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Provisional Peer-Reviewed Toxicity Values for

Ethoxyethanol Acetate
(CASRN 111-15-9)

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 reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure (oral)
RfC	reference concentration (inhalation)
RfD	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
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR ETHOXYETHANOL ACETATE (CASRN 111-15-9)

Background

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 two 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

There is no RfD, RfC, or carcinogenicity assessment for ethoxyethanol acetate (structure shown in Figure 1) on IRIS (U.S. EPA, 2009). The HEAST (U.S. EPA, 1997) lists an RfD of 0.3 mg/kg-day for both subchronic and chronic exposure based on an oral acceptable daily intake (ADI) of 0.3 mg/kg-day for ethoxyethanol acetate derived in a Health and Environmental Effects Profile (HEEP) on 2-ethoxyethanol esters (U.S. EPA, 1985). The ADI was derived from an oral NOAEL of 30.1 mg/kg-day estimated by route-to-route extrapolation from an inhalation NOEL of 50 ppm for developmental toxicity in rats exposed for 6 hours/day on Gestation Days (GDs) 6–15 (Union Carbide Corporation, 1984; later published as Tyl et al., 1988). The Chemical Assessments and Related Activities (CARA) database (U.S. EPA, 1994a, 1991a) lists no other documents besides the aforementioned HEEP. There is no entry for ethoxyethanol acetate in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006).

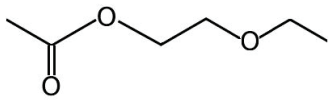

Figure 1. Chemical Structure of Ethoxyethanol Acetate

CalEPA (2009a,b,c) derived a chronic inhalation Reference Exposure Level (REL) of 0.3 mg/m^3 (0.06 ppm) for ethoxyethanol acetate based on developmental toxicity in rabbits (Tyl et al., 1988) but no chronic oral REL or cancer potency factor. There is no ATSDR (2009) Toxicological Profile or World Health Organization (WHO, 2009) Environmental Health Criteria Document for ethoxyethanol acetate. The carcinogenicity of ethoxyethanol acetate has not been evaluated by the National Toxicology Program (NTP, 2009, 2005) or the International Agency for Research on Cancer (IARC, 2009).

Occupational health guidelines and standards are available for ethoxyethanol acetate. ACGIH (2008, 2001) recommends a Threshold Limit Value-Time-Weighted Average (TLV-TWA) of 5 ppm (27 mg/m^3) to minimize the potential for reproductive effects. The TLV-TWA is based on testicular effects of ethoxyethanol acetate in mice and by analogy to the TLV for 2-ethoxyethanol. The National Institute for Occupational Safety and Health (NIOSH, 2005) has set a Recommended Exposure Limit (REL) of 0.5 ppm (2.7 mg/m^3) TWA. The Occupational Safety and Health Administration (OSHA, 2009) has promulgated a Permissible Exposure Limit (PEL) of 100 ppm (540 mg/m^3) TWA. Sweeney et al. (2001) proposed an Occupational Exposure Limit (OEL) of 2 ppm (11 mg/m^3), which was derived by using a probabilistic physiologically based pharmacokinetic (PBPK) model to estimate a NOAEL in humans from developmental toxicity data in rats.

Literature searches were conducted for studies relevant to the derivation of provisional toxicity values for ethoxyethanol acetate. Databases searched include MEDLINE, TOXLINE (BIOSIS and NTIS), TOXCENTER, CCRIS, DART/ETIC, TSCATS/TSCATS 2, GENETOX, HSDB, RTECS, and Current Contents. The time period covered by most of the searches ranged from the 1960s through early February 2010, although some searches covered earlier years. Reviews by Environment Canada (2009) and Johnson (2002) were also examined for relevant information.

REVIEW OF PERTINENT DATA

Human Studies

Epidemiology studies have noted hematological, reproductive, and developmental effects in workers exposed to mixtures of glycol ethers, including ethoxyethanol acetate.

Leucopenia was observed in male shipyard painters exposed to mixed solvents containing ethoxyethanol acetate (Kim et al., 1999). Air monitoring revealed that these workers were exposed to mean concentrations of ethoxyethanol acetate at 1.76–3.03 ppm (9.7–16.2 mg/m^3) with peak exposures of up to 8.12–18.27 ppm (44–97 mg/m^3). However, other solvents also detected in the air samples at higher concentrations included methyl isobutyl ketone, xylene, and toluene.

Workers at a silk-screening plant that used a cleaning solvent primarily composed of ethoxyethanol acetate and small amounts of methyl isobutyl ketone and toluene to clean the printing screens were evaluated for hematological effects (Loh et al., 2003). Women exposed to a geometric mean concentration of ethoxyethanol acetate in the atmosphere at 9.34 ppm (50.2 mg/m^3) had a significant ($p < 0.05$) reduction in hemoglobin (Hgb) and hematocrit (Hct) compared to the reference population, but men exposed to a geometric mean concentration of 4.87 ppm (27.0 mg/m^3) of ethoxyethanol acetate in the atmosphere did not exhibit any significant hematological changes. In follow-up surveys, the hematological effects observed in the female workers were no longer significant or present after the implementation of engineering controls at the factory for ≥1 year to decrease atmospheric concentrations, and protective measures including wearing rubber gloves (Chen et al., 2007). Loh et al. (2008) reported that there is no evidence based on evaluations of liver function profiles of the silk-screening workers that ethoxyethanol acetate is hepatotoxic.

No effects were observed on the menstrual patterns of women occupationally exposed to a mean TWA concentration of 0.51 ppm (3 mg/m^3) of ethoxyethanol acetate in the atmosphere at a liquid crystal display manufacturing facility (Chia et al., 1997). Several epidemiological studies have shown an association between maternal occupational exposure to glycol ether mixtures including 2-ethoxyethanol, ethoxyethanol acetate, 2-methoxyethanol, and 2-methoxyethanol acetate and increased risk of spontaneous abortion, conception delays, and congenital malformations (Cordier et al., 2001, 1997; Correa et al., 1996; Schenker, 1996, 1995; Beaumont et al., 1995; Swan et al., 1995). However, in a review of some of these studies, Maldonado et al. (2003) concluded that there is not enough evidence to determine whether occupational exposure to glycol ethers causes human congenital malformation. In addition, the relative contribution of ethoxyethanol acetate to the observed developmental effects among workers exposed to glycol ether mixtures is not known.

Animal Studies

Oral Exposure

Subchronic Studies—In a study from the Japanese literature, Nagano et al. (1984, 1979) administered ethoxyethanol acetate via gavage at 500, 1000, 2000, or 4000 mg/kg-day to groups of five male JCL-ICR mice, 5 days/week, for 5 weeks. An additional 20 mice served as the control group. Evaluations included hematology (white blood cell [WBC] count, red blood cell [RBC] count, Hct, and Hgb content), testes weights, combined weights of seminal vesicles and the coagulating gland, and histopathology of the testis. Three high-dose mice died prior to study termination. The English language report of this study (Nagano et al., 1984) included no details on the observed mortality and no mention of any effects on body weight. Dose-dependent decreases in absolute and relative testicular weights were observed. Table 1 summarizes the effects on organ weights. Decreased testicular weights were statistically significantly ($p < 0.05$) different than controls at ≥1000 mg/kg-day, and absolute weight of combined vesicular and coagulating glands was statistically significantly ($p < 0.05$) decreased compared to controls at 4000 mg/kg-day. Other significant findings include a reduction in WBC count at ≥2000 mg/kg-day and a decrease in Hct at 4000 mg/kg-day (see Table 1). Nagano et al. (1984) reported that histopathology revealed dose-related epithelial degeneration of the seminiferous tubules; however, the authors provided no further details regarding incidence or severity of these effects (data not shown). For the purposes of this review, the NOAEL and LOAEL are identified as 500 and 1000 mg/kg-day, respectively, based on decreased testicular weight.

Table 1. Organ Weights and Hematology in Mice Treated with Ethoxyethanol Acetate by Gavage for 5 Weeks

Parameter	Dose (mg/kg-day)				
	0	**500**	**1000**	**2000**	**4000**
Number of mice	20	5	5	5	2[a]
Absolute testes weight (mg)	291 ± 25[b]	269 ± 62	231 ± 66[c]	173 ± 39[c]	83 ± 7[c]
Relative testes weight (%)	0.76 ± 0.08	0.69 ± 0.18	0.66 ± 0.11[d]	0.44 ± 0.10[c]	0.21 ± 0.01[c]
Absolute vesicular and coagulating glands weight (mg)	376 ± 59	366 ± 80	341 ± 52	369 ± 36	299 ± 44[d]
Relative vesicular and coagulating glands weight (mg)	0.99 ± 0.16	0.94 ± 0.22	0.87 ± 0.14	0.93 ± 0.09	0.76 ± 0.07
WBC count (per mm^3)	3810 ± 1572	2940 ± 482	3940 ± 1380	2030 ± 606[d]	1100 ± 243[c]
RBC count ($10^4/mm^3$)	764 ± 79	685 ± 84	701 ± 60	719 ± 71	679 ± 32
Hct (%)	39.3 ± 2.7	37.5 ± 3.1	39.7 ± 3.1	37.8 ± 1.7	35.0 ± 0.8[d]
Hgb (g/dl)	12.7 ± 0.9	12.4 ± 0.7	12.8 ± 1.0	12.6 ± 1.1	11.7 ± 1.0

[a]3/5 animals were dead before examination.
[b]Mean ± standard deviation (SD).
[c]Significantly different from controls (Student's *t*-test, $p < 0.01$).
[d]Significantly different from controls (Student's *t*-test, $p < 0.05$).

Source: Nagano et al. (1979).

Reproductive/Developmental Studies—Following the NTP Reproductive Assessment by Continuous Breeding (RACB) protocol, groups of 20 male and 20 female CD-1 mice were allowed access ad libitum to drinking water containing 0.5, 1, or 2% ethoxyethanol acetate for 18 weeks (7 days premating, 98 days continuous breeding, and 21 days postmating) (Morrissey et al., 1989; Lamb et al., 1987; Gulati et al., 1985). Lamb et al. (1987) reported the corresponding doses as 930, 1860, and 3000 mg/kg-day. An additional group of 40 male and 40 female mice served as controls. The selected test concentrations were based on an initial range-finding study conducted by these researchers wherein ethoxyethanol acetate treatment significantly affected body-weight gain in mice at 5%, and to a lesser degree, at 2.5% in the drinking water. For the continuous breeding study, mice were monitored for survival, changes in body weight, and water consumption. Reproductive performance was assessed by evaluating fertility, pup survival, and sex ratio. At the high-dose, body weights were slightly reduced (<10%), and water consumption was reduced by about 20%. Table 2 summarizes results based on reproductive performance. The fertility index (number of fertile pairs per number of cohabited pairs) was significantly reduced only at the high-dose. At ≥1860 mg/kg-day, the mean number of litters per pair, the number of live pups per litter, and the adjusted live pup weights were significantly reduced.

Table 2. Reproductive Performance in Mice Treated with Ethoxyethanol Acetate in Drinking Water During a Continuous Breeding Study

Reproductive Parameter	Dose (mg/kg-day)			
	0	930	1860	3000
Fertility index (%)[a]	95 (36/38)	95 (19/20)	100 (19/19)	74 (14/19)[b]
Litters per pair	4.92 ± 0.05[c]	4.74 ± 0.10	4.53 ± 0.16[d]	1.64 ± 0.20[d]
Live pups per litter				
Male	5.77 ± 0.24	5.77 ± 0.34	4.07 ± 0.37[d]	0.32 ± 0.41[d]
Female	5.52 ± 0.22	5.40 ± 0.34	4.16 ± 0.31[d]	0.21 ± 0.21[d]
Combined	11.29 ± 0.43	11.17 ± 0.55	8.22 ± 0.62[d]	0.54 ± 0.30[d]
Proportion of pups born alive	0.96 ± 0.02	0.99 ± 0.01	0.88 ± 0.04[d]	0.17 ± 0.09[d]
Live pup weight (g)				
Male	1.66 ± 0.02	1.67 ± 0.02	1.66 ± 0.02	1.50 ± 0.13[e]
Female	1.58 ± 0.01	1.60 ± 0.02	1.55 ± 0.02	1.46[f]
Combined	1.62 ± 0.01	1.64 ± 0.02	1.60 ± 0.02	1.59 ± 0.12[e]
Adjusted live pup weight (g)[g]				
Male	1.69 ± 0.02	1.69 ± 0.02	1.62 ± 0.02[d]	1.40 ± 0.06[d,e]
Female	1.60 ± 0.01	1.61 ± 0.02	1.52 ± 0.02[d]	1.35 ± 0.09[d,f]
Combined	1.65 ± 0.01	1.66 ± 0.02	1.57 ± 0.02[d]	1.44 ± 0.05[d,e]

[a]Number of fertile pairs per number of cohabited pairs in parentheses.
[b]Significantly different from controls (Fisher's exact test, $p < 0.05$).
[c]Mean ± standard error.
[d]Significantly different from controls (Kruskal-Wallis test, $p < 0.05$).
[e]Ten litters in this group contained no live pups.
[f]Only one litter in this group contained live female pups.
[g]Means adjusted for total number of live and dead pups per litter by analysis of covariance.

Source: Gulati et al. (1985).

Based on the above findings, two additional studies were conducted as part of the NTP RACB protocol including (1) a cross-over mating study to determine if males or females were more sensitive to 2-ethoxyethanol treatment and (2) an assessment of the reproductive performance of the second generation (Morrissey et al., 1989; Lamb et al., 1987; Gulati et al., 1985).

The cross-over mating study was conducted using the animals that received 2% ethoxyethanol acetate (3000 mg/kg-day) in drinking water (Morrissey et al., 1989; Lamb et al., 1987; Gulati et al., 1985). Exposed mice of each sex were mated with control. A control group consisted of control males mated with control females. Test animals were necropsied, and reproductive organs, liver, and kidneys were weighed. Sperm morphology and vaginal cytology studies were also conducted. The litters of the crossover matings were evaluated for litter size, sex ratio, and pup weights. Table 3 summarizes effects on body and organ weights and results from sperm and vaginal cytology studies. There were no significant changes in female body or organ weights. Male mice demonstrated statistically significant ($p < 0.05$) decreases in body weight (magnitude was <10%) and absolute right testis weights

(7%) compared to controls. When adjusted for body weight by analysis of covariance, the change in testis weight was no longer significant. Sperm studies did not show any difference between control and treated males based on count or motility, but there was a significant increase in abnormal sperm compared with controls. There were no apparent effects on the estrous cycle in females. Table 4 summarizes results based on reproductive performance. No significant effects on fertility index, litter size, pup survival, or growth were observed among litters from treated males mated with control females. However, the fertility index of treated females mated with control males was significantly reduced compared to controls. In addition, there were marked decreases in the number of live pups per litter and proportion of pups born alive to treated female mice mated with control males. Based on these findings, female mice were subjected to a detailed histological examination, which did not reveal any significant treatment-related lesions. Gulati et al. (1985) concluded that the findings of the cross-over mating study suggest that the reduction in the number of litters per fertile pair observed in the continuous breeding study described above is attributable to effects in the female mice treated with ethoxyethanol acetate, even though histopathology of reproductive organs was observed for males (see below) and not females.

To assess the effects on the second generation, ethoxyethanol acetate was administered again in the drinking water ad libitum at 0, 0.5, or 1% (0, 930, and 1860 mg/kg-day) to F1 mice from weaning until mating at approximately 74 days of age (Morrissey et al., 1989; Lamb et al., 1987; Gulati et al., 1985). Mating was only allowed between female and male offspring from the same treatment group (20/sex/group). There were a limited number of live pups from dams treated with 2% (3000 mg/kg-day) ethoxyethanol acetate for this evaluation. F1 adults were evaluated for body weight, water consumption, and organ weights (reproductive organs, liver, and kidneys). Mating and fertility indexes were also calculated. F2 litters were evaluated for litter size, sex ratio, and pup weights. Table 5 summarizes effects in F1 adults on body and organ weights and results from sperm and vaginal cytology studies. No significant effects on growth were observed. F1 females from the high-dose group exhibited significant decreases in absolute and adjusted (for body weight by analysis of covariance) group mean liver weights. In F1 males, significant changes in organ weights include increased absolute and adjusted liver weights among the low-dose group, and decreased absolute right cauda weight among the high-dose group. Sperm studies did not reveal any significant effects on sperm motility or morphology, but there was a decrease in sperm density among F1 mice in the high-dose (1860 mg/kg-day) group that was significantly different from controls. There were no apparent effects on the estrous cycle in females. Based on these effects, high-dose mice were subjected to a detailed histological examination. No significant histological changes were observed among females. However, degeneration of seminiferous tubules, interstitial cell hyperplasia, reduction of sperm content, and accumulation of fluid and degenerated cells in the epididymis were noted in males. Table 6 summarizes effects on reproductive performance. There was a 50% reduction in the number of F1 pairs that were confirmed sperm positive at 1860 mg/kg-day. However, the fertility indexes for the treated and control pairs were similar. There was a reduction in the proportion of pups born alive at 1860 mg/kg-day compared to controls, but this difference is not significant.

Table 3. Body and Organ Weights in Mice Treated with Ethoxyethanol Acetate in Drinking Water During a Cross-Mating Study

Parameter	Dose (mg/kg-day)			
	0		3000	
	Males	Females	Males	Females
Number of mice	40	36	20	15
Body weight (g)	41.6 ± 0.77[a]	40.0 ± 0.99	38.8 ± 0.88[b]	37.1 ± 0.90
Organ weights				
Liver (g)				
Absolute	2.16 ± 0.05	2.25 ± 0.06	2.08 ± 0.08	2.07 ± 0.06
Adjusted for body weight	2.10 ± 0.03	2.21 ± 0.05	2.19 ± 0.05	2.16 ± 0.7
Kidneys (g)[c]				
Absolute	0.79 ± 0.02	0.58 ± 0.01	0.77 ± 0.02	0.60 ± 0.02
Adjusted for body weight	0.78 ± 0.02	0.58 ± 0.01	0.79 ± 0.02	0.62 ± 0.02
Right epididymis (mg)				
Absolute	55.8 ± 1.0	N/A	53.4 ± 1.1	N/A
Adjusted for body weight	55.4 ± 0.9		54.3 ± 1.3	
Right cauda (mg)				
Absolute	19.6 ± 0.4	N/A	18.9 ± 0.4	N/A
Adjusted for body weight	19.5 ± 0.4		19.1 ± 0.5	
Right testes (g)				
Absolute	0.14 ± 0.004	N/A	0.13 ± 0.004[d]	N/A
Adjusted for body weight	0.14 ± 0.003		0.13 ± 0.005	
Seminal vesicles (g)				
Absolute	0.62 ± 0.02	N/A	0.57 ± 0.03	N/A
Adjusted for body weight	0.61 ± 0.02		0.59 ± 0.03	
Prostate gland (mg)				
Absolute	31.7 ± 1.4	N/A	31.3 ± 1.4	N/A
Adjusted for body weight	31.0 ± 1.2		32.6 ± 1.7	
Sperm				
Motility (%)	95.3 ± 0.54[e]	N/A	93.3 ± 0.99	N/A
Density ($\times 10^6$ per gram caudal tissue)	1097 ± 54	N/A	1012 ± 80	N/A
Morphology (% abnormal sperm)	3.03 ± 0.23[e]	N/A	5.80 ± 1.71[b,e]	N/A
Length of estrous cycle (days)	N/A	4.96 ± 0.10[f]	N/A	5.00 ± 0.10[g]

[a]Mean ± standard error.
[b]Significantly different from controls (F test, $p < 0.05$).
[c]Kidneys weighed with adrenal glands attached.
[d]Significantly different from controls (F test, $p < 0.01$).
[e]No sperm present for one animal in this group.
[f]Estrous cycle length could not be accurately estimated for 11 of 36 control females.
[g]Estrous cycle length could not be accurately estimated for 4 of 15 treated females.

N/A = not applicable.

Source: Gulati et al. (1985).

Table 4. Reproductive Performance in Mice Treated with Ethoxyethanol Acetate in Drinking Water During a Cross-Mating Study

Reproductive Parameter	Treatment Group		
	Control Male × Control Female	Control Male × High-Dose Female	High-Dose Male × Control Female
Fertility index (%)[a]	59 (10/17)	27 (4/15)[b]	74 (14/19)
Live pups per litter			
Male	4.70 ± 0.92[c]	0.25 ± 0.25[d]	3.07 ± 0.58
Female	3.40 ± 0.70	0.25 ± 0.25[d]	4.50 ± 0.86
Combined	8.10 ± 1.33	0.50 ± 0.29[d]	7.57 ± 1.31
Proportion of pups born alive	0.85 ± 0.11	0.07 ± 0.04[d]	0.87 ± 0.08
Live pup weight (g)			
Male	1.69 ± 0.04[e]	2.04[f]	1.77 ± 0.05[g]
Female	1.66 ± 0.05[g]	1.53[f]	1.62 ± 0.05[g]
Combined	1.69 ± 0.03[g]	1.78 ± 0.25[e]	1.70 ± 0.05
Adjusted live pup weight (g)[h]			
Male	1.70 ± 0.06[e]	2.04 ± 0.16[f]	1.76 ± 0.04[g]
Female	1.66 ± 0.06[g]	1.50 ± 0.18[f]	1.62 ± 0.05[g]
Combined	1.69 ± 0.06[g]	1.76 ± 0.12[e]	1.70 ± 0.04

[a]Number of fertile pairs per number of cohabited pairs in parentheses.
[b]Significantly different from controls (Fisher's exact test, $p < 0.01$).
[c]Mean ± standard error.
[d]Significantly different from controls (Kruskal-Wallis test, $p < 0.05$).
[e]Two litters in this group contained no live pups.
[f]Based on only one litter.
[g]One litter in this group contained no live pups.
[h]Least squares estimate of mean ± standard error adjusted for average litter size.

Source: Gulati et al. (1985).

Table 5. Body and Organ Weights in Second Generation Mice Treated with Ethoxyethanol Acetate in Drinking Water

Parameter	Dose (mg/kg-day)					
	0		930		1860	
	Males	Females	Males	Females	Males	Females
Number of mice	20	20	20	20	20	20
Body weight (g)	35.98 ± 0.93[a]	32.5 ± 0.45	36.9 ± 0.69	32.6 ± 0.71	35.5 ± 0.91	31.1 ± 0.49
Organ weights						
Liver (g)						
Absolute	1.79 ± 0.06	1.88 ± 0.05	2.00 ± 0.05[b]	1.93 ± 0.04	1.90 ± 0.06	1.69 ± 0.05[b]
Adjusted for body weight	1.80 ± 0.04	1.86 ± 0.04	1.97 ± 0.04[d]	1.90 ± 0.04	1.92 ± 0.04[b]	1.75 ± 0.04[b]
Kidneys (g)[c]						
Absolute	0.69 ± 0.02	0.49 ± 0.01	0.71 ± 0.02	0.49 ± 0.02	0.71 ± 0.03	0.48 ± 0.01
Adjusted for body weight	0.69 ± 0.02	0.49 ± 0.01	0.70 ± 0.02	0.48 ± 0.01	0.72 ± 0.02	0.48 ± 0.01
Right epididymis (mg)						
Absolute	51.2 ± 1.4	N/A	49.0 ± 1.7	N/A	46.1 ± 2.0	N/A
Adjusted for body weight	51.4 ± 1.5		48.3 ± 1.4		46.8 ± 1.4	
Right cauda (mg)						
Absolute	18.8 ± 0.71	N/A	17.2 ± 0.64	N/A	15.0 ± 0.63[d]	N/A
Adjusted for body weight	18.9 ± 0.58		16.9 ±0.58		15.2 ± 0.58	
Right testes (g)						
Absolute	0.14 ± 0.004	N/A	0.14 ± 0.009	N/A	0.13 ± 0.008	N/A
Adjusted for body weight	0.14 ± 0.007		0.14 ± 0.007		0.13 ± 0.007	
Seminal vesicles (g)						
Absolute	0.44 ± 0.02	N/A	0.44 ± 0.02	N/A	0.40 ± 0.02	N/A
Adjusted for body weight	0.44 ± 0.02		0.43 ± 0.02		0.40 ± 0.17	
Prostate gland (mg)						
Absolute	24.2 ± 1.4	N/A	21.3 ± 1.5	N/A	20.7 ± 1.4	N/A
Adjusted for body weight	24.3 ± 1.2		20.7 ± 1.2		21.2 ± 1.2	
Sperm						
Motility (%)	91.0 ± 1.1	N/A	87.6 ± 2.5	N/A	87.9 ± 3.7	N/A
Density ($\times 10^6$ per gram caudal tissue)	1378 ± 101	N/A	1247 ± 92	N/A	973 ± 93[b]	N/A
Morphology (% abnormal sperm)	4.24 ± 1.2	N/A	4.30 ± 0.78	N/A	6.03 ± 1.47	N/A
Length of estrous cycle (days)	N/A	5.19 ± 0.2[e]	N/A	5.17 ± 0.1[f]	N/A	4.94 ± 0.2[g]

[a]Mean ± standard error.
[b]Significantly different from controls (F test, $p < 0.05$).
[c]Kidneys weighed with adrenal glands attached.
[d]Significantly different from controls (F test, $p < 0.01$).
[e]Estrous cycle length was > 7 days or could not be accurately estimated for 4 of 20 control females.
[f]Estrous cycle length was > 7 days or could not be accurately estimated for 2 of 20 low-dose females.
[g]Estrous cycle length could not be accurately estimated for 2 of 20 high-dose females.

N/A = not applicable.

Source: Gulati et al. (1985).

Table 6. Reproductive Performance in Second Generation Mice Treated with Ethoxyethanol Acetate in Drinking Water

Reproductive Parameter	Dose (mg/kg-day)		
	0	930	1860
Mating Index (%)[a]	90 (18/20)	95 (19/20)	50 (10/20)
Fertility index (%)[b]	55 (11/20)	65 (13/20)	45 (9/20)
Live pups per litter			
Male	5.73 ± 0.65[c]	4.92 ± 0.68	4.00 ± 1.05
Female	5.02 ± 0.57	5.31 ± 0.72	4.22 ± 0.78
Combined	11.55 ± 0.61	10.23 ± 0.96	8.22 ± 1.53
Proportion of pups born alive	0.96 ± 0.04	0.99 ± 0.01	0.77 ± 0.13
Live pup weight (g)			
Male	1.63 ± 0.04	1.72 ± 0.06	1.68 ± 0.06[d]
Female	1.55 ± 0.03	1.59 ± 0.04[e]	1.55 ± 0.04
Combined	1.59 ± 0.03	1.68 ± 0.07	1.60 ± 0.04
Adjusted live pup weight (g)[f]			
Male	1.69 ± 0.03	1.69 ± 0.03	1.66 ± 0.04[d]
Female	1.59 ± 0.03	1.58 ± 0.02[e]	1.52 ± 0.03
Combined	1.65 ± 0.03	1.65 ± 0.03	1.57 ± 0.04

[a]Number with copulatory plugs per number of cohabited pairs in parentheses.
[b]Number of fertile pairs per number of cohabited pairs in parentheses.
[c]Mean ± standard error.
[d]One litter in this group contained no live male pups.
[e]One litter in this group contained no live female pups.
[f]Least squares estimate of mean ± standard error adjusted for average litter size.

Source: Gulati et al. (1985).

Based on the three companion mouse studies conducted under the NTP RACB protocol, Gulati et al. (1985) concluded that ethoxyethanol acetate is a reproductive toxicant in mice based on effects on reproductive performance in F0 mice characterized by decreases in fertility, the number of litters per fertile pair, live pups per litter, proportion of pups born alive, and pup weights at ≥1860 mg/kg-day. Gulati et al. (1985) also concluded that females appeared more sensitive to these effects based on a nearly 50% decline in fertility and decreased number of live pups per litter in the crossover mating study. Sperm parameters, testes weights, and an increased incidence of abnormal sperm suggested modest effects on the male mice as well. Second-generation animals also exhibited a slight reduction in fertility at 1860 mg/kg-day and prominent histopathologic changes in the testes and epididymis of males. Based on these findings, Lamb et al. (1987) identified a NOAEL of 930 mg/kg-day for reproductive toxicity. For the purpose of this review, a NOAEL of 930 mg/kg-day and a LOAEL of 1860 mg/kg-day are identified for reproductive toxicity.

Inhalation Exposure

Subchronic Studies—Truhaut et al. (1979) exposed a group of 40 male and 40 female Wistar rats and a group of 2 male and 2 female New Zealand rabbits to ethoxyethanol acetate (≥99% purity) vapor at 200 ppm (1081 mg/m^3), 4 hours/day, 5 days/week, for 10 months.

Groups of 10 male and 10 female Wistar rats and 2 male and 2 female New Zealand rabbits served as controls. Evaluations included body weight, hematology (RBC and WBC counts and Hgb content), urinalysis (pH, protein, glucose, ketone bodies, and nitrites), gross pathology, and detailed histopathology. Data showed no significant effects on growth or hematology, and Truhaut et al. (1979) reported that no hematuria or ketonuria was observed. The authors reported histological lesions described as "tubular nephritis with clear degeneration of the epithelium with hyaline and granular tubular casts" in the kidneys of male rats and rabbits of both sexes (data not shown). The authors did not observe any significant lesions in female rats, and they reported a progressive restoration of the renal parenchyma in surviving animals following the exposure period. Based on the evidence of renal damage in rabbits and male rats, a freestanding LOAEL of 200 ppm (1081 mg/m^3) is identified for this study, although interpretation of these results is limited by the small group sizes for rabbits and incomplete reporting of study details.

Carpenter (1947) exposed groups of three adult male dogs to 0 or 600 ppm (0 or 3243 mg/m^3) ethoxyethanol acetate vapor, 7 hours/day, 5 days/week, for 24 weeks. The available study description was very brief. Evaluations included body weight, hematology (complete blood counts and reticulocyte count), serum phosphorus, blood urea nitrogen, sulfobromophthalein excretion, urinalysis (endpoints not specified), gross pathology, and histopathology (liver, kidney, adrenal, thyroid, bladder, heart, intestine, lung, pancreas, spleen, and testis). The author reported that no significant treatment-related effects were observed in dogs exposed to ethoxyethanol acetate vapor for 24 weeks (data not shown). Although 600 ppm (3243 mg/m^3) appears to be a NOAEL for this study, the interpretation of these results is limited by the small group sizes and incomplete reporting of study details.

Reproductive/Developmental Studies—Groups of Sprague-Dawley rats were exposed to ethoxyethanol acetate vapor at 130, 390, or 600 ppm (703, 2108, or 3243 mg/m^3), 7 hours/day, on GDs 7–15 (Nelson et al., 1984; NIOSH, 1982). Group sizes were 15, 15, and 9 for the low-, mid-, and high-concentrations, respectively. Data were compared to a pooled sham-exposed control group of 34 rats. Evaluations included maternal body weights and number of resorption sites and live fetuses. Upon sacrifice of the dams, fetuses were removed, weighed, sexed, and examined for visceral abnormalities and skeletal defects. Nelson et al. (1984) reported that maternal body weights were reduced at higher concentrations (data not shown). They considered the weight reduction among dams at the higher exposure concentrations likely to be due to increased resorptions among these groups (see below). The authors did not report corrected maternal body weights based on gravid uterine weights. Table 7 summarizes pregnancy outcome data. All implants were resorbed in the 600-ppm group. Mean number of resorptions per litter were also significantly ($p < 0.05$) increased in the 390-ppm group. There were significant decreases in fetal weights at 130 (<5%) and 390 (21%) ppm. Visceral and skeletal malformations were significantly increased (on a litter basis) in the 390-ppm group, including malformations of the heart, umbilicus, and ribs. One fetus from the 130-ppm group also exhibited a heart malformation. Nelson et al. (1984) argued that as heart defects rarely occur spontaneously and in the absence of a similar malformation in any control rat, this defect was likely related to ethoxyethanol acetate treatment. There were also significant increases in the incidences of visceral variations at 390 ppm and skeletal variations at 130 and 390 ppm. Nelson et al. (1984) concluded that ethoxyethanol acetate was teratogenic at ≥130 ppm in rats. Based on increased resorptions, decreased fetal weights, and increased incidences of malformations and

Table 7. Developmental Effects in Rats Exposed to Ethoxyethanol Acetate Vapor During Gestation

Parameter	Exposure Concentration (mg/m^3)			
	0	**703**	**2108**	**3243**
Number pregnant/number mated	34/41	15/15	15/20	9/9
Mean number of implants per dam	12.7	14.5[a]	12.9	14.7[a]
Litters with resorptions (%)[b]	14 (42)	7 (47)	9 (56)	9 (100)
Mean number of resorptions per litter	0.64	0.49	2.3[a]	14.7[a]
Resorptions (% of implants)[b]	23 (5)	8 (4)	35 (17)	103 (100)
Mean number of live fetuses per litter[b]	12.2	14.0	10.8	0
Mean live fetal weights (g) Female Male	 3.46 3.64	 3.31[c] 3.46[c]	 2.74[c] 2.85[c]	 N/A N/A
Incidence of visceral malformations Total (based on number of litters) Total (based on number of fetuses) Cardiac IV septal defect Ringed aortic arch Rt.-sided ductus arteriosus Umbilical hernia	 0/34 0/270 0/270 0/270 0/270 0/270	 1/15 1/142 0/142 1/142 0/142 0/142	 3/15[d] 7/116 6/116 2/116 1/116 2/116	 N/A
Incidence of skeletal malformations Total (based on number of litters) Total (based on number of fetuses) Ribs Wavy Fused	 0/34 0/137 0/137 0/137	 0/15 0/69 0/69 0/69	 3/15[d] 4/59 2/59 1/59	 N/A
Incidence of visceral variations Total (based on number of litters) Total (based on number of fetuses)	 26/34 79/270	 14/15 47/142	 15/15[d] 58/116	 N/A
Incidence of skeletal variations Total (based on number of litters) Total (based on number of fetuses)	 19/34 37/137	 14/15[e] 39/69	 15/15[d] 56/59	 N/A

[a]Significantly different from controls (Kruskal-Wallis test, $p < 0.05$).
[b]Statistical analysis was not conducted for this endpoint.
[c]Significantly different from controls (mixed model analysis of covariance using MLE, $p < 0.05$).
[d]Statistical significance was evaluated using the litter as the experimental unit. Significantly different from controls (Kruskal-Wallis test, $p < 0.01$).
[e]Statistical significance was evaluated using the litter as the experimental unit. Significantly different from controls (Kruskal-Wallis test, $p < 0.05$).
Source: Nelson et al. (1984).

variations among fetuses of treated dams, the low exposure level of 130 ppm (703 mg/m^3) is identified as a LOAEL for this study; a NOAEL is not identified.

Tyl et al. (1988) exposed groups of 30 pregnant Fischer 344 rats to ethoxyethanol acetate (99.8% purity) vapor at 0, 50, 100, 200, or 300 ppm (0, 270, 541, 1081, or 1622 mg/m^3), 6 hours/day on GDs 6–15. Evaluations of dams included clinical signs, food and water consumption, body weights, hematology (RBC, WBC, and platelet counts, Hgb, Hct, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]), organ weights (liver, kidneys, thymus, spleen, uterus), number of corpora lutea, number of resorption sites, and gross examination of reproductive, abdominal, and thoracic organs and cavities. Fetuses were weighed and examined for external, visceral, and skeletal malformations and variations. Table 8 summarizes maternal effects. Food consumption and maternal body-weight gain were both significantly ($p < 0.05$) reduced at ≥200 ppm during the exposure period. However, Tyl et al. (1988) reported that by study termination, maternal body weight, as well as gravid uterine weight, was similar to controls (data not reported). During the postexposure period, food consumption was significantly ($p < 0.05$) reduced only at 300 ppm. Tyl et al. (1988) reported that treated dams exhibited periocular wetness and encrustation; these data were not shown. Hematological changes included increased (15%) WBC count and decreased (7–9%) platelet count at ≥200 ppm, and decreased RBC count, Hgb, Hct, and MCV at ≥100 ppm. Tyl et al. (1988) reported that all maternal organ weights were similar to controls except for increased absolute liver weights in all treatment groups and increased relative liver weights at ≥100 ppm. Tyl et al. (1988) considered increased liver weights to be an adaptive response rather than a pathological response because the liver is the presumed site of metabolism.

The pregnancy rate was high and uniform across all treatment groups, and there was no treatment-related effect on the number of corpora lutea (Tyl et al., 1988). Table 9 summarizes significant developmental effects. There was a small significant increase in the number of nonviable implantations per litter at 300 ppm. Fetal body weights were significantly reduced at ≥200 ppm. Although no external malformations were observed, there were significant increases in the incidences of visceral (cardiovascular and renal) malformations at 300 ppm and skeletal (cervical rib) and total malformations at ≥200 ppm. The incidences of numerous individual visceral (again, primarily cardiovascular and renal) and skeletal variations (and one external variation) were increased as well. The most sensitive visceral variations were increased at ≥100 ppm, while the most sensitive skeletal variations were increased at ≥50 ppm. Tyl et al. (1988) did not consider 50 ppm to be a LOAEL because there were no other indications of fetotoxicity at this level other than an increase in two indications of reduced ossification in the rat fetal skeleton. Therefore, Tyl et al. (1988) identified a NOAEL of 50 ppm for rats in this study. However, for the purpose of this review, based on evidence of a developmental delay at 50 ppm characterized by reduced ossification and increased incidence and severity of developmental effects at higher concentrations, the low concentration of 50 ppm (270 mg/m^3) is identified as a LOAEL for developmental toxicity; a NOAEL is not identified. Maternal effects occurred with a LOAEL of 100 ppm (541 mg/m^3) and NOAEL of 50 ppm (270 mg/m^3), based on decreases in RBC parameters (RBC count, Hgb, Hct) in dams.

Table 8. Significant Maternal Changes in Rats and Rabbits Treated with Ethoxyethanol Acetate Vapor via Inhalation During Gestation

Parameter	Exposure Concentration (mg/m^3)				
	0	**270**	**541**	**1081**	**1622**
Rats					
Number of dams pregnant at termination	28	28	28	28	29
Maternal weight change (g) GDs 6–15	25.5 ± 4.5[a]	25.6 ± 4.4	24.5 ± 4.6	20.8 ± 4.1[b]	16.2 ± 3.6[b]
Maternal food intake (g/day) GDs 6–15	15.82 ± 1.12	15.47 ± 1.17	15.38 ± 0.91	14.75 ± 0.79[b]	13.73 ± 0.84[b]
Hematology					
WBC count	6.7 ± 1.3	7.1 ± 0.9	6.8 ± 1.0	7.8 ± 1.0[b]	8.1 ± 1.0[b]
RBC count	6.3 ± 0.5	6.2 ± 0.3	6.0 ± 0.3[c]	5.9 ± 0.4[b]	5.9 ± 0.5[b]
Hgb	12.6 ± 1.0	12.3 ± 0.6	11.8 ± 0.8[c]	11.7 ± 1.0[b]	11.6 ± 1.1[b]
Hct	34.6 ± 2.7	33.6 ± 2.0	32.4 ± 1.7[c]	32.0 ± 2.5[b]	31.8 ± 2.8[b]
MCV	54.6 ± 0.6	54.3 ± 0.6	54.1 ± 0.7[d]	54.1 ± 0.8[c]	54.1 ± 0.5[c]
Platelets	1072 ± 98	1075 ± 74	1038 ± 59	982 ± 124[b]	1001 ± 79[c]
Rabbits					
Number of does pregnant at termination	22	21	23	19	19
Maternal weight change GDs 6–9 GDs 6–18	 -58 ± 60 12 ± 117	 -77 ± 72 9 ± 125	 -111 ± 5[d] -60 ± 211	 -173 ± 86[b] -107 ± 150	 -241 ± 111[c] -231 ± 130[c]
Hematology					
MCV	66.5 ± 2.5	66.4 ± 2.0	66.1 ± 1.7	66.5 ± 2.7	68.4 ± 2.5[c]
Platelets	487 ± 102	471 ± 117	417 ± 138[d]	395 ± 103[c]	257 ± 88[b]

[a]Mean ± SD.
[b]Significantly difference from controls (*t*-test, $p < 0.001$).
[c]Significantly different from controls (*t*-test, $p < 0.01$).
[d]Significantly different from controls (*t*-test, $p < 0.05$).

Source: Tyl et al. (1988).

Table 9. Developmental Effects in Rats Exposed to Ethoxyethanol Acetate Vapor via Inhalation During Gestation

Parameter	Exposure Concentration (mg/m^3)				
	0	**270**	**541**	**1081**	**1622**
Number of dams pregnant at termination	28	28	28	28	29
Viable implants/litter[a]	10.4 ± 2.6	10.9 ± 1.1	10.8 ± 1.9	10.3 ± 1.5	10.8 ± 1.2
Nonviable implants/litter[a]	0.1 ± 0.4	0.3 ± 0.6	0.4 ± 0.6	0.4 ± 0.6	0.5 ± 0.7[b]
Number of litters examined	28	28	28	28	29
Fetal body weights/litter (g)[a]					
All fetuses	4.3 ± 0.19	4.3 ± 0.10	4.3 ± 0.10	4.1 ± 0.30[c]	3.7 ± 0.12[c]
Male fetuses	4.4 ± 0.19	4.4 ± 0.19	4.5 ± 0.14	4.2 ± 0.24[c]	3.9 ± 0.11[c]
Female fetuses	4.2 ± 0.12	4.1 ± 0.19	4.2 ± 0.11	3.9 ± 0.32[c]	3.6 ± 0.13[c]
Malformations[d]					
Visceral	5/28	3/28	2/28	7/28	26/29[e]
Skeletal	2/27	4/28	5/28	15/28[e]	21/29[e]
Total	7/28	6/28	6/28	18/28[e]	27/29[e]
Most sensitive external variations[d]					
Cranial ecchymosis	7/28	11/28	11/28	7/28	22/29[e]
Most sensitive visceral variations[d]					
Irregular rugae on palate	10/28	11/28	21/28[e]	26/28[e]	24/29[e]
Left subclavian branches distal to ductus arteriosus	0/28	4/28	6/28[e]	7/28[e]	16/29[e]
Most sensitive skeletal variations[d]					
Unossified anterior arch of atlas	9/27	20/28[e]	24/28[e]	27/28[e]	29/29[e]
Poorly ossified metatarsals (hindlimb)	7/27	15/28[e]	16/28[e]	25/28[e]	4/29

[a]Mean ± SD.
[b]Significantly different from controls (Mann-Whitney U test, $p < 0.05$).
[c]Significantly different from controls (Mann-Whitney U test, $p < 0.001$).
[d]Incidence based on number of litters.
[e]Significantly different from controls (Fisher's exact test, $p < 0.05$).

Source: Tyl et al. (1988).

In a companion rabbit study, Tyl et al. (1988) exposed groups of 24 pregnant New Zealand white rabbits to ethoxyethanol acetate (99.8% purity) vapor at 0, 50, 100, 200, or 300 ppm (0, 270, 541, 1081, or 1622 mg/m^3), 6 hours/day on GDs 6–18. Aside from not measuring food and water consumption, rabbits were evaluated for the same endpoints as outlined above in the companion rat study through GD 29. Table 8 summarizes maternal effects. Rabbits experienced significant decreases in body-weight gain at ≥100 ppm during the first few days of the exposure period (GDs 6–9), but only at 300 ppm, based on the full exposure period. During the postexposure period, rabbits exposed to 300 ppm exhibited a significant increase in weight gain over controls. Clinicals signs reported by the researchers included scant feces on paperboard (indirect evidence of reduced feed consumption) at ≥100 ppm, and occult blood predominately at ≥200 ppm. Tyl et al. (1988) reported that gravid uterine weights were 73.99% of controls at 200 ppm and 18.77% of controls at 300 ppm. These findings were consistent with 5/19 and 16/19 resorbed litters observed at 200 and 300 ppm, respectively, as reported by the

authors. Tyl et al. (1988) also reported that absolute liver weights were significantly increased (121.24%) at 300 ppm compared to controls. Tyl et al. (1988) noted that relative liver weights were not significantly different from controls at this level. As mentioned above, Tyl et al. (1988) considered increased liver weights to be an adaptive response rather than a pathological response because the liver is the presumed site of metabolism. Hematological data showed changes including significant elevation of MCV at 300 ppm and a dose-related decrease in the number of platelets achieving significance at ≥100 ppm (see Table 8).

The pregnancy rate of rabbits at ≥200 ppm was slightly reduced compared to controls, but this difference was not statistically significant (Tyl et al., 1988). Table 10 summarizes developmental effects in rabbits. At the highest exposure level, there was a significant reduction in corpora lutea per doe and a significant increase in early resorptions per litter. The number of viable implants per litter was significantly reduced at 200 and 300 ppm in dose-related fashion, and the number of nonviable implants per litter was increased accordingly at these same concentrations. The number of litters with live fetuses was markedly reduced at both 200 ppm and 300 ppm, with only three surviving litters at 300 ppm. The small number of litters in the 300-ppm group influenced the results of statistical testing of fetal data for this group. Fetal weights per litter were comparable to controls at 50, 100, and 200 ppm but appeared to be reduced by about 10% at 300 ppm compared to controls (difference was not significant). External, visceral, and skeletal malformations were significantly increased on a litter basis at 200 and (in some cases) 300 ppm. Only 11 fetuses from three surviving litters were available for examination at 300 ppm, and all were malformed. External malformations were predominantly in the tail, which Tyl et al. (1988) notes as a finding to which New Zealand white rabbits are predisposed. Visceral malformations included ventricular septal defects and absent postcaval lung lobes and kidneys. Only one skeletal malformation was significantly increased in rabbits exposed at the highest concentration—rudimentary 14th ribs. The data on developmental variations showed that the most sensitive individual external and visceral variations occurred at 200 ppm, while the most sensitive skeletal variations were increased at 100 and 200 ppm. Tyl et al. (1988) identified a NOAEL of 50 ppm in this study for rabbits for both maternal and developmental toxicity. For the purpose of this review, a NOAEL of 50 ppm (270 mg/m^3) and a LOAEL of 100 ppm (541 mg/m^3) are identified based on decreased body weight and hematological changes in dams and skeletal variations in fetuses.

Imperial Chemical Industries (1983a,b) conducted two inhalation studies with ethoxyethanol acetate on groups of pregnant Dutch rabbits to assess maternal and developmental effects. In this first study, groups of eight rabbits were exposed to ethoxyethanol acetate (99% purity) vapor at mean measured exposure concentrations of 0, 111, 224, or 420 ppm (0, 600, 1211, or 2270 mg/m^3) (Imperial Chemical Industries, 1983a). In the second study, larger groups (24/group) were exposed to mean measured exposure concentrations of 0, 25, 99, or 412 ppm (0, 135, 535, or 2227 mg/m^3) (Doe, 1984; Imperial Chemical Industries, 1983b). In both studies, rabbits were exposed 6 hours/day on GDs 6–18. Maternal evaluations included survival, body weight, food consumption, hematology (Hgb, Hct, total WBC count, RBC count, MCV, MCH, MCHC), spleen and uterus weights, and a detailed pathological examination. In addition, implantation loss was calculated based on numbers of corpora lutea, implantations, and live fetuses. In both studies, fetuses were examined for weight and gross abnormalities. However, examinations for visceral and skeletal abnormalities were only conducted in the second study (Doe, 1984; Imperial Chemical Industries, 1983b).

Table 10. Developmental Effects in Rabbits Exposed to Ethoxyethanol Acetate Vapor via Inhalation During Gestation

Parameter	Exposure Concentration (mg/m^3)				
	0	**270**	**541**	**1081**	**1622**
Number of does pregnant at termination	22	21	23	19	19
Corpora lutea/doe[a]	11.3 ± 2.3	10.2 ± 1.5	11.0 ± 2.1	10.9 ± 2.0	9.4 ± 2.4[b]
Viable implants/litter[a]	8.3 ± 2.1	7.5 ± 2.7	8.3 ± 2.6	5.4 ± 4.1[b]	0.6 ± 1.6[b]
Nonviable implants/litter[a]	0.7 ± 0.8	0.4 ± 0.8	0.7 ± 1.0	3.5 ± 3.6[b]	6.8 ± 3.2[b]
Early resorptions/litter[a]	0.3 ± 0.6	0.0 ± 0.2	0.1 ± 0.3	2.3 ± 3.6	6.5 ± 3.4[b]
Number of litters with no live fetuses	0	0	1	5	16
Number of litters examined	22	21	22	14	3
Fetal body weights/litter (g)[a]					
All fetuses	41.8 ± 5.1	45.2 ± 5.8	39.8 ± 6.3	40.8 ± 5.9	36.4 ± 1.3
Male fetuses	41.4 ± 6.5	45.9 ± 5.8	40.0 ± 6.0	40.1 ± 6.0[c]	37.1 ± 2.3
Female fetuses	41.5 ± 5.6	43.8 ± 5.9[c]	39.7 ± 7.2	41.0 ± 6.7	37.4 ± 3.3[c]
Malformations[d]					
External	1/22	2/21	1/22	7/14[e]	3/3[e]
Visceral	9/22	12/21	11/22	12/14[e]	3/3
Skeletal	1/22	5/20	1/22	12/14[e]	2/3[e]
Total	10/22	15/21	12/22	14/14[e]	3/3
Most sensitive external variations[d]					
Blunt-tipped tail	0/22	1/21	1/22	5/14[e]	1/3
Most sensitive visceral variations[d]					
Irregular rugae on palate	11/22	11/21	14/22	13/14[e]	2/3
Incomplete septation of lung lobes	2/22	1/21	0/22	7/14[e]	3/3[e]
Partial fetal atelectasis	0/22	1/21	2/22	5/14[e]	0/3
Most sensitive skeletal variations[d]					
Extra thoracic centrum and arch (Number 13)	6/22	5/20	15/22[e]	13/14[e]	2/2
Extra ribs on thoracic centra and arch 13, bilateral	6/22	5/20	14/22[e]	13/14[e]	2/2
Poorly ossified sternebra 6	9/22	10/20	17/22[e]	11/14[e]	0/2
Misshapen sternebrae	2/22	0/20	10/22[e]	6/14[e]	1/2
Split sternebrae	0/22	1/20	5/22[e]	1/14	0/2
Unossified sternebrae	6/22	7/20	16/22[e]	11/14[e]	1/2

[a]Mean ± SD.
[b]Significantly different from controls (Mann-Whitney U test, $p < 0.05$; Dunnett's test for viable implants/litter).
[c]At 50 ppm, $n = 19$; at 200 ppm; $n = 13$; and, at 300 ppm, $n = 2$.
[d]Incidence based on number of litters.
[e]Significantly different from controls (Fisher's exact test, $p < 0.05$).

Source: Tyl et al. (1988).

Imperial Chemical Industries (1983a) observed a reduction in body-weight gain and food consumption among all treatment groups compared to controls during the first few days of exposure (GDs 5–10) (see Table 11). These differences only achieved statistical significance ($p < 0.05$) at 420 ppm. Subsequent weight gain was comparable to controls. Food consumption was significantly higher than controls at 420 ppm during the postexposure period (GDs 19–21). Aside from a single rabbit exposed to 420 ppm that exhibited marked ataxia, loss of withdrawal reflex, and slight head tremors, the study authors noted no other clinical signs. Postmortem examination of the observably sick rabbit revealed 100% postimplantation loss but no indication of the cause of the clinical signs. Mean gravid uterine weights at sacrifice were reduced among all treatment groups compared to controls, but the difference was only significant at 420 ppm. The data showed no significant maternal effects based on hematology, spleen weights, or pathology. Table 11 summarizes litter data. There was a dose-related increase in group mean percentage preimplantation loss that was statistically different from controls at 111 and 420 ppm—but not at 224 ppm. There were also apparent increases in postimplantation loss and decreases in number of viable fetuses at 420 ppm, although the differences from controls were not statistically significant. The number of early intrauterine deaths was significantly increased at 420 ppm. Mean fetal weights per litter were significantly reduced in all treatment groups. Imperial Chemical Industries (1983a) reported that gross fetal examination did not reveal any significant abnormalities (data not shown). For the purpose of this review, a NOAEL of 224 ppm (1211 mg/m^3) and a LOAEL of 420 ppm (2270 mg/m^3) are identified for maternal toxicity based on slight reductions in gestational body-weight gains. A LOAEL of 111 ppm (600 mg/m^3) (lowest concentration tested) is identified for developmental toxicity based on reductions in mean fetal weights.

In the second study, reductions in maternal body-weight gain and food consumption were observed among all treatment groups compared to controls (Doe, 1984; Imperial Chemical Industries, 1983b) (see Table 12). Similar to the first study, these reductions were mainly confined to the first few days of exposure (GDs 5–8). These differences only achieved statistical significance ($p < 0.05$) at 412 ppm. Subsequent recovery towards control values was observed for both body-weight gain and food consumption. During the postexposure period, body-weight gain and food consumption were significantly increased over controls at 412 ppm. The data showed no significant ($p < 0.05$) changes in spleen weights or pathology. Hematological changes included a significant ($p < 0.05$) reduction in Hgb concentration at 412 ppm (see Table 12). The other hematological parameters exhibited a dose-related reduction, but none were significantly different from controls at any exposure level.

Table 11. Important Maternal and Developmental Effects in Rabbits Exposed to Ethoxyethanol Acetate Vapor During Gestation

Parameter	Exposure Concentration (mg/m^3)			
	0	**600**	**1211**	**2270**
Number of does	5	5	7	6
Maternal body-weight gain (g) GDs 5–10 GDs 0–20	 23.8 ± 27.3[a] 103.6 ± 152.2	 0.0 ± 77.6 117.6 ± 208.4	 -46.6 ± 90.5 140.7 ± 158.6	 -115.2 ± 71.5[b] 89.0 ± 110.3
Gravid uterine weight (g)	121.2 ± 46.1	113.7 ± 21.5	116.9 ± 42.0	70.7 ± 30.5[c]
Number of implantations	7.4 ± 1.1	7.0 ± 1.6	6.7 ± 2.6	7.2 ± 1.9
Preimplantation loss Mean ± SD Percentage litters affected	 0.0 ± 0.0 0	 15.0 ± 9.9[b] 80.0[d]	 19.4 ± 25.5 57.1	 27.1 ± 25.4[c] 83.3[d]
Postimplantation loss Mean ± SD Percentage litters affected	 20.0 ± 44.7 20.0	 11.7 ± 16.2 40.0	 11.3 ± 13.3 57.1	 37.5 ± 39.4 66.6
Number of viable fetuses	6.0 ± 3.5	6.2 ± 1.9	6.0 ± 2.4	4.3 ± 3.0
Intrauterine deaths Early Late	 0.0 ± 0.0 1.4 ± 3.1	 0.6 ± 0.9 0.2 ± 0.4	 0.4 ± 0.5 0.3 ± 0.5	 2.3 ± 2.7[c] 0.5 ± 0.8
Fetal weight/litter (g)	5.2 ± 0.2[e]	4.3 ± 0.4[b]	4.2 ± 0.3[b]	3.4 ± 0.6[b,e]

[a]Mean ± SD.
[b]Significantly different from controls (Student's *t*-test, $p < 0.01$).
[c]Significantly different from controls (Student's *t*-test, $p < 0.05$).
[d]Significantly different from controls (Fisher's exact test, $p < 0.05$).
[e]One rabbit had no live fetuses.

Source: Imperial Chemical Industries (1983a).

Table 12. Significant Maternal and Developmental Effects in Rabbits Exposed to Ethoxyethanol Acetate Vapor During Gestation

Parameter	Exposure Concentration (mg/m^3)			
	0	**135**	**535**	**2227**
Number of pregnant does at termination	16	15	17	19
Maternal body-weight gain (g)				
GDs 5–8	-5.8 ± 25.6[a]	-10.9 ± 26.4	-33.5 ± 59.7	-61.4 ± 55.4[b]
GDs 5–18	94.8 ± 109.8	73.9 ± 91.5	62.3 ± 117.0	-1.5 ± 123.4[c]
Hematology				
Number of animals examined	13	14	16	18
Hgb (g/dl)	12.6 ± 1.1	12.5 ± 1.5	12.0 ± 0.8	11.8 ± 0.9[c]
Hct	0.38 ± 0.3	0.38 ± 0.4	0.37 ± 0.02	0.37 ± 0.03
RBC count ($\times 10^{12}$/l)	5.65 ± 0.4	5.76 ± 0.57	5.60 ± 0.24	5.50 ± 0.41
WBC count ($\times 10^{9}$/l)	3.64 ± 1.9	3.18 ± 2.1	2.96 ± 1.6	2.92 ± 1.5
Number of implantations	7.3 ± 1.8	6.3 ± 3.4	8.1 ± 3.3	6.5 ± 3.0
Preimplantation loss (%)[d]	14.0	19.1	8.2	12.3
Postimplantation loss (%)[d]	9.4	18.1	6.7	24.4[c]
Number of live fetuses/litter	6.6 ± 1.6	5.1 ± 2.8	7.4 ± 3.0[e]	4.9 ± 3.2[c]
Total litter weight (g)	230 ± 63	194 ± 83[f]	223 ± 68[e]	179 ± 72[c,f]
Live fetal weight (g)	34.7 ± 4.9	35.2 ± 5.9[f]	30.1 ± 6.1[b,e]	30.8 ± 4.2[b,f]
Number of fetuses	106	77	111	93
External and visceral defects				
No. (%) showing any defects	22 (20.8)	18 (23.4)	30 (27.0)	51 (54.8)[g]
No. (%) showing major defects	0	1 (1.3)	2 (1.8)	3 (3.2)
Skeletal defects				
No. (%) variants	50 (47.2)	40 (51.9)	72 (64.9)[g]	92 (98.9)[g]
No. (%) showing any defects	23 (21.7)	14 (18.2)	37 (33.3)[h]	91 (97.8)[g]
No. (%) showing major defects	1 (0.9)	0	0	6 (6.5)[h]

[a]Mean ± SD, unless otherwise noted.
[b]Significantly different from controls (Student's t-test, $p < 0.01$).
[c]Significantly different from controls (Student's t-test, $p < 0.05$).
[d]Values reported as percentages.
[e]Excludes two mid-dose females who littered early and whose fetuses were partially eaten.
[f]Excludes four females with total resorptions (1 low-dose and 3 high-dose).
[g]Significantly different from controls (Fisher's exact test, $p < 0.01$).
[h]Significantly different from controls (Fisher's exact test, $p < 0.05$).

Sources: Doe (1984); Imperial Chemical Industries (1983b).

Four rabbits (three from the 412-ppm group and one from the 25-ppm group) experienced 100% resorptions (Doe, 1984; Imperial Chemical Industries, 1983b). These animals demonstrated vaginal bleeding, weight loss, lethargy, and fatty tissue in the excreta tray. There was a significant increase in postimplantation loss at 412 ppm (see Table 12). Doe (1984)

reported that when data based on the three rabbits that experienced 100% resorptions at this level were excluded, there were no statistically significant differences in percentage postimplantation loss. Other findings included significant decreases in the number of viable fetuses at 412 ppm and significant reductions in live fetal weights at ≥99 ppm. Mean litter weights were only significantly lower than controls at 412 ppm. While the researchers recognized that the reduction in mean fetal weight at 99 ppm may be attributable in part to the higher proportion of litters containing a large number of fetuses with subsequent intralitter competition, they suggested that it may also be evidence of a slight fetotoxic effect at 99 ppm. The incidence of external/visceral defects was significantly increased at 412 ppm, while the incidences of skeletal defects and skeletal variations were increased at ≥99 ppm (see Table 12). External and visceral defects included moderately dilated brain ventricles, malrotated forelimbs, and agenesis of the right kidney. There was also a significant difference in the incidence of pale and reduced spleens at 99 and 412 ppm. However, Imperial Chemical Industries (1983b) points out that this finding is difficult to interpret and is of unknown biological significance. Skeletal defects included misaligned vertical arches, additional hemivertebrae, increased numbers of thoracic ribs, and retarded ossification in the vertebrae and sternebrae. Doe (1984) concluded that ethoxyethanol acetate was teratogenic at 412 ppm. Based on these findings, the researchers identified 25 ppm as a NOAEL, 99 ppm as fetotoxic, and 412 ppm (2227 mg/m^3) as teratogenic. For the purposes of this review, A NOAEL of 25 ppm (135 mg/m^3) and a LOAEL of 99 ppm (535 mg/m^3) are identified for developmental toxicity based on reduced fetal body weights and increased skeletal variations and malformations. A NOAEL of 99 ppm (535 mg/m^3) and a LOAEL of 412 ppm (2227 mg/m^3) are identified for maternal toxicity based on reduced weight gain and a marginal reduction in blood Hgb concentration.

Other Studies

Genotoxicity

Ethoxyethanol acetate tested negative for mutagenicity in bacterial tests using *Salmonella typhimurium* strains TA98, TA100, TA102, TA104, TA1535, TA1537, and TA1538 (JCIETIC, 2000 as cited in Environmental Canada, 2009; Slesinkski et al., 1988), *Escherichia coli* strain WP2uvrA/pKM101 (JCIETIC, 2000 as cited in Environmental Canada, 2009), and Chinese hamster ovary (CHO) cells at the HGPRT locus (Slesinski et al., 1988) with and without metabolic activation. Slesinski et al. (1988) also reported negative findings in vitro for SCE in CHO cells with and without activation. Positive results were obtained in the presence of metabolic activation in CHO cells during a clastogenicity test (not further described; Slesinski et al., 1988). In the absence of metabolic activation, results were only weakly positive. In vivo, ethoxyethanol acetate was negative for micronuclei induction in mouse bone marrow cells following intraperitoneal injection (Slesinski et al., 1988). An epidemiological investigation evaluated the genotoxic potential of glycol ethers among workers at a varnish production plant with known exposure to 2-ethoxyethanol, ethoxyethanol acetate, and 2-butoxyethanol (Sohnlein et al., 1993). No cytogenetic effects based on micronuclei induction or SCE were observed.

DERIVATION OF SUBCHRONIC AND CHRONIC PROVISIONAL ORAL RfD VALUES FOR ETHOXYETHANOL ACETATE

Oral studies of ethoxyethanol acetate are limited to a subchronic study specifically designed to evaluate effects on the male reproductive system (Nagano et al., 1984, 1979) and an NTP reproductive toxicity study in mice following the RACB protocol (Morrissey et al., 1989; Lamb et al., 1987; Gulati et al., 1985). There are no chronic oral data available for ethoxyethanol acetate. Table 13 summarizes the available data. Nagano et al. (1984, 1979) observed significant decreases in testes weights and a dose-related atrophy of the seminiferous epithelium in male mice at ≥1000 mg/kg-day. Similar effects on the male reproductive system were noted at ≥1860 mg/kg-day in the NTP study (degeneration of seminiferous tubules, interstitial cell hyperplasia, reduction of sperm content, accumulation of fluid and degenerated cells in the epididymis, increased incidence of abnormal sperm, decreased absolute testis weights). The NTP evaluation also found functional effects on reproductive parameters at these doses, including fewer litters per mated mouse pair, decreased numbers of pups per litter, and depressed body weights of pups born alive. Based on a cross-over mating study, these researchers concluded that the observed functional reproductive changes were due primarily to an effect on the females.

Subchronic p-RfD

The lowest LOAEL by oral exposure was observed by Nagano et al. (1984, 1979), and it was for reduced testicular weight at 1000 mg/kg-day. The corresponding NOAEL was 500 mg/kg-day. Dose-response modeling of the data for both absolute and relative testicular weights (see Table 1) was attempted. BMD modeling was also attempted for the most sensitive endpoints from the Gulati et al. (1985) study, including right cauda weights, sperm density, estrous cycle length (see Table 5), and live pups per litter (see Table 6). Appendix A contains details of the modeling. Data based on absolute testes weights, sperm density, and estrous cycle length were not amenable to dose-response modeling (i.e., no adequate fit was achieved with any model). Model fit based on relative testes weights was achieved after dropping the high-dose group, which had experienced a high incidence of early mortality (Nagano et al., 1984, 1979). As shown in Table 14, modeling of the data based on reduced relative testes weights in mice (Nagano et al., 1984, 1979) resulted in the lowest $BMDL_{1SD}$ value across the endpoints where model fit was achieved (relative testes weight, absolute and adjusted right cauda weights, and live pups per litter). The BMD_{1SD} was 663 mg/kg-day, and the $BMDL_{1SD}$ was 499 mg/kg-day. The $BMDL_{1SD}$ (499 mg/kg-day) based on gavage dosing 5 days/week was converted to an equivalent continuous (7 days/week) dose of 356 mg/kg-day. The $BMDL_{1SD}$ of 499 mg/kg-day, which is virtually identical to the NOAEL of 500 mg/kg-day, was selected as the point of departure (POD) for derivation of the subchronic p-RfD value.

Table 13. Summary of Oral Noncancer Dose-Response Information

Species (*n*/sex/ group)	Exposure	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Duration-adjusted[a] NOAEL (mg/kg-day)	Duration-adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Mouse (20/sex/ group)	0, 930, 1860, or 3000 mg/kg-day in drinking water continuously for 126 days	930	1860	930	1860	Decreased mean number of litters per pair, number of live pups per litter, and adjusted live pup weights.	Cross-mating study suggested that decreased reproductive performance was due primarily to an effect on females, even though pathological effects were observed on the male (and not female) reproductive tract.	Morrissey et al., 1989; Lamb et al., 1987; Gulati et al., 1985
Mouse (5 males/ group)	0, 500, 1000, 2000, or 4000 mg/kg-day via gavage 5 days/week for 5 weeks	500	1000	357	714	Decreased testicular weight.	Study was specifically designed to assess effects on the male reproductive system.	Nagano et al., 1984, 1979

[a]Adjusted to continuous exposure.

Table 14. Summary of BMDs and BMDLs for Endpoints in Mice Treated Orally with Ethoxyethanol Acetate

Endpoint	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)	$BMDL_{1SDADJ}$ (mg/kg-day)	Reference
Absolute testes weight	NA[a]			Nagano et al. (1979)
Relative testes weight	663	499	356	Nagano et al. (1979)
Absolute right cauda weight	1412	992	992	Gulati et al. (1985)
Body-weight-adjusted right cauda weight	1271	917	917	Gulati et al. (1985)
Sperm density	Inadequate for modeling (no significant trend, $p > 0.05$)			Gulati et al. (1985)
Length of estrous cycle	NA			Gulati et al. (1985)
Live pups per litter	1279	676	676	Gulati et al. (1985)

[a]No model adequately fit the data.

A **subchronic p-RfD of 1 mg/kg-day** was derived for ethoxyethanol acetate by dividing the duration-adjusted $BMDL_{1SD}$ of 356 mg/kg-day (Nagano et al., 1984, 1979) by an uncertainty factor (UF) of 300, as shown below:

Subchronic p-RfD = $BMDL_{1SD} \div UF$
= 356 mg/kg-day ÷ 300
= **1 mg/kg-day**

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 because data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient.
- UF_D: The database for oral exposure to ethoxyethanol acetate consists of a single subchronic toxicity study in mice specifically evaluating the effects on the male reproductive system and an NTP reproductive evaluation in mice. A factor of $3(10^{0.5})$ is applied for database inadequacies because data for evaluating developmental toxicity are insufficient and might have identified toxic effects at lower levels.
- UF_L: A factor of 1 is applied, additional UF is not warranted when the POD is based on $BMDL_{1SD}$.
- UF_S: A factor of 1 is applied; additional UF for subchronic duration is not warranted when the POD is based on subchronic exposure.

Confidence in the principal study (Nagano et al., 1984, 1979) is medium. Evaluations were limited to the male reproductive tract, size of treated groups was small, and reporting of histopathology results was qualitative. However, a wide range of doses were tested, organ weight data were provided, and a NOAEL and LOAEL were identified. Confidence in the database is medium. Reproductive toxicity has been evaluated based on a multigenerational study in mice that followed a continuous breeding protocol. This study demonstrated reproductive effects to be a sensitive endpoint for ethoxyethanol acetate and supported the findings of Nagano et al. (1979, 1984). However, the database is limited because studies are available on only a single species (mouse), and no multigenerational developmental toxicity studies are available (developmental effects were a sensitive endpoint for ethoxyethanol acetate in inhalation studies). Thus, confidence in the subchronic p-RfD is medium.

Chronic p-RfD

To derive the chronic p-RfD in the absence of chronic data, the POD from the subchronic p-RfD is used along with a composite UF that includes the same areas of uncertainty enumerated above for the subchronic p-RfD, as well as the application of a subchronic to chronic UF of 10, as follows:

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 because data for evaluating susceptible human response are insufficient.

- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient.
- UF_D: The database for oral exposure to ethoxyethanol acetate consists of a single subchronic toxicity study in mice specifically evaluating the effects on the male reproductive system and an NTP reproductive evaluation in mice. A factor of $3(10^{0.5})$ is applied for database inadequacies because data for evaluating developmental toxicity are insufficient and might have identified toxic effects at lower levels.
- UF_L: A factor of 1 is applied, additional UF is not warranted when the POD is based on $BMDL_{1SD}$.
- UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure because data for evaluating response after chronic exposure are not available.

This results in a total UF of 3000 for derivation of the chronic p-RfD.

A **chronic p-RfD of 0.1 mg/kg-day** for ethoxyethanol acetate based on the duration-adjusted $BMDL_{1SD}$ of 356 mg/kg-day in mice (Nagano et al., 1984, 1979) is derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfD} &= BMDL_{1SD} \div UF \\ &= 356 \div 3000 \\ &= \textbf{0.1 mg/kg-day} \end{aligned}$$

As discussed for the subchronic p-RfD, confidence in the principal study is medium. Confidence in the database is reduced to low due to the absence of chronic data. Overall confidence in the chronic p-RfD is low.

DERIVATION OF SUBCHRONIC AND CHRONIC PROVISIONAL INHALATION RfC VALUES FOR ETHOXYETHANOL ACETATE

Human inhalation data are limited to epidemiology studies among workers exposed to mixed atmospheres of glycol ethers. These data suggest that the critical effects in humans associated with exposure to glycol ethers are hematological, reproductive, and developmental. These data also suggest that in addition to the inhalation route, potential human health effects may occur from exposure via the dermal route. However, due to concurrent exposures to multiple chemicals, the relative contribution of ethoxyethanol acetate to the observed effects reported in the epidemiology studies is unknown. Therefore, these data are inadequate for deriving the p-RfC.

Animal data also suggest that ethoxyethanol acetate produces hematological (reduced hemoglobin and increased WBC levels) and developmental effects. Inhalation studies of ethoxyethanol acetate include subchronic studies in rats, rabbits, and dogs (Truhaut et al., 1979; Carpenter, 1947) and developmental studies in rats and rabbits (Tyl et al., 1988; Doe, 1984; Nelson et al., 1984; Imperial Chemical Industries, 1983a,b). Table 15 summarizes these data.

Table 15. Summary of Inhalation Noncancer Dose-Response Information

Species (*n*/sex/group)	Exposure	NOAEL[a] (mg/m^3)	LOAEL[a] (mg/m^3)	Responses at the LOAEL	Comments	Reference
Subchronic toxicity						
Rat (40/sex/group)	0 or 1081 mg/m^3 4 hours/day, 5 days/week for 10 months	NA	1081 HEC: 129	Renal tubular nephritis with clear degeneration of the epithelium with hyaline and granular tubular casts (males only).	Study limited by incomplete reporting of study details.	Truhaut et al., 1979
Rabbit (2/sex/group)	0 or 1081 mg/m^3 4 hours/day, 5 days/week for 10 months	NA	1081 HEC: 129	Renal tubular nephritis with clear degeneration of the epithelium with hyaline and granular tubular casts.	Study limited by small group size and incomplete reporting of study details.	Truhaut et al., 1979
Dog (3/group)	0 or 3243 mg/m^3 7 hours/day, 5 days/week for 24 weeks	3243 HEC: 676	NA	NA	Study limited by small group size and incomplete reporting of study details.	Carpenter, 1947
Developmental toxicity						
Rat (9–15 pregnant females/group)	0, 703, 2108, or 3243 mg/m^3 7 hours/day on GDs 7–15	Developmental: NA	Developmental: 703 HEC: 205	Decreased fetal weight and increased fetal skeletal variations; cardiovascular malformation.	Increased resorptions and visceral and skeletal malformations at higher exposure concentrations. Data are inadequate for assessing maternal effects.	Nelson et al., 1984
Rat (30 pregnant females/group)	0, 270, 541, 1081, or 1622 mg/m^3 6 hours/day on GDs 6–15	Maternal: 270 HEC: 68 Developmental: NA	Maternal: 541 HEC: 135 Developmental: 270 HEC: 68	Maternal: decreased red cell parameters (RBC count, Hgb, Hct). Developmental: increased fetal skeletal variations.	Increased nonviable implants, decreased fetal body weights, and increased malformations and variations at higher exposure concentrations.	Tyl et al., 1988

Table 15. Summary of Inhalation Noncancer Dose-Response Information

Species (*n*/sex/group)	Exposure	NOAEL[a] (mg/m^3)	LOAEL[a] (mg/m^3)	Responses at the LOAEL	Comments	Reference
Rabbit (24 pregnant females/group)	0, 270, 541, 1081, or 1622 mg/m^3 6 hours/day on GDs 6–18.	Maternal and developmental: 270 HEC: 68	Maternal and developmental: 541 HEC: 135	Maternal: reduced gestational body-weight gains and hematological changes. Developmental: increased fetal skeletal variations.	Increased resorptions, decreased viable implants, decreased fetal weight, and increased malformations and variations at higher exposure concentrations.	Tyl et al., 1988
Rabbit (8 pregnant females/group)	0, 600, 1211, or 2270 mg/m^3 6 hours/day on GDs 6–18	Maternal: 1211 HEC: 303 Developmental: NA	Maternal: 2270 HEC: 568 Developmental: 600 HEC: 150	Maternal: reduced gestational body-weight gain. Developmental: decreased fetal body weight.	Increased preimplantation loss at higher exposure concentrations. Preliminary study with no fetal evaluations for malformations or variations.	Imperial Chemical Industries, 1983a
Rabbit (24 pregnant females/group)	0, 135, 535, or 2227 mg/m^3 6 hours/day on GDs 6–18	Maternal: 535 HEC: 134 Developmental: 135 HEC: 34	Maternal: 2227 HEC: 557 Developmental: 535 HEC: 134	Maternal: reduced gestational body-weight gain and marginal reduction in blood Hgb concentration. Developmental: decreased fetal body weights and increased fetal skeletal variations.	Decreased fetal survival and increased fetal malformations observed at higher exposure concentrations.	Doe, 1984; Imperial Chemical Industries, 1983b

[a]HEC calculated as follows: $NOAEL_{HEC}$ = NOAEL × exposure hours/24 hours × exposure days/7 days × dosimetric adjustment. For nonrespiratory effects, the chemical is treated as a Category 3 gas (U.S. EPA, 1994b) and the dosimetric adjustment is the ratio of the animal:human blood:gas partition coefficients for ethoxyethanol acetate (in the absence of experimental values, a default value of 1 was used).

To provide a basis for comparing the studies, LOAEL and NOAEL values were adjusted for continuous exposure and then converted to human equivalent concentrations (HECs). First, exposure is adjusted to equivalent continuous exposure according to the below equation:

$$LOAEL_{ADJ} = LOAEL\ (mg/m^3) \times \text{hours per day}/24 \times \text{days per week}/7$$

EPA currently performs this adjustment to continuous exposure for gestational exposure studies, as for other types of studies (U.S. EPA, 2002). Then, treating ethoxyethanol acetate as a Category 3 gas for effects on extrarespiratory endpoints, the dosimetric adjustments are made using the ratio of animal:human blood:gas partition coefficients for ethoxyethanol acetate (U.S. EPA, 1994b). Johanson and Dynesius (1988) attempted to experimentally determine a human blood:gas partition coefficient for ethoxyethanol acetate but could not, apparently due to rapid hydrolysis of the chemical by blood esterases. Gargas et al. (2000) used a saline:air partition coefficient of 3822 reported by Johanson and Dynesius (1988) for ethoxyethanol acetate as the blood:air partition coefficient for both rats and humans in their PBPK model. In the absence of species-specific blood:air partition coefficients for rats and humans, the default ratio of 1.0 is used to perform the dosimetric adjustment. For each study, the duration-adjusted effect level is multiplied by the corresponding dosimetric adjustment to calculate the HEC:

$$LOAEL_{HEC} = LOAEL_{ADJ} \times \text{Dosimetric Adjustment}$$

where:
Dosimetric Adjustment = ratio of animal:human blood:gas partition coefficients (default = 1)

Table 15 includes the HECs.

Maternal effects mainly characterized by decreased gestational weight gains and hematological effects have been observed at HEC $\geq$135 mg/m^3 ethoxyethanol acetate vapor following inhalation exposure during gestation in rabbits and rats (Tyl et al., 1988; Doe, 1984; Imperial Chemical Industries, 1983a,b). Evidence of a treatment-related delay in development characterized by retarded ossification has been observed in rats at HEC $\geq$68 mg/m^3 (Tyl et al., 1988). At higher concentrations, developmental effects including decreased fetal survival, depressed fetal weights, and increases in the incidence and severity of developmental malformations and variations have been observed in both rats and rabbits (Tyl et al., 1988; Nelson et al., 1984; Doe, 1984; Imperial Chemical Industries, 1983a,b).

Dose-response modeling was performed on the incidence data (see Table 9) for delayed skeletal ossification in rats (Tyl et al., 1988). BMD modeling was also performed for skeletal variations in rats (see Table 7) and rabbits (see Table 12) in the studies by Nelson et al. (1984) and Doe (1984), respectively. Doe (1984) only reported the incidence of skeletal defects in rabbits based on individual fetuses, whereas Nelson et al. (1984) and Tyl et al. (1988) reported data in rats for both fetuses and litters. When possible, incidence of affected litters, rather than individual fetuses, was modeled for developmental variants to take into account potential litter effects. The litter is considered the experimental unit in developmental toxicity studies, and statistical analyses are generally performed based on incidence per litter or number of litters affected (U.S. EPA, 1991b). Appendix B contains details of the modeling and plots of the best fitting models.

For comparison across endpoints, the $BMCL_{10}$ values, which were calculated using the experimental exposure concentrations, were adjusted for continuous exposure and converted to HECs, as described above for the LOAEL values:

$BMCL_{10ADJ}$ = $BMCL_{10}$ × hours per day/24 × days per week/7

$BMCL_{10HEC}$ = $BMCL_{10ADJ}$ × Dosimetric Adjustment

As shown in Table 16, modeling of the data based on the incidence of unossified anterior arch of atlas in rats as reported by Tyl et al. (1988) resulted in the lowest $BMCL_{HEC}$ estimate. The BMC_{10} and $BMCL_{10}$ for the incidence of unossified anterior arch of atlas in rats are 36 and 26 mg/m^3, respectively. The corresponding $BMCL_{10HEC}$ value is 6.5 mg/m^3. Modeling of the data on total skeletal variations in rats from Nelson et al. (1984) produced similar results (BMC_{10} = 112.5 mg/m^3, $BMCL_{10}$ = 26 mg/m^3, $BMCL_{10HEC}$ = 7.6 mg/m^3).

In addition to providing a slightly lower POD for derivation of the p-RfC, the Tyl et al. (1988) study is preferable as the basis for the p-RfC because there is less uncertainty in the modeling results. Uncertainty in the modeling results from Nelson et al. (1984) is relatively high because the data set included only two dose groups other than controls; only one of those showed a fractional incidence (the other was 100%), and the fractional incidence in the low-dose group was very high (93%), leaving no data points to inform the curve in the vicinity of the BMR (10% extra risk). Relative to the Nelson el. (1984) study, the Tyl et al. (1988) study included more dose groups, more dose groups with fractional responses, larger group sizes, a broader range of exposure concentrations (low concentration of 270 mg/m^3 versus 703 mg/m^3), and a broader range of responses (low response incidence of 71% versus 93%). Therefore, the $BMCL_{10HEC}$ of 6.5 mg/m^3 based on unossified anterior arch in rats reported by Tyl et al. (1988) is selected as the POD for derivation of the subchronic and chronic p-RfC values.

The provisional **subchronic and chronic p-RfC of 0.06** mg/m^3 for ethoxyethanol acetate, based on the $BMCL_{10HEC}$ of 6.5 mg/m^3 for unossified anterior arch in fetal rats exposed during gestation (Tyl et al., 1988), is derived as follows:

Subchronic and Chronic p-RfC = $BMCL_{10HEC}$ ÷ UF
= 6.5 mg/m^3 ÷ 100
= **0.06 or 6 × 10^{-2} mg/m^3**

Table 16. BMCs and BMCLs Based on Incidence of Skeletal Variations in Rats and Rabbits Exposed to Ethoxyethanol Acetate via Inhalation

Endpoint	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)	$BMCL_{10\ ADJ}$ (mg/m^3)	$BMCL_{10HEC}$ (mg/m^3)	Reference
Litter incidence of combined skeletal variations (rats)	112.5	26	7.6	7.6	Nelson et al. (1984)
Litter incidence of unossified anterior arch (rats)	36	26	6.5	6.5	Tyl et al. (1988)
Litter incidence of poorly ossified metatarsals (rats)	121	97	24	24	Tyl et al. (1988)
Fetal incidence of skeletal variants (rabbits)	133	109	27	27	Doe (1984); Imperial Chemical Industries (1983b)

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 partial UF of 3 ($10^{0.5}$) is applied for interspecies extrapolation to account for potential pharmacodynamic differences between rats and humans. Converting the rat data to HECs by the dosimetric equations accounts for pharmacokinetic differences between rats and humans; thus, it was not necessary to use the full UF of 10 for interspecies extrapolation.
- UF_D: The database includes limited subchronic studies in rats, rabbits, and dogs and developmental studies in rats and rabbits. A factor of 3 ($10^{0.5}$) is applied for database inadequacies, including a lack of a multigeneration reproduction study following inhalation exposure.
- UF_S: A factor of 1 is applied to derive the chronic p-RfC, as an additional factor for extrapolation from subchronic–to-chronic exposure duration is not warranted when developmental toxicity data are used.
- UF_L: A factor of 1 is applied; as an additional factor is not warranted when the POD is based on $BMCL_{10HEC}$.

Confidence in the principal study (Tyl et al., 1988) 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. The database includes multiple high-quality developmental toxicity studies in two species. Reproduction has not been evaluated following inhalation exposure; a continuous breeding study in mice by oral exposure showed that ethoxyethanol acetate can act as a reproductive toxicant. Subchronic studies are available in rats, rabbits, and dogs but were all limited by incomplete reporting of study methods and results. Medium confidence in the subchronic and chronic p-RfC value follows.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ETHOXYETHANOL ACETATE

Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess [the] Carcinogenic Potential"* of ethoxyethanol acetate. No information was located on the carcinogenicity of ethoxyethanol acetate in humans or animals. Genotoxicity data for ethoxyethanol acetate were primarily negative.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for ethoxyethanol acetate is precluded by the lack of suitable data.

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APPENDIX A. DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC AND CHRONIC RfD

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. 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 of the models providing adequate fit to the data, the lowest 95% lower confidence limit of benchmark dose (BMDL) is selected as the POD when the difference between the BMDLs estimated from these models is more than 3-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 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. The models are run with a BMR of 1 SD from the control mean, as recommended by EPA (2000).

Model Fitting Results for Testicular Atrophy in Mice (Nagano et al., 1984, 1979)

Following the above procedure, the continuous models in the EPA BMDS (version 2.1.1) were fit to the data shown in Table 1 for testicular weight in mice (based on both absolute and relative testes weights). The results based on absolute testes weights are shown in Table A-1. The assumption of constant variance did not hold, and the nonhomogenous variance model did not provide adequate fit based on absolute testes weights. Due to the deaths of three of the five high-dose animals, the mean testes weight for the high-dose group was based on only two animals. Therefore, the procedure for continuous data was also applied to absolute testes weights excluding the high-dose group. Again, the assumption of constant variance did not hold, and the nonhomogenous variance model did not provide adequate fit.

Table A-2 shows the results based on relative testes weights. The assumption of constant variance did not hold, and the nonhomogenous variance model did not provide adequate fit based on relative testes weights. As mentioned above, only two animals were examined in the high-dose group. Excluding the high-dose group, the constant variance model provided adequate fit to the variance data, and the linear model provided the best fit to the means. There were insufficient data points to fit the Hill model. Figure A-1 shows the fit of the linear model to the data. The resulting benchmark dose (BMD_{1SD}) and associated 95% lower confidence limit ($BMDL_{1SD}$) are 663 and 499 mg/kg-day, respectively.

Model Fitting Results for Changes in Right Cauda Weights, Sperm Density, Length of Estrous Cycle, and Number of Live Pups per Litter in Mice (Gulati et al., 1985)

Following the above procedure, the continuous models in the EPA BMDS (version 2.1.1) were fit to the data shown in Table 5 for decreases in right cauda weights in mice (based on both absolute and body-weight-adjusted right cauda weights), sperm density, and estrous cycle duration, and to the data shown in Table 6 for reduced number of live litters per pair. Table A-3 shows the results based on right cauda weights. The constant variance model provided adequate fit to the variance data based on both absolute and adjusted right cauda weights. Only the linear model fit the means data based on the absolute right cauda weights. The BMD_{1SD} and $BMDL_{1SD}$ estimates are 1412 and 992 mg/kg-day, respectively. Figure A-2 shows the fit of the linear model to the data for absolute right cauda weight. All models based on the adjusted right cauda weights defaulted to the linear model, with the resulting BMD_{1SD} and $BMDL_{1SD}$ of 1272 and 917 mg/kg-day, respectively (see Table A-3). Figure A-3 shows the fit of the linear model to the data for adjusted right cauda weight.

Table A-4 shows the results based on the decreased sperm density and shortened estrous cycle length. As shown, data on sperm density were inadequate for modeling (no statistically significant trend, $p < 0.05$). For estrous cycle length, the assumption of constant variance did not hold, and the nonhomogenous variance model did not provide adequate fit.

Table A-5 shows the results based on the number of live pups (males and females combined) per litter. The assumption of constant variance did not hold, but the nonhomogenous variance model provided adequate fit to the variance data. All models defaulted to the linear model. Figure A-4 shows the fit of the linear model to the data is shown. The resulting BMD_{1SD} and $BMDL_{1SD}$ are 1279 and 676 mg/kg-day, respectively.

Table A-1. Model Predictions for Testicular Atrophy in Mice Based on Absolute Testes Weights

Model	Variance *p*-Value[a]	Means *p*-Value[a]	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
All dose groups					
Linear (constant variance)[b]	0.002	0.889	311.0	684	541
Linear (modeled variance)[b]	0.001	0.875	312.8	724	507
Without high-dose group					
Linear (constant variance)[b]	0.014	0.916	296.0	646	488
Linear (modeled variance)[b]	0.031	0.430	295.8	551	371

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be negative.

Sources: Nagano et al. (1984, 1979).

Table A-2. Model Predictions for Testicular Atrophy in Mice Based on Relative Testes Weights

Model	Variance *p*-Value[a]	Means *p*-Value[a]	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
All dose groups					
Linear (constant variance)[b]	0.008	0.642	-128.9	684	541
Linear (modeled variance)[b]	0.008	0.508	-128.2	785	576
Without high-dose group					
Linear (constant variance)[b]	**0.144**	**0.500**	**-119.9**	**663**	**499**
1-degree polynomial (constant variance)[b]	0.144	0.500	-119.9	663	499
2-degree polynomial (constant variance)[b]	0.144	0.533	-118.8	901	526
3-degree polynomial (constant variance)[b]	0.144	0.604	-119.0	921	530
Power (constant variance)[c]	0.144	0.477	-118.7	898	523
Hill (constant variance)[c]	0.144	NA[d]	-116.7	898	522

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be negative.
[c]Power restricted to ≥1.
[d]Not available; insufficient degrees of freedom.

Sources: Nagano et al. (1984, 1979).

Table A-3. Model Predictions for Decreased Right Cauda Weights in Mice					
Model	**Variance *p*-Value[a]**	**Means *p*-Value[a]**	**AIC**	**BMD_{1SD} (mg/kg-day)**	**$BMDL_{1SD}$ (mg/kg-day)**
Absolute Right Cauda Weight					
Linear (constant variance)[b]	**0.8415**	**0.7039**	**193.1**	**1412**	**992**
2-degree polynomial (constant variance)[b]	0.8415	NA[c]	195.0	1501	1000
Power (constant variance)[d]	0.8415	NA	195.0	1490	1000
Hill (constant variance)[d]	NA				
Body-Weight-Adjusted Right Cauda Weight					
Linear (constant variance)[b]	**1**	**0.8285**	**177.4**	**1271**	**917**
2-degree polynomial (constant variance)[b]	1	0.8285	177.4	1271	917
Power (constant variance)[d]	1	0.8285	177.4	1271	917
Hill (constant variance)[d]	NA				

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be negative.
[c]Not available; insufficient degrees of freedom.
[d]Power restricted to ≥1.

Sources: Gulati et al. (1985).

Table A-4. Model Predictions for Decreased Sperm Density and Shortened Estrous Cycle Length in Mice

Model	Variance *p*-Value[a]	Means *p*-Value[a]	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Sperm Density					
Linear (constant variance)[b]	No significant trend (Test 1 *p*-value = 0.053)				
Estrous Cycle Length					
Linear (constant variance)[b]	0.005501	0.6111	32.2	5615	2179
Linear (modeled variance)[b]	0.3678	0.001695	34.2	5618	2150
2-degree polynomial (modeled variance)[b]	0.3678	0.002365	33.6	3069	1924
Power (modeled variance)[c]	0.09448	0.01323	32.5	1972	1870
Hill (modeled variance)[c]	NA[d]				

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be negative.
[c]Power restricted to ≥1.
[d]Not available; insufficient degrees of freedom.

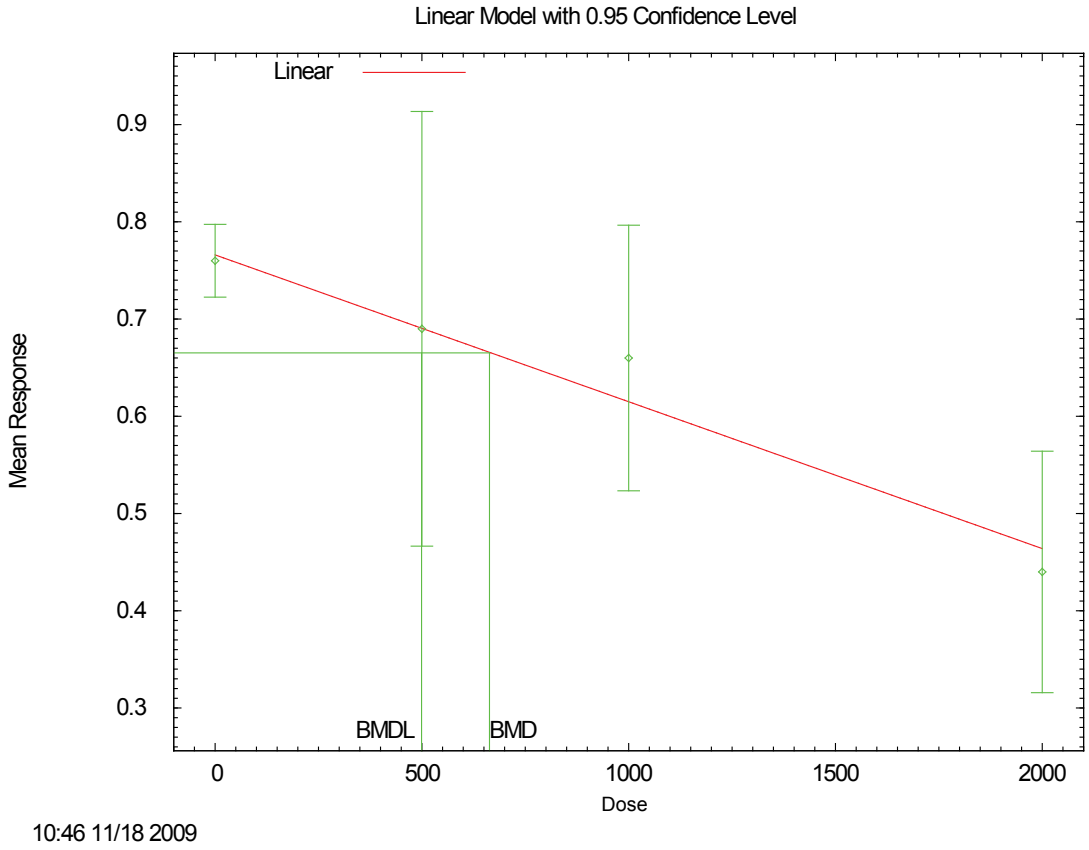
Sources: Gulati et al. (1985).

Table A-5. Model Predictions for Decreased Numbers of Live Mouse Pups Per Litter

Model	Variance *p*-Value[a]	Means *p*-Value[a]	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Linear (constant variance)[b]	0.04581	0.7678	117.3	1845	1048
Linear (modeled variance)[b]	**0.5295**	**0.6888**	**113.6**	**1279**	**676**
2-degree polynomial (modeled variance)[b]	0.5295	0.6888	113.6	1279	676
Power (modeled variance)[c]	0.5295	0.6888	113.6	1279	676
Hill (modeled variance)[c]	NA[d]				

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be negative.
[c]Power restricted to ≥1.
[d]Not available; insufficient degrees of freedom.

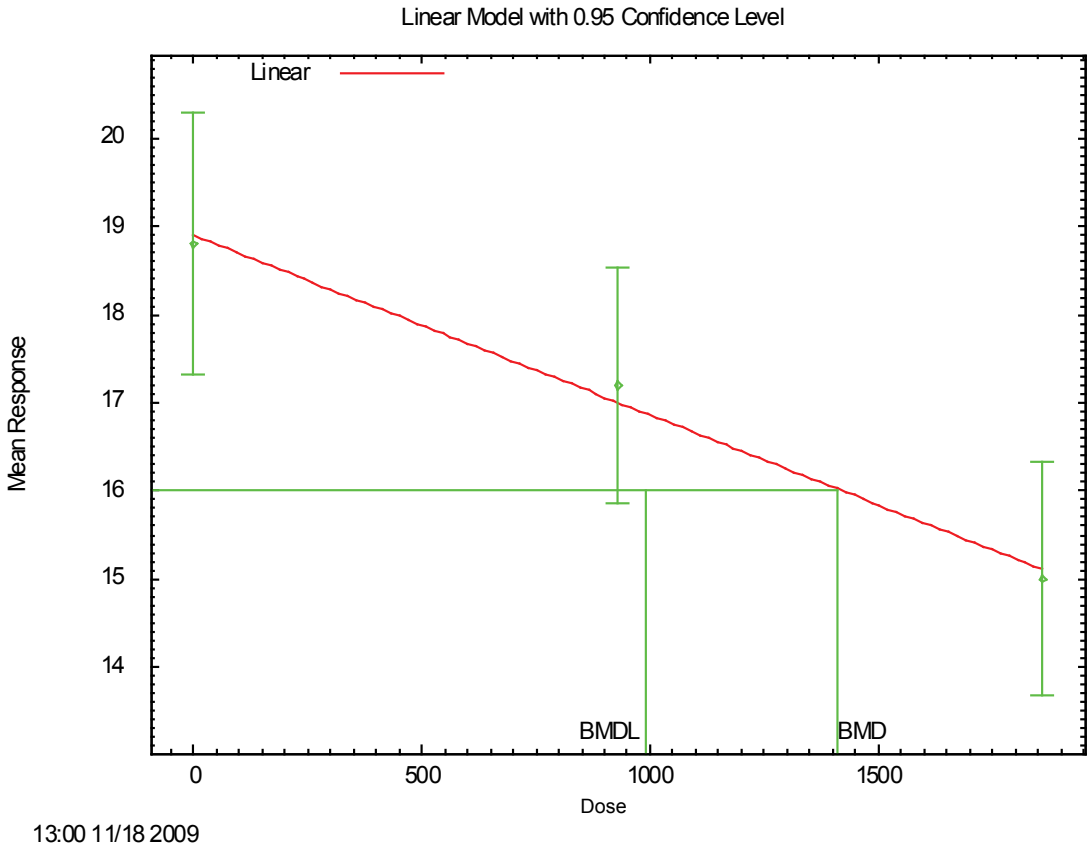
Sources: Gulati et al. (1985).



BMDs and BMDLs indicated are associated with a change of 1 SD from the control and are in units of mg/kg-day (5 day/week).

Sources: Nagano et al. (1984, 1979).

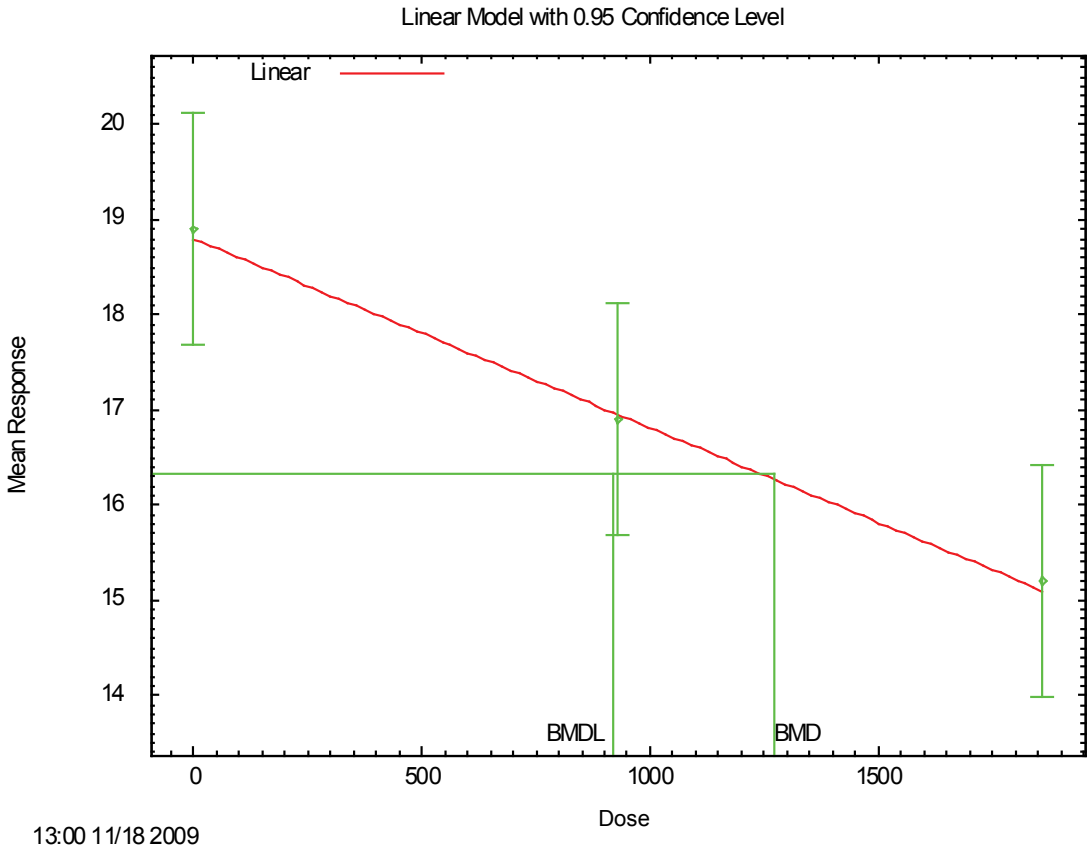
Figure A-1. Fit of Linear Model to Data for Relative Testes Weights in Mice



BMDs and BMDLs indicated are associated with a change of 1 SD from the control and are in units of mg/kg-day.

Source: Gulati et al. (1985).

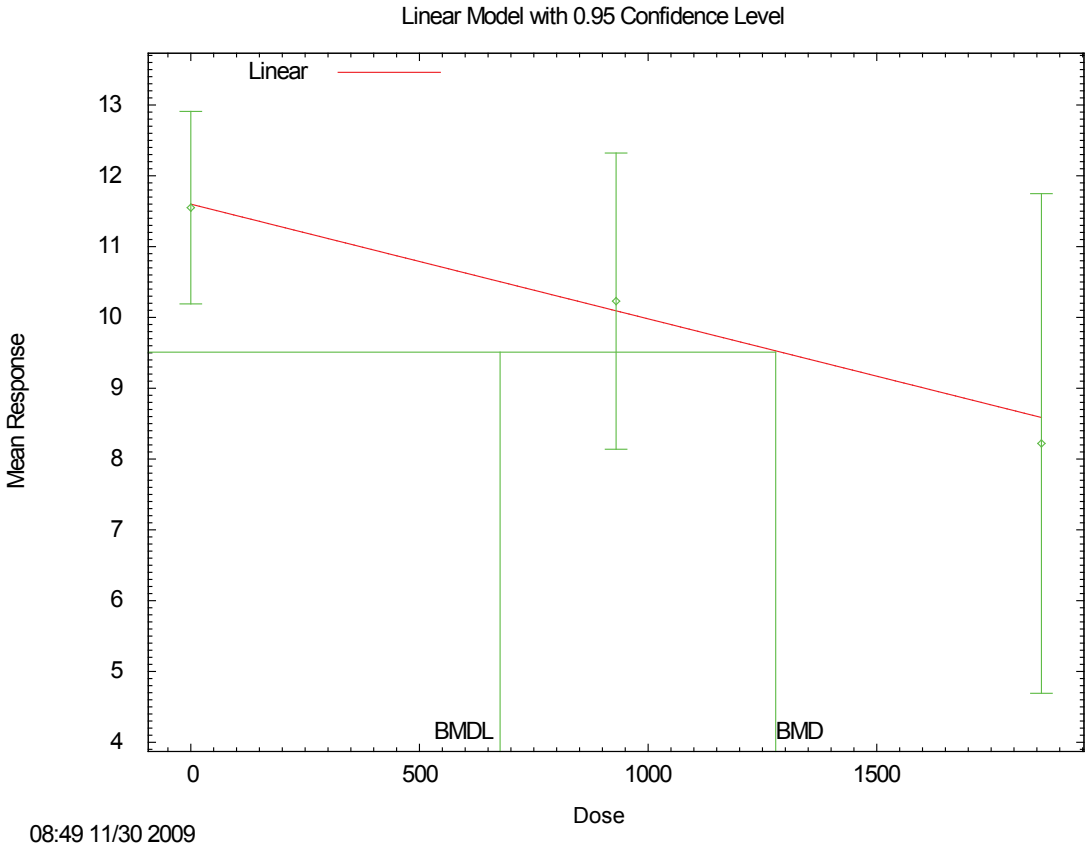
Figure A-2. Fit of Linear Model to Data for Absolute Right Cauda Weights in Mice



BMDs and BMDLs indicated are associated with a change of 1 SD from the control and are in units of mg/kg-day.

Source: Gulati et al. (1985).

Figure A-3. Fit of Linear Model to Data for Body-Weight-Adjusted Right Cauda Weights in Mice



BMDs and BMDLs indicated are associated with a change of 1 SD from the control and are in units of mg/kg-day.

Source: Gulati et al. (1985).

Figure A-4. Fit of Linear Model to Data for Number of Live Mice Pups (Male and Female Combined) per Litter

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC AND CHRONIC RfC

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 (version 2.1.1) 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). 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 of the models providing adequate fit to the data, the lowest BMCL is selected as the POD when the difference between the BMCLs estimated from these models are more than 3-fold (unless it appears to be an outlier); otherwise, the BMCL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMCs and BMCLs associated with an extra risk of 10% benchmark response (BMR) are calculated for all models.

Model Fitting Results for Skeletal Variations in Rats (Nelson et al., 1984)

Following the above procedure, the quantal models in the EPA BMDS (version 2.1.1) were fit to the litter incidence data shown in Table 7 for the total number of skeletal variations observed in rats. No live fetuses were born to rats exposed at the highest concentration; therefore, data are only available for the control, low- and mid-exposure groups. Table B-1 shows the modeling results. There were insufficient degrees of freedom available to fit the gamma, log logistic, log probit, or weibull models. The remaining models (logistic, 1-degree multistage, 2-degree multistage, probit, and quantal-linear) all provided adequate fit. The $BMCL_{10}$ estimates for these models differed by less than 3-fold. The AIC for the 2-degree multistage model (AIC = 58.0102, BMC_{10} = 166 mg/m^3, $BMCL_{10}$ = 18 mg/m^3) was just slightly lower than that of the probit model (AIC = 58.0106, BMC_{10} = 59 mg/m^3, $BMCL_{10}$ = 34 mg/m^3). Given the proximity of the AIC values for these models, the BMC_{10} and $BMCL_{10}$ values were averaged across both models to give representative values of 112.5 mg/m^3 (BMC_{10}) and 26 mg/m^3 ($BMCL_{10}$) for this endpoint. Figures B-1 and B-2 show the fit of the 2-degree multistage and probit models to these data.

The excellent fit of the 2-degree multistage, probit, and other models requiring few enough parameters to the Nelson et al. (1984) skeletal variation data is misleading, as it reflects primarily the lack of information in the data set. There is high uncertainty with these modeling results. This is because the data set included only two dose groups other than controls; only one of those showed a fractional incidence (the other was 100%), and the fractional incidence in the low-dose group was very high (93%), leaving no data points to inform the curve in the vicinity of the BMR (10% extra risk).

Model Fitting Results for Skeletal Variations in Rats (Tyl et al., 1988)

Following the above procedure, the quantal models in the EPA BMDS (version 2.1.1) were fit to the litter incidence data shown in Table 9 for the most sensitive skeletal variations in rats (unossified anterior arch of atlas and poorly ossified hindlimb metatarsals). Table B-2 shows the modeling results based on unossified anterior arch of atlas in rats. Adequate model fit was achieved with all models. The BMCLs differed by approximately 3-fold. The log-logistic model gave the lowest BMCL estimate but appears to be an outlier, as the BMCL estimates from

all of the other models fall within approximately a factor of 2 of each other. Moreover, there is high uncertainty in the BMCL estimate from the log-logistic model. Although this model gave the lowest BMCL estimate, it also gave the highest BMC estimate, and the spread between them was much larger than for any of the other models. Therefore, the log-logistic model was not considered further for this endpoint. In accordance with EPA (2000) guidance, the lowest AIC was selected from among the remaining models. The gamma, 1-degree multistage, and quantal-linear models all converged on the same parameters. The resulting benchmark concentration (BMC_{10}) and associated 95% lower confidence limit ($BMCL_{10}$) are 36 and 26 mg/m^3, respectively. Figure B-3 shows the fit of the gamma model to these data.

Table B-3 shows the modeling results for poorly ossified metatarsals of the hindlimb in rats. For this data set, adequate model fit could only be achieved by dropping the highest exposure group. The incidence of poorly ossified metatarsals was very low in the high exposure group because almost all of the fetuses at this level exhibited totally unossified metatarsals (a progression of effect from the poorly ossified variation but quantified by the researchers separately). After dropping the high exposure level, all of the models provided adequate fit. BMCLs from the models differed by a factor of 3 (rounded). The log-logistic model provided the lowest BMCL estimate, but as for unossified atlas arch discussed above, this appears to reflect primarily greater uncertainty in the log-logistic results, as the spread between the BMC and BMCL for the log-logistic was much larger than for any of the other models. In addition, the BMCL estimate based on the log-logistic appears to be an outlier in comparison with the BMCL estimates based on the other models, which are all within a factor of 2 of each other. Therefore, the log-logistic was not considered any further for this endpoint, and in accordance with EPA (2000) guidance, the lowest AIC was selected from among the remaining models. For incidence data based on poorly ossified hindlimb metatarsals in rats, the probit model provided the best fit. The resulting BMC_{10} and associated $BMCL_{10}$ are 121 and 97 mg/m^3, respectively. Figure B-4 shows the fit of the probit model to these data.

Model Fitting Results for Skeletal Variations in Rabbits (Doe, 1984; Imperial Chemical Industries, 1983b)

Following the above procedure, the quantal models in the EPA BMDS (version 2.1.1) were fit to the fetal incidence data shown in Table 12 for the number of fetuses with skeletal variants. Table B-4 shows the modeling results. There were insufficient degrees of freedom available to fit the 3-degree multistage model. All other models provided adequate fit to the data. The BMCL estimates differed by a factor of more than 3, with the 1-degree multistage and quantal-linear models converging with the lowest BMCL estimate. However, these models provide relatively poor fit to the data, as shown by low goodness-of-fit *p*-value, high AIC, high scaled residuals at 3 of the 4 data points, and visual inspection. Furthermore, the BMCL estimate from these models appears to be an outlier, as the BMCL estimates from the remaining models are all within a factor of 2.5 of each other. Therefore, the quantal-linear/1-degree multistage model was not considered further for this endpoint. In accordance with EPA (2000) guidance, the lowest AIC was selected among these remaining models. The probit model had the lowest AIC. Figure B-5 shows the fit of the probit model to these data. The resulting BMC_{10} and $BMCL_{10}$ are 133 and 109 mg/m^3, respectively.

Table B-1. Model Predictions for the Total Number of Skeletal Variations in Rats

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma (power ≥ 1)	0	0	NA[b]	60.010	294.91	17.97
Logistic	1	0.01	0.9253	58.027	52.48	26.97
Log logistic (slope ≥ 1)	0	0	NA	60.010	531.75	1.34
Log probit (slope ≥ 1)	0	0	NA	60.010	391.23	23.02
Multistage (degree = 1, betas ≥ 0)	1	0.02	0.8802	58.052	38.04	17.87
Multistage (degree = 2, betas ≥ 0)	**1**	**0**	**0.9996**	**58.0102**	**165.99**	**17.97**
Probit	**1**	**0**	**0.9888**	**58.0106**	**58.67**	**34.32**
Weibull (power ≥ 1)	0	0	NA	60.010	156.06	17.97
Quantal-linear	1	0.02	0.8802	58.052	38.04	17.87

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Not available; insufficient degrees of freedom.

Source: Nelson et al. (1984).

Table B-2. Model Predictions for the Skeletal Variation Unossified Anterior Arch of Atlas in Rats

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma (power ≥ 1)	**3**	**0.28**	**0.96**	**103.9**	**35.69**	**26.11**
Logistic	3	1.3	0.73	104.7	61.21	46.73
Log logistic (slope ≥ 1)	2	0.74	0.69	106.6	87.50	17.19
Log probit (slope ≥ 1)	2	0.51	0.78	106.2	82.53	43.04
Multistage (degree = 1, betas ≥ 0)	**3**	**0.28**	**0.96**	**103.9**	**35.69**	**26.11**
Multistage (degree = 2, betas ≥ 0)	2	0.3	0.86	105.9	37.24	26.13
Multistage (degree = 3, betas ≥ 0)	2	0.29	0.86	105.8	37.47	26.20
Multistage (degree = 4, betas ≥ 0)	2	0.27	0.87	105.8	37.55	26.28
Probit	3	2.17	0.54	105.5	67.83	53.27
Weibull (power ≥ 1)	2	0.28	0.87	105.9	35.81	26.11
Quantal-linear	**3**	**0.28**	**0.96**	**103.9**	**35.69**	**26.11**

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.

Sources: Tyl et al. (1988).

Table B-3. Model Predictions for the Skeletal Variation Poorly Ossified Hindlimb Metatarsals in Rats, After Excluding the High Exposure Group

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma (power ≥ 1)	1	1.54	0.21	134.4	106.96	51.36
Logistic	2	1.35	0.51	132.2	121.17	94.48
Log logistic (slope ≥ 1)	1	2.13	0.14	135.0	135.17	31.01
Log probit (slope ≥ 1)	1	2.08	0.15	134.9	140.43	92.48
Multistage (degree = 1, betas ≥ 0)	2	1.66	0.44	132.5	71.46	50.96
Multistage (degree = 2, betas ≥ 0)	1	1.25	0.26	134.1	101.77	52.27
Multistage (degree = 3, betas ≥ 0)	1	1.02	0.31	133.9	97.02	53.02
Probit	**2**	**1.26**	**0.53**	**132.1**	**121.48**	**96.95**
Weibull (power ≥ 1)	1	1.46	0.23	134.3	111.19	51.62
Quantal-linear	2	1.66	0.44	132.5	71.46	50.96

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.

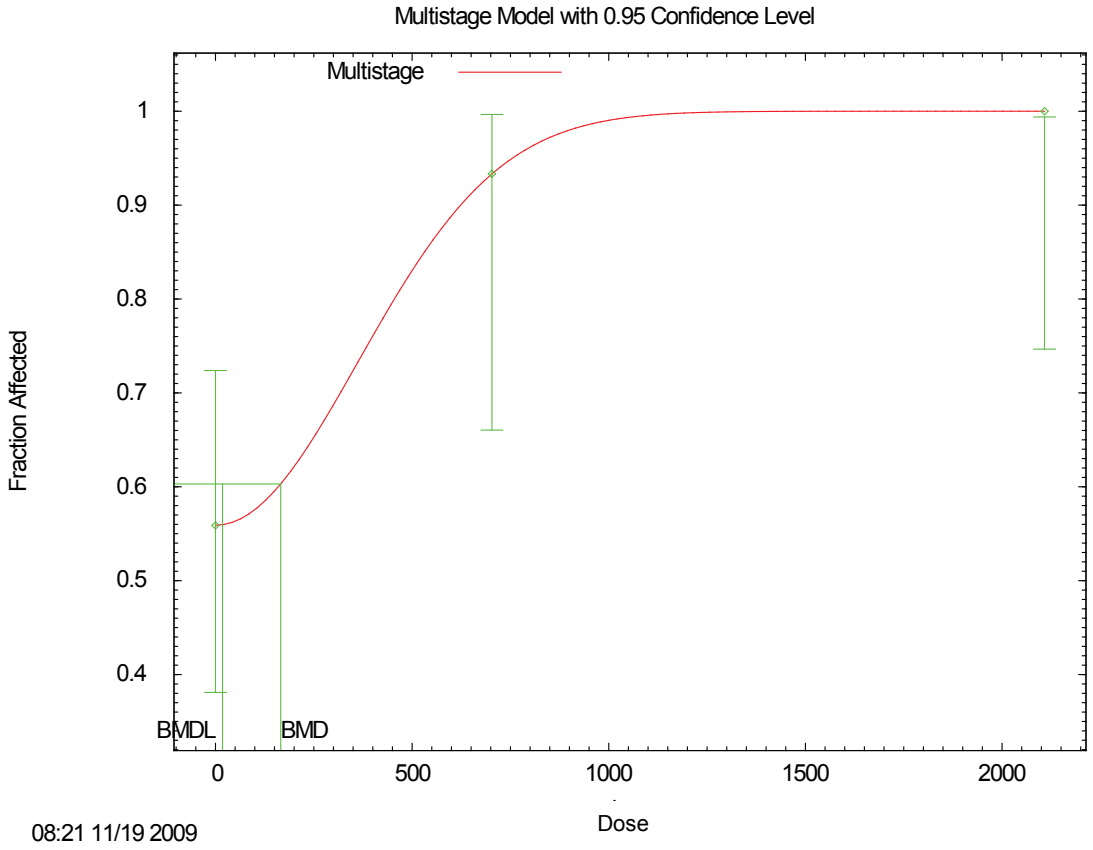
Sources: Tyl et al. (1988).

Table B-4. Model Predictions for the Number of Rabbit Fetuses with Skeletal Variations

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma (power ≥ 1)	1	0.24	0.6219	414.5	273.00	116.26
Logistic	2	1.34	0.5128	413.6	120.98	97.33
Log logistic (slope ≥ 1)	1	0.36	0.5465	414.6	345.98	220.31
Log probit (slope ≥ 1)	1	0.39	0.5307	414.6	342.78	215.05
Multistage (degree = 1, betas ≥ 0)	2	4.23	0.1204	417.0	84.89	65.79
Multistage (degree = 2, betas ≥ 0)	1	0.03	0.8683	414.2	188.05	91.17
Multistage (degree = 3, betas ≥ 0)	0	0	NA[b]	416.2	149.82	85.35
Probit	**2**	**0.45**	**0.7995**	**412.7**	**132.65**	**108.51**
Weibull (power ≥ 1)	1	0.12	0.7303	414.3	230.83	107.88
Quantal-linear	2	4.23	0.1204	417.0	84.89	65.79

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Not available; insufficient degrees of freedom.

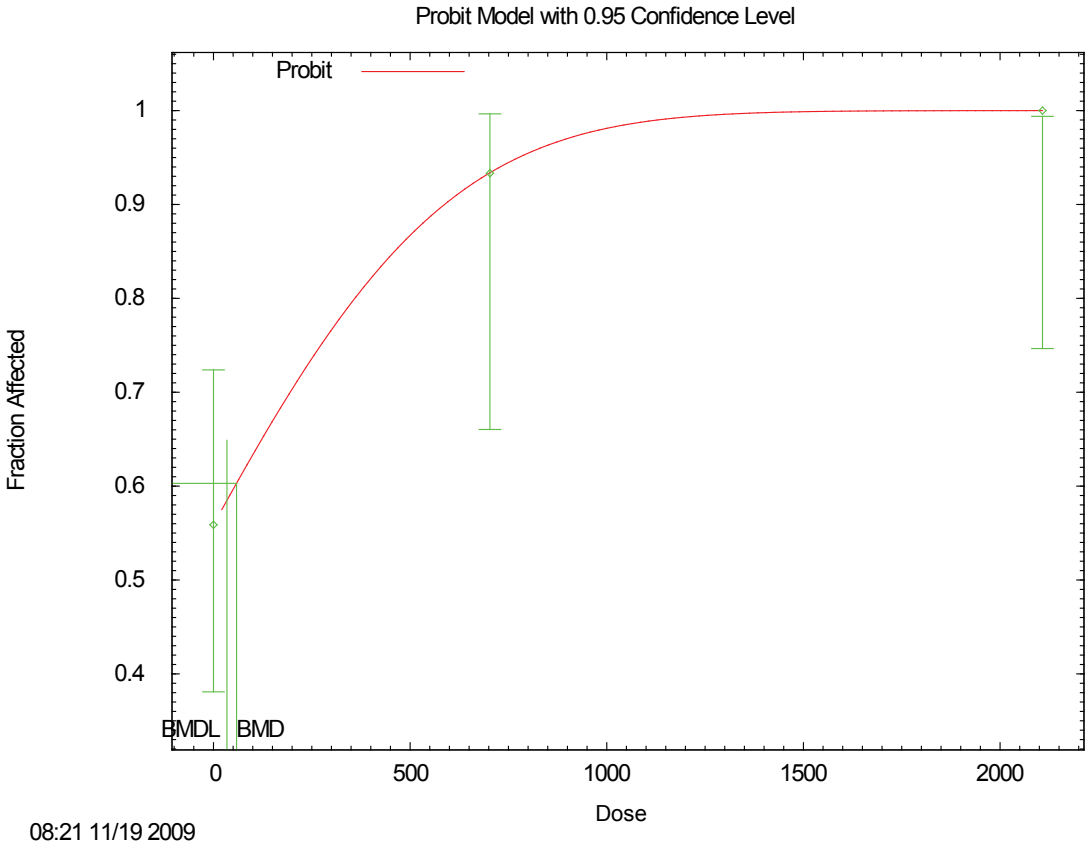
Sources: Doe (1984); Imperial Chemical Industries (1983b).



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

Source: Nelson et al. (1984).

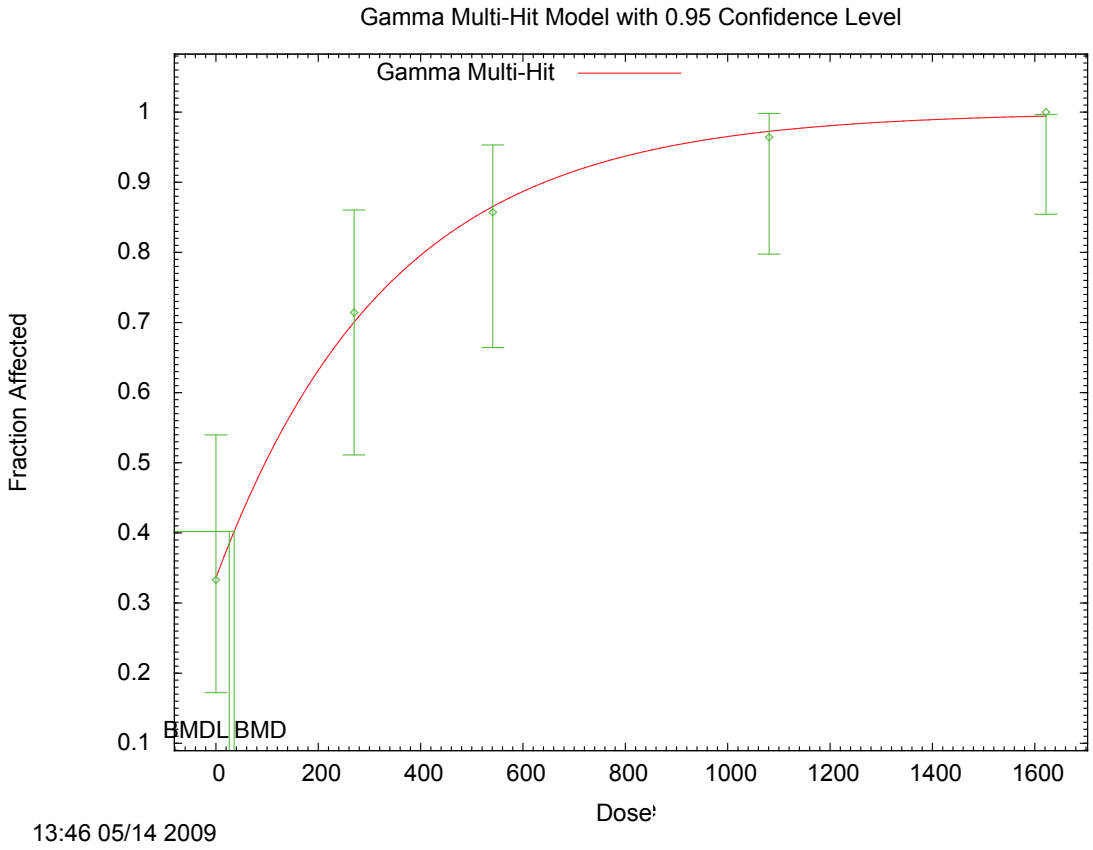
Figure B-1. Fit of 2-Degree Multistage Model to Litter Data on Incidence of Total Skeletal Variations in Rats



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

Source: Nelson et al. (1984).

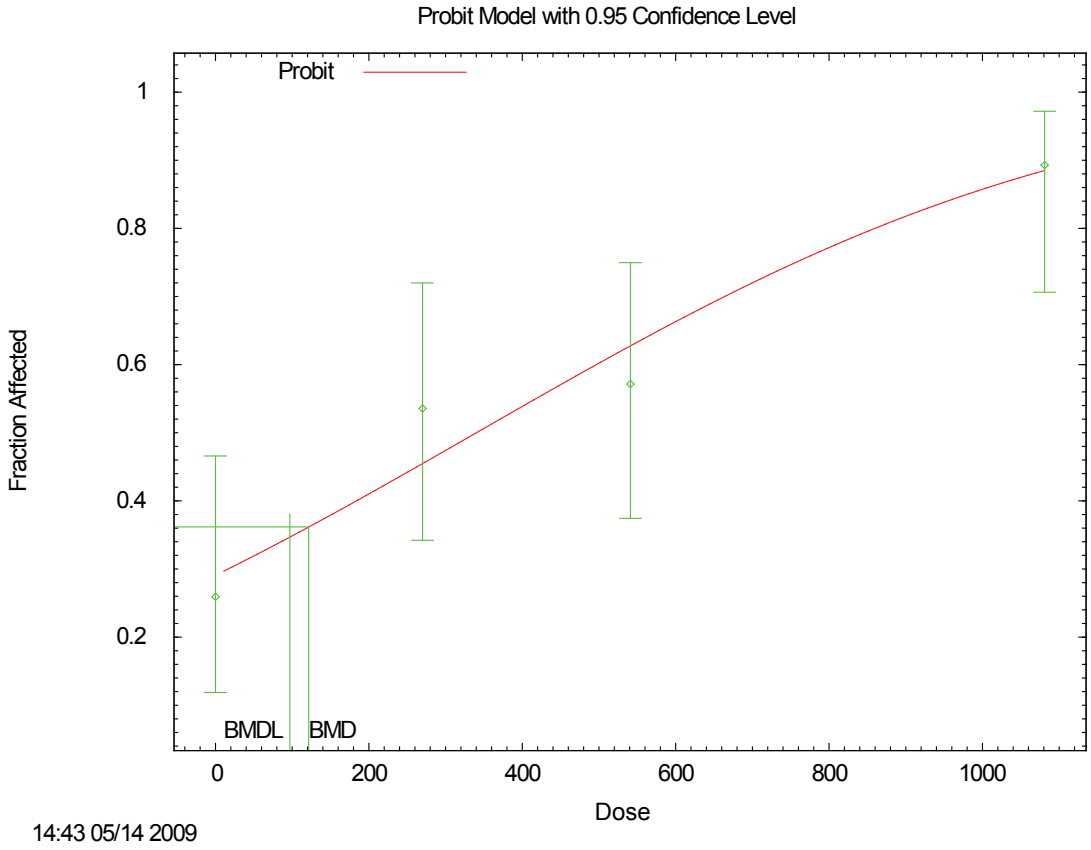
Figure B-2. Fit of Probit Model to Litter Data on Incidence of Total Skeletal Variations in Rats



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

Source: Tyl et al. (1988).

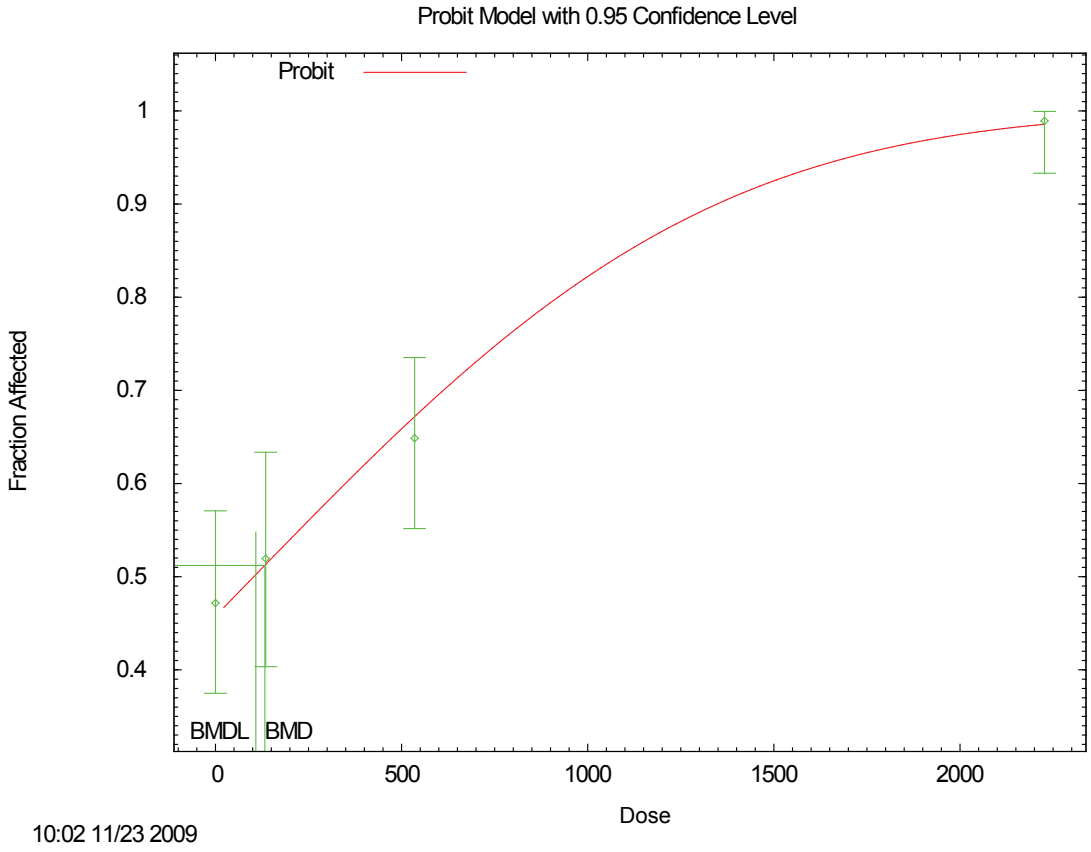
Figure B-3. Fit of Gamma Multihit Model to Data on Litter Incidence of Unossified Anterior Arch of Atlas in Rats



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

Source: Tyl et al. (1988).

Figure B-4. Fit of Probit Model to Data on Litter Incidence of Poorly Ossified Hindlimb Metatarsals in Rats



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

Sources: Doe (1984); Imperial Chemical Industries (1983b).

Figure B-5. Fit of Probit Model to Data on Fetal Incidence of Skeletal Variants in Rabbits