Splenic congestion	0/10	0/10	1/9	5/10[c]
Renal proteinaceous casts, hemosiderin	0/10	0/10	0/10	3/10

[a] Kodak, 1982.
[b] Significantly different from control at $p < 0.05$.
[c] Significantly different from control by Fisher's exact test performed for this review; $p < 0.05$.
[d] Observed only in animals that died before study termination.

Table 2. Changes in Wistar Rats Fed DGEE for 90 Days[a]

Males				
Dose (mg/kg-day)	**Control**	**195**	**750**	**3750**
No. Animals Examined	12	12	12	12
Body Weight at 12 Weeks (g)	473	440	454	393[b]
Relative Organ Weight				
Right Kidney (g/100 g BW)	0.33	0.32	0.34	0.41[b]
Left Kidney (g/100 g BW)	0.33	0.34	0.34	0.39[b]
Testis (g/100 mg BW)	0.38	0.40	0.35	0.45[b]
Brain (g/100 mg BW)	0.45	0.46	0.47	0.52[c]
Urinalysis				
Protein concentration (mg/100 mL)	25	25	70[f]	200[f]
AST activity (IU/mL)	28.5[e]	30.3	31.2	41.8
Females				
Dose (mg/kg-day)	**Control**	**205**	**810**	**4000**
No. Animals Examined	12	12	12	12
Body Weight at week 12 (g)	284	266	296	255[b]
Relative Organ Weight				
Right Kidney (g/100 g BW)	0.36	0.34	0.34	0.40[b]
Left Kidney (g/100 g BW)	0.36	0.33	0.33	0.38[d]
Urinalysis				
AST activity (IU/mL)	20.3[e]	25.2	30.0	35.5

[a] Hall et al., 1966.
[b] Significantly different from control at $p < 0.001$.
[c] Significantly different from control at $p < 0.01$.
[d] Significantly different from control at $p < 0.05$.
[e] No statistical comparison or variability data reported
[f] Significantly different from control by t-test performed for this review; $p < 0.05$.

A series of subchronic toxicity studies was conducted in which CFE rats, CD-1 mice, and "Large White" pigs (no strain reported) of both sexes were fed DGEE (purity not stated; reported to contain up to 0.4% ethylene glycol, 2 ppm arsenic and 10 ppm lead) for 90 days (Gaunt et al., 1968). In the rat study, groups of 15 males and 15 females were fed a diet containing 0, 0.5, or 5.0% DGEE. Doses were 0, 375, and 3950 mg/kg-day in the males and 0, 410, and 4380 mg/kg-day in the females[3]. Endpoints that were evaluated included mortality, food consumption, body weight, organ weights (brain, pituitary, heart, liver, kidneys, adrenals, spleen, and gonads), hematology (RBC counts, total and differential WBC counts, hemoglobin, and hematocrit), serum chemistry (AST and ALT activities), serum urea, urinalysis (color, pH, microscopic constituents, protein and crystal content, reducing substances, bile salts, blood, AST, and kidney concentrating ability), and gross pathology and histology of 23 tissues. Table 3 shows the dose-related changes. There were no statistically or biologically significant effects in low-dose animals of either sex. Effects observed in the high-dose groups included reduced body weight (<10% difference from controls) and increased relative kidney weight (with no changes in absolute kidney weights) in both sexes. Signs of anemia were observed in high-dose animals of both sexes (significantly reduced hemoglobin level in females at 45 days and in males at 90 days; significantly reduced red blood cell count in females at 45 days). Evidence of renal toxicity was obtained from the urinalysis and histopathology findings in the high-dose animals; these included oxalate crystals in the urine of both sexes (incidence data not reported), calcification of the renal cortex in males, and hydropic degeneration in the renal proximal

[3] Approximate time-weighted average chemical intakes, based on reported monthly values.

tubules in the males. The study authors identified the low-dose level of 0.5% as a NOEL. For this review, a NOAEL of 0.5% (males, 375 mg/kg-day; females, 410 mg/kg-day) and LOAEL of 5% (males, 3950 mg/kg-day; females, 4380 mg/kg-day) were identified for signs of anemia and renal toxicity in rats.

Table 3. Changes in CFE Rats Fed DGEE for 90 Days[a]

Males			
Dose (mg/kg-day)	**Control**	**375**	**3950**
No. Animals Examined	15	15	15
Body Weight at 13 Weeks (g)	456	458	426[c]
Hematology			
Hemoglobin concentration: day 90 (g/100 mL)	14.6	13.9	13.4[c]
Relative Organ Weights			
Right kidney (g/100 g BW)	0.35	0.36	0.40[d]
Left kidney (g/100 g BW)	0.35	0.36	0.40[d]
Histopathology			
Hydropic degeneration of renal tubules	0/15	0/15	6/15[e]
Calcification of renal cortex	0/15	0/15	3/15
Females			
Dose (mg/kg-day)	**Control**	**410**	**4380**
No. Animals Examined	15	15	15
Body Weight at 13 Weeks (g)	286	276	269[b]
Hematology			
Hemoglobin concentration: day 45 (g/100 mL)	15.4	14.8	13.2[c]
RBC count: day 45 (10^6/mm^3)	7.86	7.65	7.25[c]
Relative Organ Weights			
Right kidney (g/100 g BW)	0.34	0.36	0.39[d]
Left kidney (g/100 g BW)	0.34	0.36	0.40[d]
Thyroid (g/100 g BW)	7.02	6.67	8.19[b]

[a] Gaunt et al., 1968.
[b] Significantly different from control at $p < 0.05$.
[c] Significantly different from control at $p < 0.01$.
[d] Significantly different from control at $p < 0.001$.
[e] Significantly different from control by Fisher's exact test performed for this review; $p < 0.05$.

In the Gaunt et al. (1968) mouse study, groups of 20 males and 20 females were fed a diet containing 0, 0.2, 0.6, 1.8, or 5.4% DGEE. Doses were 0, 318, 905, 2800, and 8840 mg/kg-day in the males and 0, 350, 1000, 4000, and 10,680 mg/kg-day in the females[4]. Endpoints that were evaluated included mortality, food consumption, body weight, organ weights (brain, heart, liver, kidneys, and spleen), hematology (RBC counts, total and differential WBC counts, hemoglobin and hematocrit), serum chemistry (AST and ALT activities), serum urea, urinalysis (color, pH, microscopic constituents, protein and crystal content, reducing substances, bile salts, blood, AST and kidney concentrating ability), and gross pathology and histology of 23 tissues. Table 4 shows the dose-related changes. Half of the 20 males treated at 8840 mg/kg-day died. Of these, six exhibited hydropic degeneration of the renal tubule, two died from lung infection, and two were cannibalized, precluding determination of cause of death. Inspection of body weight data showed no dose-related changes. Hematology analysis showed significantly ($p < 0.05$) reduced

[4] The values are approximate time-weighted average chemical intakes that were calculated from the monthly intakes reported by the study authors.

RBC counts in high-dose males but no other changes. Increased relative kidney weight was seen in males at ≥2800 mg/kg-day, while increased relative brain (males), and heart, liver and kidney (female) weights were seen at ≥8840 mg/kg-day. Histopathology examination revealed changes in the liver, kidney, and bladder—particularly in high-dose animals. Centrilobular hepatocyte enlargement (with no indication of increased intracellular fat or fluid) was observed at increased incidence in both sexes at ≥8840 mg/kg-day and was also observed in a few males at 2800 mg/kg-day. Kidney changes in mid- and high-dose animals included proximal tubular hydropic degeneration, mucoid degeneration, and tubular degeneration and atrophy, as shown in Table 4. Even though there were areas of tubular degeneration and atrophy in all dose groups including the control group (6/20; see Table 4), they appeared with "greater frequency" at the higher dose levels. Urinary oxalate crystals were seen in males at 8840 mg/kg-day. No exposure-related changes were observed at ≤1000 mg/kg-day in either sex. The study authors identified this dose level as a NOEL. For this review, a NOAEL and LOAEL of 905 and 2800 mg/kg-day, respectively, were identified, based on renal and liver effects in male mice. The high dose of 8840 mg/kg-day is a FEL based on mortality in male mice.

Table 4. Changes in CD-1 Mice Fed DGEE for 90 Days[a]

Males					
Dose (mg/kg-day)	**0**	**318**	**905**	**2800**	**8840**
Mortality	0/20	0/20	0/20	0/20	10/20
Hematology					
RBC counts (10^6/mm^3)	8.69	8.05	8.23	8.36	7.68[b]
Organ Weights					
Relative brain (g/100 g BW)	1.23	1.20	1.26	1.28	1.44[b]
Relative kidney (g/100 g BW)[e]	0.88	0.92	0.98	1.02[b]	1.02[b]
Histopathology					
Centrilobular hepatocyte enlargement in liver	0/20	0/10	0/10	2/20	8/16[f]
Advanced intracellular edema (hydropic degeneration) in kidney	0/20	0/10	0/10	0/20	7/16[f]
Mucoid degeneration in kidney	0/20	0/10	0/10	0/20	4/16[f]
Renal tubular degeneration and atrophy	6/20	0/10	4/10	7/20	13/16[f]
Protein inclusions in lumen of bladder	0/20	0/10	0/10	0/20	3/16
Females					
Dose (mg/kg-day)	**0**	**350**	**1000**	**4000**	**10680**
Organ Weights					
Relative heart (g/100 g BW)	0.43	0.43	0.43	0.45	0.53[d]
Relative liver (g/100 g BW)	4.84	4.88	4.58	4.66	6.17[d]
Relative kidney (g/100 g BW)[e]	0.68	0.64	0.62	0.68	0.80[b]
Histopathology					
Centrilobular hepatocyte enlargement in liver	0/20	0/9	0/10	0/20	5/20[f]
Renal tubular degeneration and atrophy	3/20	0/9	1/10	4/20	8/20

[a] Gaunt et al., 1968.
[b] Significantly different from control at $p < 0.05$.
[c] Significantly different from control at $p < 0.01$.
[d] Significantly different from control at $p < 0.001$.
[e] Mean of right and left kidney weights.
[f] Significantly different from control by Fisher's exact test performed for this review; $p < 0.05$.

These researchers also conducted an experiment using pigs (strain not reported) (Gaunt et al., 1968). Groups of three male and three female 6-week-old animals were fed DGEE in reported dietary doses of 0, 167, 500, or 1500 mg/kg-day for 90 days. The 1500 mg/kg-day dose was reduced to 1000 mg/kg-day on day 21 due to severe toxicity. For this review, the high dose was first represented by 1117 mg/kg-day, which is a time-weighted average (TWA) value reflecting treatment with 1500 mg/kg-day for 21 days and subsequent reduction of the dose to 1000 mg/kg-day. Endpoints that were evaluated included mortality, food consumption, body weight, organ weights (brain, heart, liver, kidneys, adrenals, spleen, thyroid and gonads), hematology (RBC counts, total and differential WBC counts, Hgb and Hct), serum chemistry (AST and ALT activities), serum urea, urinalysis (color, pH, microscopic constituents, protein and crystal content, reducing substances, bile salts, blood, AST and kidney concentrating ability), and gross pathology and histology of 23 tissues. Table 5 shows the dose-related changes. Half of the 6 pigs in the high-dose group were killed *in extremis* or died after exposure to 1500 mg/kg-day for 14–21 days. Effects observed in the pigs that were moribund or died included clinical signs of CNS depression, severe anemia, severe RBC crenation (notching due to shrinkage), gross pulmonary edema, clinical changes indicative of renal toxicity (e.g., increased serum urea levels, and numerous castes and increased protein content in urine), and histopathological damage to the kidneys and liver, including glomerular atrophy, renal tubular hydropic degeneration and desquamation, and extensive hepatic hydropic degeneration. For the surviving animals, no dose-related changes were observed in body weight, organ weight, serum chemistry, or urinalysis. Slight, but not statistically significant, reductions in RBC counts were observed in all groups of treated males. No oxalate crystals were found in the urine of pigs, in contrast to findings in mice and rats. Histopathological effects in the surviving pigs included hydropic degeneration of the renal proximal tubules and hydropic degeneration and fatty changes in the liver at ≥500 mg/kg-day. The study authors identified a NOAEL and LOAEL of 167 and 500 mg/kg-day, respectively, based on kidney and liver lesions in female pigs.

Chronic Studies—Chronic studies of limited quality have been conducted by oral exposure. Groups of 20 albino rats (12 males and 8 females) were exposed to 0 or 2.16% (21,600 ppm) DGEE (purity not reported) in the diet for 2 years (Morris et al., 1942). The 21,600 ppm diet provided an estimated dose of 1840 mg/kg-day[5]. Body-weight gain, food consumption, and survival were monitored. Limited histological examinations (liver, kidney, adrenal, lung, heart, spleen, and testes in all animals, and pancreas, stomach, intestines, and lymph nodes in about half the animals) were performed on animals surviving the longest (number not reported). The only effects reported were testicular enlargement and histopathology (interstitial edema and tubular atrophy) in a few of the exposed males (incidences not reported). The limited scope of this study and poor reporting of methods preclude identification of a NOAEL or LOAEL.

Hanzlik et al. (1947) reported chronic studies in rats and mice. Rats (6 weeks old, strain unspecified) were exposed to 0% (13 males, 8 females) or 1% (10 males, 5 females) DGEE (purity not reported) in drinking water for 2 years. Reported chemical intakes were approximately 1.30 and 1.63 mL/kg-day (approximately 1286 and 1612 mg/kg-day[6]) in the males and females, respectively. Endpoints included clinical condition, food and water consumption, body weight, and gross pathology and histology on unspecified organs from approximately a third of the animals in each group. All of the exposed rats died by the end of 16 months. An unspecified number of deaths occurred by 4 months in the control group. The

[5] A food factor of 0.085 kg food/kg-bw/day was applied to dietary DGEE based on the average of male and female chronic reference values for food consumption and body weight in F344 rats (U.S. EPA, 1987).
[6] This value was calculated based on a density of 0.989 g/mL (HSDB, 2008).

cause of death in the control and treated rats was not reported. No changes in other endpoints were attributable to DGEE. The unexplained deaths in the control group as well as limited scope and inadequate reporting of the study preclude identification of a NOAEL or LOAEL.

Table 5. Changes in Pigs Fed DGEE for 90 Days[a]

Males				
Dose (mg/kg-day)	**Control**	**167**	**500**	**1117[b]**
No. Animals Examined	3	3	3	2
Hematology				
RBC counts (10^6/mm^3)	7.05	6.25	6.12	6.65
Histopathology				
Advanced intracellular edema (hydropic degeneration) and fatty changes in liver	0/3	0/3	0/3	2/2
Hydropic tubule degeneration in kidney	0/3	0/3	0/3	1/2
Females				
Dose (mg/kg-day)	**Control**	**167**	**500**	**1117[b]**
No. Animals Examined	3	3	2[c]	1
Histopathology				
Advanced intracellular edema (hydropic degeneration) and fatty changes in liver	0/3	0/3	1/2	1/1
Hydropic tubule degeneration in kidney	0/3	0/3	1/2	1/1

[a] Gaunt et al., 1968.
[b] Including only animals that survived 90 days of treatment.
[c] Only two females were given 500 mg/kg-day because one died from an intestinal infection during the 2-week acclimatization period before treatment.

In the mouse study, groups of 10 male and 10 female mice (approximately 10 weeks old, strain unspecified) were exposed to 0 or 5% DGEE (purity not reported) in the diet for 20 months (Hanzlik et al., 1947). Reported chemical intakes were approximately 7.54 and 6.14 ml/kg-day (7457 and 6072 mg/kg-day[7]) in the males and females, respectively. Endpoints included clinical condition, food and water consumption, growth rate and gross pathology, and histology in unspecified organs from approximately a third of the animals in each group. Reduced food intake and decrease in body-weight gain with comparison to the control group (data shown graphically) were the only effects observed in the treated mice. The limited scope of this study and poor reporting of methods precludes identification of a NOAEL or LOAEL.

Reproductive/Developmental Studies—A developmental toxicity screening assay was conducted in which groups of 50 pregnant CD-1 mice were treated with 0 or 5500 mg/kg-day of DGEE (99% pure) by gavage in aqueous solution on days 7–14 of gestation (Schuler et al., 1984). Maternal indices were limited to body weight on days 7 and 18 of gestation and day 3 postpartum. Developmental endpoints included pup survival *in utero* (percent of live litters/pregnant survivors), pup perinatal and postnatal survival (numbers of live and dead pups per litter at birth and pup survival to age 2.5 days), and pup body weights (at birth and age 2.5 days). Exposure to DGEE caused 14% maternal mortality and slightly reduced mean pup birth weight (6% lower than controls, $p < 0.05$), but did not affect viability of the litters, or postnatal survival, or weight gain of the pups. The maternal mortality data indicate that 5500 mg/kg-day is a FEL.

[7] A food factor of 0.085 kg food/kg-bw/day was applied to dietary DGEE based on the average of male and female chronic reference values for food consumption and body weight in F344 rats (U.S. EPA, 1987).

Groups of eight male and eight female weanling albino rats were exposed to DGEE ("Carbitol GF", purity not specified but reported to contain <0.2% ethylene glycol) in drinking water at reported chemical intake levels of 0, 10, 40, 200, or 950 mg/kg-day (Smyth et al., 1964). The rats were allowed to breed such that F_1 and F_2 generations received the same dose levels as the parental rats. All surviving rats were killed 718 days after the start of the study; however, the durations of exposure for the F_1 and F_2 generations were not reported. This study is limited by poor reporting of methods and results. Endpoints included growth and survival, limited hematology (RBC and total and differential WBC counts measured four times per year in 2 rats/sex/group) and clinical biochemistry (serum protein, blood urea, and glucose measured at 6 months and 2 years) indices, fertility, gross pathology and histology (kidney and liver in all animals, and adrenal, small intestine, spleen, ovary and testis in unspecified dose groups and number of animals). Effects included reduced growth at ≥200 mg/kg-day, and increased RBCs, increased urinary protein, and gross or histopathological changes (kidney or liver lesions, incidences not reported) at 950 mg/kg-day. It is not clear from the report which specific lesions were observed in DGEE-treated animals or which generation was affected. The report does state that bladder protein calculi were observed in four F_2 males at 950 mg/kg-day (total number of F_2 animals not reported). The study authors identified a maximum safe dosage of 200 mg/kg-day. However, it is not clear if 200 mg/kg-day, which was associated with reduced growth, actually represents a NOAEL. Therefore, the data are inadequate to define effect levels for this study.

Reproductive toxicity was evaluated in orally exposed mice using a continuous breeding protocol (Williams et al., 1990; Lamb and Reel, 1997). DGEE (>99% pure) was provided in drinking water at concentrations of 0, 0.25, 1.25 or 2.5% (2500, 12,500, or 25,000 ppm), which yielded reported average chemical intake estimates of 0, 0.44, 2.2 and 4.4 g/kg-day (0, 440, 2200 and 4400 mg/kg-day), respectively. Groups of 20 male and 20 female mice per dose level (40/sex in control group) were exposed during a l-week pre-cohabitation period and subsequently for 14 weeks as breeding pairs (F_0 generation). The F_0 pairs were then separated and exposed for a further 3 weeks, during which time offspring from the last litter produced by the control and high-dose groups (F_1 generation) were reared and weaned. Endpoints that were examined during the 17-week cohabitation/post-cohabitation periods included clinical signs and body weights in parental mice, gestation length, number of fertile pairs, numbers of litters/pair and live pups/litter, sex ratio, and body weight of pups. The F_1 mice were continuously treated, and at 74 days of age were paired with non-siblings from the same control and high-dose groups. These animals continued on treatment until F_2 litters were produced; these litters were evaluated for the same endpoints as the F_1 litters. Necropsies were performed on the F_1 parents; these included organ weights of liver, brain, and pituitary and weights and histology of selected male (testes with attached epididymis, prostate and seminal vesicles) and female (uterus and ovary with attached oviduct) reproductive tissues. The F_1 parental males were additionally evaluated for effects on cauda epididymal sperm (concentration, motility, and abnormalities). There were few significant findings in any of the generations; effects were mainly observed in the high-dose F_1 generation, which essentially consisted of a 34% decrease in sperm motility ($p < 0.05$) in the males and slightly (10–14%) increased absolute/relative liver weights in both sexes ($p < 0.01$). Although sperm motility was reduced in the F_1 males, there were no DGEE-related effects on reproduction in either the F_0 or F_1 generation. According to Williams et al. (1990), the study authors considered DGEE as a “weak male reproductive toxicant in mice” even though there was a lack of a functional impact on reproduction in either the F_0 or F_1 generation. Since there was a statistically significant systemic effect, which indicates a presence of general toxicity (>10%

increase in liver weight[8]), the 4400 mg/kg-day dose level is classified as a LOAEL for reproductive and systemic effects in this review. No NOAEL is identified, because the study authors only administered one dose level (4400 mg/kg-day).

Inhalation Exposure

Subchronic or Chronic Studies—No subchronic or chronic inhalation studies in animals were identified in the available literature for DGEE.

A short-term study by the inhalation route was located. Groups of five male and five female Sprague-Dawley CD rats were exposed (nose-only) to mean DGEE (purity 98.6%) concentrations of 0, 0.09, 0.27, or 1.1 mg/L (0, 90, 270, or 1100 mg/m^3) for 6 hours/day, 5 days/week for 28 days (Hardy et al., 1997). DGEE was present entirely as a vapor at the two lowest exposure levels. The high concentration was approximately equally divided by mass into respirable aerosol droplets and vapor and was considered to be the maximum exposure level that could be reliably produced over the study period. The mass median aerodynamic diameter of the aerosol component of the high concentration atmosphere was 3.8 μm with a geometric standard deviation of 1.68. Endpoints assessed include clinical signs, food and water consumption, body weight, organ weight (liver, kidneys, adrenals, testes and lungs), hematology (Hgb, RBC counts, total and differential WBC counts, Hct, platelet counts, and thrombotest), and serum chemistry (total protein, creatine phosphakinase, albumin, globulin, glucose, BUN, bilirubin, creatinine, electrolytes, ALT, AST and γ-glutamyltransferase [GGT]). Gross and histopathological examinations (liver, kidneys, adrenals, testes, lungs, heart, larynx, pharynx, trachea, and the rostral and caudal nasal passages) were performed in the control and high-exposure groups. Due to pathology findings at the high concentration, the larynx (males only) and nasal turbinates from rats in the low and middle exposure-level groups were also examined histologically. Table 6 shows the dose-related changes. The only effects considered to be toxicologically important were slightly increased incidences of histological changes indicative of mild upper respiratory tract irritation in the two highest exposure groups. Focal necrosis in the ventral cartilage of the larynx, with no damage to the overlying squamous epithelium, was observed in males at ≥270 mg/m^3. Minimally increased numbers of eosinophilic inclusions in the olfactory epithelium of the nasal mucosa were detected in females at 1100 mg/m^3. The investigators noted that these changes in the olfactory epithelium and ventral cartilage of the larynx are nonspecific indicators of irritation that have been observed with various other chemicals and that the human relevance of these changes is unclear because rats are obligate nose breathers. However, in the absence of information clearly showing that these effects are not relevant to humans, the histological evidence of mild upper respiratory tract irritation is used as the basis for the NOAEL and LOAEL values of 90 and 270 mg/m^3 (respectively) identified for this review.

Reproductive/Developmental Studies—Developmental toxicity was evaluated in groups of 15 and 21 Sprague-Dawley female rats that were exposed to DGEE (98–99.5% pure) by inhalation at concentrations of 0 or 100 ppm (549 mg/m^3), respectively, for 7 hours/day on days 7–15 of gestation (Nelson et al., 1984). Concentrations higher than 549 mg/m^3 were not tested due to probable aerosol formation. No observations for maternal toxicity were reported. The animals were sacrificed on gestation day 20 for determination of resorption site and live fetus numbers, fetal weight, external malformations, visceral malformations (two thirds of fetuses), and skeletal defects (remaining one third of fetuses). No maternal toxicity (endpoints not specified) was reported. The data showed no statistically significant differences in

[8]The study authors have inadvertently stated ">11% decrease relative liver weight" for the wrong chemical (diethylene glycol) in the Discussion section, but they actually intent to state ">10% decrease in liver weight" as described in the text and tables.

developmental endpoints—indicating that 549 mg/m^3 is a NOAEL (highest concentration tested) for developmental effects.

Table 6. Changes in Sprague-Dawley Rats Inhaling DGEE, 6 hrs/day, 5 days/wk, for 28 Days[a]

Exposure Level (mg/m^3)	Control	90	270	1100
Males				
Histopathology				
Focal necrosis in the ventral cartilage of the larynx	0/5	0/5	2/5	3/5
Females				
Histopathology				
Minimal eosinophilic inclusions in the olfactory epithelium of the nasal mucosa	0/ 5	0/5	0/5	3/5

[a] Hardy et al., 1997.

Other Studies

Other Routes

A dermal study was performed in which 0.35 mL (346 mg) of DGEE (purity not reported) was applied to the shaved skin of Sprague-Dawley rats four times daily on days 7–16 of gestation (Hardin et al., 1984). The dams were sacrificed on gestation day 21 and examined for external abnormalities (all fetuses), visceral abnormalities (half the fetuses), and skeletal abnormalities (other half of fetuses). Inspection of the data revealed no evidence of fetotoxicity or teratogenicity, although maternal body weight was significantly lower (5%) than controls.

Genotoxicity

Little information was located on the genotoxicity of DGEE. *In vitro* mutagenicity testing in *Salmonella typhimurium* was negative in strains TA97, TA100, and TA102, and weakly positive in strains TA1535, TA1537 and TA1538 (Berte et al., 1986). DGEE was not mutagenic in *Saccharomyces cerevisiae* D7 *in vitro* and did not induce micronuclei in CD-1 mice *in vivo* (Berte et al., 1986).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR DGEE

A number of subchronic studies of oral DGEE exposure in laboratory animals identified adverse effects such as mortality (Gaunt et al., 1968; Kodak, 1982), CNS effects, blood in mouth, nose, and urine (Kodak, 1982), reduced water consumption and body weight (Smyth and Carpenter, 1948; Hall et al., 1966; Gaunt et al., 1968), increased relative organ weight (Hall et al., 1966; Gaunt et al., 1968), changes in urine chemistry reflective of renal damage (Hall et al., 1966; Gaunt et al., 1968; Kodak, 1982), and histopathological lesions in the kidneys, liver and/or testes (Gaunt et al., 1968; Hall et al., 1966; Kodak, 1982). Of these studies, only Hall et al. (1966), Gaunt et al. (1968), and Williams et al. (1990; Lamb and Reel, 1997) provided sufficient study details to adequately identify effect levels. Table 7 provides an overview of these studies and their findings. Chronic oral studies are available (Hanzlik et al., 1947; Morris et al., 1942), however these studies were too limited in scope and detail to reliably identify effect levels. No reproductive or developmental effects were seen in single-generation study (Schuler et al., 1984), and only minor toxic effects were observed in multi-generational oral studies (Smyth et al., 1964;

Table 7. Summary of Oral Noncancer Dose-Response Information Potentially Useful for p-RfD Derivation

Species and Study Type (n/sex/group)	Exposure (mg/kg-day)	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Rats Diet 90 days 12/sex/group	Males: 0, 195, 750, or 3750 Females: 0, 205, 810, or 4000	195	750	Proteinuria in males	Additional renal effects at higher dose level in both sexes	Hall et al., 1966
Rats Diet 90 days 15/sex/group	Males: 0, 375 or, 3950 Females: 0, 410, or 4380	375 (M) 410 (F)	3950 (M) 4380 (F)	Reduced hemoglobin and RBC counts; hydropic degeneration of renal tubules		Gaunt et al., 1968
Mice Diet 90 days 20/sex/group	Males: 0, 318, 905, 2800, or 8840 Females: 0, 350, 1000, 4000, or 10,680	905	2800	Increased relative kidney weight, centrilobular hepatocyte enlargement in males	Mortality at higher dose level in males	Gaunt et al., 1968
Pigs Diet 90 days 3/sex/group	0, 167, 500, or 1117	167	500	Hydropic degeneration of hepatocytes and renal tubules in females	Mortality at higher dose level in both sexes	Gaunt et al., 1968
Mice Drinking water Continuous breeding,14 weeks 20–40 breeding pairs	0, 440, 2200, or 4400	NA	4400	Increased absolute and relative liver weight in both sexes; decreased copulatory plugs in males		Williams et al., 1990; Lamb and Reel, 1997

NA = Not Applicable

Williams et al., 1990; Lamb and Reel, 1997; see Reproductive/Developmental Studies). There was no evidence of fetotoxicity or teratogenicity in rats in inhalation or dermal exposure studies (Nelson et al., 1984; Hardin et al., 1984). The Schuler et al. (1984) study identified a FEL for the maternal mortality and is, therefore, not suitable for deriving a potential point of departure (POD) in the assessment. Furthermore, the Williams et al. (1990) and Lamb and Reel (1997) studies focused primarily on the developmental and reproductive effects by DGEE. They are not considered principal studies based on the identified critical effects (hydropic degeneration in kidneys and hydropic degeneration and fatty changes in livers) observed at lower doses in other studies.

The available information identifies the liver and kidney as critical targets of DGEE toxicity across multiple animal species, with the pig being the most sensitive species tested (Gaunt et al., 1968). The lowest LOAELs were identified for liver and kidney lesions in pigs by Gaunt et al. (1968) and for proteinuria in male rats by Hall et al. (1966). Although only 3 pigs/sex/group were tested by Gaunt et al. (1968), the critical effects (hydropic degeneration in the kidneys and liver and fatty changes in the liver) are consistent with those observed at higher doses in rats and mice (Gaunt et al., 1968; Hall et al., 1966; Smyth et al., 1964) and show a dose-response trend (see Table 5). Thus, the pig study of Gaunt et al. (1968) was selected as the principal study for p-RfD derivation. The incidence data for liver and kidney effects were candidates for the critical effect. However, based on Gaunt et al. (1968)'s conclusion, "Varying degrees of hydropic degeneration of the renal tubules was the only pathological finding common to all three species," and other kidney effects in the supporting studies (dose-related proteinuria in Hall et al. 1966; increased proteinuria, kidney lesions, and bladder calculir in Smyth et al., 1964), more emphasis may be placed on the kidney effects.

Subchronic p-RfD

A **subchronic p-RfD** is derived as follows.

Subchronic p-RfD = NOAEL ÷ UF
= 167 mg/kg-day ÷ 300
= 0.6 mg/kg-day or 6×10^{-1} mg/kg-day

The composite uncertainty factor (UF) of 300 is composed of the following UFs:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation, as data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation, as data for evaluating relative interspecies sensitivity are insufficient.
- UF_D: A factor of 3 ($10^{0.5}$) is applied for database inadequacies, as data for evaluating developmental toxicity are inadequate. The database for oral DGEE includes subchronic toxicity studies in several species, chronic studies in two species, and multigeneration reproductive toxicity studies in mice and rats.
- UF_L: A factor of 1 is applied as a NOAEL was selected as the POD.

Confidence in the key study (Gaunt et al., 1968) is medium. Although only 3 animals/sex/dose were tested, the study is well designed with respect to number and variety of endpoints, it identifies critical effects that showed a dose-response relationship, and the findings are consistent with those observed in other species and supporting studies. Confidence in the database is medium because a number of studies in rats and mice provide some support to the critical study with respect to effect levels and types of effects, but the database lacks adequate oral developmental toxicity data. Confidence in the subchronic p-RfD is medium.

Chronic p-RfD

A **chronic p-RfD of 0.06 mg/kg-day** is similarly derived from the same data as follows.

Chronic p-RfD = NOAEL/UF
= 167 mg/kg-day/3000
= **0.06 mg/kg-day or 6×10^{-2} mg/kg-day**

The composite UF of 3000 is composed of the following UFs:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation, as data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation, as data for evaluating relative interspecies sensitivity are insufficient.
- UF_D: The database for oral DGEE includes subchronic toxicity studies in several species, chronic studies in two species, and multigeneration reproductive toxicity studies in mice and rats. A factor of 3 ($10^{0.5}$) is applied for database inadequacies, as data for evaluating developmental toxicity are inadequate.
- UF_L: A factor of 1 is applied as a NOAEL was selected as the POD.
- UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure, as data for evaluating response after chronic exposure are insufficient.

Confidence in the chronic p-RfD is medium, as detailed above for the subchronic p-RfD.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR DGEE

Information on the systemic toxicity of repeated inhalation exposures to DGEE is limited to the results of a short-term study in which groups of male and female rats were exposed for 28 days (Hardy et al., 1997) and a developmental toxicity study (Nelson et al., 1984). Toxicologically relevant findings in the 28-day study were slightly increased incidences of histological changes indicative of mild upper respiratory tract irritation at ≥270 mg/m^3. These effects included focal necrosis in the ventral cartilage of the larynx in males at ≥270, and minimally increased numbers of eosinophilic inclusions in the nasal mucosal olfactory epithelium in females at 1100 mg/m^3. The only other inhalation study identified a NOAEL of 549 mg/m^3 (the lowest dose tested) for developmental toxicity in rats (Nelson et al., 1984), which is two-fold higher than the observed LOAEL of 270 mg/m^3 for respiratory tract irritation (Hardy et al., 1997). The 28-day study was selected as the basis for p-RfC derivation.

The data of Hardy et al. (1997) for focal necrosis in the ventral cartilage of the larynx in male rats (see Table 6) were used for BMD modeling. Details of model fitting and selection of the best model are given in Appendix B. In accordance with U.S. EPA (2000) guidance, the lowest $BMCL_{10}$ (30 mg/m^3) was selected from among models providing adequate fit, as the BMDLs are not sufficiently close.

Using the $BMCL_{10}$ of 30 mg/m^3 for respiratory tract irritation in rats (Hardy et al., 1997) and the U.S. EPA (1994b) RfC methodology (treating DGEE as a Category 1 gas), a human equivalent concentration ($BMCL_{10\ HEC}$) can be calculated and used for deriving a subchronic and chronic p-RfC. Irritation effects can be solely a function of concentration rather than the product

of concentration and time. However, a duration adjustment was applied to the $BMCL_{10}$ for DGEE since there are no data to determine whether the observed effects are a result of the exposure regimen. The $BMCL_{10}$ was multiplied by the exposure period to obtain a duration-adjusted $BMCL_{10\ ADJ}$, as follows:

$$BMCL_{10\ ADJ} = 30\ mg/m^3 \times 6/24\ hr \times 5/7\ d = 5.4\ mg/m^3$$

The $BMCL_{10\ ADJ}$ was then multiplied by the RGDR (regional gas dose ratio) for extrathoracic (ET) respiratory effects to obtain a human equivalent concentration ($BMCL_{10\ HEC}$). Using default values for minute volume (V_E) (L/min) and ET region surface area (SA) (cm^2) for the animals (male Sprague-Dawley rat) and humans and the equation given by U.S. EPA (1994b), the $RGDR_{ET}$ and $BMCL_{10\ HEC}$ were calculated as follows:

$$RGDR_{ET} = (V_E/SA_{ET})_A/(V_E/SA_{ET})_H$$
$$RGDR_{ET} = (0.19/15.0)_A/(13.8/200)_H = 0.18$$

$$BMCL_{10\ HEC} = BMCL_{10\ ADJ} \times RGDR_{ET}$$
$$BMCL_{10\ HEC} = 5.4\ mg/m^3 \times 0.18 = 1.0\ mg/m^3$$

Subchronic p-RfC

A **subchronic p-RfC** is derived as follows.

$$\textbf{Subchronic p-RfC} = BMCL_{10\ HEC} / UF$$
$$= 1.0\ mg/m^3 / 300$$
$$\mathbf{= 0.003\ mg/m^3\ or\ 3 \times 10^{-3}\ mg/m^3}$$

The composite UF of 300 is composed of the following UFs:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation, as data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 3 is applied for animal-to-human extrapolation, as the dosimetric equations were used to account for kinetic differences across species but data for evaluating relative interspecies toxicodynamic differences are insufficient.
- UF_D: The database for inhaled DGEE is limited to a short-term and a developmental toxicity study in rats. A factor of 10 is applied for database inadequacies, as data for evaluating developmental/reproductive toxicity are incomplete.
- UF_L: A factor of 1 is applied as a $BMCL_{10}$ was selected as the POD.

The critical study (Hardy et al., 1997) is well conducted with respect to scope of examinations, number of exposure levels, identification of a NOAEL and LOAEL, and its consistency with European Community test guidelines, but it is given medium confidence due to the relatively short duration (28 days) and small number of animals (5/sex/level) used. Confidence in the database is low due to the lack of subchronic or chronic inhalation study and the lack of reproductive toxicity data by inhalation exposure. Confidence in the subchronic p-RfC is low.

Chronic p-RfC

A chronic p-RfC is similarly derived as follows.

Chronic p-RfC = $BMCL_{10\ HEC}$/ UF
= 1.0 mg/m^3/ 3000
= **0.0003 mg/m^3 or 3×10^{-4} mg/m^3**

The composite UF of 3000 is composed of the following UFs:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation, as data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 3 is applied for animal-to-human extrapolation, as the dosimetric equations were used to account for kinetic differences across species but data for evaluating relative interspecies toxicodynamic differences are insufficient.
- UF_D: The database for inhaled DGEE is limited to a short-term study and a developmental toxicity study in rats. A factor of 10 is applied for database inadequacies, as data for evaluating developmental/reproductive toxicity are incomplete.
- UF_L: A factor of 1 is applied as a $BMCL_{10}$ was selected as the POD.
- UF_S: A factor of 10 is applied for using data from a short-term study to assess potential effects from chronic exposure, as data are insufficient for evaluating response after chronic exposure.

There is low confidence in the chronic p-RfC, as detailed above for the subchronic p-RfC.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR DGEE

Weight-of-Evidence Descriptor

There are no indications that DGEE is carcinogenic in rats or mice based on results of available chronic oral toxicity studies (Hanzlik et al., 1947; Morris et al., 1942; Smyth et al., 1964). However, these studies were not designed as cancer bioassays and do not provide an adequate evaluation of carcinogenicity due to limited or unknown scope of histological examinations, insufficient numbers of animals and dose levels, and/or poor reporting of methods and results. In genotoxicity testing, DGEE induced mixed mutagenic responses in bacteria *in vitro*, was not mutagenic in yeast *in vitro*, and did not induce micronuclei in mice *in vivo*. Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), the available evidence provides *"Inadequate Information to Assess the Carcinogenic Potential"* of DGEE.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for DGEE is precluded by the lack of cancer data for DGEE.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2007. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2008. Toxicological Profile Information Sheet. U.S. Department of Health and Human Services, Public Health Service. Online. http://www.atsdr.cdc.gov/toxpro2.html.

Berte, F., A. Bianchi, C. Gregotti et al. 1986. In vivo and in vitro toxicity of carbitol. Bol. Chim. Farm. 125:401–403.

Gaunt, I.F., J. Colley, P. Grasso et al. 1968. Short-term toxicity of diethylene glycol monoethyl ether in the rat, mouse and pig. Food Cosmet. Toxicol. 6:689–705.

Hall, D.E., F.S. Lee, P. Austin et al. 1966. Short-term feeding study with diethylene glycol monoethylether in rats. Food Cosmet. Toxicol. 4:263–268.

Hanzlik, P.J., W.S. Lawrence and G.L. Laqueur. 1947. Comparative chronic toxicities of diethylene glycol monoethyl ether (Carbitol) and related glycols: Results of continued drinking and feeding. J. Ind. Hyg. Toxicol. 29:233–241.

Hardin, B.D., P.T. Goad and J.R. Burg. 1984. Developmental toxicity of four glycol ethers applied cutaneously to rats. Environ. Health Perspect. 57:69–74.

Hardy, C.J., D.W. Coombs, D.J. Lewis et al. 1997. Twenty-eight-day repeated-dose inhalation exposure of rats to diethylene glycol monoethyl ether. Fund. Appl. Toxicol. 38(2):143–147.

HSDB (Hazardous Substances Data Bank). 2008. Diethylene glycol monoethyl ether. National Library of Medicine. Online. http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~wNcQqJ:1.

IARC (International Agency for Research on Cancer). 2008. Search IARC Monographs. Online. http://monographs.iarc.fr/ENG/Monographs/allmonos90.php.

Kodak. 1982. Comparative toxicology of nine glycol ethers. III. Six-weeks repeated dose study. Eastman Kodak Co., Rochester, NY. Submitted to U.S. EPA under TSCA Section 8E, Fiche No. OTS0570960.

Lamb, J.C. and I.R. Reel. 1997. Reproductive toxicology. Diethylene glycol monoethyl ether. Environ. Health Perspect. 105(Suppl 1):209–210.

Morris, H.J., A.A. Nelson and H.O. Calvery. 1942. Observations on the chronic toxicities of propylene glycol, ethylene glycol, diethylene glycol, ethylene glycol mono-ethyl-ether, and diethylene glycol mono-ethyl-ether. J. Pharmacol. Exp. Ther. 74:266–273.

Nelson, B.K., J.V. Setzer, W.S. Brightwell et al. 1984. Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. Environ. Health Perspect. 47:261–271.

NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards. Online. http://www.cdc.gov/niosh/npg/.

NTP (National Toxicology Program). 2005. 11th Report on Carcinogens. Online. http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932.

NTP (National Toxicology Program). 2008. Management Status Report. Online. http://ntp.niehs.nih.gov/index.cfm?objectid=78CC7E4C-F1F6-975E-72940974DE301C3F.

OECD SIDS (Organization for Economic Co-operation and Development Screening Information Data Set). 2005. Diethylene Glycol Ethers Category. SIDS Initial Assessment Report for SIAM 21. Washington DC, United States, 18–21 October 2005. Online. http://www.chem.unep.ch/irptc/sids/OECDSIDS/.

OSHA (Occupational Safety and Health Administration). 2008. OSHA Standard 1910.1000 Table Z–1. Part Z, Toxic and Hazardous Substances. Online. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

Schuler, R.L., B.D. Hardin, R.W. Niemeier et al. 1984. Results of testing fifteen glycol ethers in a short-term *in vivo* reproductive toxicity assay. Environ. Health Perspect. 57:141–146.

Smyth, H.F. and C.P. Carpenter. 1948. Further experience with the range finding test in the industrial toxicology laboratory. J. Ind. Hyg. Toxicol. 30:63–68.

Smyth, H.F., C.P. Carpenter and C.B. Shaffer. 1964. A 2-year study of diethylene glycol monoethyl ether in rats. Food Cosmet. Toxicol. 2:641–642.

SRC (Syracuse Research Corporation). 1992. Health and Environmental Effects Document on Glycol Ethers. Prepared by Syracuse Research Corporation, Syracuse, NY for the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. SRC TR-92-007.

U.S. EPA. 1984. Health Effects Assessment for Glycol Ethers. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, D.C. EPA/540/1-86-052.

U.S. EPA. 1987. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/600/6-87/008. NTIS PB 88-179874.

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.
U.S. EPA. 1994a. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1994b. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. October. EPA/600/8-90/066F.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA. 2000. Benchmark Dose Technical Guidance Document. External Review Draft. Risk Assessment Forum. EPA/630/R-00/001. October.

U.S. EPA. 2005. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, National Center for Environmental Assessment, Washington, DC.

U.S. EPA. 2006. 2006 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. EPA 822-R-06-013. Washington, DC. http://www.epa.gov/water science/drinking/standards/dwstandards.pdf.

U.S. EPA. 2008. Integrated Risk Information System (IRIS). Online. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. http://www.epa.gov/iris/.

WHO (World Health Organization). 1976. Diethylene glycol monoethyl ether. In: WHO Food Additive Series No. 10. Toxicological evaluation of certain food additives. Twentieth report of the Joint FAO/WHO Expert Committee on Food Additives (JEFCA), Geneva, 1967. WHO Technical Report Series No. 599, FAO Food and Nutrition Series No. 1. Online. http://www.in chem.org/documents/jecfa/jecmono/v10je04.htm.

WHO (World Health Organization). 1993. Diethylene glycol monoethyl ether. In: WHO Food Additive Series No. 30. Toxicological evaluation of certain food additives and naturally occurring toxicants. Thirty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives (JEFCA), Geneva, 1993. Online. http://www.inchem.org/documents/jecfa/jecmono/ v30je01.htm.

WHO (World Health Organization). 1995. JEFCA evaluation of diethylene glycol monoethyl ether. Joint FAO/WHO Expert Committee on Food Additives. Online. http://www.inchem.org/ documents/jecfa/jeceval/jec_d67.htm.

WHO (World Health Organization). 2008. Online catalogs for the Environmental Health Criteria Series. Online. http://www.who.int/ipcs/publications/ehc/ehc_alphabetical/en/ index.html.

Williams, J., J.R. Reel, J.D. George et al. 1990. Reproductive effects of diethylene glycol and diethylene glycol monoethyl ether in Swiss CD-1 mice assessed by a continuous breeding protocol. Fund. Appl. Toxicol. 14:622–635.

APPENDIX A. DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC AND CHRONIC p-RfCs

Model Fitting Procedure for Quantal Noncancer Data:

The model fitting procedure for dichotomous noncancer data is as follows. All available dichotomous models in the U.S. EPA Benchmark Dose Software (BMDS, version 2.0) are fit to the incidence data using the extra risk option. The multistage model is run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Goodness-of-fit is assessed by the χ^2 test. When several models provide adequate fit to the data (χ^2 $p \geq 0.1$), and the estimated BMDLs from these models differ by $\geq$3-fold, then the model with the lowest BMDL is selected. Otherwise, models with adequate fit are compared using the AIC. The model with the lowest AIC is considered to provide the best fit to the data. When several models have the same AIC, the model resulting in the lowest BMDL is selected. In accordance with U.S. EPA (2000) guidance, benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with an extra risk of 10% (BMD_{10} and $BMDL_{10}$) are calculated for all models.

Model Fitting Results for Mild Upper Respiratory Tract Irritation in Rats, Hardy et al., 1997:

Applying the procedure outlined above to the data on focal necrosis of the ventral cartilage of the larynx in male rats (see Table 6), adequate model fit was achieved with several models. Table A-1 shows the modeling results. The BMCLs from models providing adequate fit differed by more than 3-fold. Thus, in accordance with U.S. EPA (2000) guidance, the lowest BMCL was selected from among models providing adequate fit. The resulting benchmark concentration (BMC_{10}) and associated 95% lower confidence limit ($BMCL_{10}$) were 109 and 30 mg/m^3, respectively. Figure A-1 shows the model fit of the log logistic model, which is representative of those resulting in the lowest $BMCL_{10}$.

Table A-1. Model Predictions for Mild Upper Respiratory Tract Irritation in Male Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Log Logistic	**2**	**1.07**	**0.5847**	**18.8845**	**108.674**	**30.174**
Gamma	3	1.32	0.7238	17.1128	106.956	54.004
Multistage (degree of polynomial = 1)[b]	3	1.32	0.7238	17.1128	106.956	54.004
Multistage (degree of polynomial = 2)[b]	3	1.32	0.7238	17.1128	106.956	54.004
Multistage (degree of polynomial = 3)[b]	3	1.32	0.7238	17.1128	106.956	54.004
Weibull	3	1.32	0.7238	17.1128	106.956	54.004
Quantal Linear	3	1.32	0.7238	17.1128	106.956	54.004
Log Probit	3	1.58	0.665	17.0282	161.063	85.429
Probit	2	3.14	0.208	20.9637	285.087	160.062
Logistic	2	3.21	0.2004	21.1292	308.151	163.835

[a] Hardy et al., 1997.
[b] Degree of polynomial initially set to (n - 1) where n = number of dose groups including control. Betas restricted to ≥0.

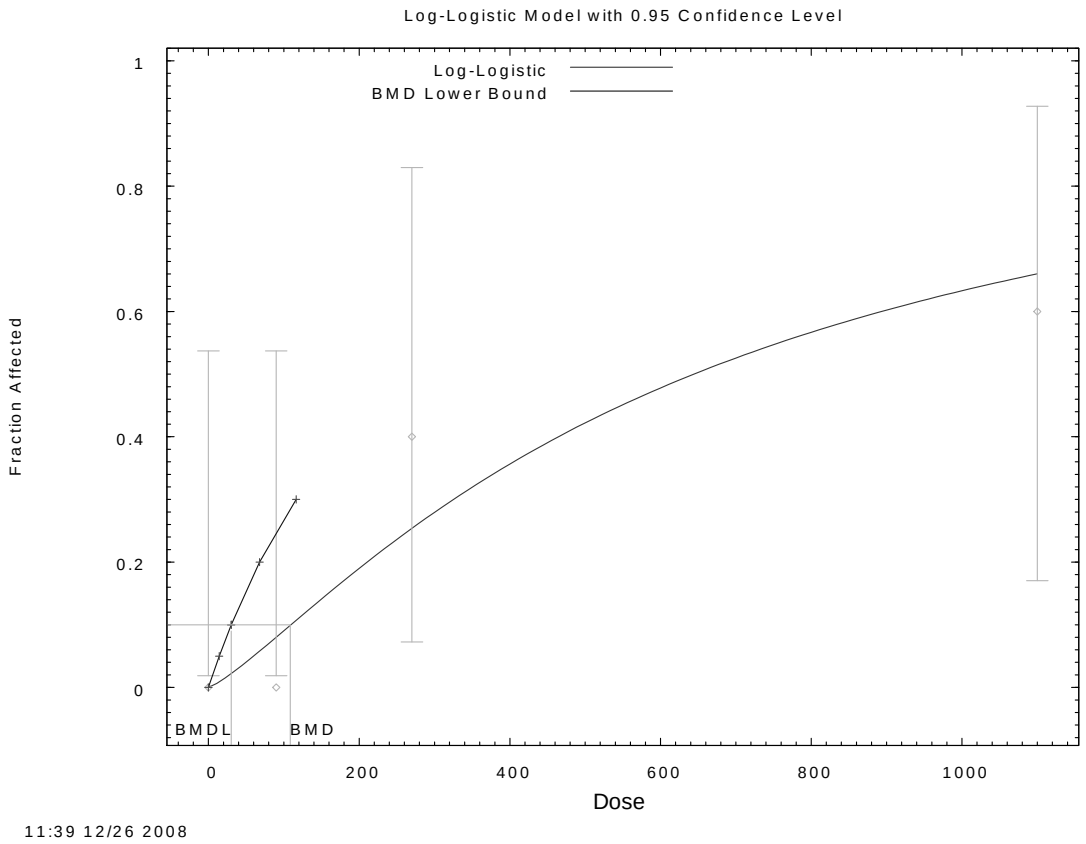

Figure A-1. Fit of Log Logistic Model to Data on Mild Upper Respiratory Tract Irritation in Male Rats, Hardy et al., 1997

BMCs and BMCLs indicated are associated with an extra risk of 10% and are in units of mg/m^3

```
 ================================================================
         Logistic Model. (Version: 2.12; Date: 05/16/2008)
         Input Data File: C:\USEPA\BMDS2\DGEE\Hardy_BMD\LogHarSet.(d)
         Gnuplot Plotting File:  C:\USEPA\BMDS2\DGEE\Hardy_BMD\LogHarSet.plt
                                                 Fri Dec 26 11:39:50 2008
 ================================================================

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

   The form of the probability function is:

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


   Dependent variable = incidence
   Independent variable = DOSE
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   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
                     intercept =    -7.04239
                         slope =      1.0952


          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        -0.99

     slope        -0.99            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    background                0            *               *                   *
     intercept         -8.02007            *               *                   *
         slope          1.24198            *               *                   *

* - Indicates that this value is not calculated.


                       Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -6.73012         4
   Fitted model        -7.44224         2       1.42424      2          0.4906
  Reduced model        -11.2467         1       9.03317      3         0.02885

          AIC:         18.8845


                                Goodness  of  Fit
                                                        Scaled
```

Dose	Est._Prob.	Expected	Observed	Size	Residual
0.0000	0.0000	0.000	0.000	5	0.000
90.0000	0.0808	0.404	0.000	5	-0.663
270.0000	0.2560	1.280	2.000	5	0.738
1100.0000	0.6632	3.316	3.000	5	-0.299

Chi^2 = 1.07 d.f. = 2 P-value = 0.5847

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 108.674

BMDL = 30.1739