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Provisional Peer-Reviewed Toxicity Values for

Diisopropyl ether
(CASRN 108-20-3)

Superfund Health Risk Technical Support Center
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TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR DIISOPROPYL ETHER (CASRN 108-20-3)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency'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) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR);
   - California Environmental Protection Agency (CalEPA) values; and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by a panel of six 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 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVS

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

INTRODUCTION

No RfD, RfC, or cancer assessment for diisopropyl ether (DIPE; see Figure 1 for chemical structure) is available on IRIS (U.S. EPA, 2009), in the HEAST (U.S. EPA, 1997), or in the *Drinking Water Standards and Health Advisories list* (U.S. EPA, 2006). No relevant documents were located in the *Chemical Assessments and Related Activities* (CARA) list (U.S. EPA, 1991a, 1994a). The ATSDR (2008) has not published a Toxicological Profile for DIPE, and no Environmental Health Criteria Document is available from the World Health Organization (WHO, 2008). The carcinogenicity of DIPE has not been assessed by the International Agency for Research on Cancer (IARC, 2008) or the National Toxicology Program (NTP, 2005, 2008). The American Conference for Governmental Industrial Hygienists (ACGIH, 2007) has adopted a threshold limit value-time-weighted average (TLV-TWA) of 250 ppm (1040 mg/m^3) and a threshold limit value-short-term exposure limit (TLV-STEL; not to exceed 15-minute exposure over an 8-hour work shift) of 310 ppm (1300 mg/m^3) as protective against irritation. The National Institute of Occupational Safety and Health-recommended exposure limit (REL) is 500 ppm (2090 mg/m^3) based on irritation of eyes, skin, and respiratory system and central nervous system effects (NIOSH, 2008). The Occupational Safety and Health Administration permissible exposure limit (PEL) is 500 ppm (OSHA, 2008).

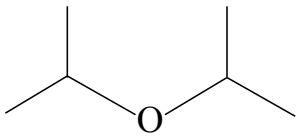

Figure 1. Chemical Structure of DIPE

Literature searches were conducted from the 1960s through March 2011 for studies relevant to the derivation of provisional toxicity values for DIPE. Databases searched include MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents (last 6 months). An IUCLID Data

Set for DIPE submitted by ExxonMobil Biomedical Sciences (2005) under EPA's High Production Volume (HPV) Challenge Program was also reviewed for relevant information.

An evaluation of the cancer literature indicates that a major study related to the carcinogenicity of DIPE has been conducted by the Ramazzini Institute. Following a report from the National Toxicology Program (NTP), EPA has placed the development of health assessments, such as DIPE, that may rely on Ramazzini Institute cancer data on hold. The NTP report, referred to in EPA's June 15, 2010 press release (U.S. EPA, 2010), recommended that pathology reviews be carried out to resolve differences of opinion in the diagnoses of certain tumors reported in a methanol research study completed by the Ramazzini Institute. As a result, EPA and the National Institute of Environmental Health Sciences (NIEHS) are jointly sponsoring an independent Pathology Working Group (PWG) review of select studies conducted at the Institute. The cancer assessment for DIPE will remain on hold until the completion of the PWG review.

REVIEW OF PERTINENT DATA

HUMAN STUDIES

Silverman et al. (1946) exposed a mixed-sex group of 12 human subjects to 300 ppm (1250 mg/m^3) of DIPE vapor for 15 minutes. No irritation of the eyes, nose, or throat was reported; although, about one-third of study subjects objected to the unpleasant odor of the solvent at this concentration. No studies were located examining the effects of longer-term inhalation exposure or oral exposure in humans.

ANIMAL STUDIES

Oral Exposure

No relevant noncancer studies on oral exposure to DIPE have been located.

Inhalation Exposure

Subchronic and developmental inhalation studies were conducted by Dalbey and Feuston (1996). In the subchronic study, groups of Sprague-Dawley rats (14/sex) were whole-body exposed to 0 (untreated), 0 (sham-exposed), 2000, 13,800, or 29,700 mg/m^3 (0, 480, 3300, or 7100 ppm) of DIPE 6 hours/day, 5 days/week, for approximately 13 weeks. Because commercial grade (92% pure) test material was used, test animals were also exposed to low concentrations of a mixture containing more than 20 low molecular weight alkanes, cycloalkanes, alkenes, alcohols, and ketones. The DIPE concentrations reported above represent 91–95% of the total chemical exposures in the treatment groups. Sham-exposed controls were individually housed in the inhalation chambers, and untreated controls were observed in a separate animal room. Food and water were provided ad libitum but not during exposures. Test animals were monitored daily during the week (not on weekends) for clinical signs, and individual body weights were recorded weekly. Blood samples collected prior to terminal sacrifice were analyzed for serum chemistry (glucose, urea nitrogen [BUN], total protein, albumin, globulin, A/G ratio, sorbitol dehyrogenase [SDH], aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin, creatinine, cholesterol, triglycerides, uric acid, chloride, calcium, sodium, potassium, and phosphorus) and hematology (white blood cells [WBCs], red blood cells [RBCs], hemoglobin [Hgb], hematocrit [Hct], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean

corpuscular hemoglobin concentration [MCHC], platelets, and differential cell count). Following sacrifice, all test animals were necropsied, and organ weights (adrenals, kidney, spleen, brain, liver, testes, epididymides, ovaries, thymus, heart, prostate, uterus, and the right middle lung lobe) were collected. Slides for histopathological examination were prepared from over 40 tissues, and all gross lesions in the sham-exposed and high-dose groups; liver and kidney in the mid-dose males; and lungs, tracheobronchial lymph nodes, and gross lesions in the untreated control group. The left cauda epididymides from 10 male rats in each control group and the high-dose group were used for evaluation of sperm morphology and number.

No mortality was reported, and there were no treatment-related clinical signs observed over the course of the study (Dalbey and Feuston, 1996). Treated males tended to gain more weight compared to controls during the first half of the study. A statistically significant ($p < 0.05$) difference was seen in mid-dose males (see Table 1). Similar trends were not observed in female rats. Serum chemistry and hematology analyses were generally unremarkable, except for a statistically significant ($p < 0.05$) increase in serum cholesterol in high-dose males (see Table 2). Absolute liver weights were statistically significant increased ($p < 0.05$) in males and females in the mid- and high-dose groups in a dose-related manner (see Table 1). Relative liver weights were not reported, but a comparison of the ratio of mean liver weight to mean terminal body weight in the different study groups suggests that relative liver weights were also increased in these groups in relation to dose. Microscopic examination revealed mild hepatocellular hypertrophy only in the male rats from the high-dose group. Absolute kidney weights of mid- and high-dose males were significantly increased (see Table 1). Comparison of the ratio of mean kidney weight to mean terminal body weight in the different study groups suggests that relative kidney weight was not increased in the mid-dose group and only slightly increased in the high-dose group. Microscopic examination of the kidney showed a mild increase in hyaline droplets in the proximal convoluted tubules of males of the high-dose group only. No other organs had changes in weight or morphology attributed to exposure to DIPE. There were no differences between treated males and controls (both untreated and sham-exposed) in sperm or spermatid counts. The number of abnormal sperm was significantly increased in high-dose males (5.3% versus 2.8% in control rats), but this increase was not considered by the researchers to be of biological significance because no specific type of abnormality was increased and because the prevalence of abnormal sperm in the high-dose group was within the range of historical controls (2.8–5.6%).

Table 1. Absolute Body and Organ Weights of Sprague-Dawley Rats Exposed to DIPE by Inhalation for 90 Days[a,b]

Organ	Exposure Group (mg/m^3)				
	0 (untreated)	0 (sham-exposed)	2000	13,800	29,700
Males					
Body weight (g)	438 ± 28	449 ± 34	466 ± 34	482 ± 32[c]	462 ± 36
Liver (g)	12.1 ± 1.4	12.3 ± 1.3	12.8 ± 1.5	15.4 ± 1.1[d]	16.9 ± 2.2[d]
Kidneys (g)	2.92 ± 0.26	2.86 ± 0.36	2.96 ± 0.33	3.24 ± 0.27[d]	3.26 ± 0.43[d]
Females					
Body weight (g)	287 ± 20	276 ± 24	280 ± 19	276 ± 17	280 ± 17
Liver (g)	8.04 ± 0.81	7.45 ± 1.09	7.64 ± 0.68	8.23 ± 1.16[e]	9.11 ± 0.81[d]
Kidneys (g)	1.86 ± 0.14	1.81 ± 0.15	1.79 ± 0.11	1.90 ± 0.15	1.94 ± 0.18[e]

[a]Dalbey and Feuston (1996).
[b]Values are presented as means ± SD.
[c]Reported to be significantly different from untreated controls by the researchers but *p*-values not shown. Following methods reported by the researchers, ANOVA was performed for this review, followed by group comparisons using Duncan's multiple range test. Based on this evaluation, it appears the study authors were evaluating statistical significance at $p < 0.05$. However, not all of the statements about statistical significance made by the authors were validated at this level. Discrepancies were that the re-analysis showed a statistically significant ($p < 0.05$) difference from both control groups, rather than just untreated controls, for body weight in mid-dose males and no difference from sham-exposed controls for liver weight in mid-dose females.
[d]Significantly different from both control groups (*p*-value not reported, see footnote c for further discussion).
[e]Significantly different from sham-exposed controls (*p*-value not reported, see footnote c for further discussion).

Table 2. Serum Chemistry and Hematology Values in Sprague-Dawley Rats Exposed to DIPE by Inhalation for 90 Days[a,b]

Parameter	Exposure Group (mg/m^3)				
	0 (untreated)	0 (sham-exposed)	2000	13,800	29,700
Males					
Creatinine (mg/dL)	0.61 ± 0.06	0.64 ± 0.04	0.64 ± 0.04	0.67 ± 0.06[c]	0.69 ± 0.03[c]
Cholesterol (mg/dL)	71 ± 10	74 ± 13	77 ± 17	77 ± 9	95 ± 22[d]
SDH (IU/L)	11 ± 5	16 ± 7	13 ± 6	9 ± 3[f]	9 ± 3[f]
Lymphocytes[c]	92 ± 3	92 ± 4	90 ± 6	90 ± 4	87 ± 6[c]
Monocytes[c]	1 ± 2	1 ± 2	2 ± 2	2 ± 2	3 ± 2[c]
Females					
Potassium (mmol/L)	4.96 ± 0.35	4.68 ± 0.24	4.58 ± 0.41	4.51 ± 0.37[c]	4.45 ± 0.4[c]
Lymphocytes[c]	92 ± 3	88 ± 5	86 ± 6[c]	85 ± 7[c]	86 ± 3[c]

[a]Dalbey and Feuston (1996).
[b]Values are presented as means ± SD.
[c]Reported to be significantly different from untreated controls by the researchers, but *p*-values not shown. Following methods reported by the researchers, ANOVA was performed for this review, followed by group comparisons using Tukey's studentized range test. Based on this evaluation, it appears the study authors were evaluating statistical significance at $p < 0.05$. However, not all of the statements about statistical significance made by the authors were validated at this level. Discrepancies were that the re-analysis showed statistically significant ($p < 0.05$) differences from both control groups, rather than just untreated controls, for creatinine in high-dose males and that levels of lymphocytes and monocytes in high-dose males were not different than untreated controls.
[d]Significantly different from both control groups (*p*-value not reported, see footnote d for further discussion)
[e]Percent of total WBCs.
[f]Significantly different from sham-exposed controls (*p*-value not reported, see footnote d for further discussion).

Dalbey and Feuston (1996) identified the liver as the most sensitive target in male rats for DIPE, with no effects at 2000 mg/m^3, increases in liver weight at 13,800 mg/m^3 and larger increases in liver weight, hepatocellular hypertrophy, and increased serum cholesterol at 29,700 mg/m^3. The changes observed in this study were increased liver weights, hepatocellular hypertrophy, and elevated levels of serum cholesterol. The only other target identified in this study was the kidney in male rats. Some of the experimental data suggest that development of kidney toxicity in male rats following exposure to DIPE may involve an α_{2u}-globulin-mediated mode of action. Generally, kidney effects observed in animals are assumed to be relevant for assessment of human toxicity. However, a number of chemicals have been shown to induce accumulation of $_{2u}$-globulin in hyaline droplets in male rat kidney. The $_{2u}$-globulin accumulation in hyaline droplets initiates a sequence of events that leads to renal nephropathy and, eventually, to renal tubular tumor formation. The phenomenon is unique to the male rats since female rats and other laboratory mammals administered the same chemicals do not accumulate $_{2u}$-globulin in the kidney and do not develop renal tubule tumors (U.S. EPA, 1991b). However, there is a lack of α_{2u}-globulin immunohistochemical data for DIPE-induced nephrotoxicity. In the absence of minimum information demonstrating the involvement of α_{2u}-globulin processes, male rat renal toxicity associated with exposure to DIPE is considered relevant for risk assessment purposes. The study authors identified a no-observed-effect-level (NOEL) of 2000 mg/m^3. For the purpose of this review, a LOAEL of 13,800 mg/m^3 based on the increased liver weight (~28% in males; 6% in females) and a NOAEL of 2000 mg/m^3 are identified.

In the developmental study, groups of 22 mated female Sprague-Dawley rats were whole-body exposed to 0 (untreated), 0 (sham-exposed), 1800, 12,940, or 28,200 mg/m^3 (0, 430, 3095, or 6745 ppm) DIPE vapor for 6 hours/day on Days 6–16 of gestation (Dalbey and Feuston, 1996). Because commercial grade (92% pure) test material was used, test animals were also exposed to low concentrations of other chemicals, but the DIPE concentrations reported above represent 92–95% of the total chemical exposures in the treatment groups. The sham-exposed controls were housed in the study chambers without chemical treatment, and untreated controls were observed in a separate animal room. Food and water were provided ad libitum, but not during exposures. Dams were observed daily for clinical signs, and body-weight and food consumption were recorded periodically throughout gestation. Dams were sacrificed on GD 20, at which time blood samples were collected for serum chemistry analyses of the same parameters as in the subchronic study. In addition, all organs were examined grossly, the ovaries were inspected for corpora lutea, and the gravid uterus was weighed and examined for numbers of implantation sites, early and late resorptions, and live and dead fetuses. All fetuses were weighed, sexed, and examined for external anomalies. Half of the fetuses from each litter were processed and examined for visceral anomalies, while the other half were processed and examined for skeletal anomalies (due to overmaceration, roughly 23–32% of the litters processed for skeletal evaluation could not be examined, spread evenly across the different treatment groups).

Transient lacrimation and salivation were observed in some of the pregnant rats in the high-dose group during exposure; in these cases, normal behaviors resumed shortly after the daily exposure ended (Dalbey and Feuston, 1996). As shown in Table 3, there was a general decrease in body-weight gain during the exposure period for all females housed in the inhalation chambers relative to the untreated controls (including sham-exposed controls, indicating a possible effect from handling and treatment). Compared to sham-exposed controls, the decrease

in average body-weight gain was statistically significant ($p < 0.05$) only for the high-dose group. Food consumption was statistically significantly ($p < 0.05$) reduced in comparison to untreated and sham-exposedcontrols in both the mid- and high-dose groups during the first week of treatment (see Table 3). This indicates a possible food aversion during the first week of the study that may have affected initial body-weight gains. No serum chemistry or gross pathology changes were found in the treated dams. Reproductive parameters were not affected by exposure, and there was no effect on fetal body weight. The only significant developmental finding was a dose-related increase in the incidence of rudimentary ("small, discrete ossification") or short ("less than one half the length of the preceding rib") 14th ribs in fetuses from both the mid- and high-dose groups, both on the basis of number of fetuses affected and number of litters affected (see Table 4). The study authors did not identify any effect levels. A NOAEL of 1800 mg/m^3 and a LOAEL of 12,940 mg/m^3 for both maternal (reduced feed consumption and body weight) and developmental (increased incidence of rudimentary 14th ribs in fetuses) effects are identified for this review.

Table 3. Body-Weight Gain and Food Consumption in Dams Exposed to DIPE by Inhalation[a,b]

	Exposure Group (mg/m^3)				
Parameter	**0 (untreated)**	**0 (sham-exposed)**	**1800**	**12,940**	**28,200**
Number of pregnant females	22	20	21	21	22
Body-weight gain (g) (GDs 6–16)	69 ± 11	50 ± 9[c]	58 ± 14[c]	42 ± 9[c]	33 ± 13[d]
Net weight gain (g)[e]	51.7 ± 13.8	37.3 ± 11.3[c]	41.5 ± 13.3[c]	31.9 ± 11.5[c]	29 ± 8.1[c]
Food Consumption (g/kg-d)					
GDs 6–13	92.8 ± 6.5	88.0 ± 6.8	88.4 ± 5.4	77.7 ± 8.4[d]	68.5 ± 6.7[d]
GDs 13–16	87.2 ± 7.7	84.4 ± 5.2	84.0 ± 4.4	81.3 ± 7.4[c]	76.1 ± 7.0[c]

[a]Dalbey and Feuston (1996).
[b]Values are presented as means ± SD.
[c]Reported to be significantly different from untreated controls by the researchers but *p*-values not shown. Following methods reported by the researchers, ANOVA was performed for this review, followed by group comparisons using Dunnett's test. Based on this evaluation, it appears the study authors were evaluating statistical significance at $p < 0.05$. The critical effect of reduced maternal weight gain at 12,940 mg/m^3 was found to be statistically significantly ($p < 0.05$) different from untreated controls, as reported by the study authors. Minor discrepancies were that the re-analysis showed statistically significant differences from both control groups, rather than just untreated controls, for net weight gain and GDs 13–16 food consumption in the mid- and high-dose groups.
[d]Significantly different from both control groups (*p-value* not reported, see footnote c for further discussion).
[e]Carcass weight minus GD 6 weight.

Table 4. Selected Developmental Anomalies in Fetuses from Dams Exposed to DIPE by Inhalation[a,b]

Rudimentary/ short 14th ribs	Exposure Group (mg/m^3)				
	0 (untreated)	0 (sham-exposed)	1800	12,940	28,200
Number of viable fetuses examined for skeletal anomalies[c]	168	155	167	156	173
Number of fetuses affected	4 (3)	4 (3.5)	6 (5)	20 (17)[d]	33 (28)[d]
Number of litters examined for skeletal anomalies[e]	17	14	15	15	15
Number of litters affected	4 (24)	1 (7)	4 (27)	7 (47)[f]	13 (87)[d]

[a]Dalbey and Feuston (1996).
[b]Values are number affected (%).
[c]Approximately one-half of fetuses examined for skeletal anomalies.
[d]Significantly different from both control groups (*p-value* not reported, see footnote c for further discussion).
[e]Due to overmaceration, not all litters were evaluated for abnormal skeletal development.
[f]Reported to be significantly different from sham-exposed controls by the researchers, but *p*-value not shown.
Following methods reported by the researchers, group comparisons were performed using Fisher's exact test. The author's claims of statistical significance were validated at $p < 0.05$.

A subchronic neurotoxicity screening study was performed on groups of 10 male and 10 female Sprague-Dawley rats whole-body exposed 5 days/week, 6 hours/day, for 13 weeks to 0, 1900, 13,600, or 29,500 mg/m^3 (0, 450, 3250, or 7060 ppm) of DIPE (Rodriguez and Dalbey, 1997). Because commercial grade (92% pure) test material was used, test animals were also exposed to low concentrations of other chemicals, but the DIPE concentrations reported above represent 91–94% of the total chemical exposures in the treatment groups. The rats were housed in the inhalation chambers for the study duration, except for scheduled behavioral testing when the rat to be tested was removed from the chamber to another room overnight and evaluated the following day. Rats were observed for clinical signs prior to the daily exposure, and body weight was recorded weekly. Neurotoxicity potential was evaluated via a functional observational battery (FOB), measurement of motor activity in a figure-8 maze, and neuropathology. The FOB was conducted following Weeks 0, 2, 4, 8, and 13 of exposure, and the motor activity was determined following Weeks 0, 4, 8, and 13 of exposure. At study termination, the rats were anesthetized; intravascularly perfused; and the brain, spinal cord, and peripheral nerves were removed and processed for microscopic examination.

Clinical signs and body weight were not affected by exposure to DIPE (Rodriguez and Dalbey, 1997). The FOB identified no effects clearly related to treatment; although, a few sporadic, statistically significant ($p < 0.05$) changes were observed (reduced pinna reflex in low-dose males during Week 2, reduced general activity of low- and high-dose females during Week 4, increased rectal temperature of low-dose males during Week 4). Motor activity in the figure-8 maze decreased in all groups as the animals aged but decreased significantly faster in high-dose females than in controls. No treatment-related effects on morphology were observed in either the central or peripheral nervous system. A single low-dose female rat had a

hypoplastic condition of the cortex (the 2 × 4-mm cavity), but this incident was not considered to be associated with the exposure to DIPE by the study authors. The study authors concluded that "only minor neurological changes were observed" and considered the neurological effects of DIPE in rats as "minimal" at concentrations up to 29,500 mg/m^3. In addition, they did not identify any effect levels. A NOAEL of 29,500 mg/m^3 is identified for this review.

Other Studies

Acute or Short-term Studies

Machle et al. (1939) exposed six rabbits to DIPE via gavage at doses ranging from 1620–8200 mg/kg. A rapid intense intoxication, including narcosis, was produced, and two rabbits dosed at 7200 and 8200 mg/kg died from respiratory failure within the first hour following dosing. Another rabbit dosed at 6000 mg/kg died within 15 hours from irritation of the intestinal tract. The minimal lethal dose for rabbits was found to be between 5075 and 6525 mg/kg. Kimura et al. (1971) determined the acute oral LD50 for DIPE in 14-day old, young adult, and adult rats as 4640, 11,963, and 11,600 mg/kg, respectively. DIPE was significantly more toxic to immature rats than adult rats ($p < 0.05$) (Kimura et al., 1971).

Machle et al. (1939) also exposed test animals (monkey, rabbit, and guinea pig) to vapor concentrations of DIPE at 0.1%, 0.3%, 1.0%, 3.0% and 6.0% by volume in air (approximately 1000, 3000, 10,000, 30,000, and 60,000 ppm). All animals exposed to 6.0% DIPE died from respiratory failure. A monkey and two rabbits exposed to 3.0% DIPE exhibited signs of anesthesia, and the monkey showed signs of beginning respiratory failure. Overall, concentration-dependent acute toxicity to DIPE treatment was observed.

DIPE applied to the clipped skin of rabbits for 1 hour produced no deleterious effects (Machle et al., 1939). However, repeated dermal exposures of 1 hour each for 10 days caused skin reddening and a well-developed dermatitis in rabbits (Machle et al., 1939). In addition, a review by Mehlman (2000) indicated that DIPE produced minor injury and irritation to rabbit eyes in an unpublished study conducted by the Union Carbide Chemical Company.

Genotoxicity

Limited genotoxicity testing of DIPE has produced negative results. Studies in *Salmonella typhimurium* (strains TA98, TA100, TA 1535, TA1537, TA1538) and *Escherichia coli* (strain WP_2 *uvr A* pKM101) using a modified assay for volatile solvents found that DIPE is not mutagenic in bacteria, with or without metabolic activation (Brooks et al., 1988). DIPE did not induce mitotic gene conversion in *Saccharomyces cerevisiae* JD1 or chromosome damage in the rat liver RL4 chromosome assay (Brooks et al., 1988), nor sister chromatid exchanges (SCEs) in Chinese hamster ovary (CHO) cells (Brooks et al., 1988).

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR DIISOPROPYL ETHER

Oral data are limited to acute studies in rats (Kimura et al., 1971) and rabbits (Machle et al., 1939). The available data are not sufficient for derivation of a subchronic or chronic p-RfD for DIPE.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR DIISOPROPYL ETHER

Noncancer inhalation effects are summarized in Table 5. The Dalbey and Feuston (1996) study presents the most sensitive effects (maternal and developmental effects) in comparison to other studies. It is selected as the principal study. The developmental study found both maternal and developmental effects at 12,940 and 28,200 mg/m^3 (Dalbey and Feuston, 1996), with a NOAEL of 1800 mg/m^3 for both. Effects seen in the developmental toxicity study included a statistically significant increased ($p < 0.05$) incidence of rudimentary and short 14th ribs among rat fetuses and litters, and reduced body-weight gain and food consumption in the dams at ≥12,940 mg/m^3. Occasional lacrimation and salivation by the dams during exposure were also observed at 28,200 mg/m^3. Even though the body weight of female rats was not affected at any concentration in the subchronic study (Dalby and Feuston, 1996), there was a statistically significant decrease ($p < 0.05$) in the body-weight gain (GDs 6–16) for the pregnant female rats at ≥1800 mg/m^3 concentration levels in the developmental study. This observation suggests that pregnant female rats may be more sensitive to DIPE.

Dose-response modeling was performed for the maternal body-weight changes and fetal skeletal variations in the developmental toxicity study (Dalbey and Feuston, 1996). For the maternal body-weight change, both body-weight gain during GDs 6–16 and net weight gains (carcass weight minus GD 6 weight) were modeled (see Table 3). Treated groups were compared to the sham-exposed control group only. Body-weight gains were significantly different in the sham-exposed controls in comparison to the untreated controls, suggesting that handling and treatment procedures may have had some effect on the exposed rats, and the untreated controls may not be an appropriate comparison group for this analysis.

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Table 5. Summary of Inhalation Noncancer Dose-Response Information for DIPE

Species	Sex	Exposure Concentration (mg/m^3)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses	Comments	Reference
Subchronic Exposure								
Rat, 14/sex	M/F	0, 0 (sham), 2000, 13,800, 29,700	Whole-body, 6 hours/day, 5 days/week, 13 weeks	2000	13,800	Increased liver weight.		Dalbey and Feuston, 1996
Rat, 10/sex	M/F	0, 1900, 13,600, 29,500	Whole-body, 6 hours/day, 5 days/week, 13 weeks	29,500	--	Only minor, sporadic neurological effects were observed.		Rodriguez and Dalbey, 1997
Developmental Toxicity								
Rat, 22/dose	F	0, 0 (sham), 1800, 12,940, 28,200	Whole-body, 6 hours/day on GDs 6–15	1800	12,940	Decreased body-weight gains and food consumption in dams; increased incidence of rudimentary/short 14^{th} ribs in fetuses.		Dalbey and Feuston, 1996

For the skeletal variations, only the data for number of litters affected were modeled. Incidence of affected litters, rather than individual fetuses, was modeled because fetuses or pups within litters do not respond independently. The litter is generally considered the experimental unit in most developmental toxicity studies, and statistical analyses are generally performed based on incidence per litter (not reported for the skeletal variations in the Dalbey and Feuston [1996] study) or number of litters affected with a particular endpoint (U.S. EPA, 1991c). These data are shown in Table 4. There was some indication of an effect of handling on the incidence of skeletal variations (4/17 for untreated vs. 1/14 for sham-exposed), the sham-exposed controls were therefore used in the analysis rather than the untreated controls. The sham-exposed controls represent the closest control condition to the treated rats and are consistent with the analysis of the maternal data.

Appendix A contains details of the modeling. No model provided an adequate fit to the maternal body-weight gain data from GDs 6–16. Based on net maternal weight gain, the BMC with a benchmark response (BMR) of 10% relative deviation is 10,141 mg/m^3, and the BMCL is 7261 mg/m^3. Based on the incidence of rudimentary and short 14th ribs, the BMC_5 is 652 mg/m^3, and the $BMCL_5$ is 264 mg/m^3. The BMCL of 264 mg/m^3 was selected as the point of departure (POD) for the derivation of the subchronic and chronic p-RfCs

In order to derive the subchronic p-RfC, the rat BMCL was first converted to a human equivalent concentration (HEC). According to the EPA guidance document, *A Review of the Reference Dose and Reference Concentration Processes* (2002), an adjustment to continuous exposure for inhalation developmental effects is typically made. In general, any chemical in vapor form that leads to inhalation toxicity outside of the respiratory tract or results in systemic toxicity would require use of the Category 3 gas equation for calculating a HEC. The $BMCL_{HEC}$ of 66 mg/m^3 was calculated from the rat BMCL of 264 mg/m^3 using EPA (1994b) methodology for an extrarespiratory effect produced by a Category 3 gas, as follows:

$$BMCL_{ADJ} = 264 \text{ mg/m}^3 \times 6 \text{ hrs} \div 24 \text{ hrs}$$
$$= 66 \text{ mg/m}^3$$

$$BMCL_{HEC} = BMCL_{ADJ} \times (H_{b/g})_A \div (H_{b/g})_H$$
$$= 66 \text{ mg/m}^3 \times 1$$
$$= 66 \text{ mg/m}^3$$

where:

$(H_{b/g})_A \div (H_{b/g})_H$ = the ratio of the blood:gas (air) partition coefficient of the chemical for the laboratory animal species to the human value. In the absence of data for DIPE, a default value of 1 is used.

The **subchronic p-RfC** for DIPE, based on the $BMCL_{HEC}$ of 66 mg/m^3 for rudimentary and short 14th ribs in fetal rats exposed during gestation (Dalbey and Fueston, 1996), is derived as follows:

Subchronic p-RfC = $BMCL_{HEC} \div UF$
= 66 mg/m^3 ÷ 100
= **0.7 mg/m^3**

The composite UF of 100 is composed of the following:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 3 is applied to account for interspecies extrapolation (toxicodynamic portion only) because a dosimetric adjustment was made.
- UF_D: A factor of 3 is applied for database deficiencies because data for a inhalation multigeneration reproduction study are not available. The database includes a subchronic study and a developmental study in rats.
- UF_S: A factor of 1 is applied for subchronic-to-chronic extrapolation because a rat developmental study is chosen as the principal study. The effects associated with this study represent a sensitive lifestage and is not considered to be duration-dependent.
- UF_L: A factor of 1 is applied for LOAEL-to-NOAEL extrapolation because the current approach is to address this factor as one of the considerations in selecting a BMR for benchmark dose modeling. In this case, a BMR of 5% change in the incidence of rudimentary and short 14th ribs in fetal rats (a developmental effect) was selected under an assumption that it represents a minimal biologically significant change.

Confidence in the principal study (Dalbey and Feuston, 1996) is high. This study included an appropriate number of animals and exposure levels and investigated a suitable range of endpoints. Confidence in the database is medium. Only one species has been evaluated (rat) in a subchronic study, a neurotoxicity study, and a developmental study. A multigeneration reproduction study is not available. Confidence in the subchronic p-RfC is medium.

CHRONIC p-RfC

The **chronic p-RfC** for DIPE, based on the $BMCL_{HEC}$ of 66 mg/m^3 for rudimentary and short 14th ribs in fetal rats exposed during gestation (Dalbey and Fueston, 1996), is derived as follows:

Chronic p-RfC = $BMCL_{HEC} \div UF$
= 66 mg/m^3 ÷ 100
= **0.7 mg/m^3**

The composite UF of 100 is composed of the following:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 3 is applied to account for interspecies extrapolation (toxicodynamic portion only) because a dosimetric adjustment was made.
- UF_D: A factor of 3 is applied for database deficiencies because data for a inhalation multigeneration reproduction study are not available. The database includes a subchronic study and a developmental study in rats.
- UF_S: A factor of 1 is applied for subchronic-to-chronic extrapolation because a rat developmental study is chosen as the principal study. The effects associated with this study represent a sensitive lifestage and is not considered to be duration-dependent.
- UF_L: A factor of 1 is applied for LOAEL-to-NOAEL extrapolation because the current approach is to address this factor as one of the considerations in selecting a BMR for benchmark dose modeling. In this case, a BMR of 5% change in the incidence of rudimentary and short 14th ribs in fetal rats (a developmental effect) was selected under an assumption that it represents a minimal biologically significant change.

As stated in the derivation of a subchronic p-RfC, confidence in the principal study (Dalbey and Feuston, 1996) is high. Confidence in the database is medium because there are no multigenerational reproductive toxicity studies. Confidence in the chronic p-RfC is medium.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR DIISOPROPYL ETHER

As stated in **Introduction** on page 4, an evaluation of the cancer literature indicates that a major study related to the carcinogenicity of DIPE has been conducted by the Ramazzini Institute. As specified earlier, the cancer assessment for DIPE will remain on hold until the completion of the PWG review.

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APPENDIX A. DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC RfC

MODEL-FITTING PROCEDURE FOR CONTINUOUS DATA:

The model-fitting procedure for continuous data using the EPA benchmark dose software (BMDS) is as follows. The simplest model (linear) is first applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means is evaluated, and the polynomial, power, and Hill models are fit to the data while assuming constant variance. An adequate model fit is judged by three criteria: goodness-of-fit *p*-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all the models providing adequate fits to the data, the lowest BMD (BMDL) is selected as the point of departure (POD) when the difference between the BMDLs estimated from these models is more than three-fold (unless it appears to be an outlier); otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) is chosen. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means is evaluated, and the polynomial, power, and Hill models are also fit to the data and evaluated while the variance model is applied. Model fit and POD selection proceed as described earlier. If the test for constant variance is negative and the nonhomogenous variance model does not provide an adequate fit to the variance data, then the data set is considered unsuitable for modeling.

MODEL-FITTING RESULTS FOR MATERNAL BODY-WEIGHT GAINS IN RATS (DALBEY AND FEUSTON, 1996):

Following the above procedure, the continuous models in the EPA BMDS (version 2.1) were fit to the data shown in Table 5 for maternal body-weight gains in rats using the sham-exposed group as controls for both body-weight gain during GDs 6–16 and net weight gain (carcass weight minus GD 6 weight). The models were run with a BMR of 1 standard deviation (SD) from the control mean, as generally recommended by EPA (2000), and also with a relative deviation of 10% from the control mean (10% change is generally considered to be biologically significant for body weight). The results are shown in Table A-1. For the GDs 6–16 body-weight gain data, the assumption of constant variance did not hold, and the nonhomogenous variance model did not provide an adequate fit. For the net weight gain data, the constant variance model provided an adequate fit to the variance data, and the linear model provided an adequate fit to the means. The power and higher-degree polynomial models all defaulted back to the linear model. There were insufficient data points to fit the Hill model. The fit of the linear model to the data is shown in Figure A-1. Benchmark concentration (BMC) and the lowest bound of the BMC (BMCL) values were considerably higher using the BMR of 1 SD (28,820 and 19,552 mg/m^3) than using the BMR of 10% relative deviation (10,141 and 7261 mg/m^3). The lower BMCL values based on the 10% relative deviation were chosen to represent the modeling results for this endpoint.

Table A-1. Model Predictions for Maternal Weight Gain in Pregnant Rats[a]					
Model	**Variance *p*-Value[b]**	**Means *p*-Value[b]**	**AIC**	**BMC (mg/m^3)**	**BMCL (mg/m^3)**
GDs 6–16 BW gain (BMR = 1 SD)					
Linear (constant variance)[c]	0.078	0.02	504.3	15346	12038
Linear (modeled variance)[c]	0.033	0.02	506.3	15179	11488
Net BW gain (BMR =1 SD)					
Linear (constant variance)[c]	0.1599	0.207	494.5	28820	19552
Polynomial (constant variance)[c,d]	0.1599	0.207	494.5	28820	19552
Power (constant variance)[e]	0.1599	0.207	494.5	28820	19552
Hill (constant variance)[e]	0.1599	NA	496.9	NA	NA
Net BW gain (BMR = 10%)					
Linear (constant variance)[c]	**0.1599**	**0.207**	**494.5**	**10,141**	**7261**

[a]Dalbey and Feuston, 1996.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be negative.
[d]One degree polynomial shown. Higher degree polynomials default back to one degree.
[e]Power restricted to ≥1.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC; NA = Not applicable; SD = standard deviation.

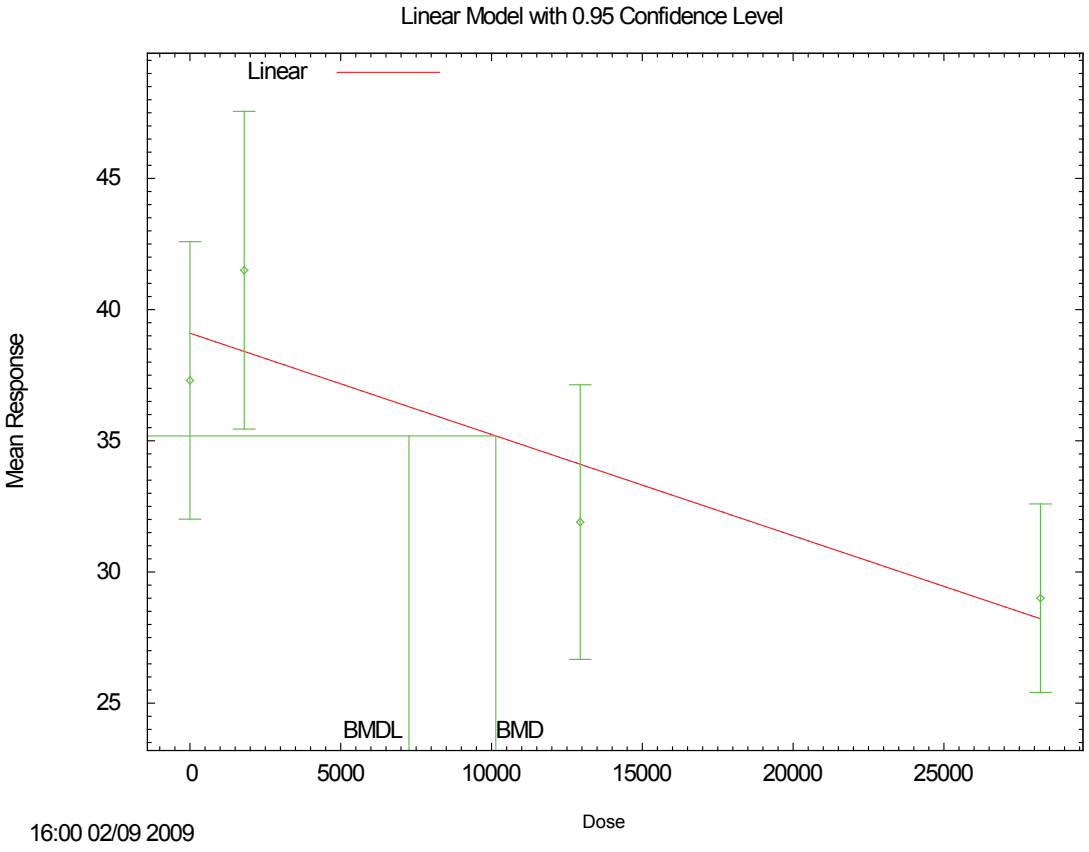

Figure A-1. Fit of Linear Model to Data on Net Maternal Body-Weight Gain in Rats (Dalbey and Feuston, 1996)

BMC and BMCL indicated are associated with a change of 10% from the control and are in units of mg/m^3.

```
================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File: C:\USEPA\BMDS21Beta\Data\10LinPTVLin.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21Beta\Data\10LinPTVLin.plt
                                          Mon Feb 09 16:00:39 2009
 ================================================================

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

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   The polynomial coefficients are restricted to be negative
   A constant variance model is fit

   Total number of dose groups = 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

Default Initial Parameter Values
alpha = 124.834
rho = 0 Specified
beta_0 = 39.0576
beta_1 = -0.000384966

Asymptotic Correlation Matrix of Parameter Estimates

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

	alpha	beta_0	beta_1
alpha	1	-2.6e-010	1.4e-010
beta_0	-2.6e-010	1	-0.7
beta_1	1.4e-010	-0.7	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	123.433	19.0461	86.1029	160.762
beta_0	39.094	1.69475	35.7723	42.4156
beta_1	-0.000385502	0.000106983	-0.000595185	-0.00017582

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	20	37.3	39.1	11.3	11.1	-0.722
1800	21	41.5	38.4	13.3	11.1	1.28
1.294e+004	21	31.9	34.1	11.5	11.1	-0.91
2.82e+004	22	29	28.2	8.1	11.1	0.328

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)

```
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                     Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
              A1         -242.684177            5     495.368354
              A2         -240.100150            8     496.200300
              A3         -242.684177            5     495.368354
          fitted         -244.259175            3     494.518350
               R         -250.296021            2     504.592043


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              20.3917          6        0.002358
   Test 2              5.16805          3          0.1599
   Test 3              5.16805          3          0.1599
   Test 4                 3.15          2           0.207

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


              Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =     Relative risk

Confidence level =          0.95
```

BMD = 10141.1

BMDL = 7261.4

MODEL-FITTING PROCEDURE FOR QUANTAL NONCANCER DATA:

The model-fitting procedure for dichotomous noncancer data is as follows. All available dichotomous models in the EPA BMDS 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). An adequate model fit is judged by three criteria: goodness-of-fit *p*-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMDL is selected as the POD when the difference between the BMDLs estimated from these models is more than three-fold (unless it appears to be an outlier); otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Although a 10% BMR is the default, in this case a 5% BMR was used because the developmental effect (i.e., short ribs) was observed during a potentially sensitive lifestage.

MODEL-FITTING RESULTS FOR INCIDENCE OF RUDIMENTARY/SHORT 14TH RIBS IN FETAL RATS (DALBEY AND FEUSTON, 1996):

Following the above procedure, the dichotomous models in the EPA BMDS (version 2.1) were fit to the data shown in Table 4 for incidence of rudimentary and short 14th ribs in the number of litters affected from the pregnant rats treated with DIPE during gestation. The incidence of affected litters, rather than individual fetuses, was modeled because fetuses or pups within litters do not respond independently. The sham-exposed group was used as the controls. The results are shown in Table A-2. All models fit the data adequately. The BMCLs from the models providing adequate fit differed by more than 3-fold. In accordance with EPA (2000) guidance, the lowest BMCL was selected from among the models providing adequate fit. The resulting benchmark concentration (BMC_5) and associated 95% lower confidence limit ($BMCL_5$) were 652 and 264 mg/m^3, respectively, based on the log-logistic model. The fit of the log-logistic model to the data is shown in Figure A-2.

Table A-2. Model Predictions for Incidence of Rudimentary/Short 14th Ribs in Fetal Rats[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)	Scaled Residual of Interest
Gamma (power ≥ 1)	2	1.6	0.4486	62.69	901.32	589.84	0.76
Logistic	2	1.42	0.4921	62.59	2356.76	1606.75	0.857
Log-Logistic (slope ≥ 1)	**1**	**2.26**	**0.1326**	**65.43**	652.399	264.336	**-0.202**
Log Probit (slope ≥ 1)	1	1.93	0.1643	65.17	6221.59	1667.01	0.967
Multistage (degree = 1, betas ≥ 0)	2	1.6	0.4486	62.69	901.319	589.84	0.76
Multistage (degree = 2, betas ≥ 0)	1	1.37	0.2411	64.46	1379.01	599.884	0.875
Multistage (degree = 3, betas ≥ 0)	1	1.16	0.2815	64.25	1304.77	609.616	0.845
Probit	2	1.38	0.5017	62.55	2213.23	1576.94	0.85
Weibull (power ≥ 1)	2	1.6	0.4486	62.69	901.319	589.84	0.76
Quantal-Linear	2	1.6	0.4486	62.69	901.319	589.84	0.76

[a]Dalbey and Feuston (1996).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC.

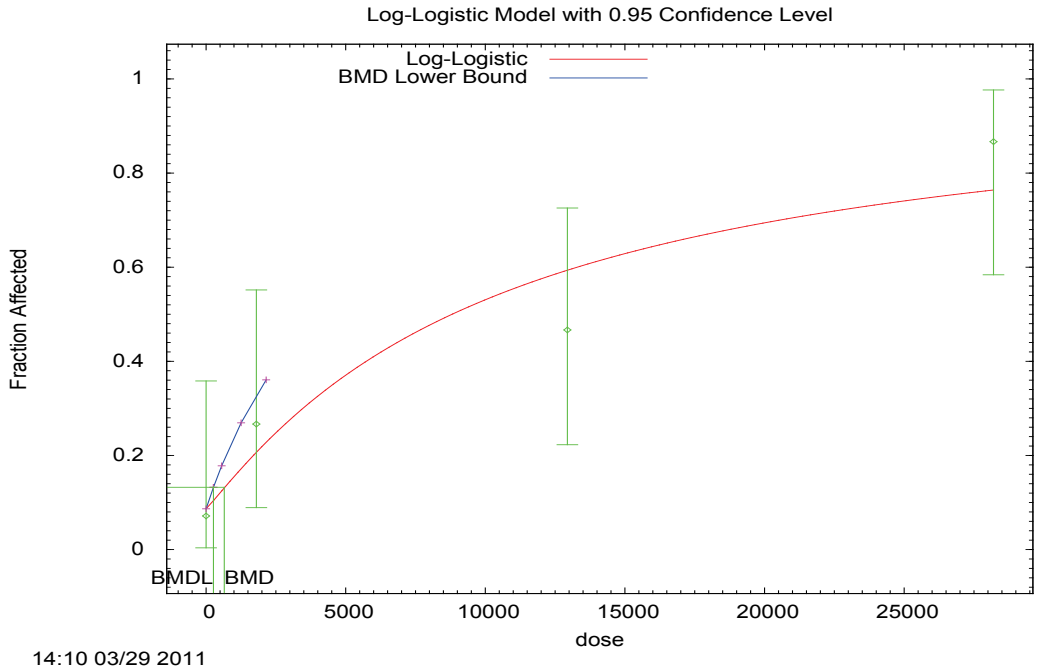

Figure A-2. Fit of Log-Logistic Model to Data on Incidence of Rudimentary/Short 14th Ribs in Fetal Rats (Dalbey and Feuston, 1996)

BMC and BMCLs indicated are associated with an extra risk of 5% and are in units of mg/m^3.

```
================================================================
        Dichotomous Hill Model. (Version: 1.0; Date: 09/24/2006)
        Input Data File:
C:\USEPA\BMDS21\Data\dhl_DIPE_inh_dich_dev_litters_Dhl-BMR05-Restrict.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\Data\dhl_DIPE_inh_dich_dev_litters_Dhl-BMR05-Restrict.plt
                                        Tue Mar 29 15:10:23 2011
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 BMDS Model Run
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   The form of the probability function is:

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

        where: 0 <= g < 1, 0 < v <= 1

               v is the maximum probability of response predicted by the
model,

               and v*g is the background estimate of that probability.


   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


                  Default Initial Parameter Values
                              v =        -9999
                              g =        -9999
                      intercept =     -9.11383
                          slope =      1.01079


           Asymptotic Correlation Matrix of Parameter Estimates

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

                       g    intercept

         g             1         -0.4

 intercept         -0.4            1


                                Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
              v                1              NA
              g           0.0625        0.0575656          -0.0503265
0.175327
      intercept         -9.13496         0.407024            -9.93271
-8.33721
          slope                1              NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test d.f.   P-value
     Full model         -28.5552
   Fitted model         -29.7575       2.40467      2          0.3005
  Reduced model         -40.2066       23.3028      3         <.0001

           AIC:           63.515
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0625	0.875	1	14	0.138
1800.0000	0.2149	3.223	4	15	0.4883
12940.0000	0.6086	9.129	7	15	-1.126
28200.0000	0.7680	11.520	13	15	0.9054

Chi^2 = 2.345887 d.f. = 2 P-value = 0.3095

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 488.101

BMDL = 162.338