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Provisional Peer-Reviewed Toxicity Values for

Diethanolamine
(CASRN 111-42-2)

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

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGERS

Chris Cubbison, PhD (Mentor)
Custodio V. Muianga, PhD, MPH (Student Services Contractor)
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

ICF International
9300 Lee Highway
Fairfax, VA 22031

PRIMARY INTERNAL REVIEWERS

Q. Jay Zhao, PhD, MPH, DABT
National Center for Environmental Assessment, Cincinnati, OH

Ghazi Dannan, PhD
National Center for Environmental Assessment, Washington, DC

This document was externally peer reviewed under contract to
Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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COMMONLY USED ABBREVIATIONS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR DIETHANOLAMINE (CASRN 111-42-2)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Diethanolamine (DEA) is produced in large amounts and is used as a chemical intermediate and as a corrosive inhibitor and surface-active agent in metal working fluids, fuels, cosmetic formulations, paints, and inks. It is also used as a dispersing agent for agricultural chemicals and as an absorbent for acidic gases (NTP, 1992a,b,c,d; IARC, 2010). The empirical formula for diethanolamine is $C_4H_{11}NO_2$ (see Figure 1). A table of the other relevant physicochemical properties is provided below (see Table 1).

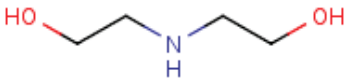

Figure 1. Diethanolamine Structure

Table 1. Physicochemical Properties Table (Diethanolamine, CAS Registry Number 111-42-2)[a]

Property (unit)	Value
Boiling point (ºC)	268.8
Melting point (ºC)	28
Density (g/cm^3)	1.0966[b]
Vapor pressure (Pa at 25ºC)	0.037
pH (of 0.1 N aqueous solution)	0.1[b]
Solubility in water (mg/L at 20ºC)	1×10^6
Relative vapor density (air = 1)	3.65[c]
Molecular weight (g/mol)	105.136

[a]ChemIDplus, 2010. Values from ChemIDplus Advanced, unless otherwise specified.
[b]HSDB, 2010.
[c]IPCS, 2002.

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for diethanolamine is included on the Integrated Risk Information System (IRIS) (U.S. EPA, 2010) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006). No RfD or RfC values are reported in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 2011a). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a) does not include a Health and Environmental Effects Profile (HEEP) for diethanolamine (U.S. EPA, 1985). The toxicity of diethanolamine has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2010) or the World Health Organization (WHO, 2010). CalEPA (2008) has derived a chronic inhalation reference exposure level (REL) of 3.0 µg/m^3 for cardiovascular, respiratory, and nervous system effects following continuous exposure to diethanolamine. The American Conference of Governmental Industrial Hygienists (ACGIH) has classified diethanolamine as a Group A3 carcinogen (*Confirmed Animal*

Carcinogen with Unknown Relevance to Humans) (HSDB, 2010). The ACGIH has established a threshold limit value time-weighted average (TLV-TWA) of 0.2 ppm (1 mg/m^3) for inhalable fraction and vapors of diethanolamine (ACGIH, 2009). Due to dose-related increases in liver tumors in female—but not male—mice and no tumors in rats after dermal exposure, ACGIH (2009) recommends a skin notation and A3 classification—"*Confirmed Animal Carcinogen with Unknown Relevance to Humans*." The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) is 3 ppm (13 mg/m^3), based on a TWA concentration for a 10-hour workday/40 hours per week (NIOSH, 2010). The Occupational Safety and Health Administration (OSHA) has no permissible exposure limit (PEL) published (OSHA, 2004).

HEAST (U.S. EPA, 2011a) does not list any cancer values or a cancer weight-of-evidence classification for diethanolamine. The International Agency for Research on Cancer (IARC, 2010, 2000) has reviewed the carcinogenic potential of diethanolamine in both humans and animals and concluded that there is inadequate evidence in humans and limited evidence in experimental animals on the carcinogenic potential of diethanolamine. Based on this evaluation, IARC has classified diethanolamine as a Group 3 carcinogen, "*Not Classifiable as to its Carcinogenicity to Humans.*" Diethanolamine is not included in the *12th Report on Carcinogens* (NTP, 2011); however, NTP (2002) published a report on carcinogens background document for diethanolamine. The document reviewed literature including NTP (1992a,b), a 13-week drinking water study in F344/N rats and B6C3F$_1$ mice, and concluded that DEA manifests toxicity in various organs in both rats and mice. NTP (2002) reported that the DEA-induced hepatocarcinogenesis observed might be related to choline deficiency, and DEA was not mutagenic, nor were its metabolites mutagenic. CalEPA (2008) has not prepared a quantitative estimate of carcinogenic potential for diethanolamine.

Literature searches were conducted on sources published from 1900 through August 2011 for studies relevant to the derivation of provisional toxicity values for diethanolamine, CAS No. 111-42-2. Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for relevant health information: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for diethanolamine and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. Principal studies are identified in bold. The phrase, "statistical significance" used throughout the document, indicates a *p*-value of <0.05.

Table 2. Summary of Potentially Relevant Data for Diethanolamine (CASRN 111-42-2)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Human								
1. Oral (mg/kg-day)[a]								
No data								
2. Inhalation (mg/m^3)[a]								
Acute	37 workers in 9 machine shops, exposure study, 2 hours of work	Median concentration of 64 µg/m^3 (range: <4−180 µg/m^3) diethanolamine in workers' breathing zones; estimated exposure via inhalation over 2 hours of work was 0.19-mg diethanolamine	N/A	Not estimated	Not estimated	Not estimated	Henriks et al. (2007)	PR
Subchronic	No data							

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Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Chronic	1 worker, 1−2 years of exposure, followed up to 1 year after study cessation	At work: unknown For bronchial provocation tests: 5 mL pure diethanolamine in aqueous solution of 0.25 mg/mL or 0.63 mg/mL (aerosolized)	After working with cutting fluids for 1−2 years, worker experienced chronic sinusitis, bronchitis, cough, sneezing, breathlessness, and wheezing; indications of occupationally-induced asthma Bronchial provocation test led to drops of 20−27% in forced expiratory volume (FEV), wheezing, and breathlessness that persisted under conditions of heated fluids and higher concentrations of diethanolamine Symptoms persisted 1 year after cutting fluids with amines were replaced	Not estimated	Not estimated	Not estimated	Piipari et al. (1998)	PR
Developmental	No data							
Reproductive	No data							
Carcinogenic	219 men, occupational study, 10-year latency, followed for 17 years	Not available; men worked with machines that used cutting fluids containing amines and nitrites	Mortality and cancer incidence were similar to general population of Gothenburg, Sweden; no significant differences were observed	Not estimated	Not estimated	Not estimated	Järvolm et al. (1986); authors noted that number of cancer cases were insignificant and concluded that the association between cutting fluids and cancer incidence should be studied further	PR

Table 2. Summary of Potentially Relevant Data for Diethanolamine (CASRN 111-42-2)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
3. Dermal								
Acute	37 workers in 9 machine shops, exposure study, 2 hours of work	The median amount of diethanolamine on skin after 2 hours of work was 12 mg/hand (1.8−37 mg); estimation of workers' dermal exposure after 2 hours is 19 mg/dominant hand retained on the skin	N/A	Not estimated	Not estimated	Not estimated	Henriks et al. (2007); authors concluded that skin was major route of exposure for diethanolamine in this study	PR
Short-term	3 premenopausal women; dermal exposure via lotion; 1 month	1.8-mg/g lotion	No critical effects reported; study conducted to assess dermal absorption potential	Not estimated	Not estimated	Not estimated	Craciunescu et al. (2009); authors estimated concentration of diethanolamine and metabolites in blood 1 month after application of lotion containing diethanolamine	PR

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Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Animal								
			1. Oral (mg/kg-day)[a]					
Short-term	5/5, F344 rat, drinking water, 2 weeks	0, 77, 162, 319, 622, or 1016 (males); 0, 79, 158, 371, 670, or 1041 (females)[d]	Increased kidney weights beginning at the lowest dose in female rats; renal tubular cell necrosis at the highest dose in males and ≥371 mg/kg-day in females; degeneration of the seminiferous tubules of the testis in males at the highest dose	Not identified	Not estimated	77 (males); 79 (females)	NTP (1992c)	NTP Report
	10, male albino rat, exposure via diet, 32 days	0, 17, 75, or 330 mg/kg-day[d]	Body weight-loss in the 330 dose group; death of 9 out of 10 animals in the 330 dose group; increased relative liver weight at the two lowest doses	Not identified	Not estimated	0.01% (~17.0 mg/kg-day)	Eastman Kodak Company (1989a)	NPR
	5/5, B6C3F$_1$ mouse, drinking water, 2 weeks	0, 110, 205, 415, 909, or 1362 (males); 0, 197, 326, 793, 1399, or 2169 (females)[d]	Increased in absolute and relative liver weight starting at 326 in female mice and 415 hepatocellular cytologic alteration in both sexes and increased serum sorbitol dehydrogenase (SDH) activity in females were seen at the highest doses	197 (females); 205 (males)	Not estimated	326 (females); 415 (males)	NTP (1992d)	NTP Report

Table 2. Summary of Potentially Relevant Data for Diethanolamine (CASRN 111-42-2)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Subchronic	**10/10, F344 rat, drinking water, 13 weeks**	**0, 25, 48, 97, 202, or 436 (males); 0, 14, 32, 57, 124, or 242 (females)[d]**	**Statistically significant reduction of mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH]) and statistically significant increases in relative kidney weights at all doses supported by renal nephropathy in both male and female rats. Relative organ-weight changes for testis (beginning at 202), and epididymis weights (beginning at 25) in males supported by renal nephropathy and lesions in the testis along with significant changes in hemoglobin [HGB]) were observed in higher doses**	**Not identified**	**6.85 (changes in MCV in male rats)**	**25 (males); 14 (females)**	**NTP (1992a)[e]**	**PS, NTP Report**
	10/10, B6C3F$_1$ mouse, drinking water, 13 weeks	0, 104, 178, 422, 807, or 1674 (males); 0, 142, 347, 884, 1154, or 1128 (females)[d]	Dose-dependent increase in relative liver and kidney weights beginning at the lowest dose in both males and females; significant changes in the serum alanine aminotransferase and sorbitol dehydrogenase levels in males at the highest dose and at the two highest doses in females; hepatocellular cytologic alteration (beginning at the lowest dose in both sexes) and necrosis (beginning at 422 in males and at 347 in females) also observed; increased relative heart weight at 422 for males and at 347 and 884 for females	Not identified	Not estimated	104 (males); 142 (females)	NTP (1992b)[e]	NTP Report

Table 2. Summary of Potentially Relevant Data for Diethanolamine (CASRN 111-42-2)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Chronic	None							
Developmental	Groups of 12 females, Sprague-Dawley rat, gavage, GDs 6−19	0, 50, 125, 200, 250, or 300	Excessive toxicity in high-dose group (sacrificed early); maternal body weight-reductions at ≥200; reduced feed consumption at ≥200; increased absolute kidney weight at 125, 200, and 250; significant increase in postimplantation loss in 200 and 250 groups; significant increase in incidence of full litter loss at 250; significant increase in pup mortality from PNDs 0−4 at ≥125; live pup weights reduced at ≥200	50 (maternal and developmental)	Not estimated	125 (maternal and developmental)	Price et al. (2005); RTI (1999)	PR
	50 female, CD-1 albino mouse, gavage, GDs 6−15, 17	Phase III: 0, 450	Significant increase in maternal weight on Postpartum Day 0 and decreases in maternal weight on Postpartum Day 3; overall, weight gain statistically significantly higher compared to controls; statistically significant reduction in neonatal survival; significant increase in duration of gestation; significant decrease in average pup weight	Not identified	Not estimated	450 (maternal and developmental)	Environmental Health Research and Testing, Inc. (1987). This study was divided in three phases. Phase I and Phase II were intended as range-finding studies and are not reported in this Table 2	NPR
Reproductive	No data							
Carcinogenic	No data							

Table 2. Summary of Potentially Relevant Data for Diethanolamine (CASRN 111-42-2)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
2. Inhalation (mg/m^3)[a]								
Short-term	10/10, Wistar rat, nose-only inhalation, 6 hours/day, 2 weeks	0, 17.9, 35.7, or 71.4	High-dose males experienced decreased body weight and body-weight gain; female rats at high-dose had increased relative and absolute liver weights; no respiratory effects seen, but larynx not examined. No statistical or biological significance was reported	Not identified	Not estimated	Not identified	Gamer et al. (2008a). $Conc_{AJD}$ is reported instead of HEC because no MMAD and GSD values	PR
	3(sex not reported): Beagle dog, 6 hours/day, 5 days/week, 9 weeks	0, 0.46, and 0.53 in Chambers 1 and 2, respectively	Slightly increased liver weights. No statistical or biological significance was reported	0.46[f] (Chamber 1) or 0.53[f] (Chamber 2)	Not estimated	Not estimated	Eastman Kodak Company (1989b)	NPR
	6 (sex not reported): Hartley-derived guinea pig, 6 hours/day, 5 days/week, 9 weeks	0, 0.46, and 0.53 in Chambers 1 and 2, respectively	Increased kidney weights. No statistical or biological significance was reported	0.46[f] (Chamber 1) or 0.53[f] (Chamber 2)	Not estimated	Not estimated	Eastman Kodak Company (1989c)	NPR
	10 (sex not reported): Sprague-Dawley rat, 6 hours/day, 5 days/week, 9 weeks	0, 0.46, and 0.53 in Chambers 1 and 2, respectively	No organ weight effects	0.46[f] (Chamber 1) or 0.53[f] (Chamber 2)	Not estimated	Not estimated	Eastman Kodak Company (1989d)	NPR

Table 2. Summary of Potentially Relevant Data for Diethanolamine (CASRN 111-42-2)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Subchronic	13/13, Wistar rat, nose-only inhalation, 6 hours/day for 65 exposure days (90-day study)	RESP: Male: 0, 5.6, 55.4, or 146.2 Female: 0, 4.8, 47.7, or 129.8 EXRESP: Male: 0, 6.8, 67.9, or 181.3 Female: 0, 6.8, 68.1, or 181.7	Significant decreases in hematological parameters (HGB, HCT, and MCV) at the highest concentration; lesions in the upper respiratory tract including focal squamous metaplasia of the ventral laryngeal epithelium at all concentrations and a diethanolamine-dependent increase in laryngeal squamous hyperplasia and tracheal inflammation at the mid- and high-concentrations	Not identified	Not estimated	RESP: Male: 5.6 Female: 4.8	Gamer et al. (2008b) Study 1	PR
	10/10, Wistar rat, nose-only inhalation, 6 hours/day for 65 days (90-day study)	RESP: Male: 0, 1.07, 2.15, or 5.66 Female: 0, 0.86, 1.71, or 4.61 EXRESP: Male: 0, 0.55, 1.11, or 2.95 Female: 0, 0.55, 1.10, or 2.93	**Significant increase in liver weight in the high-concentration females; increased incidences of squamous metaplasia of the epiglottis and the larynx in both males and females beginning at mid concentration**	**RESP: 1.07 in male rats** **EXRESP: 1.10 in female rats**	**RESP: 0.63 in male rats** **EXRESP: 2.03 in female rats**	**RESP: 2.15 in male rats** **EXRESP: 2.93 in female rats**	**Gamer et al. (2008c)** **Study 2**	**PS, PR**
	2/2, Beagle dog, 24 hours/day, 7 days/week, 90 days	0, 1.12	Blackish, elevated regions of the spleen (chemical-specific diagnosis regarding these effects could not be made)	1.12[f]	Not estimated	Not identified	Eastman Kodak Company (1989e)	NPR

Table 2. Summary of Potentially Relevant Data for Diethanolamine (CASRN 111-42-2)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Subchronic	5/5, guinea pig (strain not reported), 24 hours/day, 7 days/week, 90 days	0, 1.12	Initial weight loss and some mortality (mortalities in all groups increased towards the termination of the study period due to pneumonia)	1.12[f]	Not estimated	Not identified	Eastman Kodak Company (1989f)	NPR
	10/10, Albino rat (weanling), 24 hours/day, 7 days/week, 90 days	0, 1.12	Congested areas to blanched spots in the lung, as well as abnormal coloration in the liver	1.12[f]	Not estimated	Not identified	Eastman Kodak Company (1989g)	NPR
	10/10, Albino rat (adult), 24 hours/day, 7 days/week, 90 days	0, 1.12	Decreased body weights of male and female rats; lung abnormalities and abnormal coloration in the liver	1.12[f]	Not estimated	Not identified	Eastman Kodak Company (1989h)	NPR
Chronic	No data							
Developmental	No data							
Reproductive	No data							
Carcinogenicity	No data							

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-day) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects. All long-term exposure values (4 weeks and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure.
HEC_{RESP} = (mg/m^3) × (hours per day exposed ÷ 24) × (days exposed ÷ total days in study) × regional gas deposition ratio.
HEC_{EXRESP} = (mg/m^3) × (hours per day exposed ÷ 24) × (days exposed ÷ total days in study) × blood:gas partition coefficient.
[b]Not reported by the study author but determined from data.
[c]Notes: PS = principal study; NPR = not peer reviewed.
[d]Dosimetric conversions reported by study authors 0, 0.01, 0.1, or 1% in diet (dose conversion for 0.1 and 1% provided by study authors; dose conversion for 0.01% not provided).
[e]Laboratory report of these two studies (Battelle, 1989a,b) submitted to the Office of Toxic Substances, U.S. EPA, under 40 CFR Part 716, 54 Fed. Reg. 8484 and 8(d) Health and Safety Reporting Rule, has been reviewed, along with the final report published by the National Toxicology Program (NTP, 1992a,b).
[f]HEC conversions not presented because three different animal species were tested, and study details are not well reported.

HUMAN STUDIES

Oral Exposures

The effects of oral exposure of humans to diethanolamine have not been evaluated in subchronic, chronic, developmental, reproductive, or carcinogenic studies.

Inhalation Exposure

The effects of chronic and carcinogenic inhalation exposure of humans to various ethanolamines, including diethanolamine, were explored in two occupational studies (i.e., Järvolm et al., 1986 and Piipari et al., 1998). The effects of inhalation exposure of humans to diethanolamine have not been evaluated in subchronic, developmental, or reproductive studies.

In an occupational cohort study conducted by Gothenburg, Sweden, Järvolm et al. (1986) investigated cancer morbidity and mortality in men who worked with cutting fluids containing nitrites and amines. The study authors reported that between 1956 and 1978, the Gothenburg plant mainly used sodium nitrite and amines with alkanoamines, such as triethanolamine, diethanolamine, or monoethanolamine, occurring simultaneously in some of the products produced at the plant in varying concentrations. While specific concentrations of these alkanoamines were not available, the study authors reported that there was a persistent oil mist in the atmosphere in the grinding departments with an average concentration of 3 mg/m^3 noted in 1978, and 5 mg/m^3 or higher noted prior to 1965.

Five hundred fifty-six men, who were employed at a firm that manufactured bearing rings between 1950 and 1966 and who had been employed in certain grinding departments for at least 5 years, were selected for the study. Of these 556 men, 219 were chosen for inclusion because they had worked for at least 1 year on machines where cutting fluids with amines and nitrites were used. In order to account for long-term effects, a latent period of at least 10 years was considered, and the study authors set the first year of observation as 1966. Mortality data for the 219 men were obtained, and the underlying cause of death was used in the analysis. All 219 men were followed up to December 31, 1983. The study authors reported that besides the 7 of the 219 men that emigrated, there were no additional losses in the cohort size.

Cancer morbidity and mortality rates observed in employees were compared with those observed in the general population of Gothenburg, Sweden (440,000 residents). Death and cancer registers were used to assess cause-specific outcomes of workers and the general population. Incidence rates were stratified by age (5-year classes), calendar year (death register: 1866−1882; tumor register: 1966−1980), and gender. Expected deaths and cancer cases were stratified by calendar year, age class, exposure time, latency, and gender. Poisson distribution was applied to calculate the difference in rate ratio between observed and expected incidence rates and confidence intervals. Only two-tailed tests yielding a p-value <0.05 were considered significant.

The study authors found that mortality in grinders was similar to the general population (≥1-year exposure, standardized mortality ratio [SMR] was 0.6−1.4 for all causes; ≥5 years exposure, SMR was 0.5−1.3 for all causes). Grinders experienced fewer cases of cancer (all types) than the reference group although the difference was not statistically significant (≥1-year exposure, SMR was 0.2−1.1 for all cases of cancer; ≥5-years exposure, SMR was 0.2−1.1 for all cases of cancer). The study authors reported that the cancer records were reviewed, and "none seemed to be misclassified" (Järvolm et al., 1986, p. 564) and stated that all cancer diagnoses

were made following histopathological examination. Because this study examined mortality and cancer among workers exposed to a variety of cutting fluids at varying concentrations, specific conclusions about the effects of diethanolamine cannot be made. The study authors concluded that, although their analysis of cancer morbidity and mortality from exposures to cutting fluids was negative, an increased risk for site-specific cancer cannot be excluded given the small number of cases examined in their study. However, the results also indicated that exposures to cutting fluids in an industrial setting had not resulted in an increased risk of cancer. Because diethanolamine was not the only chemical considered in this evaluation, the results of this study do not provide support regarding the toxicity and carcinogenic potential specific to diethanolamine.

Piipari et al. (1998) reported an occupational case study of diethanolamine-induced asthma in a worker with potential exposure to cutting fluid containing triethanolamine and diethanolamine. The case study was reported on a 39-year-old male individual who had been a metal worker for 19 years in the same workplace. His primary occupation consisted of gas-shielded welding of black iron; however, in the same work area, cutting fluid containing 0.32%-triethanolamine and 0.15%-diethanolamine was used (purpose of use not specified) and was heated to a temperature of 40−60ºC, providing potential for exposure to the 39-year-old patient. The patient was considered healthy, other than mild hypertension, did not smoke, and had no or very limited exposure to second hand smoke. Beginning 1−2 years after the introduction of cutting fluids in his work area, the patient experienced chronic sinusitis, bronchitis, cough, sneezing, breathlessness, and wheezing during work hours with the symptoms increasing at the end of the work day and tapering off during holidays. Total serum IgE levels were 1260 kU/L, while the blood eosinophil count (0.089×10^9) was in the normal range. Spirometry analysis exhibited a single mild reversible obstruction that was not seen again. The patient had mild bronchial hyperactivity when given a histamine provocation test. Peak expiratory flow (PEF) readings indicated asthma, and the comparison of work-versus-home-PEF-readings suggested that it was occupationally induced because PEF readings got progressively worse during the first workweek and the first 2 days of the second workweek. However, the study authors reported that the PEF readings for the last 3 days of the second workweek did not fit the occupationally-induced asthma pattern and stated that this finding may be related to changes in exposure patterns that could not be obtained from the patient. The study authors also performed bronchial provocation tests in which 5 mL of pure diethanolamine in an aqueous solution of 0.25 mg/mL (lower concentration) and 0.63 mg/mL (higher concentration) were aerosolized into a chamber. Both of these levels are below the ACGIH TLV for diethanolamine. In addition, a placebo challenge was performed using 2 mL of cold polyol mixed with 2 mL of water. In addition to lung function, forced expiratory volume in 1 second (FEV_1) measurements were performed using a spirometer by a qualified nurse.

Results of the bronchial provocation tests indicated a number of outcomes. Exposure of the patient to heated (40ºC) cutting fluid diluted in 1:1 water for 45 minutes caused a 20% drop in FEV_1, wheezing, and breathlessness for 1 hour after the test. Exposure to heated (40ºC) fluids undiluted for 45 minutes led to a drop of 23% in FEV_1, wheezing, and breathlessness for 2 hours after the test. A concentration of 0.75-mg/m^3 aerosolized diethanolamine for 15 minutes caused a drop of 14% in FEV_1 and mild subjective breathlessness although it did not last beyond 45 minutes. A concentration of 1.0-mg/m^3 aerosolized diethanolamine for 15 minutes caused a drop of 27% in FEV_1 and breathlessness although no abnormal auscultatory findings remained 7 hours after the test. In contrast, results of the placebo challenge for 15 minutes and cold

cutting fluid for 30 minutes did not cause a drop in FEV_1 reading or cause any other symptoms noted above. One year later, even though the patient was prescribed regular anti-inflammatory asthma medication, and the workplace switched to the use of cutting fluids without amines, the patient's symptoms persisted and could not be controlled with increased medication. Following this finding, transfer of the patient was recommended to a workplace with fewer irritants.

In this study, asthmatic airway obstruction occurred at lower levels than the ACGIH threshold values, confirming that diethanolamine exposure may have caused sensitization that led to symptoms. Results of the bronchial provocation tests indicated a slight dose-response relationship. However, diethanolamine-specific IgE antibodies could not be detected due to the patient's dermatographism. The study authors concluded that it is not common to develop sensitization from exposure to ethanolamines such as that observed in this case study, and those that do develop sensitization generally only experience symptoms after an extended latent period of exposure (in this case, 1−2 years).

Other Studies

In a human dermal study, which was done in conjunction with a mouse developmental toxicity study via dermal exposure (see Table 3 for mouse study overview), Craciunescu et al. (2009) recruited three local, healthy premenopausal women (ages 30, 30, and 29) that were not pregnant or planning to get pregnant for a 1-month human study to assess the exposure potential of diethanolamine and its metabolites in human subjects. Based on Craciunescu et al. (2009), the study protocol was approved by the Public Health Institutional Review Board at the University of North Carolina at Chapel Hill. After the first visit, the three subjects were instructed to use lotion supplied to them (929 g containing 1.8-mg diethanolamine/g lotion) and to apply it to their entire body twice a day (after showering in the morning and before bedtime) from the following day onward. Participants kept a log of their application; authors also inspected and weighed the bottle 1 week and 1 month later to ensure compliance with the body lotion regimen. Whole blood was collected 1 day before treatment, 1 week after treatment, and 1 month after treatment (end of study); diethanolamine and metabolites were analyzed. Only two of the three participants completed the 1-month study; the third voluntarily dropped out after 3 weeks of participation. For this subject, a 3-week whole-bood sample was collected in place of the 1-month measurement.

Concentrations of diethanolamine and its metabolite dimethyldiethanolamine in plasma increased after 1 month of lotion application. When Craciunescu et al. (2009) compared these concentrations to those in mice, they were 100- to 200-fold lower than those in the mouse study, which is not surprising considering that the human doses were about 133-fold lower compared with doses administered to mice. Although this finding indicated that human exposure in the study was much lower than that required to impede brain development in mice, studies with a large number of participants are required before any conclusions can be drawn regarding the toxicity potential of diethanolamine to humans via the dermal route of exposure. Furthermore, this study only evaluated exposure for 1 month, though people use personal care products over a lifetime. The study also did not address exposure from other personal care products that may contain diethanolamine besides the lotion that was administered in this study. Although this study is not directly applicable to developmental toxicity, the study does provide some useful information regarding potential human exposure via the dermal route.

Henriks et al. (2007) assessed exposure to several metal-working fluids (including diethanolamine) in machinists. The study authors collected air samples and rinse-off samples from hands of 37 workers in 9 machine shops. After 2 hours of work, hand samples were collected by rinsing the dominant hand with 200 mL of 20% isopropanol for 1 minute in a plastic bag (recovery efficiency = ~55%). Workers then washed their hands with soap and water, and the process was repeated. During the same 2-hour working period, air samples were collected using personal air pumps with acid-treated glass fiber filters. The study authors determined that diethanolamine samples remained stable when analyzed within 4 days of sampling.

The median amount of diethanolamine on the skin (n = 5) was 12 mg/hand (range: 1.8−37 mg). A median concentration of 64-µg/m^3 (range: <4−180 µg/m^3) diethanolamine was measured in air samples from five workers' personal breathing zones. Estimations of workers' exposure during 2 hours of work were 0.19 mg/dominant hand (median; range: <0.02−0.44 mg/dominant hand) from dermal exposure to diethanolamine in inhaled air and 19 mg/dominant hand (median; range: 2.8−56 mg/dominant hand) retained on the skin. When machinists used only diethanolamine-containing fluids, the median amount of diethanolamine on the skin was 100 times the median amount in inhaled air, indicating that the primary exposure route of diethanolamine was through the skin. Based on their analysis regarding occupational exposures to diethanolamine, the study authors concluded that dermal exposure to diethanolamine was considerably higher compared to exposure via inhalation and recommended the use of protective gloves.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to diethanolamine have been evaluated in two short-term (i.e., NTP, 1992c,d and Eastman Kodak Company, 1989a), two subchronic-duration (i.e., NTP, 1992a,b), and two developmental toxicity studies (i.e., Price et al., 2005 or RTI, 1999; and Environmental Health Research and Testing, Inc., 1987). Studies pertaining to the chronic-duration toxicity and carcinogenicity and multigeneration reproductive effects following oral exposure to diethanolamine could not be located.

Short-term Studies

NTP (1992c) conducted a study in accordance with Good Laboratory Practice (GLP) in which they administered 0-, 630-, 1250-, 2500-, 5000-, or 10,000-ppm diethanolamine (purity >99%) in the drinking water (deionized) to F344 rats of both sexes for 2 weeks (5/sex/dose). Animals were obtained from Simonsen Labs, Inc., of Gilroy, CA, and were approximately 6 weeks old at study initiation. The estimated average daily converted doses reported by the study authors were 0, 77, 162, 319, 622, and 1016 mg/kg-day for male rats and 0, 79, 158, 371, 670, and 1041 mg/kg-day for females.

The frequency with which body-weight determinations were made is not reported. Urine samples were collected for about 16 hours from animals on Day 12 of the 2-week study. Urine was measured for volume, appearance, specific gravity, and pH; concentrations of glucose, protein, urea nitrogen, and creatinine; and activities of alkaline phosphatase and lactate dehydrogenase. Blood samples were collected from all animals and analyzed for sorbitol dehydrogenase (SDH), alanine aminotransferase (ALT), total protein (TP), albumin, urea nitrogen (UN), creatinine, glucose, total bile acids, erythrocyte count (RBC), leukocyte count (WBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean

corpuscular hemoglobin concentration (MCHC), hemoglobin (HGB), hematocrit (HCT), leukocyte differential count, erythrocyte morphologic assessment, reticulocyte count, platelet count, and platelet morphologic assessment. All animals underwent a complete necropsy. The study authors examined all organs and tissues for gross lesions and weighed the brain, heart, thymus, right kidney, liver, lung, right testis, and thymus. The authors performed complete histopathologic examinations on all early death and control animals, and animals in the highest dose groups that had at least 60% survivors. Vaginal cytology and vaginal lavage were performed on females exposed to 0-, 79-, 158-, or 371-mg/kg-day diethanolamine 7 days prior to sacrifice to identify stages of estrous cycle using preponderance of leukocytes, nucleated epithelial cells, and large squamous epithelial cells as markers. Males exposed to 0, 77, 162, or 319 mg/kg-day were subjected to sperm morphology exams at necropsy, which included analysis of sperm motility, density, and spermatogenesis.

Numerical data were analyzed using group means and standard deviations (SDs). Bartlett's test was used to test body weight, organ weight, and clinical pathology data. Nonhomogenous data were analyzed with a separate *t*-test, and homogenous data were analyzed using a one-way analysis of variance (ANOVA), followed by a Dunnett's test for a pairwise comparison to controls.

All female rats in the 670- and 1041-mg/kg-day dose groups and two males from the 1016-mg/kg-day dose group died or were sacrificed due their moribund condition before study termination. All female rats in the 1041-mg/kg-day dose group were dead by Day 6 of the study. Primary clinical signs observed included abnormal posture, tremors, and hypoactivity. Males in the 622- and 1016-mg/kg-day dose groups and females in the 371- and 670-mg/kg-day dose groups exhibited reduced body-weight gains compared to the concurrent controls (see Tables B.1 and B.2). The study authors stated that water consumption was reduced in all treatment groups when compared with controls, especially in the two highest dose groups and concluded that reduced palatability of drinking water at the two highest dose groups may have contributed to the reduced body-weight gain at these two doses. Dose-related decreases in erythrocyte and reticulocyte counts, MCV, MCHC, and HCT indicated moderate normochromatic and microcytic anemia in both sexes. Treatment with diethanolamine also led to increases in serum concentrations of creatinine, TP, UN, and albumin in both sexes and bile acids in male rats. In addition, ALT activity was increased in female rats at the 371-mg/kg-day dose level; however, changes in ALT levels were not supported by histopathological lesions in the liver. The kidney and testis were identified as target organs. Both sexes exhibited increased absolute and relative kidney weights, with the relative kidney weights exhibiting a statistically significant ($p \leq 0.05$ or $p \leq 0.01$) increase beginning at 79 mg/kg-day in females and 162 mg/kg-day in males compared with the concurrent control group (see Tables B.1 and B.2). In addition, an increased incidence of renal tubular epithelial necrosis was noted along with increased urinary concentration of UN, glucose, protein, and lactate dehydrogenase activity in both males and females (see Tables B.1 and B.2). Renal tubular necrosis characterized by tubules denuded with epithelium, tubule lumens filled with eosinophilic debris of sloughed epithelial cells, and karyorrhexis indicated regenerative changes in the renal tubules. Tubular necrosis was observed in rats treated with diethanolamine at 371 mg/kg-day (females only), 670 mg/kg-day (females only), or 1016 mg/kg-day (males) and 1041 mg/kg-day (females). The study authors reported that the lesions were more severe in animals that died early during the course of the study compared to animals that survived until study termination. Additionally, a minor amount of mineralization of necrotic renal tubules was also noted in animals (sex and dose-specific information not reported).

High-dose males experienced mild-to-noticeable degeneration of the seminiferous tubules that was characterized by a reduction in tubule size and the number of spermatogenic cells. In addition to these changes, a large number of degenerate cells were observed in the lumen of the epididymal tubules. Based on the results presented above, a LOAEL of 79 mg/kg-day for significant ($p \leq 0.05$) increases in relative kidney weight in female F344 rats is identified for this study. A NOAEL cannot be identified.

The Eastman Kodak Company (1989a) sponsored an unpublished, non-peer-reviewed, 32-day, subacute oral toxicity study in male albino rats. Animals were exposed to 0-, 0.01-, 0.1-, or 1.0%-diethanolamine (purity unreported) via diet (10 animals per dose group). Animals were housed five per cage with the dose levels randomly distributed to the cages. The study authors calculated adjusted daily doses of 75 mg/kg-day for the 0.1%-dose and 330 mg/kg-day for the 1%-dose. An adjusted calculated dose for the 0.01%-dose was not reported (estimated to be 17 mg/kg-day). The study authors recorded feed consumption and body weights at unspecified time periods. Hematological analysis (hemoglobin, hematocrit, white and differential cell counts, and serum protein) was performed on the control, 75-, and 330-mg/kg-day dose groups at Day 28. Animals were sacrificed on Day 32 or 33, and body weights and organ weights (liver, kidney, spleen, heart, lung, brain, and testes) were measured. Tissues (trachea, lung, heart, tongue, esophagus, stomach, small intestine, large intestine, liver, kidney, urinary bladder, pituitary, thyroid, adrenal, pancreas, testis, spleen, femoral bone marrow, cerebrum, cerebellum, and eye) were removed and fixed for examination. No information regarding compliance with GLP was provided. Though diethanolamine-related results are discussed by the study authors, the raw data are not presented in the study report.

The study authors reported body-weight loss in the 330-mg/kg-day dose group from study initiation until Day 14, which was observed in conjunction with reduced food intake and anorexia. Also, at the dose group level, nine out of 10 animals (90%) died between Days 13 and 21. The sole survivor appeared to improve from Days 21−32. The 75-mg/kg-day dose group showed reduced weight gain and anorexia between Days 4 and 8. Animals appeared to largely recover on Day 8 although food consumption and diet efficiency were slightly reduced compared to controls. The mortality in the 330-mg/kg-day dose group prevented organ-weight analysis; however, animals in the 75-mg/kg-day dose group had increased liver weights compared to controls. Liver weights relative to body weights were statistically significantly (level not specified) increased in the 17-mg/kg-day and 75-mg/kg-day dose groups. Relative testis weights at the 0.01% (converted dose not reported by study authors) and 75-mg/kg-day dose levels were not different from the concurrent controls, but they were different from each other (data not shown). The sole survivor in the 330-mg/kg-day dose group had decreased hemoglobin and hematocrit and a large increase in white blood cells. Hemoglobin and hematocrit in the 75-mg/kg-day dose group were within normal range but were statistically significantly ($p = 0.05$) decreased as compared to controls. The sole survivor of the 330-mg/kg-day dose group did not show any pathological abnormalities. Two rats that died during the course of the study were examined and found to have pulmonary lesions and hemorrhagic gastroenteritis, which may have been the result of diethanolamine exposure or spontaneous disease. The study authors concluded that spontaneous disease was more likely the cause of gastroenteritis because the animals at this dose level had reduced food intake.

Due to lack of clarity in the study description and unreported quantitative data, this study cannot be used as a principal study to support derivation of a provisional toxicity value. The mortality observed at the 330-mg/kg-day dose level represents a frank effect; however, a LOAEL of 0.01% (~17-mg/kg-day) diethanolamine is identified in this study for a significant increase in liver weight. A NOAEL cannot be identified.

In addition to the rat study, NTP (1992d) also examined the effects of diethanolamine in male and female $B6C3F_1$ mice. The dosing regimen, study design, and methods (diethanolamine [purity >99%] in the drinking water [deionized] to mice of both sexes for 2 weeks) for assessing toxicological endpoints were similar to what is described above for the rat study. The estimated average daily converted doses reported by the study authors were 0, 110, 205, 415, 909, and 1362 mg/kg-day for male mice and 0, 197, 326, 793, 1399, and 2169 mg/kg-day for female mice.

There were no unscheduled deaths for males or females in the control or any of the treatment groups. Body weights of the 1362-mg/kg-day (male), and 2169-mg/kg-day (female) mice and the 1399-mg/kg-day female mice were reduced compared to the control group. Primary clinical signs were seen only in the highest dose group in males and females and included emaciation, abnormal posture, and rough haircoat. Water consumption in the highest dose group was reduced in males and females, and the study authors stated that the palatability of water at this dose may have contributed to reduced body weights in males and females. While treatment-related gross lesions were not noted at necropsy, dose-dependent increases in absolute and relative liver weights were observed in both male and female mice with the relative liver weights exhibiting statistically significant ($p \leq 0.01$) increases starting at doses of 326 mg/kg-day in females and 415 mg/kg-day in males (see Tables B.3 and B.4). Increases in absolute and relative liver weights were corroborated with cytologic alterations observed following microscopic examination of the liver tissues (see Tables B.3 and B.4). Cytological alterations included cellular enlargement, increased cytoplasmic eosinophilia, and increased occurrence of binucleated hepatocytes. In addition, the study authors stated that necrosis of random, single hepatocytes were noted and could be associated with cytological alterations. Females in the 2169-mg/kg-day group experienced an increase in sorbitol dehydrogenase (SDH) activity compared with controls (see Table B.4). The study authors also reported minor incidences of myocardial degeneration in one male and one female in the 1362-mg/kg-day (male) and 2169-mg/kg-day (female) dose group. Based on these results, LOAELs of 326 mg/kg-day and 415 mg/kg-day for significant ($p \leq 0.01$) increases in relative liver weight in female and male $B6C3F_1$ mice, respectively, are identified for this study. The NOAELs for this study are 197 mg/kg-day for female mice and 205 mg/kg-day for male mice.

Subchronic-duration Studies

The NTP (1992a) rat study is selected as the principal study for the derivation of the subchronic and chronic p-RfDs. In a 13-week subchronic-duration, GLP-compliant drinking water study by NTP (1992a; Melnick et al., 1994), groups of 10 male F344 rats were exposed to 0-, 320-, 630-, 1250-, 2500-, or 5000-ppm diethanolamine, and groups of 10 female F344 rats were exposed to 0-, 160-, 320-, 630-, 1250-, or 2500-ppm diethanolamine (purity >99%) dissolved in drinking water (deionized). The estimated average daily converted doses reported by the study authors were 0, 25, 48, 97, 202, and 436 mg/kg-day for males and 0, 14, 32, 57, 124, and 242 mg/kg-day for females.

Methods used for toxicological evaluation were similar to the 2-week study and are described in detail under "Short-Term Studies." The only difference between the 2-week study and the 13-week study was in urine collection: the urine in the subchronic-duration study was collected from animals during Week 12 of the study. A description of the statistical analysis performed as part of this study is presented in detail under "Short-term Studies."

Mortality was noted in two males in the high-dose group (436 mg/kg-day), while one female was found dead in the 14-mg/kg-day dose group. The study authors stated that the death of the female rat was not considered to be treatment related. Body-weight gains were reduced in a dose-dependent manner in both sexes (see Table B.5). Decreased water consumption observed in the higher dose groups was partly attributed to decreased body-weight gains. Primary clinical signs noted in the two highest dose groups in males and females included emaciation, abnormal posture, tremors, and rough hair coat. Hematological parameters such as erythrocyte and reticulocyte counts, HGB, HCT, MCV, and MCH exhibited a dose-dependent decrease when compared to controls in both sexes, with the majority of the parameters exhibiting statistical significance ($p \leq 0.05$ or $p \leq 0.01$) at all doses when compared to the corresponding controls (see Tables B.6 and B.7). The study authors reported that the magnitude of the responses in these hematological parameters was greater in the 13-week study compared to the 2-week study. In addition, males and females treated with diethanolamine showed signs of moderate, poorly regenerative microcytic normochromatic anemia. There was no association between hematological effects and microscopic changes in the femoral bone marrow.

Necropsy examination did not reveal any significant gross lesions as a result of exposure to diethanolamine (see Tables B.10 and B.11). Relative kidney weights exhibited a dose-dependent and statistically significant ($p \leq 0.05$ or $p \leq 0.01$) increase beginning at the lowest doses (25 mg/kg-day in males and 14 mg/kg-day in females) compared to the control group (see Tables B.8 and B.9). The study authors stated that relative kidney-weight changes were well supported by increased incidence and severity of nephropathy, renal tubular cell necrosis, and tubular mineralization (see Tables B.10 and B.11). Pathological changes related to nephropathy included tubules lined with epithelial cells with more basophilic staining of the cytoplasm along with higher nuclear/cytoplasmic ratio and occasional thickening of the basement membranes. These lesions were also noted in the control group (particularly in males), but the incidence of these lesions was higher and more severe in the high-dose (436-mg/kg-day) males and at almost all doses in females (see Tables B.10 and B.11). Increase in nephropathy was considered to be a regenerative change and was well supported by the tubular necrosis observed at higher doses in both males and females. The severity of tubular necrosis was minimal and was characterized by eosinophilic tubular epithelial cells with pyknotic nuclei that were frequently observed as desquamation in the lumen of the renal tubules. Mineralization was also observed and was present in all female control rats, but the severity of mineralization was dose dependent and higher in both females and males treated with various doses of diethanolamine (see Tables B.10 and B.11).

In addition to changes in relative kidney weights, a dose-dependent and statistically significant ($p \leq 0.05$ or $p \leq 0.01$) increase was noted in relative liver weights in females at the 32-mg/kg-day dose level and above and in males at the 48-mg/kg-day dose level and above. In males, a dose-dependent and statistically significant ($p \leq 0.05$ or $p \leq 0.01$) decrease in relative epididymis and testis weights was noted at and above the 97-mg/kg-day dose level for the epididymis and the 202-mg/kg-day dose level for the testis (see Table B.8). Decreases in relative

weights of the testis and epididymis were corroborated with microscopic degeneration of seminiferous epithelium and hypospermia. Testicular lesions were morphologically similar to the ones seen in animals exposed to diethanolamine in drinking water for 2 weeks and consisted of fewer spermatogenic cells, smaller seminiferous tubules, and very little intraluminal sperm. Testicular degeneration was reported in all males at 436 mg/kg-day and in 3 out of 10 males at 202 mg/kg-day. Fewer sperm cells and intraluminal cellular debris were also observed in the epididymis. The study authors reported that these findings correlated well with decreases in sperm motility and sperm count per gram of caudal tissue. In addition to these effects, atrophy of the seminal vesicle and prostate glands was noted in males treated with 436-mg/kg-day diethanolamine. No changes in female rat estrous cycle length were reported. The dose-related increases seen in relative liver weights in both males and females were not associated with any microscopic lesions in the liver. However, mild-to-moderate increases in serum concentrations of total bile acids in females at all dose levels and in males at all dose levels (except at the 25 mg/kg-day in males and 32 mg/kg-day in females) were reported. Other biochemical changes in male and female rats included increased concentrations of albumin, TP, and UN in the serum.

In addition to the hematological endpoints and effects noted in the kidneys, the study authors also identified the brain and the spinal cord as potential target organs of diethanolamine toxicity (see Tables B.10 and B.11). Microscopic examination in the brain revealed changes in the coronal sections of the medulla oblongata, which were made of bilaterally symmetrical areas of vacuolization of the neuropil. In addition, vacuoles were consistently seen as "sharply delimited, round-to-oval, clear spaces arranged symmetrically around the midline of the medulla in areas of transversely sectioned white matter identified as the tectospinal tract" (NTP, 1992a, p. 31). In more severe cases, the peripheral white matter tracts were also involved at the same level as the medulla. In general, the vacuoles were empty and were not associated with a glial response. However, some vacuoles contained debris and exhibited a minimal cellular reaction. Transverse sections of the spinal cord showed randomly scattered vacuoles in the dorsal, ventral, and lateral columns on the white matter and in the spinal nerves. No lesions were noted in sections of the sciatic nerve. Demyelination of the brain and spinal cord was not observed at the lower doses and was limited to male rats treated with 202 or 436 mg/kg-day and female rats exposed to 124 and 242 mg/kg-day (see Tables B.10 and B.11). No neurological clinical signs could be associated with these lesions.

In addition to the observations presented above, treatment-related effects in the cytoplasmic vacuolization of the zona glomerulosa of the adrenal cortex were noted in 9 out of 10 males in the 436-mg/kg-day dose group as well as 2 out of 10 females in the 242-mg/kg-day dose group. The authors stated that this change was minimal and may be related to an increase in mineralocorticoid production secondary to renal damage and/or dehydration. Based on the results presented above, a LOAEL of 14 mg/kg-day is identified for a statistically significant ($p \leq 0.05$ or $p \leq 0.01$) increase in relative kidney weights supported by renal nephropathy and significant changes in hematological parameters in females. A LOAEL of 25 mg/kg-day is identified for significant ($p \leq 0.05$ or $p \leq 0.01$) changes in relative kidney, testis, and epididymis weights in males supported by renal nephropathy and lesions in the testis along with significant changes in hematological parameters. A NOAEL cannot be identified.

In a 13-week subchronic-duration, GLP-compliant drinking water study by NTP (1992b), groups of 10 $B6C3F_1$ mice/sex were exposed to 0-, 630-, 1250-, 2500-, 5000-, or 10,000-ppm diethanolamine (purity >99%) dissolved in drinking water (deionized). The estimated average

daily converted doses reported by the study authors were 0, 104, 178, 422, 807, and 1674 mg/kg-day for males and 0, 142, 347, 884, 1154, and 1128 mg/kg-day for females.

Methods used for toxicological evaluation were similar to the 2-week study and are described in detail under "Short-term Studies." The only difference between the 2-week study and the 13-week study was in urine collection, with the urine in the subchronic-duration study collected from animals during Week 12 of the study. A description of the statistical analysis performed as part of this study is presented in detail under "Short-term Studies."

Mortality was noted in all male and female mice in the highest dose group (1674 and 1128 mg/kg-day in males and females, respectively) and the second highest dose group (807 and 1154 mg/kg-day in males and females, respectively); three females were found dead in the third highest dose group (884 mg/kg-day). Body-weight gains were reduced in the 422-mg/kg-day dose group for males and in the 347- and 884-mg/kg-day dose group for females (see Table B.12). Water consumption did not change across dose groups. Primary clinical signs noted in the two highest dose groups in males and females included emaciation, abnormal posture, tremors, hypoactivity, and rough hair coat. Clinical chemistry parameters such as TP, albumin, and alanine aminotransferase exhibited a dose-dependent increase when compared to controls in both sexes with most of the parameters exhibiting statistical significance ($p \leq 0.05$ or $p \leq 0.01$) at all doses when compared to the corresponding controls (see Tables B.13 and B.14). Similar to the liver effects in the 2-week study, multiple hepatocytic changes including hypertrophy and increased eosinophilia and hepatic cord disruption occurred. These lesions were seen in both mice that died early and those that survived for 13 weeks. The study authors also noted an increase in nuclear pleomorphism and the presence of large, multinucleated hepatocytes, frequently containing more than 10 nuclei and randomly distributed among single cells and small foci.

Necropsy examination did not reveal any significant gross lesions as a result of exposure to diethanolamine. Relative liver and kidney weights exhibited a dose-dependent increase beginning at the lowest doses in both males and females compared to the control group, with relative liver weights exhibiting statistical significance ($p \leq 0.05$ or $p \leq 0.01$) at the lowest dose group in both sexes (see Tables B.15 and B.16). The study authors stated that relative liver-weight changes were well supported by changes in the serum alanine aminotransferase and sorbitol dehydrogenase levels in both sexes, with a significant ($p < 0.01$) increase seen in males at the 422 and nonsignificant in females at 884 mg/kg-day level, respectively (see Tables B.13 and B.14). In addition to these enzyme changes, hepatocellular cytologic alteration and necrosis were also reported by the study authors. Pathological changes related to nephropathy included tubules lined with epithelial cells with more basophilic staining of the cytoplasm along with a higher nuclear/cytoplasmic ratio. The study authors noted that this finding was a "regenerative response" and was only observed in a small number of early-death mice and the two highest dose groups. Relative heart weight increased in the 422-mg/kg-day dose group for males and in the 347- and 884-mg/kg-day dose groups for females (see Tables B.15 and B.16). The study authors noted that these observations were important because minimal-to-marked degeneration and necrosis of cardiac myocytes were seen at 422 and 884 mg/kg-day in males and females, respectively, and in higher dose groups in both male and female mice. These lesions consisted of degenerated and fragmented myofibers in the ventricles and were linked with mineralization and inflammatory cells. The study authors noted that the myocardial degeneration was more common in mice that died early compared to those that survived for 13 weeks. Lesions in the

submandibular salivary gland increased in a dose-dependent manner in the 422, 807, and 1674 mg/kg-day (males); 884, 1154, and 1128 mg/kg-day (females) dose groups. These lesions were characterized by a decrease in loss of eosinophilic granules and change in size of the secretory duct cells.

Based on the results presented above, a LOAEL of 104 mg/kg-day in males and 142 mg/kg-day in females is identified for statistically significant ($p \leq 0.05$ or $p \leq 0.01$) increases in relative liver weights supported by increased serum alanine aminotransferase and sorbitol dehydrogenase levels along with hepatocellular cytologic alteration and necrosis in male and female mice. A NOAEL cannot be identified in this study.

Chronic-duration Studies

Studies pertaining to chronic systemic toxicity of diethanolamine via oral exposure could not be located.

Developmental and Reproductive Toxicity Studies

No oral studies pertaining to the reproductive toxicity of diethanolamine were identified. In a peer-reviewed, developmental toxicity study (i.e., Price et al., 2005; RTI, 1999; Price et al. and RTI are the same study), the study authors orally administered 0-, 50-, 125-, 200, 250, or 300 mg/kg-day diethanolamine (purity ≥98%) in distilled Pico water (dose volume of 5 mL/kg, based on body weight) to time-mated Sprague-Dawley rats on gestational days (GDs) 6−19. The rats were obtained from Charles River Laboratories, Inc. in Raleigh, NC. Animals were stratified into groups of 12 confirmed-mated females, with an additional 10 used as sentinel females. Animals were kept individually in polycarbonate cages, and environmental conditions were maintained with temperatures of 65.6−75.2°F, relative humidity of 39.3−69.7%, and a 12-hour-light/dark cycle. Purina Certified Rodent Chow and water were provided ad libitum. The body weights of confirmed-mated females were recorded on GD 0 and GDs 6−20. Dams with litters were weighed on Postnatal Days (PNDs) 0, 4, 7, 14, and before sacrifice on PND 21. The study authors observed dams for clinical signs once daily on GDs 0−5 and from GD 20 through study termination. Females were also observed for clinical signs at dosing and 1−2 hours after dosing (GDs 6−19). The study authors measured food and water consumption on GDs 0, 6, 9, 12, 15, 18, and 20 for all timed-mated females and on PNDs 0, 4, 7, 14, and 21 for dams with litters.

Time-mated females that did not produce litters by GD 24 were terminated and examined for early resorptions. Dams producing only dead pups or those who lost entire litters after delivery were also sacrificed, and their implantation sites were counted. All surviving dams and pups were sacrificed on PND 21. After sacrifice, authors recorded weights of the whole body, liver, and paired kidneys for each time-mated female, examined the thoracic and abdominal cavities, and counted uterine implantation sites. Litter size, pup sex, and pup body weights were recorded, and clinical examinations of pups were conducted on PNDs 0, 4, 7, 14, and 21. Pups were examined for malformations and abnormalities on PND 0 and culled to litter sizes of eight on PND 7 (one litter in the 250-mg/kg-day dose group was culled to nine pups). Culled pups were necropsied on PND 7 while all others were necropsied at termination on PND 21. The study authors did not provide a GLP-compliance statement.

Statistical analysis was done using SAS software, with the significance level set at $p < 0.05$. The Kruskal-Wallis one-way analysis by ranks was used for differences between treatment groups, and the Mann-Whitney U-test for pairwise comparison was used to compare treated groups to controls. The authors used a one-tailed Mann-Whitney U-test for all parameters other than maternal and pup body weights and feed/water consumption, which were determined via a two-tailed test. Dose-response trends were identified using Jonckheere's test. For nominal scale measures, the χ^2 test for independence was used to determine differences between treatment groups, and the Cochran-Armitage test was used to determine linear trends on proportions. When the results of χ^2 tests were significant, a one-tailed Fisher's exact test was used for comparison between control and treated animals. The authors determined maternal LD_{10} using probit analysis.

Due to excessive toxicity at 300 mg/kg-day, all females in this group were sacrificed before schedule and excluded from further analysis. All 12 females from the control, 50-mg/kg-day, and 125-mg/kg-day groups as well as 11/12 females in the 200-mg/kg-day group delivered viable litters. One female in the 200-mg/kg-day group was terminated while attempting to deliver a litter of 15 dead pups. In the 250-mg/kg-day group, one female was found dead on GD 15, and one female with 12 dead pups was sacrificed due to its moribund condition on GD 21. Among the remaining females, five females delivered viable litters, one delivered a litter of dead pups, three had resorbed litters, and one was not pregnant. The study authors calculated an LD_{10} of 218 mg/kg-day. The study authors noted weight loss, piloerection, and lethargy at ≥200 mg/kg-day. Piloerection was also seen on PNDs 0 and 1 in dams treated with 125-, 200-, and 250-mg/kg-day diethanolamine. Reduction in maternal body weight was noted in dams dosed with ≥200-mg/kg-day diethanolamine, predominantly during treatment and gestation. Across the treatment period, average maternal relative feed consumption was reduced at ≥200 mg/kg-day, and water intake was not affected. Maternal kidney weight was increased in a dose-dependent manner, and absolute paired kidney weights were statistically significantly ($p < 0.05$) increased in the 125-, 200-, and 250-mg/kg-day groups at PND 21. The study authors concluded that there was persistent diethanolamine-induced toxicity noted in dams up to PND 21 after exposure to diethanolamine had ceased. Based on these results, the study authors identified a maternal toxicity LOAEL of 125 mg/kg-day for significant increases in absolute kidney weight and a maternal toxicity NOAEL of 50 mg/kg-day.

Developmental toxicity observations included postimplantation loss that was statistically significantly ($p < 0.05$) increased in the 200- and 250-mg/kg-day dose groups and exhibited a dose-response trend (see Table B.18). There was a biologically and statistically significant ($p < 0.05$) increase in the incidence of full litter loss in the 250-mg/kg-day group. Exposure to diethanolamine was associated with a decreasing trend for number of live pups on PNDs 4 and 7 (see Table B.18). Percentages of live pups were 91, 97, 85, and 55% of the controls at 50, 125, 200, and 250 mg/kg-day, respectively. There was a statistically significant ($p < 0.05$) increase in pup mortality during PNDs 0−4 at ≥125 mg/kg-day (see Table B.17). Live pup body weights were statistically significantly reduced at ≥200 mg/kg-day, both at birth and at the end of lactation (see Table B.18). Based on these results, the study authors identified a developmental toxicity LOAEL of 125 mg/kg-day for significant increases in early postnatal mortality (PNDs 0−4) and a NOAEL of 50 mg/kg-day.

In another developmental toxicity study, Environmental Health Research and Testing, Inc. (1987) conducted a three-phase GLP-compliant drinking water study on diethanolamine and related chemicals with 50 CD-1 albino mice, 6−8-week-old obtained from Charles River Breeding Laboratories in Kingston, New York. The study does not appear to be peer reviewed. Phases I and II were intended as range-finding studies to identify a dose for Phase III, which focused on reproductive outcomes. Body weights were measured within 2 days of receipt, and mice were quarantined for 5 days in the room where the study took place. Animals were kept individually in polycarbonate shoebox cages; cages were sanitized, and bedding was replaced at least once during the study period. Mice were given Purina Certified Rodent Chow #5002 (although Phase III animals were given Ziegler Brothers NIH-07 Rodent Chow for 1 day due to a supplier problem) and water ad libitum. The temperature of the room was kept at 72 ± 3°F, and a 12-hour-light/dark cycle was maintained. Throughout the various phases, animals were observed twice per day (once in the morning and once at night) for signs of toxicity and mortality. Animals were observed once a day for toxicity and mortality on days when not dosed (7 days post treatment for Phases I and II and after completion of Phase III). Bartlett's test for homogeneity of variance and F-tests were completed for weight data of each group at study initiation. Probit analysis was used for mortality and morbidity data in Phase II. ANOVA (two-tail) was used for random weights; survival was measured using Fisher's exact test; weight gains and other group/control comparisons (e.g., number of live pups/litter) were made using the Mann-Whitney U-Test (two-tail); the proportion of viable litters was analyzed using Fisher's exact test; and survival of pups was analyzed using the χ^2 test (one-tail).

In Phase I, virgin females (3 per group) were dosed with 10-, 100-, or 1000-mg/kg-day diethanolamine (purity confirmed, but unreported) in distilled water for 5 days. Body weights were recorded at randomization and on Days 1 and 5 during treatment and Days 3 and 7 after treatment. One death occurred at 100 mg/kg. Other clinical signs including hunched appearance, rough haircoat, and pale eyes and extremities. Based on the mortality, doses of 200, 380, 720, 1370, and 2605 mg/kg-day were chosen for Phase II (no control group; 4 mated females per group). Pregnant mice were dosed from GDs 6−15 (10 days). Body weights were recorded every day. Systemic toxicity was evidenced by a rough haircoat at all doses; hunched posture, languid behavior, and squinted eyes (≥720 mg/kg); bloody vaginal discharge (≥1370 mg/kg); labored breathing (≥1370 mg/kg); unsteady gait and underweight animals (1370 mg/kg); prostrate behavior (2605 mg/kg); and pale eyes/extremities (2605 mg/kg). Death occurred in one animal at 200 mg/kg from dosing trauma. All other deaths were not related to trauma and included three animals at 720 mg/kg, four animals at 1370 mg/kg, and all animals at 2605 mg/kg by Day 5. Surviving females were sacrificed and weighed, and uteri were removed and examined; no significant results were found.

After probit analysis, authors selected a dose of 450 mg/kg-day for Phase III; this dose represented the LD_{10}. A vehicle control received distilled water; dosed animals (50 treated pregnant females and 50 controls) were administered diethanolamine on GDs 6−15 and GD 17. Weights were recorded at randomization, every day of gestation, and on Postpartum (PP) Days 0 and 3. All mice that did not deliver by GD 22 were sacrificed, and their uteri were examined. No maternal toxicity was observed in this phase. There were significant increases in maternal weight on PP Day 0 ($p < 0.001$) and decreases in weight on PP Day 3 ($p = 0.01$) compared to controls (see Table B.19). Overall, weight gain was statistically significantly different from the control group, with treated dams gaining an average of 6.4 grams from pretreatment to PP Day 0. There was also a statistically significant reduction in neonatal survival ($p < 0.001$), a significant

increase ($p \leq 0.001$) in duration of gestation compared to control animals, and a significant decrease in average pup weight on PND 3 ($p \leq 0.001$) (see Tables B.20 and B.21). Based on these results, maternal and developmental LOAELs of 450 mg/kg-day are identified in this study. A NOAEL cannot be identified.

Inhalation Exposures

The effects of inhalation exposure of animals to diethanolamine have been evaluated in four short-term- (i.e., Gamer et al., 2008a; Eastman Kodak Company, 1989b,c,d) and six subchronic-duration (i.e., Gamer et al., 2008b,c; Eastman Kodak Company, 1989e,f,g,h) toxicity studies. Studies pertaining to the chronic toxicity, carcinogenicity, developmental toxicity, and multigeneration reproductive effects following inhalation exposure to diethanolamine could not be located.

Short-term Studies

In a range-finding study, Gamer et al. (2008a) exposed 10 Wistar rats per sex to 100-, 200-, or 400-mg/m^3 diethanolamine for 6 hours/day, for 2 weeks (totaling 10 exposures). The corresponding adjusted continuous exposure concentrations are 17.9, 35.7, and 71.4 mg/m^3, respectively. Animals were housed individually in wire cages between exposure periods and were given KLIBA laboratory diet (Lingenthalmüle AG, Kaiseraugust, Switzerland) and tap water ad libitum. The room was kept at a temperature of 20−24°C and a relative humidity of 30−70% with a 12-hour-light/dark cycle. During administration of diethanolamine, animals were transferred to glass exposure tubes with only their snouts inside the inhalation systems. Liquid diethanolamine was aerosolized and then pumped into stainless steel cylindrical past-flow nose exposure systems. Infusion pump rates were adjusted to control the concentration of diethanolamine. Prior to study initiation, animals were adapted to the administration system for 3−5 days using clean air.

The study authors found no diethanolamine-related effects at 17.9 and 35.7 mg/m^3. However, male rats exposed to 71.4 mg/m^3 experienced decreased body weight and body-weight gain, and both sexes showed a slight decrease in serum cholesterol. Females had increased relative and absolute liver weights. No effects were seen in the nasal cavity, trachea, or lungs following histopathological examination. The larynx was not examined in this study. The results of this study were used to determine the dose range for the first 90-day nose-only study.

Eastman Kodak Company (1989b,c,d) sponsored an unpublished, 9-week, subchronic-duration inhalation toxicity study on diethanolamine and Bimat Imbitant (used in photography) in dogs, guinea pigs, and rats (sex and number not reported). A gas chromatographic analysis of diethanolamine supplied to the study authors by Elon Department, Kodak Park, indicated that the only impurity in the supplied sample was 1% water. The Bimat Imbitant (referred to as 485K hereafter) was obtained from the Powder and Solution Department, Kodak Park, and consisted of approximately 80% water and <20% diethanolamine. Three chambers, each consisting of 3 dogs, 6 guinea pigs, and 10 rats were used in the study. In one chamber, a concentration of about 0.5-ppm (2.2-mg/m^3) undiluted diethanolamine was maintained, while in a second chamber, 485K was injected to an approximate concentration of 0.5-ppm (2.2-mg/m^3) diethanolamine. The third chamber received air alone with no known contaminants and served as the study control. Animals were exposed to diethanolamine and 485K for 6 hours/day, 5 days/week, for 9 weeks, totaling 45 exposures. The study authors stated that the actual measured concentrations were 0.6 ppm (2.6 mg/m^3) of undiluted diethanolamine (Chamber 1)

and 0.7 ppm (3.0 mg/m^3) of 485K (Chamber 2). The corresponding continuous exposures are 0.46 mg/m^3 in Chamber 1 and 0.53 mg/m^3 in Chamber 2. The dogs used in this study were beagles from Marshall Research Animals, Inc.; Sprague-Dawley rats and Hartley-derived guinea pigs both from A and E Farms were also used in this study. Animals were allowed to acclimate to the chambers for 6 hours/day, for 8 days. The study authors used an assumed minute volume of 5.2 L/min (7.49 m^3/day) for dogs and 0.1 L/min (0.14 m^3/day) for rats to calculate total daily doses of 0.5 mg/kg for dogs and 0.2 mg/kg for rats, respectively. Calculations were not reported for guinea pigs. No information on GLP compliance was presented.

The study authors made clinical observations before and during each exposure. Animals were weighed before each exposure. Hematological analysis was performed (hemoglobin, hematocrit, white and differential cell counts, and serum protein). Animals were sacrificed 18 hours following the last exposure period. Lungs, livers, and kidneys were weighed. Organs (respiratory, cardiovascular, digestive, urinary, endocrine, reproductive, hematopoietic, lymphopoietic, sensory, integumentary, muscular, and central nervous system) were removed and fixed for sectioning and staining with hematoxylin and eosin. Livers were also stained, fixed, examined for glycogen, and stained with Oil Red O for fat. Data were analyzed using the test for variance and the Duncan's Multiple Range Test. Data were discussed by the study authors, but raw data and data tables were not presented in the study report.

No abnormal behavior or mortalities were observed in the exposed animals. Body weights were not affected, except for the rats exposed to neat diethanolamine; these rats reportedly gained less weight than the 485K group or the controls. Organs weight effects were seen in the liver of the dogs, with those exposed to neat diethanolamine slightly increased over the control and those exposed to 485K slightly decreased compared to the control. Organ weight effects were seen in the kidneys of exposed guinea pigs, with those exposed to the neat diethanolamine increased over control. No organ weight effects were noted in the rats. No significant changes were seen in the hematological analysis. No lesions were noted in the necropsy. Microscopic examination of organs revealed no treatment-related effects. The liver was closely examined for vacuolization, fat, and glycogen, but no effects related to exposure were observed.

Due to lack of clarity in the study description and unreported quantitative data, this study cannot be used as a principal study to support derivation of a provisional toxicity value. NOAELs of 0.46- or 0.53-mg/m^3 diethanolamine in Chambers 1 and 2, respectively, are identified because no effects in any of the diethanolamine-treated animals were observed at these two dose levels in the two chambers.

Subchronic-duration Studies

The Gamer et al. (2008c) study is selected as the principal study for the derivation of subchronic and chronic p-RfCs. In two peer-reviewed nose-only inhalation studies, Gamer et al. exposed Wistar rats to concentrations of 0-, 15-, 150-, or 400-mg/m^3 (2008b; *n* = 13/sex/dose group; hereafter referred to as Study 1) or 0-, 1.5-, 3-, or 8-mg/m^3 (2008c; *n* = 10/sex/dose group; hereafter referred to as Study 2) diethanolamine (purity >99%) 6 hours per day, for a total of 65 exposures over a time period of 99 days (90-day study; as specified by the study authors). The corresponding adjusted continuous exposure concentrations are 0, 2.5, 24.6, and 65.7 mg/m^3 for Study 1 and 0, 0.25, 0.49, and 1.3 mg/m^3 for Study 2. In Study 1, authors obtained animals at 7 weeks of age from Dr. K. Thomae, Bierbach, Germany. In

Study 2, authors obtained animals at 7 weeks of age from Charles River, Sulzfeld, Germany. Environmental conditions and exposure methodology are the same as those of the 14-day range-finding study discussed previously (Gamer et al., 2008a). Observations for clinical signs and mortality were made three times per week in Study 1 and two times per week in Study 2. An ophthalmoscopy was completed on all animals in Study 1 before the preflow period. In both studies, body weight was measured at the beginning of the preflow period, before the first exposure, and once per week thereafter. Study 1 specifically investigated neurotoxicity; thus, authors administered comprehensive neurofunctional tests in 10 rats/sex. This functional observational battery (FOB) test included observations for sensory and motor functions, and was performed before the exposure and then four times (once a month) during the study. Tests covered responses to visual, auditory, olfactory, and touch stimuli, and neuromotor alterations (e.g., pain perception). Motor activity was tested on the same day as the FOB with a Multi-Varimex System.

For Study 1, blood samples were obtained from animals (10/sex) the morning after the last exposure (animals were not fasted). Urinalysis was done after animals (10/sex) were transferred to metabolism cages overnight. Hematological parameters included leukocyte count, erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and platelet count. Clinical chemistry analysis included measurement of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase, sodium, potassium, magnesium, chloride, inorganic phosphate, calcium, urea, creatinine, glucose, total bilirubin, total protein, albumin, globulins, triglycerides, and cholesterol, which were analyzed using an automatic analyzer. Urinalysis was semi-quantitative and completed either by microscopic or visual evaluation or with test strips and a reflection photometer. The study authors looked at volume, color, turbidity, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, specific gravity, and sediment. In Study 2, the authors did not examine blood or urine.

In Study 1, neuropathological examinations were performed on three sacrificed animals of each sex in every test group. Organs were embedded in epoxy resin (mid-thigh sciatic nerve and tibial nerve at the knee) or paraplast (brain, spinal cord). The rest of the animals underwent a necropsy and gross pathological examination, which included cross sections of the nasal cavity and larynx. In Study 2, all animals underwent a necropsy and gross pathological and histopathological examinations. The respiratory tract was the focus of examinations; thus, the nasal cavity, larynx, and trachea were investigated in all animals. Reversibility of effects was investigated by examinations of the recovery groups (Study 2). Data from clinical examinations were analyzed using two-sided ANOVA and Dunnett's test. Clinical chemistry and hematology data were analyzed using a one-way ANOVA using the F-test, and Dunnett's tests for pairwise comparisons with the controls were done if the p-value <0.05. Organ weights were analyzed using nonparametric one-way ANOVA with the Kruskal-Wallis H-test. If that test resulted in a p-value <0.05, authors performed a pairwise comparison of each group using the Wilcoxon U-test and the hypothesis of equal medians. The relationship between the concentration of diethanolamine and laryngeal irritation was evaluated using the EPA benchmark multistage model (Gamer et al., 2008; U.S. EPA, 2011b).

There were no deaths in Study 1. Clinical effects included a diethanolamine-related decrease in body weight in males exposed to 400 mg/m^3 (equivalent HEC of 181.3 mg/m^3) compared to control animals (see Tables B.22). There were a few isolated significant differences

in motor activity measurements in treated animals compared to controls, but the authors considered these incidental. The authors observed significant ($p < 0.01$) decreases in red blood cells, hemoglobin, hematocrit, and mean corpuscular volume ($p < 0.05$) in both sexes of rats exposed to 400 mg/m^3 (equivalent HEC of 181.3 mg/m^3 and 181.7 mg/m^3 for male and female rats, respectively) diethanolamine. At 150- and 400-mg/m^3 (equivalent HEC of 67.9 and 181.3 mg/m^3 for male and 68.1 and 181.7 mg/m^3 for female rats) diethanolamine, there were slight, significant (level not reported) increases in serum alkaline phosphatase for both sexes and a decrease in serum alanine aminotransferase in males only. Serum levels of calcium, total protein, albumin, and globulin were increased in females of the mid- and high-exposure groups (see Tables B.24 and B.25). There was a significant (level not reported) increase in blood in the urine in both sexes at the high concentration. Males exposed to 150- and 400-mg/m^3 (corresponding HEC of 67.9 and 181.3 mg/m^3) diethanolamine also experienced significant (level not reported) increases in renal tubular epithelial cells and occasional granular casts.

Organ examinations revealed significant ($p < 0.05$ or $p < 0.01$) increases in the weights of the liver and kidneys in males and females at the highest concentration. Females exposed to 24.6 mg/m^3 (corresponding HEC of 68.1 mg/m^3) also experienced significant increases ($p < 0.01$) in the weights of both these organs, and males exposed to the mid-dose experienced significant ($p < 0.05$) increases in kidney weight (see Tables B.22 and B.23). The relative brain weight was statistically significantly ($p < 0.05$) increased in high-dose males, which is consistent with reduced body weights. The study authors noted gross lesions of the epithelium of the glandular stomach in females at the intermediate and high concentrations. There were apparent lesions in the upper respiratory tract when examined microscopically. These findings included focal squamous metaplasia of the ventral laryngeal epithelium at the base on the epiglottis at all concentrations and a diethanolamine-dependent increase in laryngeal squamous hyperplasia and the incidence and severity of laryngeal and tracheal inflammation at the mid- and high-concentrations (see Tables B.26 and B.27). Based on these results, a $LOAEL_{ADJ}$ of 2.5 mg/m^3 is identified in Study 1 for respiratory effects in male and female rats (corresponding $LOAEL_{HECs}$ of 5.6 mg/m^3 and 4.8 mg/m^3 for male and female rats, respectively). A NOAEL cannot be identified.

In Study 2, two females in the recovery groups died, but the study authors considered the deaths incidental. No clinical effects were seen. There were no significant differences in body weight or relative organ weight for males at any concentration compared to the control (see Table B.28). Effects in the larynx at the high concentration were similar to those seen in the first study. This finding was not seen in the low-concentration group in Study 1, indicating variability of populations. The authors noted a significant ($p < 0.05$) increase in liver weight in female rats exposed to 8 mg/m^3 (corresponding HEC of 2.93 mg/m^3) (see Table B.29). Squamous metaplasia of the laryngeal epithelium at the base of the epiglottis (Level 1) and the larynx (Level 2) and submucosal inflammation were seen in both sexes. Squamous metaplasia (without inflammatory cell infiltration) was found in 3/10 male rats exposed to 3 mg/m^3 (corresponding HEC of 1.11 mg/m^3) diethanolamine, and some inflammatory cell infiltration was seen in control animals. No histological changes were found in the respiratory tract after 3 months of recovery (see Tables B.30 and B.31).

The study authors concluded that diethanolamine is toxic to the upper respiratory tract, as evidenced by epithelial effects in the larynx. Diethanolamine also affected hematology, clinical chemistry, and urinalysis parameters, which corresponded to increases in liver and kidney

weights and lesions in the kidneys. Results from Studies 1 and 2 indicate that the respiratory tract (in particular, the trachio-bronchiolar region) is more sensitive to diethanolamine via inhalation exposure. While reversal of respiratory effects was noted in Study 2 in females followed for 3 months postexposure, it is clear that exposures to higher concentrations of diethanolamine (Study 1) led to more severe respiratory effects. Based on these results, a $LOAEL_{ADJ}$ of 0.49 mg/m^3 (corresponding to a $LOAEL_{HEC}$ of 2.15 mg/m^3 for respiratory effects due to increased incidences of squamous metaplasia in the epiglottis [Level 1] and in the larynx [Level 2]) in male rats and a $NOAEL_{ADJ}$ of 0.36 mg/m^3 (corresponding to a $NOAEL_{HEC}$ of 1.07 mg/m^{3}for respiratory effects in male rats) are identified in this study. A $LOAEL_{HEC}$ of 2.93 mg/m^3 for extrarespiratory effects due to increased relative liver weight in female rats and a $NOAEL_{HEC}$ of 1.10 mg/m^3 are considered.

Eastman Kodak Company (1989e,f,g,h) sponsored an unpublished, 90-day, subchronic-duration inhalation toxicity study in groups of beagle dogs (n = 4; equally divided by sex), guinea pigs (n = 10; equally divided by sex), and weanling and adult albino rats (n = 20; equally divided by sex). Animals were exposed to analyzed vapor concentrations of 0.26-ppm (1.12-mg/m^3) diethanolamine (purity not reported) without a vehicle or in Formulation 485k (485K), which reportedly contained 0.25-ppm (1.08-mg/m^3) diethanolamine and 0.05-ppm (0.66 mg/m^3) quinine at saturation levels. Exposure was carried out for 24 hours/day, 7 days/week, for 90 days. Control exposures of filtered laboratory air were used for comparison. Experimental vapor concentrations were generated by forcing dry air into bubblers or gallon jars with glass wool containing diethanolamine or 485K. One stainless steel inhalation chamber (3.85 m^3 in volume) was used for 2 beagle dogs per sex, 5 guinea pigs (strain unreported) per sex, 10 weanling albino rats per sex, and 10 adult albino rats per sex exposed to diethanolamine; another chamber was used for 485K; and another chamber was used for controls. No information regarding the strains or husbandry of the animals was presented in the report. No data regarding compliance with GLP were presented.

Biological observations, including those on general health conditions, were conducted throughout study duration. Animals were weighed biweekly. Hematological analysis (hemoglobin, hematocrit, and white, red, and differential cell counts) was performed on all dogs, guinea pigs, and a sample (50%/sex) of rats before and following the exposure period. In the case of abnormal hematology findings, the tests were carried out again following a 2-week period when the animals were observed. Urinalysis measuring albumin and sugar was conducted in the same number of animals. Examination of the cornea using fluorescent dye was conducted in all dogs prior to exposure and then at 5, 10, and 13 weeks. The eyes of rats and guinea pigs were visually examined "frequently" (Eastman Kodak Company, 1989a,b,c,d,e,f,g,h; p. 10). Complete necropsies were conducted on animals that died during the exposure period, as well as on animals that were sacrificed at scheduled times 24−48 hours following the exposure period and at 2 weeks following the end of the exposure period. Gross pathological examinations of the brain, thyroid, parathyroid, lung, heart, liver, kidney, spleen, trachea, large and small intestine, adrenals, urinary bladder, gall bladder, and gonads were conducted, with particular attention given to the lung. Histopathology was done on the lungs, liver, kidneys, spleen, gonads, bone marrow, and brain of 1 dog per sex per group, 5 guinea pigs per sex per group, 10 weanling rats per sex per group, and 2 adult rats per sex per group. While data were discussed in some detail by the study authors, data tables providing specific details were not presented in the study report.

Body weights recorded in dogs in the first 4 weeks declined; however, the body weights of all dogs measured at the 13-week time period was normal. Few exposure effects were noted in dogs, despite "isolated cases" of decreased food consumption, nasal discharge, and loose stool, which the study authors concluded were not related to diethanolamine exposure. Two dogs exposed to 485K were reported to have affected corneas (no further details provided). Necropsies showed dogs to have blackish, elevated regions of the spleen; however, the authors noted that a chemical-specific diagnosis regarding these effects could not be made. No changes in hematology or urinalysis were noted compared to controls in any of the tested animals. The study authors reported no compound-related mortalities in any of the exposed animals. Histopathological examination indicated no effects in the tissues of exposed dogs.

Exposed guinea pigs reportedly lost weight initially during the exposure period and experienced some mortality. The study authors attributed this finding to the stress of the experimental procedure and provided "replacement" animals. However, mortalities in all groups increased towards the termination of the study period due to pneumonia that was reportedly related to a change in the air conditioning system. Given these observations in exposed guinea pigs, limited information can be gleaned from the reported results regarding the toxicity of diethanolamine to guinea pigs. Histopathological examination of the guinea pigs concluded that the observed mortalities were incidental. No histological effects of exposure were found.

Based on Eastman Kodak Company (1989e,f,g,h), statistical evaluation of the terminal body weights and organ-weight ratios revealed several cases of statistically significantly different values, but there were no distinct trends or patterns to indicate any compound-related effects. Weanling rats were not reportedly affected for the first 6 weeks of exposure; however, beginning at Week 8, growth in males exposed to 485K and diethanolamine was suppressed compared to the concurrent controls. Generally, animals sacrificed 2 weeks following the exposure period showed a small increase in body weights when compared to those weighed at 13 weeks. All rats (adult and weanling) displayed nasal discharge, which appeared to be related to exposure, but the effect did not persist through the entire study period. Weanling rats had abnormalities ranging from congested areas to blanched spots in the lung (3/10 males exposed to diethanolamine and 4/9 males exposed to 485K, compared to 1/10 control males; "similar trends in the female animals" Eastman Kodak Company, 1989a,b,c,d,e,f,g,h, p. 22) as well as abnormal coloration in the liver (incidence not reported). Adult rats also showed lung abnormalities (3/8 males exposed to diethanolamine and 4/10 males exposed to 485K, compared to 3/10 control males) and abnormal coloration in the liver (incidence not reported). No discussion of results in the female adult rats was included. Histopathological examination showed that the brain, lung, liver, spleen, kidney, testis, and bone marrow were not affected by exposure. A "moderate incidence" of infectious disease lesions in the lungs was noted. None of the observed effects were considered treatment related and a NOAEL of 1.12 mg/m^3 is identified.

Due to lack of clarity in the study description and unreported quantitative data (Eastman Kodak Company [1989a,b,c,d,e,f,g,h] cited tables with several data and statistical inferences but did not include these tables in their report). Thus, this study cannot be used as a principal study to support derivation of a provisional toxicity value. Additionally, the study authors reported several cases of statistically significantly different values, without any trends or patterns to indicate compound-related effects or other causes. No LOAEL is identified.

Chronic-duration Studies

Studies pertaining to chronic systemic toxicity of diethanolamine via inhalation exposure could not be located.

Developmental Studies

Studies pertaining to developmental toxicity of diethanolamine via inhalation exposure could not be located.

Reproductive Studies

Studies pertaining to reproductive toxicity of diethanolamine via inhalation exposure could not be located.

Table 3 provides a summary of selected acute, dermal carcinogenicity, in vitro, toxicokinetic, genotoxicity, and mutagenicity studies.

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute oral and dermal toxicity	Acute toxicity study in calves by stomach intubation of 0.6, 1.0, 1.4, 2.0, 2.4, 3.0, or 5.0 g/kg in gum arabic solution; 10%-aqueous solution of undiluted diethanolamine was applied to the skin of rabbits (unspecified method and duration)	Low acute oral toxicity; 100% survival at 1.0 g/kg, 1 death/2 animals at 1.4 g/kg, 2/3 deaths at 2.0 g/kg, 2/5 deaths at 2.4 g/kg, 5/5 deaths at 3.0 g/kg, and 1/1 death at 5.0 g/kg No significant skin irritation; denaturation of the ear after 10 applications and denaturation of the belly after 3 applications	Moderately irritating to the skin; low acute oral toxicity	Dow Chemical Company (1944)
Acute toxicity; hepatotoxicity	Acute toxicity study in albino Swiss Webster mice given single i.p. injections of 1.1−5.5 g/kg and observed for 24 hours post dosing	LD_{50} of 2.3 g/kg; dose of 1.7 g/kg led to sedation, ataxia, loss of righting reflex; microscopy revealed many changes in organelles of synthesis, secretion, and respiration (e.g., mitochondria) in the liver; LD_{50} doses corresponded with cellular degeneration and hepatic steatosis	IP exposure caused fatty degeneration of liver and ultrastructural effects in the ER and mitochondria	Blum et al. (1972)
Dermal carcinogenicity	2-year dermal study in F344 rat (50/sex/group); males administered 0, 16, 32, or 64 mg/kg and females administered 0, 8, 16, or 32 mg/kg	Minimal-to-moderate skin conditions in both sexes; increased incidence and severity of nephropathy in treated females; increased incidences of acanthosis (males), hyperkeratosis (males and females), and exudate (males and females); no neoplastic effects	There was no evidence of carcinogenic activity. Exposure increased several skin conditions and nephropathy in females	Pathology Working Group (1997); NTP (1999)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Dermal carcinogenicity	2-year dermal study in $B6C3F_1$ mouse (50/sex/group); doses of 0, 40, 80, or 160 mg/kg	Increased incidences of multiple hepatocellular adenoma in both sexes; increased multiple hepatocellular carcinoma in both sexes; increased hepatoblastoma in treated males; increased incidences of hepatocellular carcinoma in females; increased incidences of renal tubule and multiple renal tubule carcinoma in males; low-to-moderate skin irritation in all treated animals; increased incidences of cytoplasmic alteration (males), syncytial alteration of the liver, renal tubule hyperplasia (males), thyroid gland follicular cell hyperplasia, and hyperkeratosis of the skin	There was evidence of carcinogenic activity (liver of males and kidneys of females). Exposure increased several skin conditions and thyroid gland follicular cell hyperplasia	Pathology Working Group (1997); NTP (1999)
Mode-of-action for carcinogenicity via dermal exposure	4-week dermal study in $B6C3F_1$ mouse (6 male mice/dose group); doses of 0, 10, 20, 40, 80, or 160 mg/kg; diethanolamine dissolved in ethanol; 2 control groups included ethanol treated and untreated groups	Phosphocholine levels most impacted by diethanolamine treatment by exhibiting a decrease beginning at 20 mg/kg; glycerophosphocholine, choline, and phosphatidylcholine also decreased in a dose-dependent manner; S-adenosylmethionine levels decreased at 80 and 160 mg/kg; S-adenosylhomocysteine increased at 80 and 160 mg/kg; study authors identified a NOEL of 10 mg/kg for diethanolamine-induced changes in choline homeostasis; application of ethanol alone decreased hepatic betaine levels	The study authors concluded that diethanolamine treatment leads to a range of biochemical changes in choline homeostasis; this demonstrates that there is a dose-related concordance between diethanolamine-induced choline deficiency and hepatocarcinogenicity; use of ethanol as a vehicle may exacerbate or confound the effects of diethanolamine alone	Lehman-McKeeman et al. (2002)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Mode-of-action for carcinogenicity via dermal exposure	Not applicable; review article	Diethanolamine reduced choline metabolites and S-adenosylmethionine levels in mice; no effects observed in dermally-treated rats; rats did not exhibit tumors at the maximum tolerated dose of 64 mg/kg; all diethanolamine doses that induced tumors in the NTP (1999) study also caused choline deficiency; rats and mice reported to be more susceptible to choline deficiency compared to humans and other mammalian species; diethanolamine is less readily absorbed through rat and human skin compared to mouse	NOEL of 10 mg/kg-day established in mice; this level indicates that a critical level of diethanolamine needs to be achieved to impact choline homeostasis; noncarcinogenic activity in rats indicates that a critical level of diethanolamine was not reached; because rodents are more susceptible to choline deficiency compared to humans, diethanolamine-induced hepatocarcinogenicity in mice may not be predictive of similar susceptibility in humans	Leung et al. (2005)
Predictive carcinogenicity	Computational toxicology study using rules R1 (8 sub-rules) and R3 (8 sub-rules) and reports of lesions from subchronic-duration studies as well as genotoxicity results to calculate predicted carcinogenicity	Negative in *Salmonella* assay review; applicable lesions for organ-specific toxicity included the following: ulceration, hyperkeratosis, and inflammation of skin; nephropathy, necrosis, and mineralization in kidney; degeneration in brain; necrosis in liver; degeneration in heart; rules predict that diethanolamine is carcinogenic	Diethanolamine was predicted positive using R1 and R3 but was negative in the *Salmonella* assay	Lee et al. (1996)
In vitro neurotoxicity	In vitro neurotoxicity study using mouse neural precursor cells (C57Bl/6J cortical neural precursor cells at Embryonic Day 14); 3-mM diethanolamine in culture; 72 hours; also examined fetal brains from 2 dams dermally exposed to 80 mg/kg-day on Gestation Days (GDs) 7−17	Cells proliferated 24% less than controls, had 308% more apoptosis at 72 hours compared to controls, and had reduced uptake of choline (52% of controls), which resulted in lowered intracellular concentrations of choline and phosphocholine. Effects were eliminated with supplemental choline in the cell media. Fetal brains had diethanolamine concentrations of 0.023 and 0.026 mM	Neurotoxicity may be the result of inhibition of choline transport and altered choline metabolism. Prenatal exposure to diethanolamine may inhibit brain development	Niculescu et al. (2007)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Dermal developmental/ neurotoxicity	Dermal study in C57BL/6 mouse dams (7/group) from GDs 7−17; doses of 0, 5, 40, 50, and 80 mg/kg-day	At 80 mg/kg-day, increased diethanolamine and metabolites in maternal liver and plasma; decreased maternal hepatic concentration of choline and metabolites; and, in fetal brains, diminished proportions of cells in the mitotic phase and increased number of apoptotic cells	Supports previous reports of diminished hepatic stores of choline and altered brain development	Craciunescu et al. (2009)
Dermal developmental	Dermal study in CD rat dams (25/dose group) from GDs 6−15: doses of 0, 150, 500, or 1500 mg/kg-day; New Zealand White rabbit does (15/dose group) from GDs 6−18: doses of 0, 35, 100, or 350 mg/kg-day; 6 hours/day; occluded test site	For rat dams, significant decrease (~4.5%) in body weight from GDs 15−21 at 1500 mg/kg-day; skin irritation and increased kidney weights at 500 and 1500 mg/kg-day; hematological effects in all dose groups For rat fetuses, increased incidences of skeletal alterations (6) at 1500 mg/kg-day For rabbit does, significant decrease in food consumption at 100 and 350 mg/kg-day; skin lesions For rabbit fetuses, increased poorly ossified interparietal bones at 350 mg/kg-day	No evidence for teratogenicity in either species; maternal toxicity at lower doses; rats more sensitive than rabbits	Marty et al. (1999)
Dermal developmental	Dermal study in New Zealand White rabbit does (15/group) from GDs 6−18; doses of 0, 35, 100, or 350 mg/kg-day; 6 hours/day; occluded test site	Severe skin irritation (necrosis, ecchymosis, exfoliation, excoriation, crusting, and/or scabbing) at 350 mg/kg-day; some edema in 350-mg/kg-day group; increased absolute and relative liver weights; increased relative kidney weight; no developmental effects	Maternal NOEL: 100 mg/kg-day Fetal NOEL: ≥350 mg/kg-day	Bushy Run Research Center (1993)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Dermal developmental	Dermal study in CD rat dams (25/group) from GDs 6−15; doses of 0, 150, 500, or 1500 mg/kg-day; 6 hours/day; occluded test site	Severe skin irritation at 1500 mg/kg-day (erythema, crusting, necrosis, and ecchymosis at dosing site); reductions in body weight during last third of treatment at 1500 mg/kg-day; increased kidney weights; treatment-related anemia at all doses; other changes in hematology at all doses; in fetuses, increased incidences of skeletal variations (6) in the skull, axial skeleton, and distal limb at 1500 mg/kg-day	Maternal effects starting at 150 mg/kg-day and developmental delay at 1500 mg/kg-day Fetal NOEL: 500 mg/kg-day	Bushy Run Research Center (1992)
Dermal developmental	Dermal study in C57BL/6 mouse dams (6/group) from GDs 7−17; doses of 0, 20, 80, 160, 320, or 640 mg/kg-day; fetal mouse brain analysis included only at 80-mg/kg dose	Significant decrease in maternal choline stores; decreased litter size at >80 mg/kg; decreased neuronal progenitor cell mitosis in fetal hippocampus at 80 mg/kg-day; increased apoptosis in fetal hippocampus at 80 mg/kg-day	Effects on pregnancy outcome and on fetal brain development	Craciunescu et al. (2006)
Predictive developmental	Short-term in vivo assay on 12 chemicals to rank for potential toxicity using a numerical scoring system (proportion of pregnant survivors that produced a litter of at least one live pup; average litter size and weight of pups at birth; and average pup survival and gain in weight at 3 days of age)	Diethanolamine was classified as "high priority"	Diethanolamine recommended for further testing of developmental toxicity and other effects	York et al. (1988) (abstract only)
Toxicokinetic	Distribution and excretion study in female Sprague-Dawley rat; i.v. injection of 10 or 100 mg/kg; followed through 96 hours post dosing	Clearance calculated at 84 mL/h/kg for the 10-mg/kg dose and 242 mL/h/kg for the 100-mg/kg dose; primary excretion of parent compound through urine; majority recovered from tissues (primarily in liver and kidney); some accumulation in red blood cells 6−96 hours after dosing	Evidence of tendency to bioaccumulate	Mendrala et al. (2001)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Toxicokinetic	Distribution and excretion study in male F344 rat; i.v. injection of 7.5 mg/kg; followed through 48 hours post dosing	Clearance almost entirely in urine (16% and 28% of total dose at 24 and 48 hours after administration, respectively); most found in tissues (highest in liver and kidney)	Evidence of accumulation in the liver and kidneys	RTI (1991)
Toxicokinetic	Distribution and excretion study in unspecified rat strain; unspecified oral dose; 5 days/week, for 1, 2, 4, or 8 weeks	Accumulated in tissues and reached steady-state levels around 4 weeks; highest concentrations in liver and kidney	Evidence of accumulation in the liver and kidneys	RTI (1991) in NTP (1992a,b,c,d)
Toxicokinetic	Distribution and excretion study in $B6C3F_1$ mouse; unspecified single oral dose	25% of dose excreted in urine in 48 hours; highest concentrations in liver and kidney; lower concentrations in heart, spleen, and lung	Evidence of accumulation in the liver and kidneys	RTI (1991) in NTP (1992a,b,c,d)
Toxicokinetic	Metabolism study in male F344 rats; gavage of single dose of 7.9 mg/kg or daily repeated dose of 7.8 mg/kg, 5 days/week, for 2, 4, or 8 weeks; or i.v. injection with 7.5 mg/kg; or dermal doses of 2.l, 7.6, or 27.5 mg/kg	Less than 1% of the i.v. dose excreted in the feces; highest concentration in the liver (27%); kidney, brain, and heart also target organs; total amount absorbed by the skin increased with dose, but absorption was relatively low; 2% of the single oral dose excreted in feces and 22% excreted in urine; distribution of oral dose similar to i.v., with the lung, kidney, and liver showing high concentrations; accumulation decreased with increasing number of daily doses; rats likely reached steady state between 4 and 8 weeks	Evidence of accumulation in the liver and kidneys	RTI (1991)
Toxicokinetic	Metabolism study in male $B6C3F_1$ mouse; single i.v. injection of 14.9 mg/kg or dermal application of 81.1 mg/kg	About 25% of an i.v. dose of 14.9 mg/kg was excreted 48 hours after dosing; the liver had the highest concentration (20%), followed by the kidney; well absorbed by the skin (58 ± 5% of applied dose absorbed)	Higher dermal penetration in mice may be due to thinner skin than rats	RTI (1991)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Toxicokinetic	Metabolism study in Fischer rat; single or repeated (up to 8 weeks) oral exposure of 7 mg/kg; i.v. injection of 7 mg/kg; dermal administration of 2−28 mg/kg (48 hours)	Less than 30% of the oral or i.v. doses excreted by rats in 48 hours (as unchanged diethanolamine); most excretion through urine; highest tissue concentrations found in the liver, kidney, heart, lung, brain, and spleen; not well absorbed through rat skin (16%); over 50% of the dermal dose absorbed by mouse skin In oral dosing (7 mg/kg) for 5 days/week, steady state reached around 4 weeks of exposure; larger doses (up to 200 mg/kg) resulted in almost complete absorption; a first-order process indicates a whole-body half life of 6 days, but about 54 days in blood; methylation produced alkanolamine metabolites, and a new metabolite formed from oxidation of dimethyldiethanolamine	Metabolites changed with increased repeated oral dosing. There were significant amounts of *N*-methyl diethanolamine and more cationic metabolites along with diethanolamine	Mathews (1997)
Toxicokinetic	Metabolism study in vitro rat liver; concentrations of 100−3,000 µM; 3 weeks Metabolism study in male albino Sprague-Dawley rat (4/group); drinking water 2 mg/mL; 1, 2, or 3 weeks	Suppressed synthesis of phosphatidyl choline and phosphatidyl ethanolamine in rat liver tissue in vitro; K_1 of about 3-mM diethanolamine; no inhibition from acute in vivo administration; repeated doses of 330 mg/kg-day required to cause significant inhibition of phospholipids, most notably in the liver	The half-life of diethanolamine derivatives may cause accumulation of diethanolamine-containing phospholipid in tissues	Barbee and Hartung (1979)
Toxicokinetic	Metabolism study in male Sprague-Dawley rat : 0.25-, 1, 3-, or 5-mg/mL pH-neutralized diethanolamine in drinking water; 1, 2, or 3 weeks; in vitro experiment in hepatocytes (details not specified)	Hepatic mitochondria: declined respiratory control, increased oxygen consumption during ADP depletion in cellular respiration after repeated oral administration of diethanolamine; after 24 hours of oral exposure to 3 mg/mL, no effect on mitochondria; in vitro treatment showed no effect	Mitochondrial metabolism impaired (structure not altered) after repeated diethanolamine administration	Barbee and Hartung (1976) (abstract only)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Toxicokinetic	Metabolism study in male F344 rat; gavage or i.v. injection of 7 mg; up to 8 weeks	Less than 30% of dose (either route) excreted in 48 hours, predominantly in urine as parent compound; high concentrations in liver, kidney, heart, brain, and spleen compared to blood; liver contained predominantly parent compound but also polar metabolites; diethanolamine headgroup conjugated with endogenous ceramides to form aberrant sphingomyelins; after administration for 8 weeks, diethanolamine accumulation plateaued	Cumulative toxicity partially caused by increasing levels of aberrant phospholipids	Mathews et al. (1995)
Toxicokinetic	Metabolism study in $B6C3F_1$ mouse; gavage or dermal administration of 160 mg/kg-day; 2 weeks	Blood levels 1−1.5 hours after dosing were 5−7.7 mg/kg depending on route; dermal absorption blood levels were 65% of the oral dose blood levels; decrease in choline and metabolites in livers of all treated mice; unoccluded dermal exposure resulted in higher exposure due to contribution of oral ingestion (35% higher blood levels than dermal occluded)	Treatment-depleted choline-containing compounds, which may have a role in tumorigenesis	Stott et al. (2000)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Genotoxicity	Genotoxicity study in hepatocytes, lung cells, and kidney cells from Sprague-Dawley rat, Syrian golden hamster, and domestic pig: 12.5-, 25.0-, or 50.0-µmol diethanolamine/tube of cells (2×10^6 hepatocytes); rat lung, liver, and kidney cells: 25.0-µmol/mL diethanolamine	Positive results in hepatocytes at 12.5 µmol: the maximum observed DNA single strand break (SSB) induction—10−19% in hamsters and 40−59% in pigs; at 25.0 µmol the max SSB induction: 20−39% in rats and hamsters and 60−79% in pigs; at 50.0 µmol the max SSB induction: 10−19% in hamsters and 60−79% in pigs In liver and kidney cells, mostly negative: no difference between treated and control kidney cells at either 12.5 or 25.0 µmol; in liver cells, negative result (<10% induction) at 12.5 µmol and positive result (20−39% induction) at 25.0 µmol	Hepatocytes were most sensitive to diethanolamine genotoxicity	Pool et al. (1990)
Genotoxicity	Genotoxicity study in Wistar rat; single-dose level of 910 mg/kg; for 6 hours; rat liver cells extracted and analyzed via alkaline elution assay for DNA damage	No DNA single-strand damage found after treatment with diethanolamine	Not genotoxic in this model	Shell Oil Company (1989)
Mutagenicity	Bacterial reverse-mutation study using an Ames *Salmonella* plate-incorporation assay with and without metabolic activation by Aroclor 1254-induced rat liver homogenate mixture (S9) in strains TA98, TA100, TA1535, TA1537, and TA1538; 10.0-, 3.0-, 1.0-, 0.3-, or 0.1-µl diethanolamine with activation and 1.0-, 0.3-, 0.1-, 0.03-, or 0.01-µl diethanolamine without activation in 0.5-µl tetrahydrofuran	None of the strains had significant reversion frequencies; microcolonies seen at 10.0 for all strains except TA1535 with activation and at 1.0 for TA100 without activation	No evidence of mutagenic activity	Mobil Oil Corporation (1993)

Table 3. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Genotoxicity	Genetic toxicology study using sister chromatid exchange (SCE) and chromosomal aberration (AB) assays in cultured Chinese hamster ovary (CHO) cells with and without metabolic activation by Aroclor 1254-induced rat liver homogenate mixture (S9)	Negative for both SCE and AB with and without activation	Negative for genotoxicity	Loveday et al. (1989)
Genotoxicity	Bacterial reverse-mutation and genetic toxicology study (plate incorporation assay, preincubation assay, spot test, and treat and plate assay) in *Salmonella* strains TA1535, TA1537, TA1538, TA98, and TA100 and *E. Coli* WP 2 and WP 2 *uvrA*, in *Saccharomyces cerevisiae* JD1 yeast for mitotic gene conversion, and in a cultured rat-liver cell line for structural chromosome damage	Negative for all tests; no mutations in bacteria, gene conversion in yeast, or chromosome damage in cultured rat liver cells	Negative for genotoxicity	Dean et al. (1985)
Genotoxicity	Bacterial reverse mutation study using the Ames *Salmonella* test in strains TA1535 and TA100	No increase in the number of mutations per plate	Negative for mutagenic activity	Hedenstedt (1978) (abstract only)
Genotoxicity	Mammalian gene mutation study using the L5178Y TK+/- mutagenesis assay with and without Aroclor 1254-induced rat liver S9 activation	Negative for mutagenicity	Negative for mutagenic activity	Myhr et al. (1986) (abstract only)

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

A few studies on the acute, dermal carcinogenicity, in vitro, dermal developmental, toxicokinetic, and genotoxic effects of diethanolamine are available. The acute toxicity of diethanolamine was examined by two studies utilizing dermal administration in rabbits, oral administration in cows, and intraperitoneal (i.p.) injections in mice (i.e., Dow Chemical Company, 1944 and Blum et al., 1972). In the study by Dow Chemical Company (1944), the study authors concluded that while dermal administration caused moderate skin irritation in rabbits, oral administration in cows resulted in a low degree of toxicity. In mice, a single i.p. exposure produced liver and ultrastructural cellular effects (Blum et al., 1972).

While no chronic-duration carcinogenicity studies via oral and inhalation exposures were identified, the carcinogenic potential of diethanolamine via the dermal exposure route was studied by NTP (1999; same as Pathology Working Group, 1997). In a chronic-duration carcinogenicity assay by NTP (1999), groups of 50 male and female F344/N rats were treated with 16-, 32-, or 64-mg/kg-body weight (BW) or 8-, 16-, or 32-mg/kg-BW diethanolamine (purity >99%), respectively, dissolved in ethanol dermally for 2 years. A separate group of 50 animals/sex was administered ethanol alone. No differences in survival were noted between the control and treated animals. Mean body weights of males treated with 64 mg/kg-BW were less than the mean body weight of the control group beginning at Week 8 of diethanolamine application. In contrast, mean body weights of treated females were comparable to the concurrent controls. The only clinical finding resulting from diethanolamine exposure was irritation of the skin at the site of application. Study authors reported minimal-to-moderate nonneoplastic lesions at the site of diethanolamine application in treated males and females. Incidences of acanthosis in males treated with 64-mg/kg-BW and hyperkeratosis in the 32- and 64-mg/kg-BW males and all dosed females were reported to be greater than the control group. In addition, incidences of exudate in the 64-mg/kg-BW males and females in all dose groups were reported to be higher compared to the concurrent control group. Study authors also reported a significant (significance level not reported) increase in nephropathy in treated female rats compared to the control group. No diethanolamine-related neoplastic lesions in the liver were reported. Based on these results, the study authors concluded that there was "no evidence of carcinogenic activity of diethanolamine in male F344/N rats administered 16, 32, or 64 mg/kg diethanolamine or in female F344/N rats administered 8, 16, or 32 mg/kg" (NTP, 1999, p.7).

In a concurrent study (NTP, 1999), groups of 50 male and female B6C3F$_1$ mice were treated with 40-, 80-, or 160-mg/kg-BW diethanolamine dissolved in ethanol dermally for 2 years. A separate group of 50 animals/sex served as the vehicle control. No differences in survival were noted between the treated male and control groups. In treated females, survival was statistically significantly lower compared to the vehicle control group. Mean body weights of males treated with 80 and 160 mg/kg-BW were less than the control group after 88 and 77 weeks, respectively. Mean body weights of females were reported to be lower compared with controls during Year 2 of the study. Study authors reported treatment-related hyperkeratosis, acanthosis, and exudates at the site of application. Pathological analyses of various tissues in male mice indicated significant ($p \leq 0.01$) increases in the incidences of hepatocellular adenomas in the treated groups (36/50, 47/50, and 41/50 in the 40-, 80-, and 160-mg/kg-BW dose groups, respectively) compared with the control group (12/50); significant ($p \leq 0.01$) increases in hepatocellular adenomas or carcinomas (combined) at all doses; and significant ($p \leq 0.01$) increases in hepatocellular carcinomas and hepatoblastoma in the 80- and 160-mg/kg-BW males compared to the concurrent control group. Similarly, incidences of hepatocellular neoplasms

were statistically significantly ($p \leq 0.01$) higher in females treated with diethanolamine (43/50, 46/50, and 45/50 adenomas in treated groups, respectively) when compared with the control group (16/50). In addition to changes in the liver, incidences of renal tubule adenomas exhibited a positive trend in males. The study authors also reported that pathological analysis of kidney sections indicated adenomas and hyperplasia in all treated groups. Incidences of thyroid gland follicular cell hyperplasia were also reported to be increased in treated males and females compared with the control group. Based on these results, the study authors concluded that there was "clear evidence of carcinogenic activity of diethanolamine in male and female $B6C3F_1$ mice based on increased incidences of liver neoplasms in males and females and increased incidences of renal tubule neoplasms in males" (NTP, 1999, p.7).

The mode of action of hepatocarcinogenicity in the $B6C3F_1$ mouse was evaluated by Lehman-McKeemam et al. (2002) in a 4-week dermal study. Following application of diethanolamine in ethanol at doses of 0, 10, 20, 40, 80, or 160 mg/kg, the study authors stated that phosphocholine levels were mostly impacted following diethanolamine administration. In addition, other choline-related enzymes such as S-adenosylmethionine, glycerophosphocholine, choline, and phosphatidylcholine levels also decreased, indicating diethanolamine-induced changes in choline homeostasis. The study authors also stated that application of ethanol vehicle alone decreased hepatic betaine levels. Based on these results, the study authors concluded that diethanolamine treatment leads to a range of biochemical changes in choline homeostasis, which demonstrates that there is a dose-related concordance between diethanolamine-induced choline deficiency and hepatocarcinogenicity. A NOEL of 10 mg/kg in mice for changes in choline homeostasis was identified by the study authors. The study authors also concluded that use of ethanol as a vehicle may have exacerbated or confounded the effects of diethanolamine.

The role of choline homeostasis in diethanolamine-induced hepatocarcinogenicity was further evaluated in a review article by Leung et al. (2005). Leung et al. (2005) reported that, while diethanolamine reduced choline metabolites in mice following dermal application, similar effects were not observed in rats. The study authors stated that rats did not exhibit diethanolamine-related tumors at the maximum tolerated dose of 64 mg/kg. Rats and mice were reported to be more susceptible to choline deficiency following treatment with diethanolamine compared to humans and other mammalian species because diethanolamine is absorbed to a lesser degree through human skin compared to rodent skin. Mice, in particular, have a higher absorption rate compared with rats. Leung et al. (2005) stated that the NOEL of 10 mg/kg identified by Lehman-McKeemam et al. (2002) indicated that a critical level of diethanolamine needs to be achieved in order to see an impact on choline homeostasis. Noncarcinogenic activity in F344/N rats indicated that a critical level of diethanolamine was not reached in rats. Additionally, because rodents are reportedly more susceptible to diethanolamine-induced choline deficiency compared with humans, the implications of hepatocarcinogenicity observed in $B6C3F_1$ mice need to be further evaluated.

In a predictive carcinogenicity report, Lee et al. (1996) used a predictive model based on two sets of rules, R1 and R3 (eight sub-rules each), to predict the carcinogenic potential of diethanolamine and concluded that diethanolamine was predicted as a carcinogen by the application of these rules. Rules R1 and R3 were developed based on applicable lesions for organ-specific toxicity including ulceration, hyperkeratosis, and inflammation of skin;

nephropathy, necrosis, and mineralization in kidney; degeneration in brain; necrosis in liver; and degeneration in heart. In addition, results of the *Salmonella* assay were also used in the predictive model.

Five studies examined the maternal and developmental toxicity of dermally applied diethanolamine (i.e., Craciunescu et al., 2009, 2006; Marty et al., 1999; Bushy Run Research Center, 1993, 1992). The authors largely concluded that dermal diethanolamine administration has maternal and developmental effects although these vary by species and exposure protocol. Some common effects were noted. The studies by Craciunescu et al. (2006, 2009) implicate effects on choline regulation in potential developmental neurotoxicity. Severe skin irritation as well as increased kidney weights associated with exposure was reported in pregnant rabbits and rats in the studies conducted by Bushy Run Research Center (1992, 1993) and by Marty et al. (1999). Marty et al. (1999) and Bushy Run Research Center (1992) noted skeletal malformations in the fetuses of treated dams and does. In rats, Marty et al. (1999) and Bushy Run Research Center (1992) reported maternal hematology effects from exposure. While the complete publication could not be accessed for this review, an abstract submitted by York et al. (1988) described an assay for predictive developmental toxicity that combines a number of effects to give an indicator of a chemical's priority for future investigation.

Several studies have investigated the toxicokinetics of diethanolamine using oral, dermal, and injection dosing (Mendrala et al., 2001; RTI, 1991; NTP, 1992a,b,c,d; Mathews et al., 1997, 1995; Barbee and Hartung, 1979, 1976 [abstract only]; Stott et al., 2000). Mendrala et al. (2001) reported that diethanolamine had a tendency to accumulate in the body following intravenous (i.v.) administration. Studies by RTI (1991) reported that diethanolamine was most highly concentrated in the liver and kidneys following oral or injection administration, which is supported by the findings of NTP (1992a,b,c,d) and Mathews et al. (1997). Two studies reported diethanolamine accumulation in the tissue phospholipids (Barbee and Hartung, 1979; Mathews et al., 1995). Similar to the Craciunescu et al. (2006, 2009) findings, Stott et al. (2000) and Barbee and Hartung (1979) noted effects on choline regulation following exposure.

Diethanolamine was not reported to cause gene mutations in bacteria or mammalian cells (Dean et al., 1985; Hedenstedt, 1978 [abstract only]; Mobil Oil Corporation, 1993; Myhr et al., 1986 [abstract only]), sister chromatid exchanges (Loveday et al., 1989), or chromosomal aberrations (Loveday et al., 1989). Diethanolamine's ability to cause single-strand DNA breaks is unclear, because Pool et al. (1990) reported positive activity in hepatocytes while Shell Oil Company (1989) reported negative results in extract of rat liver.

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer reference values. Table 5 presents a summary of cancer reference values. The toxicity values were converted to human equivalent concentration (HEC)/human equivalent dose (HED) units, and the conversion process is presented in the text below. No IRIS data are available for consideration.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

There are two subchronic-duration studies and two developmental studies available involving oral exposure to diethanolamine (see Table 2). The F344 rat study by NTP (1992a) is selected as the principal study for the derivation of the subchronic p-RfD. Hematological changes indicated by statistically significant ($p \leq 0.05$ or $p \leq 0.01$) reduction of mean corpuscular volume (MCV) in male rats was chosen as the critical effect. At the same dose level, statistically significant increases in relative kidney weight supported by renal nephropathy in female and male rats, along with significant reduction of mean corpuscular hemoglobin (MCH) in males and females were observed. The reported liver and kidney effects are supported by toxicokinetic studies (Mendrala et al., 2001; RTI, 1991) that observed bioaccumulation of diethanolamine in both organs. Of the two subchronic-duration studies considered for the derivation of a subchronic p-RfD (one in rats [NTP, 1992a] and one in mice [NTP, 1992b]; see Table 6), the NTP (1992a) study was performed in the most sensitive species (rats) and provides the lowest LOAEL (14 mg/kg-day in female rats and 25 mg/kg-day in male rats due to statistically significant reduction of MCV, MCH, and statistically significant increases in relative kidney weights along with renal nephropathy in males and females). A NOAEL could not be identified for this study or for the other subchronic-duration oral study. The effects observed in the two developmental studies (one in rats [Price et al., 2005; RTI, 1999] and one in mice [Environmental Health Research and Testing, Inc., 1987]) were also less sensitive than those observed in the NTP (1992a) study, and thus, were not considered for determination of a POD. Therefore, the NTP (1992a) study is the most credible choice for the determination of a point-of-departure (POD) for deriving a subchronic p-RfD.

All continuous variable models in the U.S. EPA Benchmark Dose Software (BMDS version 2.1.1) (U.S. EPA, 2011b) were fit to NTP (1992a) endpoint data including hematological changes, and relative organ weights for male and female rats (see Tables B.6−B.9). Among the modeled endpoints in male rats, hematocrit (HCT), hemoglobin (HGB), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), reticulocytes, red blood cells (RBCs), urine lactate dehydrogenase, mean body weight at necropsy, relative brain weight, and relative heart weight provided a good fit using Continuous-Hill (HCT, HGB, MCH, MCV, RBCs, mean body weight, relative brain weight), Continuous-Power (relative heart weight and reticulocytes), and Continuous-Linear (urine lactate dehydrogenase) models (see Table C.1 in Appendix C). Among modeled endpoints in female rats, body weight at necropsy and relative brain weights were the only two endpoints that provided good fits using the Continuous-Hill model (see Table C.1 in Appendix C). The BMDLs for these endpoints ranged from 6.85 to 150 mg/kg-day (see Table C.1 in Appendix C). Among all the models providing good fits for the aforementioned endpoints in male and female rats, the Continuous-Hill model from the male rat MCV dataset provided the lowest $BMDL_{1SD}$ of 6.85 mg/kg-day (see Table 7; see Table C.1 in Appendix C). This $BMDL_{1SD}$ supports the significant changes noted in hematological parameters in both male and female rats beginning at the lowest administered dose. Therefore, the $BMDL_{1SD}$ of 6.85 mg/kg-day for MCV in male rats is used as the POD for the derivation of a subchronic p-RfD for diethanolamine.

Table 4. Summary of Noncancer Reference Values for Diethanolamine (CASRN 111-42-2)

Toxicity Type (Units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_c	Principal Study
Subchronic p-RfD (mg/kg-day)	Rat/F	Significant reduction in MCV.	2×10^{-2}	$BMDL_{1SD}$	6.85	300	NTP (1992a)
Chronic p-RfD (mg/kg-day)	Rat/F	Significant reduction in MCV.	2×10^{-3}	$BMDL_{1SD}$	6.85	3000	NTP (1992a)
Subchronic p-RfC (mg/m^3)	Rat/M	Increased incidence of squamous metaplasia Level 1 in male rats.	2×10^{-3}	$BMCL_{10HEC}$	0.63	300	Gamer et al. (2008c)
Chronic p-RfC (mg/m^3)	Rat/M	Increased incidence of squamous metaplasia Level 1 in male rats.	2×10^{-4}	$BMCL_{10HEC}$	0.63	3000	Gamer et al. (2008c)

Table 5. Summary of Cancer Values for Diethanolamine (CASRN 111-42-2)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None			
p-IUR	None			

Table 6. Summary of Relevant Oral Systemic Subchronic-Duration Toxicity Studies for Diethanolamine

Reference	# M/F, Species	Exposure (mg/kg-day)	Frequency/ Duration	$NOAEL_{ADJ}$[a] (mg/kg-day)	$LOAEL_{ADJ}$[a] (mg/kg-day)	Critical Endpoint
NTP (1992a)[b]	10/10, F344 rat	0, 25, 48, 97, 202, 436 (males); 0, 14, 32, 57, 124, 242 (females)	Daily for 13 weeks	None	25 (males); 14 (females)	Significant increase in relative kidney weight along with renal nephropathy in males and females; significant changes in hematological parameters in males and females
NTP (1992b)[b]	10/10, $B6C3F_1$ mouse	0, 104, 178, 422, 807, 1674 (males); 0, 142, 347, 884, 1154, 1128 (females)	Daily for 13 weeks	None	104 (males); 142 (females)	Relative liver and kidney weights exhibited a dose-dependent increase beginning at the lowest dose in both males and females

[a]$NOAEL_{ADJ}$/$LOAEL_{ADJ}$ = Dose (NOAEL/LOAEL) × drinking water intake per day × (1÷ BW) × (days dosed ÷ total days in study).
[b]Laboratory report of these two studies (Battelle, 1989a,b) submitted to the Office of Toxic Substances, U.S. EPA under 40 CFR Part 716, 54 Fed. Reg. 8484 and 8(d) Health and Safety Reporting Rule has been reviewed, along with the final report published by the National Toxicology Program (NTP, 1992a,b).

Table 7. Model Predictions for Mean Corpuscular Volume for Male Rats[a]

Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC[c] for Fitted Model	BMD_{1SD}[d] (mg/kg-day)	$BMDL_{1SD}$[e] (mg/kg-day)	Conclusions
Hill (constant variance)	**0.124**	**0.260**	**24.69**	**10.96**	**6.85**	**Lowest AIC Lowest BMDL**
Linear (constant variance)	0.124	<0.0001	42.70	40.14	32.41	*p*-score 4 < 0.1 Observed to modeled std. dev. ratio > 1.5
Polynomial (constant variance)	0.124	<0.0001	42.70	40.14	32.41	*p*-score 4 < 0.1 Observed to modeled std. dev. ratio > 1.5 Maximum order β = 0 β2 = 0 β3 = 0 β4 = 0
Power (constant variance)	0.124	<0.0001	42.70	40.14	32.41	*p*-score 4 < 0.1 Observed to modeled std. dev. ratio > 1.5 hit bound (power 1)

[a]NTP, 1992a.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]AIC = Akaike's Information Criteria.
[d]BMD = benchmark dose.
[e]BMDL = lower confidence limit (95%) on the benchmark dose.

Adjusted doses for daily exposure—No adjustments were made for daily exposures because the animals were dosed with diethanolamine in drinking water daily for 13 weeks. The study authors provided the dose conversions from ppm to mg/kg-day in the study report (NTP, 1992a, p. 29, Table 5).

The subchronic p-RfD for diethanolamine based on the $BMDL_{1SD}$ of 6.85 mg/kg-day in the male F344 rat (NTP, 1992a) is derived as follows:

Subchronic p-RfD = $BMDL_{1SD} \div UFc$
= 6.85 mg/kg-day ÷ 300
= **2×10^{-2} mg/kg-day**

Tables 8 and 9 summarize the uncertainty factors (UF) and the confidence descriptor, respectively, for the subchronic p-RfD for diethanolamine.

Table 8. Uncertainty Factors for Subchronic p-RfD for Diethanolamine, CAS Registry Number 111-42-2[a]

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to changes noted in the kidney following exposure to diethanolamine.
UF_D	3	A UF_D of 3 is applied because the database includes two acceptable developmental toxicity studies (Price et al., 2005; RTI, 1999; Env. Health Research and Testing Inc., 1987) via oral exposure route and five developmental studies (Craciunescu et al., 2009, 2006; Marty et al., 1999; Bushy Run Research Center, 1993, 1992) via the dermal exposure route. However, no acceptable two-generation reproduction studies were available.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a BMDL.
UF_S	1	A UF_S of 1 is applied because results from a subchronic-duration duration study (NTP, 1992a) were utilized as the principal study.
UF_C	300	

[a]NTP, 1992a.

Table 9. Confidence Descriptor for Subchronic p-RfD for Diethanolamine, CAS Registry Number 111-42-2

Confidence Categories	Designation[a]	Discussion
Confidence in study	H	Confidence in the key study (NTP, 1992a) is high. The study provides a comprehensive assessment of various toxicological endpoints, including significant changes in hematological parameters and relative organ weights in both males and females. Changes in relative organ weights are well supported by histopathological examination in an appropriate number of animals (10/sex) for 13 weeks of observation. A NOAEL could not be identified in the study. In addition to this study, the toxicological effects of diethanolamine exposure are well supported by a mouse study by NTP (1992b). Additional support is provided by short-term studies conducted by NTP (1992c,d) and the Eastman Kodak Company (1989a).
Confidence in database	M	Confidence in the database is medium because no multigeneration reproductive study could be located. The database includes short-term- (NTP, 1992c,d; Eastman Kodak Company, 1989a) and subchronic-duration (NTP, 1992a,b) toxicity studies in two species (rats and mice). Additionally, two studies (Price et al., 2005; RTI, 1999; Environmental Health Research and Testing, Inc., 1987) pertaining to developmental toxicity of diethanolamine via the oral exposure route were also identified along with five studies (Craciunescu et al., 2009, 2006; Marty et al., 1999; Bushy Run Research Center, 1993, 1992) via the dermal exposure route.
Confidence in subchronic p-RfD[b]	M	The overall confidence in the subchronic p-RfD is medium.

[a]L= Low; M= Medium; H= High.
[b]The overall confidence cannot be greater than the lowest entry in the table.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

The subchronic-duration study by NTP (1992a) in F344 rats is selected as the principal study for the derivation of a chronic p-RfD. This is the same study that was utilized in the derivation of a subchronic p-RfD; hence, study specifics and the justification for the use of this study for the derivation of a chronic p-RfD are similar to the justification provided for "*Derivation of Subchronic Provisional RfD*." The other possible studies considered for the derivation of a chronic p-RfD are presented in Table 6; there are no chronic-duration studies available. Hematological changes indicated by statistically significant ($p \leq 0.05$ or $p \leq 0.01$) reduction of mean corpuscular volume (MCV) in male rats was chosen as the critical effect. As described in the "*Derivation of Subchronic Provisional RfD*" section, the lowest BMDL was obtained by modeling the MCV data for male rats with the Continuous-Hill model, which provided a $BMDL_{1SD}$ of 6.85 mg/kg-day (see Table 7; see Figure C.1 in Appendix C). This BMDL supports the significant changes noted in hematological parameters in both male and female rats beginning at the lowest administered dose. Therefore, the $BMDL_{1SD}$ of 6.85 mg/kg-day for MCV in male rats is used as the POD for the derivation of a chronic p-RfD for diethanolamine.

Adjusted doses for daily exposure—No adjustments were made for daily exposures because the animals were dosed with diethanolamine in drinking water daily for 13 weeks. The study authors provided the dose conversions from ppm to mg/kg-day in the study report (NTP, 1992a, p. 29, Table 5).

The chronic p-RfD for diethanolamine based on the $BMDL_{1SD}$ of 6.85 mg/kg-day in the male F344 rat (NTP, 1992a) is derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfD} &= BMDL_{1SD} \div UF_C \\ &= 6.85 \text{ mg/kg-day} \div 3000 \\ &= \mathbf{2 \times 10^{-3} \text{ mg/kg-day}} \end{aligned}$$

Tables 10 and 11 summarize the UFs and the confidence descriptor, respectively, for the chronic p-RfD for diethanolamine.

Table 10. Uncertainty Factors for Chronic p-RfD for Diethanolamine, CAS Registry Number 111-42-2[a]

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. There are no data to determine whether humans are more or less sensitive than rats to changes noted in the kidney following exposure to diethanolamine.
UF_D	3	A UF_D of 3 is applied because the database includes two acceptable developmental toxicity studies (Price et al., 2005; RTI, 1999; Env. Health Research and Testing Inc., 1987) via oral exposure route and five developmental studies (Craciunescu et al., 2009, 2006; Marty et al., 1999; Bushy Run Research Center, 1993, 1992) via dermal exposure route. However, no acceptable two-generation reproduction studies were available.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a BMDL.
UF_S	10	A UF_S of 10 is applied for using data from a subchronic-duration study (NTP, 1992a) to assess potential effects from chronic exposure because data for evaluating response from chronic exposure are unavailable or insufficient.
UF_C	3000	

[a]NTP, 1992a.

Table 11. Confidence Descriptor for Chronic p-RfD for Diethanolamine, CAS Registry Number 111-42-2

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	Confidence in the key study (NTP, 1992a) is medium. The study is a subchronic-duration study that provides a comprehensive assessment of various toxicological endpoints, including significant changes in hematological parameters and relative organ weights in both males and females. Changes in relative organ weights are well supported by histopathological examination in an appropriate number of animals (10/sex) for 13 weeks of observation but a NOAEL could not be identified in the study. In addition to this study, the toxicological effects of diethanolamine exposure are well supported in a mouse study by NTP (1992b). Additional support is provided by short-term studies conducted by NTP (1992c,d) and the Eastman Kodak Company (1989a). Based on similar effects seen in these subchronic-duration studies, it may be hypothesized that similar effects may be observed in studies conducted for a chronic duration.
Confidence in database	M	Confidence in the database is medium because no multigeneration reproductive study and chronic study could be located. The database includes short-term- (NTP, 1992c,d; Eastman Kodak Company, 1989a) and subchronic-duration (NTP, 1992a,b) toxicity studies in two species (rats and mice). Additionally, two studies (Price et al., 2005; RTI, 1999; Environmental Health Research and Testing, Inc., 1987) pertaining to developmental toxicity of diethanolamine via the oral exposure route were also identified along with five studies (Craciunescu et al., 2009, 2006; Marty et al., 1999; Bushy Run Research Center, 1993, 1992) via the dermal exposure route.
Confidence in chronic p-RfD[b]	M	The overall confidence in the chronic p-RfD is medium.

[a]L= Low; M= Medium; H= High.
[b]The overall confidence cannot be greater than the lowest entry in the table.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

There are six subchronic-duration studies available involving inhalation exposure to diethanolamine (see Table 12). Four studies by Eastman Kodak Company (1989e,f,g,h) possessed deficiencies in data reporting (e.g., tables cited with several data and statistical inferences but not included in the reports). Additionally, the study authors reported several instances of statistically significantly different values without any trends or patterns to indicate compound-related effects or other causes. Thus, none of these studies were considered as the principal study to support derivation of a provisional RfC. The most sensitive effect was the increased incidence of squamous metaplasia in the epiglottis and the larynx observed in rats in the Gamer et al. (2008c) and provides the lowest $LOAEL_{ADJ}$ of 0.49 mg/m^3 ($LOAEL_{HEC}$ of 2.15 mg/m^3) and a $NOAEL_{ADJ}$ of 0.25 mg/m^3 ($NOAEL_{HEC}$ of 1.07 mg/m^3). This study is supported by the Gamer et al. (2008b) rat study which observed similar effects at a higher HEC of 4.8 mg/m^3 in female rats.

The study by Gamer et al. (2008c) is selected as the principal study for the derivation of a subchronic p-RfC value. The critical effect is increased incidence of squamous metaplasia in the epiglottis (Level 1) and in the larynx (Level 2) in male rats. Results from Gamer et al. (2008b,c) indicate that the respiratory tract (the trachea-bronchial area, in particular) is more sensitive to

diethanolamine exposure via the inhalation route. The sensitivity of the respiratory tract following exposure to diethanolamine is intensified in Gamer et al. (2008b), in which the animals were exposed to higher concentrations of diethanolamine with all 10 male and female rats exhibiting incidences of squamous metaplasia beginning at the lowest administered dose of 15 mg/m^3 (HEC respiratory effects: 5.6 mg/m^3 and 4.8 mg/m^3 for male and female rats, respectively). In addition to squamous metaplasia, relative liver weights were increased in the females at the highest administered dose of 8 mg/m^3 (HEC extrarespiratory effects: 2.93 mg/m^3) in Gamer et al. (2008c), indicating the primary respiratory effects were accompanied by systemic toxicity after exposure to diethanolamine. Like squamous metaplasia, relative organ weights (i.e., liver, kidney, brain, and lungs) in Gamer et al. (2008b) exhibited a dose-related increase supporting the intensified effects of diethanolamine exposure at higher dose levels.

Table 12. Summary of Relevant Inhalation Subchronic-duration Toxicity Studies for Diethanolamine, CAS Registry Number 111-42-2

References	# M/F, Species	Exposure (mg/m^3)	Frequency/ Duration	$NOAEL_{ADJ}$[a] (mg/m^3)	$LOAEL_{ADJ}$[a] (mg/m^3)	Critical Endpoint
Gamer et al. (2008c)	10/10, Wistar rat	0, 1.5, 3, 8	6 hours/day, 65 exposures, total study duration 99 days	RESP: 0.25 in male rats EXRESP: 1.10 in female rats	RESP: 0.49 in male rats EXRESP: 1.31 in female rats	Increased incidence of squamous metaplasia in both males and females; significant increase in liver weight in females at the highest dose
Gamer et al. (2008b)	13/13, Wistar rat	0, 15, 150, 400	6 hours/day, 65 exposures; total study duration 99 days	Not identified	RESP: 2.46 for both male and female rats	Increased incidence of squamous metaplasia in both males and females; significant increase in relative organ weights (liver, kidney, lung, and brain) in both males and females beginning at 150 mg/m^3
Eastman Kodak Company (1989e,f,g,h) (unpublished)	2/2, Beagle dog ; 5/5, guinea pig; 10/10, Albino rat (weanling and adult)	0, 1.12	24 hours/day, 7 days/week; 90 days	1.12[b]	NA[c]	Toxicological endpoints not well defined; data tables not presented; critical endpoints not easily identifiable

[a]$NOAEL_{ADJ}$/$LOAEL_{ADJ}$ = Dose (NOAEL/LOAEL) × (hours per day exposed ÷ 24) × (days exposed ÷ total number of days in study).
[b]HEC conversion not presented because three different animal species were tested and study details are not well reported.
[c]NA = not available.

HEC dosimetric adjustment: Gamer et al. (2008c) observed respiratory and extrarespiratory effects in animals treated with diethanolamine. Therefore, dosimetric adjustments using equations for respiratory and extrarespiratory effects are presented below.

1) Adjusted continuous exposure concentration ($Conc_{ADJ}$)

$Conc_{ADJ}$ (mg/m^3) = $Conc_{Gamer\ et\ al.,\ 2008c}$ (mg/m^3) × (hours per day exposed ÷ 24) × (days exposed ÷ total number of days in study)
= Conc × 6 ÷ 24 hours × 65 ÷ 99 days
= $Conc_{Gamer\ et\ al.,\ 2008c}$ × 0.16414

2) Human equivalent concentration conversion

$Conc_{HEC}$ = $Conc_{ADJ}$ × Dosimetric Adjustment Factor (DAF)

DAF = DAF for regional deposited dose ratio (RDDRr) for particles. (r = tracheobronchial [respiratory effects] and extrarespiratory or systemic effect [increased relative liver weight]).

The study by Gamer et al. (2008c) reported exposure concentrations that have been first adjusted for continuous exposure ($Conc_{ADJ}$), followed by Human Equivalent Concentration (HEC) conversions ($Conc_{HEC}$) based on $Conc_{ADJ}$ multiplied by the DAF. The DAF is calculated for respiratory (tracheobronchial region) and extrarespiratory effects (increases in relative liver weight) using the RDDR software, as specified in the RfC guidelines (U.S. EPA, 1994b). Gamer et al. (2008c) reported particle-size distribution in mass median aerodynamic diameters (MMADs) to be between 0.6 and 0.7 µm and geometric standard deviation (GSD) in the range of 2 to 3. Inputs to the RDDR software have an average MMAD of 0.65 µm, an average GSD of 2.5, and an average of initial body weight (i.e., body weight at Day 0) and terminal body weight for each exposure-level group. The average body weight was used because information was not supplied to calculate time-weighted averages. The calculations were performed separately for male and female rats.

Table 13 shows the Gamer et al. (2008c) HEC-converted exposure concentrations for respiratory and extrarespiratory effects.

Table 13. HEC Conversion for Male and Female Rats Exposed Via Inhalation to Diethanolamine Aerosol Particles for 99 Days[a]

$Conc_{Gamer\ et\ al.,\ 2008c}$ (mg/m^3)	$Conc_{ADJ}$[c] (mg/m^3)	Respiratory Effects		Extrarespiratory	
		$RDDR_{TB}$[e]	$Conc_{HEC}$[d] (mg/m^3)	$RDDR_{ER}$[e]	$Conc_{HEC}$[d] (mg/m^3)
Male Rats[b]					
0	0	ND[f]	0	ND[f]	0
1.5	0.246	4.353	1.07	2.253	0.55
3.0	0.492	4.361	2.15	2.254	1.11
8.0	1.311	4.322	5.66	2.252	2.95
Female Rats[b]					
0	0	ND[f]	0	ND[f]	0
1.5	0.246	3.492	0.86	2.236	0.55
3.0	0.492	3.470	1.71	2.236	1.10
8.0	1.311	3.514	4.61	2.236	2.93

[a]Gamer et al., 2008c.
[b]10 rats per treatment group.
[c]$Conc_{ADJ}$ = Conc × 6 ÷ 24 hours × 65 ÷ 99 days.
[d]$Conc_{HEC}$ = $Conc_{ADJ}$ × $RDDR_{TB}$ or $Conc_{HEC}$ = $Conc_{ADJ}$ × $RDDR_{ER}$.
[e]TB = tracheobronchial and ER = extrarespiratory.
[f]RDDR not determined for control group.

ND = Not determined

A POD for derivation of the subchronic p-RfC is selected as the $BMCL_{10HEC}$ of 0.63 mg/m^3 from respiratory effects (increased incidence squamous metaplasia Level 1), because it is lower than the $BMCL_{10HEC}$ of 2.03 mg/m^3 from extrarespiratory effects (increased relative liver weight). These dosimetric results are consistent with the Gamer et al. (2008b,c) conclusion that diethanolamine is toxic to the respiratory tract. The details for estimating the best $BMCL_{10HEC}$ for respiratory and extrarespiratory effects are presented below.

Respiratory effects: A benchmark concentration (BMC) analysis of the squamous metaplasia Level 1 incidence data in male rats (respiratory effects) was conducted using all dichotomous models of the EPA BMDS (version 2.1.1) (U.S. EPA, 2011b). The incidence data of squamous metaplasia Level 1 are presented in Table B.30 (BMDS input data). As recommended by EPA (2012), a 10% benchmark response (BMR) level was used for modeling purposes. The incidence of squamous metaplasia: Level 1 in female rats was only seen at the high exposure-level with an incidence of 90%, and because there is only one positive response and the control, summing two data points, this data set has not been fit to the BMD model. Of the 8 models fit to the squamous metaplasia data (respiratory effects), the Dichotomous-Multistage provided the best fit with a $BMCL_{10HEC}$ of 0.63 mg/m^3 and a BMC_{10HEC} of 1.25 mg/m^3. Of all the models run, the Multistage model exhibited the lowest Akaike's Information Criteria (AIC) with *p*-values more than 0.1, scaled residuals less than 2.0, and the range of BMCLs less than 3-fold (see Table 14; see Appendix C, Figure C.2).

Table 14. BMC Model Predictions for Incidence of Squamous Metaplasia Level 1 in Male Wistar Rats[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC[b,c] for Fitted Model	BMC_{10HEC}[d] (mg/m^3)	$BMCL_{10HEC}$[e] (mg/m^3)	Conclusion
Multistage	**0.8302**	**22.3385**	**1.25161**	**0.63**	**Lowest AIC β1 = 0 β2 = 0**
Quantal-Linear	0.2011	27.7867	0.480386	0.30	*p*-score 4 < 0.1 Residual of interest ≥2
Gamma	0.7509	23.5722	1.56303	0.85	
Logistic	0.4018	25.2414	1.66713	1.04	
Log-Logistic	0.806	23.4084	1.57738	0.95	
Log-Probit	0.8585	23.1896	1.59494	0.99	
Probit	0.4493	24.8632	1.63039	1.01	
Weibull	0.6506	24.0402	1.47536	0.74	

[a]Gamer et al., 2008c.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]AIC = Akaike's Information Criteria.
[d]BMD = benchmark dose.
[e]BMDL = lower confidence limit (95%) on the benchmark dose.

Extrarespiratory effects: A relative liver-weight increase of 14% in female rats was observed at the high-exposure level ($Conc_{HEC}$ of 2.93 mg/m^3) and was statistically significant ($p < 0.05$). All continuous variable models in the EPA BMDS (version 2.1.1) were fit to data from relative liver weight in female rats (Gamer et al., 2008c). Table B.29 presents BMDS input data for relative liver weight (extrarespiratory effect). A benchmark response (BMR) of 10% change in relative liver weight (relative risk from the BMDS options screen) was selected. An adequate fit was judged based on the goodness-of-fit *p*-value ($p > 0.1$), scaled residuals, the range of BMR, and visual inspection of the model fit. If a homogenous variance model was recommended based on statistics (Test 2) provided from the BMD model run, the final BMD results would be estimated from a homogenous variance model. If the test for homogenous variance (Test 2) was negative ($p < 0.1$), the model was run again to account for nonhomogenous variance. If the nonhomogenous variance model did not provide an adequate fit to the variance data (Test 3: $p < 0.1$), the data set would be considered unsuitable for BMD modeling. Among all the fitted continuous models, the nonhomogenous variance Power model presents the best fit (provided the lowest AIC, after all the models with good fit [*p*-value > 0.1], scaled residuals less than 2.0, and BMCLs sufficiently close) with a $BMCL_{10HEC}$ of 2.03 mg/m^3 and BMC_{10HEC} of 2.86 mg/m^3 (see Table 15 below with the BMDS predictions; Appendix C, Figure C.3).

Table 15. Model Predictions for Relative Liver Weight Changes in Female Rats Exposed Via Inhalation to Diethanolamine for 90 Days[a]

Model Name	Homogeneity Variance *p*-Value[b]	Goodness-of-Fit *p*-Value[b]	AIC[c] for Fitted Model	BMC_{10HEC}[d] (mg/m^3)	$BMCL_{10HEC}$[e] (mg/m^3)
Exponential3	<0.001	0.2166	486.61	2.87	2.04
Polynomial	<0.001	0.295	486.18	2.79	2.12
Hill	<0.001	0.217	486.61	2.58	1.21
Power	**<0.001**	**0.466**	**484.61**	**2.86**	**2.03**

[a]Gamer et al., 2008c.
[b]*p*-values <0.10 fail to meet conventional goodness-of-fit criteria. Exponential 2, Exponential 4, Exponential 5, and Linear model failed because of goodness of fit *p*-value of less than 0.1.
[c]AIC = Akaike's Information Criteria.
[d]BMC = benchmark concentration.
[e]BMCL = benchmark lower confidence limit (95%) on the benchmark concentration.

Based on respiratory and extrarespiratory effects BMDS modeling output, a $BMCL_{10HEC}$ of 0.63 mg/m^3 from respiratory effects (increased incidence squamous metaplasia Level 1) in male rats is selected as the POD for derivation of subchronic p-RfC because it is lower than the $BMCL_{10HEC}$ of 2.03 mg/m^3 from extrarespiratory effects (increased relative liver weight). The $BMCL_{10HEC}$ of 0.63 mg/m^3 is protective for both respiratory and extrarespiratory effects in both sexes.

The subchronic p-RfC for diethanolamine, based on a $BMCL_{10HEC}$ of 0.63 mg/m^3 is derived as follows:

$$\textbf{Subchronic p-RfC} = BMCL_{10HEC} \div UF_C$$
$$= 0.63\ mg/m^3 \div 300$$
$$= \mathbf{2 \times 10^{-3}\ mg/m^3}$$

Tables 16 and 17, respectively, summarize the UFs and the confidence descriptor for the subchronic p-RfC for diethanolamine.

Table 16. Uncertainty Factors for Subchronic p-RfC for Diethanolamine, CAS Registry Number 111-42-2

UF	Value	Justification
UF_A	3	A UF_A of 3 is applied for animal-to-human extrapolation to account for the toxicodynamic portion of the UF_A because the toxicokinetic portion ($10^{0.5}$) has been addressed in dosimetric conversions.
UF_D	10	A UF_D of 10 is applied because there are no acceptable two-generation reproductive or developmental studies via inhalation route of exposure. The two available acceptable developmental studies via the oral exposure route (Price et al., 2005; RTI, 1999; Environmental Health Research and Testing, Inc., 1987) and five developmental studies via the dermal exposure route (Craciunescu et al., 2009, 2006; Marty et al., 1999; Bushy Run Research Center, 1993, 1992) do not provide sufficient information to judge diethanolamine toxicity due to inhalation exposures.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of definitive information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a BMCL.
UF_S	1	A UF_S of 1 is applied because results from a subchronic-duration study (Gamer et al., 2008c) were utilized as the principal study.
UF_C	300	

Table 17. Confidence Descriptor for Subchronic p-RfC for Diethanolamine, CAS Registry Number 111-42-2

Confidence Categories	Designation[a]	Discussion
Confidence in study	H	Confidence in the key study is high. The study is well conducted, and appropriate endpoints were evaluated in an adequate number of animals (10/sex).
Confidence in database	M	Confidence in the database is medium due to a lack of a chronic-duration study and lack of multigeneration reproductive and developmental studies via inhalation exposure. However, the principal study (Gamer et al., 2008c) is well conducted, and two different assays using two different dosing regimens were used by the study authors. Results from these studies indicated that the respiratory system is the target organ following exposure to diethanolamine via the inhalation route. In addition, two developmental studies via the oral route (Price et al., 2005; RTI, 1999; Environmental Health Research and Testing, Inc., 1987) and five studies (Craciunescu et al., 2009, 2006; Marty et al., 1999; Bushy Run Research Center, 1993, 1992) via the dermal exposure route were available and lend support to the potential toxicity of diethanolamine.
Confidence in subchronic p-RfC[b]	M	The overall confidence in the subchronic p-RfC for diethanolamine is medium due to the lack of supporting studies in multiple animal species and also due to the lack of developmental and multigeneration reproduction studies via the inhalation route.

[a]L = Low, M = Medium, H = High.
[b]The overall confidence cannot be greater than lowest entry in table.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

The subchronic-duration study by Gamer et al. (2008c) in Wistar rats is selected as the principal study for the derivation of a chronic p-RfC. This study is the same study that was utilized in the derivation of a subchronic p-RfC; hence, study specifics and the justification for the use of this study for the derivation of a chronic p-RfC are similar to the justification provided for "*Derivation of Subchronic Provisional RfC*." The critical effect is increased incidence of squamous metaplasia in the epiglottis (Level 1) and in the larynx (Level 2) in male rats. The other possible studies considered for the derivation of a chronic p-RfC are presented in Table 12; there are no chronic-duration studies available. As described in the "*Derivation of Subchronic Provisional RfC*" section, the lowest BMCL was obtained by modeling the squamous metaplasia incidence rates in male rats with the Dichotomous-Multistage model, which provided a $BMCL_{10HEC}$ of 0.63 mg/m^3 and a BMC_{10HEC} of 1.25 mg/m^3 (see Table 14; see Figure C.2 in Appendix C). The female rat liver data also provided a good fit using the Continuous-Power nonconstant variance model (see Table 15); however, the $BMCL_{10HEC}$ (2.03 mg/m^3) is higher compared with the $BMCL_{10HEC}$ obtained by modeling the squamous metaplasia data. Based on this modeling outcome and the study authors' conclusion that diethanolamine is toxic to the respiratory tract, the $BMCL_{10HEC}$ of 0.63 mg/m^3 is selected as the POD for the derivation of a chronic p-RfC. The $BMCL_{10HEC}$ of 0.63 mg/m^3 as the POD is protective for both respiratory and extrarespiratory effects in both sexes.

The chronic p-RfC for diethanolamine, based on a $BMCL_{10HEC}$ of 0.63 mg/m^3, is derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfC} &= BMCL_{HEC} \div UF_C \\ &= 0.63 \text{ mg/m}^3 \div 3000 \\ &= \mathbf{2 \times 10^{-4} \text{ mg/m}^3} \end{aligned}$$

Tables 18 and 19, respectively, summarize the UFs and the confidence descriptor for the chronic p-RfC for diethanolamine.

Table 18. Uncertainty Factors for Chronic p-RfC for Diethanolamine, CAS Registry Number 111-42-2

UF	Value	Justification
UF_A	3	A UF_A of 3 is applied for animal-to-human extrapolation to account for the toxicodynamic portion of the UF_A because the toxicokinetic portion ($10^{0.5}$) has been addressed in dosimetric conversions.
UF_D	10	A UF_D of 10 is applied because there are no acceptable two-generation reproductive or developmental studies via inhalation route of exposure. The two acceptable developmental studies via the oral exposure route (Price et al., 2005; RTI, 1999; Environmental Health Research and Testing, Inc., 1987) and five developmental studies via the dermal exposure route (Craciunescu et al., 2009, 2006; Marty et al., 1999; Bushy Run Research Center, 1993, 1992) available in the database do not provide sufficient information to judge diethanolamine toxicity due to inhalation exposures.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of definitive information on the variability of response in humans.
UF_L	1	A UF_L of 1 is applied because the POD was developed using a BMCL.
UF_S	10	A UF_S of 10 is applied for using data from a subchronic-duration study (Gamer et al., 2008c) to assess potential effects from chronic exposure.
UF_C	3000	

Table 19. Confidence Descriptor for Chronic p-RfC for Diethanolamine, CAS Registry Number 111-42-2

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	Confidence in the key study is medium. The study is well conducted, and appropriate endpoints were evaluated in an adequate number of animals (10/sex) but the study is subchronic in duration and not supported by any chronic-duration studies.
Confidence in database	M	A confidence of medium is considered due to a lack of chronic-duration study and lack of multigeneration reproductive and developmental studies via inhalation exposure. However, the principal study (Gamer et al., 2008c) is well conducted, and two different assays using two different dosing regimens were used by the study author. Results from both studies indicated that the respiratory system is the target organ following exposure to diethanolamine via the inhalation route. In addition, two developmental studies via the oral route (Price et al., 2005; RTI, 1999; Environmental Health Research and Testing, Inc., 1987) and five studies (Craciunescu et al., 2009, 2006; Marty et al., 1999; Bushy Run Research Center, 1993, 1992) via the dermal exposure route were available and lend support to the potential toxicity of diethanolamine.
Confidence in chronic p-RfC[b]	M	The overall confidence in the chronic p-RfC for diethanolamine is medium due to the lack of supporting studies in multiple animal species and also due to the lack of chronic-duration, developmental, and multigeneration reproduction studies via the inhalation route.

[a]L = Low, M = Medium, H = High.
[b]The overall confidence cannot be greater than lowest entry in table.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Chronic-duration carcinogenicity studies evaluating the effects of diethanolamine exposure via oral and inhalation routes in humans and animals could not be identified. However, NTP (1999; same as Pathology Working Group, 1997) conducted a 2-year bioassay via the dermal exposure route in male and female F334/N rats and male and female $B6C3F_1$ mice to assess the carcinogenic potential of diethanolamine when administered dermally. The dermal route was specifically chosen by NTP (1999) because diethanolamine is produced on a large scale, and its pattern of use indicates that humans are likely to be exposed to the chemical primarily via the dermal route of exposure in a wide variety of products containing diethanolamine. The potential for higher dermal exposure was also reported in an occupational study by Henriks et al. (2007), in which the authors reported that dermal exposure to diethanolamine was considerably higher in machinists working with metal-working fluids containing diethanolamine compared to exposure via the inhalation route. No diethanolamine-related tumors were reported in male and female rats in the NTP study; however, hepatocelluar adenomas, hepatocellular adenomas and carcinomas, and hepatoblastoma were reported in male and female mice treated dermally with diethanolamine. In addition to liver tumors, increased incidences of renal tubule neoplasms in males were also observed. Evidence of diethanolamine carcinogenicity is limited to a single species and needs further evaluation. Additionally, mode-of-action studies by Lehman-McKeeman et al. (2002) and Leung et al. (2005) suggest that rodents are more susceptible than humans to diethanolamine absorption when administered dermally. However, unless strong evidence of noncarcinogenic activity in humans following occupational and general exposures to diethanolamine becomes available, the carcinogenic activity in the mouse needs to be taken into consideration for the carcinogenic descriptor of the chemical.

Table 20 identifies the cancer WOE descriptor for diethanolamine.

Table 20. Cancer WOE Descriptor for Diethanolamine

Possible WOE Descriptor	Designation	Route of Entry	Comments
"Carcinogenic to Humans"	N/A	N/A	One occupational study (Järvolm et al., 1986) explored the cancer morbidity and mortality of men working with cutting fluids containing nitrites and amines. The authors did not provide any firm conclusions regarding the carcinogenic potential following exposures to diethanolamine specifically.
"Likely to be Carcinogenic to Humans"	N/A	N/A	No studies pertaining to the carcinogenicity of diethanolamine in multiple species of animals are available.
"Suggestive Evidence of Carcinogenic Potential"	**Selected**	**Dermal, Oral, and Inhalation**	**No oral or inhalation studies pertaining to the carcinogenicity of diethanolamine were available. However, NTP (1999; same as Pathology Working Group [1997]) conducted a 2-year dermal carcinogenicity study in F344 rats and B6C3F$_1$ mice (see Table 3) and concluded that "There was clear evidence of carcinogenic activity" of diethanolamine in male and female B6C3F$_1$ mice based on increased incidences of liver neoplasms in males and females and increased incidences of renal tubule neoplasms in males" (NTP, 1999; p. 7). There was no evidence of carcinogenic activity in F344 rats. Studies via the oral and inhalation exposure routes in multiple species are needed to reach a firm conclusion regarding diethanolamines carcinogenic potential. Additionally, the EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005, p. 2−52) state that "when tumors occur at a site other than the point of initial contact, the descriptor generally applies to all exposure routes that have not been adequately tested at sufficient doses. An exception occurs when there is convincing information, e.g., toxicokinetic data that absorption does not occur by another route"; however, this exception is not suggested by the available toxicokinetic data on diethanolamine.**
"Inadequate Information to Assess Carcinogenic Potential"	N/A	N/A	
"Not Likely to be Carcinogenic to Humans"	N/A	N/A	

N/A = Not applicable.

DERIVATION OF PROVISIONAL CANCER VALUES

Derivation of Screening Provisional Oral Slope Factor (p-OSF)

No oral carcinogenicity studies on diethanolamine were identified.

Derivation of Screening Provisional Inhalation Unit Risk (p-IUR)

No inhalation carcinogenicity studies on diethanolamine were identified.

While EPA is aware of tumor formation in the liver and the kidney in the mouse following dermal exposure to diethanolamine, a dermal slope factor was not derived.

MODE-OF-ACTION DISCUSSION

The *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005) define mode-of-action "…as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation." Examples of possible modes of carcinogenic action for a given chemical include "mutagenicity, mitogenesis, programmed cell death, cytotoxicity with reparative cell proliferation, and immune suppression" (p. 1−10).

In studies exploring the genotoxic potential of diethanolamine, it was reported that diethanolamine did not cause gene mutations in bacteria or mammalian cells (Dean et al., 1985; Hedenstedt, 1978; Mobil Oil Corporation, 1993; Myhr et al., 1986), sister chromatid exchanges (Loveday et al., 1989), or chromosomal aberrations (Loveday et al., 1989). The ability of diethanolamine to cause single-strand DNA breaks is unclear, because Pool et al. (1990) reported positive activity in hepatocytes, while Shell Oil Company (1989) reported negative results in extract of rat liver. Based on these results there are insufficient data to determine the mode-of-action for diethanolamine. Additionally, the lack of carcinogenicity studies via the oral and inhalation route precludes a detailed mode-of-action discussion.

APPENDIX A. PROVISIONAL SCREENING VALUES

No screening values are presented.

APPENDIX B. DATA TABLES

Table B.1. Renal Toxicity in Male F344/N Rats in 2-Week Drinking Water Studies of Diethanolamine[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	**630 (77)**	**1250 (162)**	**2500 (319)**	**5000 (622)**	**10,000 (1016)**
Final body weight (g)	149	152 (102%)	149 (100%)	144 (97%)	131 (88%)*	98 (66%)[c]**
Right kidney weight	0.733	0.768 (105%)	0.848 (116%)*	0.821 (112%)	0.855 (117%)*	0.918 (125%)[c]**
Relative kidney weight	4.92	5.05 (103%)	5.69 (116%)**	5.70 (116%)*	6.53 (133%)**	9.37 (190%)[c]**
Tubular epithelial necrosis[d]	0/5	0/5	0/5	0/5	0/5	3/5*[c](2.2)
Urinalysis						
Urea nitrogen (mg/mg creatinine)	28	27 (96%)	28 (100%)	29 (104%)	32 (114%)**	62 (221%)**
Glucose (mg/mg creatinine)	0.3	0.3 (100%)	0.2 (67%)	0.2 (67%)	0.4 (133%)	4.8 (1600%)**
Protein (mg/mg creatinine)	0.7	0.4 (57%)	0.3 (43%)	0.3 (43%)	0.5 (71%)	3.1 (443%)**
Lactate dehydrogenase (IU/mg creatinine)	0.08	0.08 (100%)	0.08 (100%)	0.11 (138%)**	0.15 (188%)**	0.48 (600%)**

[a]NTP, 1992c.
[b]Unless otherwise noted, values are mean and (percentage of control).
[c]$n = 3$; $n = 5$ for all other entries.
[d]Incidence and (severity score) based on a scale of 1 to 4: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animals with lesions from groups of 5 unless otherwise noted.

*Statistically significant different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.

Table B.2. Renal Toxicity in Female F344/N Rats in 2-Week Drinking Water Studies of Diethanolamine[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	**630 (79)**	**1250 (158)**	**2500 (371)**	**5000 (670)**	**10,000 (1041)**
Final body weight (g)	136	134 (99%)	126 (93%)*	106 (78%)**	[c]	[c]
Right kidney weight (g)	0.628	0.740 (118%)*	0.696 (111%)	0.821 (131%)**	[c]	[c]
Relative kidney weight (g)	4.62	5.52 (119%)*	5.52 (119%)*	7.75 (168%)**	[c]	[c]
Tubular epithelial necrosis[d]	0/5	0/5	0/5	5/5 (1.6)	5/5 (3.4)	5/5 (3.2)
Urinalysis						
Urea nitrogen (mg/mg creatinine)	33	35 (106%)	33 (100%)	46 (139%)**	[e]	[e]
Glucose (mg/mg creatinine)	0.2	0.2 (100%)	0.3 (150%)	0.9 (450%)**	[e]	[e]
Protein (mg/mg creatinine)	0.4	0.5 (125%)	0.7 (175%)	1.8 (450%)**	[e]	[e]
Lactate dehydrogenase (IU/mg creatinine)	0.06	0.07 (117%)	0.11 (183%)*	0.21 (350%)**	[e]	[e]

[a]NTP, 1992c.
[b]Unless otherwise noted, values are mean and (percentage of control).
[c]All animals in group died before scheduled termination.
[d]Incidence and (severity score) based on a scale of 1 to 4: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animals with lesions from groups of 5 unless otherwise noted.
[e]All animals in group died before urine collection.

*Statistically significant different from the control group, $p \leq 0.05$.
**Statistically significant different from the control group, $p \leq 0.01$.

Table B.3. Liver Toxicity in Male B6C3F$_1$ Mice in 2-Week Drinking Water Studies of Diethanolamine[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	630 (110)	1250 (205)	2500 (415)	5000 (909)	10,000 (1362)
Necropsy weight (g)	25.2	24.7 (98%)	25.1 (100%)	25.3 (100%)	24.2 (96%)	19.9 (79%)
Liver weight (g)	1.50 ± 0.16	1.61 ± 0.09 (107%)	1.73 ± 0.12 (115%)	1.94 ± 0.13 (129%)**	2.18 ± 0.13 (145%)*	1.86 ± 0.32 (124%)*
Relative liver weight (g)	59.8 ± 6.6	65.1 ± 4.8 (109%)	69.1 ± 5.3 (116%)	76.5 ± 4.2 (128%)**	90.0 ± 4.4 (151%)**	93.2 ± 11.8 (156%)**
SDH, IU/L	84.5 ± 50.9	49.9 ± 4.9 (59%)	50.0 ± 7.9 (59%)	80.6 ± 17.4 (95%)	127.2 ± 33.6 (151%)	237.8 ± 163.6 (281%)
Cytologic alteration[c]	0/5	0/5	1/5 (1.0)	4/5 (1.3)	5/5 (2.4)	5/5 (1.6)

[a]NTP, 1992d.
[b]Unless otherwise noted values are means ± SD and (percentage of control).
[c]Incidence and (severity score) based on a scale of 1 (minimal) to 4 (marked). Severity scores are averages based on the number of animals with lesions from groups of 5.

*Statistically significant different from the control group, $p \leq 0.05$.
**Statistically significant different from the control group, $p \leq 0.01$.

Table B.4. Liver Toxicity in Female B6C3F$_1$ Mice in 2-Week Drinking Water Studies of Diethanolamine[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	630 (197)	1250 (326)	2500 (793)	5000 (1399)	10,000 (2169)
Necropsy weight (g)	21.0	22.3 (106%)	22.1 (105%)	22.4 (107%)	18.8 (90%)	18.0 (86%)
Liver weight (g)	1.19 ± 0.10	1.34 ± 0.10 (113%)	1.50 ± 0.26 (126%)*	1.70 ± 0.16 (143%)**	1.89 ± 0.12 (159%)**	1.97 ± 0.12 (166%)**
Relative liver weight (g)	56.5 ± 4.0	60.1 ± 2.1 (106%)	67.4 ± 7.2 (119%)*	75.8 ± 6.4 (134%)**	100.4 ± 8.3 (178%)**	109.0 ± 3.6 (193%)**
SDH, IU/L	48.3 ± 11.0	43.8 ± 13.9 (91%)	39.2 ± 4.7 (81%)	44.0 ± 9.1 (91%)	84.3 ± 29.4 (175%)	105.7 ± 30.3 (219%)*
Cytologic alteration[c]	0/5	0/5	1/5 (1.0)	1/5 (1.0)	5/5 (1.8)	5/5 (1.4)

[a]NTP, 1992d.
[b]Unless otherwise noted, values are means ± SD and (percentage of control).
[c]Incidence and (severity score) based on a scale of 1 (minimal) to 4 (marked). Severity scores are averages based on the number of animals with lesions from groups of 5.

*Statistically significant different from the control group, $p \leq 0.05$.
**Statistically significant different from the control group, $p \leq 0.01$.

Table B.5. Body-Weight Changes in F344/N Rats Administered Diethanolamine for 13 Weeks[a]

Original Dose (ppm)	Average Daily Dose (mg/kg-day)	Body-Weight Gain (g)[b]
Male F344/N Rats		
0	0	240
320	25	221 (95%)
630	48	200 (89%)
1250	97	180 (82%)
2500	202	135 (71%)
5000	436	81 (56%)
Female F344/N Rats		
0	0	120
160	14	106 (95%)
320	32	98 (91%)
630	57	95 (90%)
1250	124	85 (84%)
2500	242	63 (75%)

[a]NTP, 1992a.
[b]Number in parentheses is percentage change in body weight relative to control as provided by study authors.

Table B.6. Hematological Changes in Male F334/N Rats Administered Diethanolamine for 13 Weeks[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	320 (25)	630 (48)	1250 (97)	2500 (202)	5000 (436)[c]
RBC (10^6/uL)	8.79 ± 0.09	8.75 ± 0.11 (100%)	8.20 ± 0.06 (93%)**	7.33 ± 0.11 (83%)**	6.40 ± 0.09 (73%)**	5.71 ± 0.13 (65%)**
HGB (g/dL)	14.8 ± 0.2	14.3 ± 0.2 (97%)*	13.3 ± 0.1 (90%)**	11.6 ± 0.2 (78%)**	9.8 ± 0.2 (66%)**	8.9 ± 0.2 (60%)**
HCT (%)	47.8 ± 0.5	46.1 ± 0.7 (96%)	42.5 ± 0.5 (89%)**	36.9 ± 0.5 (77%)**	31.4 ± 0.4 (66%)**	27.8 ± 0.7 (58%)**
MCV (fL)	54.3 ± 0.2	52.6 ± 0.2 (97%)**	51.9 ± 0.4 (96%)**	50.2 ± 0.3 (92%)**	49.1 ± 0.2 (90%)**	48.5 ± 0.2 (89%)**
MCH (pg)	16.9 ± 0.1	16.4 ± 0.1 (97%)**	16.2 ± 0.1 (96%)**	15.9 ± 0.1 (94%)**	15.3 ± 0.2 (91%)**	15.5 ± 0.1 (92%)**
Reticulocytes (10^6/uL)	0.23 ± 0.02	0.23 ± 0.01 (100%)	0.23 ± 0.01 (100%)	0.24 ± 0.02 (104%)	0.14 ± 0.01 (61%)**	0.16 ± 0.01 (70%)**

[a]NTP, 1992a.
[b]Values are mean ± SD and (percentage of control). Data were reported in Standard Error by the study authors. For modeling purposes, data were converted to Standard Deviation by the following equation: SD = SE × Sqrt(n).
[c]$n = 8$; $n = 10$ for all other entries.

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.

Table B.7. Hematological Changes in Female F334/N Rats Administered Diethanolamine for 13 Weeks[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	**160 (14)**	**320 (32)[c]**	**630 (57)**	**1250 (124)**	**2500 (242)**
RBC (10^6/uL)	8.40± 0.08	8.51± 0.07 (101%)	7.84 ± 0.08 (93%)**	7.56 ± 0.07 (90%)**	6.78 ± 0.15 (81%)**	6.43 ± 0.13 (77%)**
HGB (g/dL)	15.1 ± 0.3	15.2 ± 0.1 (101%)	13.8 ± 0.1 (91%)**	13.0 ± 0.1 (86%)**	11.3 ± 0.2 (75%)**	10.5 ± 0.2 (70%)**
HCT (%)	47.3 ± 0.5	47.0 ± 0.4 (99%)	42.3 ± 0.5 (89%)**	39.7 ± 0.4 (84%)**	34.4 ± 0.7 (73%)**	31.2 ± 0.7 (66%)**
MCV (fL)	56.3 ± 0.2	55.2 ± 0.2 (98%)**	53.9 ± 0.2 (96%)**	52.5 ± 0.3 (93%)**	50.7 ± 0.3 (90%)**	48.5 ± 0.2 (86%)**
MCH (pg)	17.9 ± 0.2	17.8 ± 0.1 (99%)*	17.7 ± 0.1 (99%)**	17.2 ± 0.1 (96%)**	16.7 ± 0.1 (93%)**	16.3 ± 0.1 (91%)**
Reticulocytes (10^6/uL)	0.17 ± 0.0	0.16 ± 0.01 (94%)	0.13 ± 0.01 (76%)**	0.12 ± 0.01 (71%)*	0.09 ± 0.01 (53%)**	0.08 ± 0.01 (47%)**

[a]NTP, 1992a.
[b]Values are mean ± SD and (percentage of control). Data were reported in Standard Error by the study authors. For modeling purposes, data were converted to Standard Deviation by the following equation: SD = SE × Sqrt(n).
[c]$n = 8$; $n = 10$ for all other entries.

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.

Table B.8. Relative Organ Weights of Male F334/N Rats Administered Diethanolamine for 13 Weeks[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	**320 (25)**	**630 (48)**	**1250 (97)**	**2500 (202)**	**5000 (436)**
Number of animals	10	10	10	10	10	8
Necropsy Body Weight (g)	366 ± 9	339 ± 9 (93%)*	326 ± 9 (89%)**	302 ± 7 (83%)**	265 ± 8 (72%)**	205 ± 4 (56%)**
Relative Kidney Weight	3.54 ± 0.03	3.94 ± 0.05 (111%)**	3.99 ± 0.06 (113%)**	3.98 ± 0.05 (112%)**	4.44 ± 0.05 (125%)**	6.14 ± 0.17 (173%)**
Relative Liver Weight	41.28 ± 0.41	40.79 ± 0.69 (99%)	45.61 ± 1.06 (110%)**	48.90 ± 1.14 (118%)**	53.27 ± 0.98 (129%)**	56.71 ± 0.86 (137%)**
Relative Testis Weight	4.08 ± 0.05	4.31 ± 0.07 (106%)	4.50 ± 0.05 (110%)	4.22 ± 0.11 (103%)	3.64 ± 0.18 (89%)**	2.63 ± 0.13 (64%)**
Relative Brain Weight	5.46 ± 0.11	5.90 ± 0.13 (108%)*	6.19 ± 0.12 (113%)**	6.50 ± 0.15 (119%)**	7.28 ± 0.15 (133%)**	9.11 ± 0.14 (167%)**
Relative Heart Weight	2.98 ± 0.05	3.09 ± 0.07 (104%)	3.17 ± 0.08 (106%)	3.05 ± 0.06 (102%)	3.38 ± 0.11 (113%)**	3.73 ± 0.07 (125%)**
Relative Epididymis Weight[c]	1.17	1.34 (115%)**	1.20 (103%)	1.02 (87%)**	0.68 (58%)**	0.65 (56%)**
Right Epididymis	0.426 ± 0.009		0.392 ± 0.013 (92%)	0.309 ± 0.012 (73%)**	0.184 ± 0.019 (43%)**	
Right Epididymal Tail	0.134 ± 0.008		0.122 ± 0.006 (91%)	0.094 ± 0.006 (70%)**	0.053 ± 0.006 (40%)**	

[a]NTP, 1992a.
[b]Values are mean ± SD and (percentage of control). Data were reported in Standard Error by the study authors. For modeling purposes data were converted to Standard Deviation by the following equation: SD = SE × Sqrt(n).
[c]Standard deviation not reported by study authors.

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.

Table B.9. Relative Organ Weights of Female F334/N Rats Administered Diethanolamine for 13 Weeks[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	**160 (14)**	**320 (32)**	**630 (57)**	**1250 (124)**	**2500 (242)**
Number of animals	10	9	10	10	10	10
Necropsy Body Weight (g)	218 ± 4	208 ± 4 (95%)	201 ± 2 (92%)**	202 ± 3 (93%)**	188 ± 4 (86%)**	162 ± 4 (74%)**
Relative Kidney Weight	3.03 ± 0.05	4.12 ± 0.06 (136%)**	4.21 ± 0.14 (139%)**	4.12 ± 0.09 (136%)**	4.63 ± 0.07 (153%)**	5.67 ± 0.11 (187%)**
Relative Liver Weight	27.86 ± 0.28	30.54 ± 0.55 (110%)	35.09 ± 1.58 (126%)**	34.52 ± 0.82 (124%)**	41.41 ± 1.27 (149%)**	45.26 ± 0.80 (162%)**
Relative Brain Weight	8.25 ± 0.14	8.69 ± 0.12 (105%)	9.23 ± 0.16 (112%)**	9.04 ± 0.16 (110%)**	9.73 ± 0.27 (118%)**	11.02 ± 0.32 (134%)**
Relative Heart Weight	3.25 ± 0.06	3.20 ± 0.05 (98%)	3.50 ± 0.15 (108%)	3.42 ± 0.23 (105%)	3.65 ± 0.13 (112%)	3.89 ± 0.11 (120%)**

[a]NTP, 1992a.
[b]Values are mean ± SD and (percentage of control). Data were reported in Standard Error by the study authors. For modeling purposes, data were converted to Standard Deviation by the following equation: SD = SE × Sqrt(n).

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.

Table B.10. Incidence and Severity of Lesions in Male F334/N Rats Administered Diethanolamine for 13 Weeks[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	320 (25)	630 (48)	1250 (97)	2500 (202)	5000 (436)
Number of animals	10	10	10	10	10	10
Kidney						
Nephropathy	6 (1.0)	2 (1.0)	2 (1.0)	3 (1.0)	6 (1.0)	10 (2.4)
Tubular epithelial necrosis	0	0	0	0	0	10 (1.0)
Tubular mineralization	0	0	0	1 (1.0)	10 (1.8)	10 (1.7)
Brain, medulla						
Demyelination	0	0	0	0	10 (1.7)	10 (2.0)
Spinal Cord						
Demyelination	0	0	0	0	10 (1.9)	10 (2.0)

[a]NTP, 1992a.
[b]Incidence and (severity score) based on a scale of 1 to 4: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animals with lesions from groups of 10.

Table B.11. Incidence and Severity of Lesions in Female F334/N Rats Administered Diethanolamine for 13 Weeks[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	160 (14)	320 (32)	630 (57)	1250 (124)	2500 (242)
Number of animals	10	10	10	10	10	10
Kidney						
Nephropathy	2 (1.0)	9 (1.0)	10 (1.5)	10 (1.4)	9 (1.0)	2 (1.0)
Tubular epithelial necrosis	0	0	0	0	1 (1.0)	3 (1.0)
Tubular mineralization	10 (1.3)	10 (2.0)	10 (2.5)	10 (3.0)	10 (2.4)	10 (1.7)
Brain, medulla						
Demyelination	0	0	0	0	10 (1.5)	10 (1.9)
Spinal Cord						
Demyelination	0	0	0	0	10 (1.0)	10 (1.9)

[a]NTP, 1992a.
[b]Incidence and (severity score) based on a scale of 1 to 4: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked. Severity scores are averages based on the number of animals with lesions from groups of 10.

Table B.12. Body-Weight Changes in B6C3F$_1$ Mice Administered Diethanolamine for 13 Weeks[a]

Original Dose (ppm)	Average Daily Dose (mg/kg-day)	Body-Weight Gain (g)
Male B6C3F$_1$ Mice		
0	0	15.4
630	104	14.1
1,250	178	14.2
2,500	422	11.9
5,000	807	Died prior to study completion.
10,000	1674	Died prior to study completion.
Female B6C3F$_1$ Mice		
0	0	12.7
630	142	13.2
1,250	347	9.8
2,500	884	6.7
5,000	1154	Died prior to study completion.
10,000	1128	Died prior to study completion.

[a]NTP, 1992b.

Table B.13. Clinical Chemistry Data for Male B6C3F$_1$ Mice in 13-Week Drinking Water Studies of Diethanolamine[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	630 (104)	1250 (178)	2500 (422)	5000 (807)	10,000 (1674)
Number of animals	10	10	10	10	0	0
Clinical Chemistry						
Blood urea nitrogen (mg/dL)	30.6 ± 1.6	27.2 ± 0.9 (89%)	27.6 ± 1.2 (90%)	25.2 ± 1.1 (82%)*	-	-
Creatinine (mg/dL)	0.500 ± 0.021	0.500 ± 0.000 (100%)	0.520 ± 0.013 (104%)	0.480 ± 0.033 (96%)	-	-
Glucose (mg/dL)	164 ± 6	162 ± 7 (99%)	161 ± 4 (98%)	163 ± 7 (99%)	-	-
Total Protein (g/dL)	6.1 ± 0.1	6.3 ± 0.1 (103%)*	6.4 ± 0.1 (105%)**	6.4 ± 0.1 (105%)*	-	-
Albumin (g/dL)	4.1 ± 0.1	4.4 ± 0.1 (107%)**	4.7 ± 0.1 (115%)**	4.8 ± 0.1 (117%)**	-	-
Alanine aminotransferase (IU/L)	40 ± 5	35 ± 5 (88%)	33 ± 3 (83%)	91 ± 7 (228%)**	-	-
Sorbitol dehydrogenase (IU/L)	58 ± 2	50 ± 3 (86%)	56 ± 2 (97%)	107 ± 4 (184%)**	-	-
Bile salts (um/L)	25.90 ± 0.92	22.30 ± 0.68 (86%)**	22.10 ± 0.89 (85%)*	19.90 ± 1.45 (77%)**	-	-

[a]NTP, 1992b.
[b]Values are mean ± SD and (percentage of control). Data were reported in Standard Error by the study authors. For modeling purposes, data were converted to Standard Deviation by the following equation: SD = SE × Sqrt(n).

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.
Dash (-) indicates all animals died before study completion.

Table B.14. Clinical Chemistry Data for Female B6C3F$_1$ Mice in 13-Week Drinking Water Studies of Diethanolamine[a,b]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	630 (142)	1250 (347)	2500 (884)	5000 (1154)	10000 (1128)
Number of animals	10	10	10	7	0	0
Clinical Chemistry						
Blood urea nitrogen (mg/dL)	22.4 ± 1.4	19.4 ± 0.9 (87%)	18.6 ± 1.3 (83%)	22.3 ± 2.5 (100%)	-	-
Creatinine (mg/dL)	0.530 ± 0.021	0.530 ± 0.021 (100%)	0.500 ± 0.015 (94%)	0.486 ± 0.014 (92%)	-	-
Glucose (mg/dL)	168 ± 11	156 ± 5 (93%)	153 ± 4 (91%)	133 ± 5 (79%)**	-	-
Total Protein (g/dL)	5.8 ± 0.1	6.2 ± 0.1 (107%)**	6.2 ± 0.1 (107%)**	6.1 ± 0.2 (105%)*	-	-
Albumin (g/dL)	3.9 ± 0.1	4.5 ± 0.1 (115%)**	4.6 ± 0.1 (118%)**	4.8 ± 0.2 (123%)**	-	-
Alanine aminotransferase (IU/L)	25± 1	25 ± 1 (100%)	32 ± 3 (128%)*	74 ± 10 (296%)**	-	-
Sorbitol dehydrogenase (IU/L)	37 ± 1	36 ± 1 (97%)	36 ± 1 (97%)	47 ± 5 (127%)	-	-
Bile salts (um/L)	26.60 ± 1.47	22.70 ± 0.97 (85%)	22.60 ± 1.09 (85%)	23.86 ± 1.90 (90%)	-	-

[a]NTP, 1992b.
[b]Values are mean ± SD and (percentage of control). Data were reported in Standard Error by the study authors. For modeling purposes, data were converted to Standard Deviation by the following equation: SD = SE × Sqrt(n).

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.
Dash (-) indicates all animals died before study completion.

Table B.15. Relative Organ Weight in Male B6C3F$_1$ Mice Administered Diethanolamine for 13 Weeks[a,b,c]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	630 (104)	1250 (178)	2500 (422)	5000 (807)	10,000 (1674)
Number of animals	10	10	10	10	0	0
Necropsy Body Weight	39.08 ± 0.92	37.64 ± 0.43 (96%)	37.82 ± 1.01 (97%)	35.40 ± 1.21 (91%)**	-	-
Relative Kidney Weight	8.22 ± 0.15	8.74 ± 0.16 (106%)	9.38 ± 0.28 (114%)**	10.35 ± 0.25 (126%)**	-	-
Relative Liver Weight	42.64 ± 0.81	50.29 ± 1.00 (118%)**	54.89 ± 1.13 (129%)**	66.65 ± 1.02 (156%)**	-	-
Relative Testis Weight	2.97 ± 0.06	3.19 ± 0.05 (107%)	3.10 ± 0.08 (104%)	3.29 ± 0.11 (111%)**	-	-
Relative Brain Weight	11.37 ± 0.19	11.89 ± 0.14 (105%)	12.09 ± 0.38 (106%)	12.98 ± 0.38 (114%)**	-	-
Relative Heart Weight	4.39 ± 0.11	4.31 ± 0.09 (98%)	4.58 ± 0.11 (104%)	5.07 ± 0.15 (115%)**	-	-
Right Epididymis Weight	0.048 ± 0.001	0.049 ± 0.001 (102%)	0.051 ± 0.002 (106%)	0.049 ± 0.001 (102%)	-	-
Right Epididymal Tail Weight	0.017 ± 0.000	0.016 ± 0.001 (94%)	0.018 ± 0.001 (106%)	0.018 ± 0.001 (106%)	-	-

[a]NTP, 1992b.
[b]All body weights and organ weights are presented as weight in g; relative organ-weight-to-body-weight ratios are given in mg organ weight/gm body weight.
[c]Values are mean ± SD and (percentage of control). Data were reported in Standard Error by the study authors. For modeling purposes, data were converted to Standard Deviation by the following equation: SD = SE × Sqrt(n).

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.
Dash (-) indicates all animals died before study completion.

Table B.16 Relative Organ Weight in Female B6C3F$_1$ Mice Administered Diethanolamine for 13 Weeks[a,b,c]

Parameter	Exposure Group ppm (mg/kg-day)					
	0 (0)	**630 (142)**	**1250 (347)**	**2,500 (884)**	**5000 (1154)**	**10,000 (1128)**
Number of animals	10	10	10	7	0	0
Necropsy Body Weight	32.70 ± 0.82	33.18 ± 0.79 (101%)	29.78 ± 1.18 (91%)*	26.70 ± 0.60 (82%)**	-	-
Relative Kidney Weight	6.71 ± 0.20	6.93 ± 0.30 (103%)	7.57 ± 0.23 (113%)*	8.80 ± 0.35 (131%)**	-	-
Relative Liver Weight	41.01 ± 1.27	51.17 ± 0.91 (125%)*	62.69[d] (153%)**	91.93 ± 5.96 (224%)**	-	-
Relative Brain Weight	14.39 ± 0.39	14.29 ± 0.36 (99%)	15.74 ± 0.49 (109%)*	17.39 ± 0.42 (121%)**	-	-
Relative Heart Weight	4.42 ± 0.10	4.41 ± 0.14 (100%)	5.14 ± 0.22 (116%)**	6.03 ± 0.15 (136%)**	-	-

[a]NTP, 1992b.
[b]All body weights and organ weights are presented as weight in g; relative organ-weight-to-body-weight ratios are given in mg organ weight/gm body weight.
[c]Values are mean ± SD and (percentage of control). Data were reported in Standard Error by the study authors. For modeling purposes, data were converted to Standard Deviation by the following equation: SD = SE × Sqrt(n).
[d]Unable to determine SE from table.

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.
Dash (-) indicates all animals died before study completion.

Table B.17. Body Weights of Pups Born to Sprague-Dawley Dams Exposed Orally to Diethanolamine from GDs 6−19[a]

Parameter	Dose Group (mg/kg-day)					
	0	**50**	**125**	**200**	**250**	**300**
Dams with live litters	12	12	12	11	5	-
Average body weight (g) per litter (mean ± SD) and (percentage of control)						
PND 0[b,c]	6.10 ± 0.12	6.34 ± 0.16 (104%)[d]	6.33 ± 0.10 (104%)[e]	5.65 ± 0.19 (93%)	5.25 ± 0.19 (86%)*	-
PND 4[b,c]	9.72 ± 0.25	10.17 ± 0.35 (105%)	9.96 ± 0.29 (102%)	8.81 ± 0.47 (91%)*	8.15 ± 0.45 (84%)*	-
PND 7[b,c]	13.86 ± 0.33	14.71 ± 0.55 (106%)	14.54 ± 0.42 (105%)	12.74 ± 0.65 (92%)	11.99 ± 0.66 (87%)*	-
PND 14[b]	33.08 ± 0.55	33.88 ± 0.60 (102%)	35.53 ± 0.63 (107%)*	30.72 ± 1.10 (93%)	30.18 ± 1.83 (91%)	-
PND 21[b,c]	53.80 ± 1.09	55.26 ± 1.23 (103%)	55.96 ± 1.05 (104%)	48.02 ± 2.02 (89%)*	47.46 ± 2.22 (88%)*	-

[a]Price et al., 2005, p. 250.
[b]Significant group-wise comparison, $p < 0.05$ (Kruskal-Wallis test).
[c]Significant trend test, $p < 0.05$ (Jonckheere's test).
[d]The body weight was inadvertently not recorded for one female pup in the litter of Dam 46.
[e]The body weight was inadvertently not recorded for one female pup in the litter of Dam 56.

*Statistically significantly different from the control group, $p < 0.05$ (Mann-Whitney U-test).

Table B.18. Developmental Outcome Data in Sprague-Dawley Dams Exposed Orally to Diethanolamine from GDs 6−19[a]

Parameter	Dose Group (mg/kg-day)					
	0	50	125	200	250	300
Live litters	12	12	12	11	5	-
Total litter loss (100% postimplantation loss)						
N	0	0	0	0	4	-
Females (%)	0.0*	0.0	0.0	0.0	44.4*	-
All litter data, mean ± SD, and (percentage control)						
Gestational length (days)	21.9 ± 0.1	22.2 ± 0.1 (101%)	22.3 ± 0.1 (102%)	22.3 ± 0.1 (102%)	22.2 ± 0.2 (101%)	-
Implantation sites per litter	14.25 ± 0.46	13.75 ± 0.86 (96%)	14.33 ± 0.28 (101%)	14.42 ± 0.81 (101%)	14.91 ± 0.59 (105%)	-
% Postimplantation loss PND 0	2.48 ± 1.38	5.83 ± 1.84 (235%)	3.41 ± 1.03 (138%)	17.31 ± 4.97 (698%)*	50.98 ± 15.82 (2056%)*	-
Number of dead pups per live litter, mean ± SD, and (percentage control)						
PNDs 0−4	0.1 ± 0.1	0.1 ± 0.1 (100%)	0.7 ± 0.2 (700%)*	0.4 ± 0.2 (400%)	2.0 ± 0.9 (2000%)*	-
PNDs 7−14	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.1	0.1 ± 0.1	0.4 ± 0.2	-
% Postnatal mortality per live litter, mean ± SD, and (percentage control)						
PNDs 0−4	0.6 ± 0.6	0.6 ± 0.6 (100%)	1.8 ± 1.0 (300%)*	2.8 ± 1.2 (467%)*	13.4 ± 7.2 (2233%)*	-
PNDs 7−14	0.0 ± 0.0	0.0 ± 0.0	2.1 ± 1.4	1.1 ± 1.1	5.0 ± 3.1	-

[a]Price et al., 2005, p. 249.

*Statistically significantly different from the control group, $p < 0.05$.

Table B.19. Average Maternal Body Weight and Weight Gain (g; Mean ± SD) of CD-1 Mice Exposed Orally to 450-mg/kg-day Diethanolamine from GDs 6−15[a]

Weight Measure	Vehicle control	Diethanolamine
Random weight—pregnant only	26.1 ± 1.15 (*n* = 28)	25.9 ± 1.13 (*n* = 34)
Random weight—viable litters only	26.0 ± 1.13 (*n* = 25)	25.9 ± 1.10 (*n* = 27)
Weight gain postpartum (on Day 0)—randomization	+4.3 ± 1.60 (*n* = 25)	+6.4 ± 1.70* (*n* = 27)

[a]Environmental Health Research and Testing, Inc., 1987.

*Statistically significant different from the control group, $p < 0.01$.

Table B.20. Reproductive and Litter Data of CD-1 Mice Exposed Orally to 450-mg/kg-day Diethanolamine from GDs 6−15[a]

Parameter	Vehicle Control	Diethanolamine
Reproductive index		
Ratio	25/28	27/34
Percent	89.3	79.4
Average number/litter, mean ± SD		
Day 0 live	10.2 ± 3.1 (*n* = 25)	9.0 ± 2.7 (*n* = 27)
Day 3 live	10.1 ± 3.1 (*n* = 25)	7.0 ± 4.2*** (*n* = 27)
Postnatal survival		
Ratio	242/255	188/243
Percent	94.9	77.4***
Duration of gestation (days) (Mean ± SD)	18.2 ± 0.35	18.5*** ± 0.34 (*n* = 27)

[a]Environmental Health Research and Testing, Inc., 1987.

***Statistically different from the control group, $p \leq 0.001$.

Table B.21. Average Live Pup Weight (g; Mean ± SD) in Litters from CD-1 Mice Exposed Orally to 450-mg/kg-day Diethanolamine from GDs 6−15[a]

Parameter	Vehicle Control	Diethanolamine
Average live pup weight		
Day 0	1.5 ± 0.19 *(n =25)*	1.5 ± 0.19 (*n* = 27)
Day 3	2.1 ± 0.32 *(n = 25)*	1.6 ± 0.27*** (*n* = 23)
Change (Day 3−Day 0)	0.6 ± 0.318 *(n = 25)*	0.1 ± 0.25*** (*n* = 23)

[a]Environmental Health Research and Testing, Inc., 1987.

***Statistically significantly different from the control group, $p \leq 0.001$.

Table B.22. Body Weight and Relative Organ Weight in Male Wistar Rats Administered Diethanolamine by Inhalation for 90 Days[a,b,c,d]

Parameter	Exposure Group mg/m^3 (HEC)			
	0 (0)	15 (5.6)	150 (55.4)	400 (146.2)
Body Weight at Termination	433 ± 51	407 ± 45 (94%)	396 ± 30 (91%)	376 ±27 (87%)**
Relative Liver Weight	2834 ± 263	2793 ± 269 (99%)	2814 ± 112 (99%)	3077 ± 121 (109%)*
Relative Kidney Weight	652 ± 58	674 ± 45 (103%)	716 ± 45 (110%)*	734 ± 58 (113%)**
Relative Brain Weight	510 ± 57	538 ± 65 (105%)	546 ± 30 (107%)	578 ± 40 (113%)*
Relative Lung Weight	319 ± 38	323 ± 34 (101%)	321 ± 27 (101%)	332 ± 20 (104%)

[a]Gamer et al., 2008b.
[b]Values are mean ± SD and (percentage of control).
[c]n = 13 for body weight, measured in grams.
[d]n = 10 for organ weight, measured in g/100g bw.

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.

Table B.23. Body Weight and Relative Organ Weights of Female Wistar Rats Administered Diethanolamine by Inhalation for 90 Days[a,b,c,d]

Parameter	Exposure Group mg/m^3 (HEC)			
	0 (0)	15 (6.8)	150 (68.1)	400 (181.7)
Body Weight at Termination	266 ± 12	264 ± 19 (99%)	253 ± 21 (95%)	269 ± 19 (101%)
Relative Liver Weight	3171 ± 157	3191 ± 161 (101%)	3488 ± 215 (110%)**	3771 ± 204 (119%)**
Relative Kidney Weight	795 ± 40	811 ± 51 (102%)	891 ± 39 (112%)**	922 ± 72 (116%)**
Relative Brain Weight	787 ± 43	803 ± 46 (102%)	801 ± 65 (102%)	802 ± 53 (102%)
Relative Lung Weight	451 ± 39	410 ± 48 (91%)	419 ± 45 (93%)	418 ± 55 (93%)

[a]Gamer et al., 2008b.
[b]Values are mean ± SD and (percentage of control).
[c]n = 13 for body weight, measured in grams.
[d]n = 10 for organ weight, measured in g/100g bw.

**Statistically significantly different from the control group, $p < 0.01$.

Table B.24. Red Blood Cell Parameters of Male Wistar Rats Administered Diethanolamine by Inhalation for 90 Days[a,b]

Parameter	Exposure Group mg/m^3 (HEC)			
	0 (0)	15 (6.8)	150 (67.9)	400 (181.3)
Erythrocytes (tera/l)	8.6 ± 0.2	8.7 ± 0.4 (101%)	8.6 ± 0.5 (100%)	8.1 ± 0.3 (94%)**
Haemoglobin (mmol/l)	9.7 ± 0.3	9.6 ± 0.4 (99%)	9.5 ± 0.3 (98%)	8.8 ± 0.4 (91%)**
Haematocrit (%)	45.7 ± 1.8	45.2 ± 2.2 (99%)	45.0 ± 2.2 (98%)	41.4 ± 2.0 (91%)**
Mean corpuscular volume (femtoliter)	53.1 ± 1.5	52.0 ± 1.6 (98%)	52.6 ± 1.1 (99%)	51.0 ± 1.9 (96%)*

[a]Gamer et al., 2008b.
[b]Values are mean ± SD and (percentage of control).

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.

Table B.25. Red Blood Cell Parameters of Female Wistar Rats Administered Diethanolamine by Inhalation for 90 days[a,b]

Parameter	Exposure Group mg/m^3 (HEC)			
	0 (0)	15 (6.8)	150 (68.1)	400 (181.7)
Erythrocytes (tera/l)	7.7 ± 0.3	8.0 ± 0.5 (104%)	7.6 ± 0.5 (99%)	7.1 ± 0.2 (92%)**
Haemoglobin (mmol/l)	9.0 ± 0.3	9.3 ± 0.4 (103%)	8.7 ± 0.3 (97%)	7.9 ± 0.2 (88%)**
Haematocrit (%)	409 ± 13	424 ± 28 (104%)	396 ± 19 (97%)	367 ± 9 (90%)**
Mean corpuscular volume (femtoliter)	53.0 ± 1.3	53.0 ± 1.0 (100%)	52.1 ± 1.4 (98%)	51.7 ± 1.0 (98%)*

[a]Gamer et al., 2008b.
[b]Values are mean ± SD and (percentage of control).

*Statistically significantly different from the control group, $p \leq 0.05$.
**Statistically significantly different from the control group, $p \leq 0.01$.

Table B.26. Incidence of Changes to the Larynx in Male Wistar Rats Administered Diethanolamine by Inhalation for 90 Days[a,b]

Parameter	Severity	Exposure Group mg/m^3 (HEC)			
		(0)[c]	15 (5.6)	150 (55.4)	400 (146.2)
Metaplasia squamous: Level 1	Present	NR	10	10	10
Metaplasia squamous: Level 2	Present	NR	0	0	0
Metaplasia squamous: Level 2: Hyperplasia	Minimal	NR	0	3	0
	Slight	NR	0	3	2
	Moderate	NR	0	0	4
	Marked/Severe	NR	0	0	2
Metaplasia squamous: Level 2: Inflammatory cells	Minimal	NR	0	0	0
	Slight	NR	0	0	0
	Moderate	NR	1	0	0
Metaplasia squamous: Level 2: Chronic Inflammation	Slight	NR	0	1	2
	Moderate	NR	0	9	5
	Marked/Severe	NR	0	0	3

[a]Gamer et al., 2008b.
[b]*n* = 10/sex.
[c]Incidence in the control group was not reported by the study authors; however, the study authors stated that fields with no entries (see Table 5 in Gamer et al., 2008b) imply no findings.

Table B.27. Incidence of Changes to the Larynx in Female Wistar Rats Administered Diethanolamine by Inhalation for 90 Days[a,b]

Parameter	Severity	Exposure Group mg/m^3 (HEC)			
		0 (0)[c]	15 (4.8)	150 (47.7)	400 (129.8)
Metaplasia squamous: Level 1	Present	NR	10	10	10
Metaplasia squamous: Level 2	Present	NR	0	0	0
Metaplasia squamous: Level 2: Hyperplasia	Minimal	NR	0	1	1
	Slight	NR	0	6	7
	Moderate	NR	0	0	1
	Marked/Severe	NR	0	0	0
Metaplasia squamous: Level 2: Inflammatory cells	Minimal	NR	0	0	0
	Slight	NR	3	0	0
	Moderate	NR	0	0	0
Metaplasia squamous: Level 2: Chronic Inflammation	Slight	NR	0	4	1
	Moderate	NR	0	6	8
	Marked/Severe	NR	0	0	1

[a]Gamer et al., 2008b.
[b]*n* = 10/sex.
[c]Incidence in the control group was not reported by the study authors; however, the study authors stated that fields with no entries (see Table 5 in Gamer et al., 2008b) imply no findings.

Table B.28. Body Weight and Relative Organ Weights of Male Wistar Rats Administered Diethanolamine by Inhalation for 90 Days[a,b,c,d]

Parameter	Exposure Group mg/m^3 (HEC)			
	0 (0)	1.5 (0.55)	3 (1.11)	8 (2.95)
Body Weight at Termination	327 ± 37	335 ± 30 (102%)	336 ± 29 (103%)	327 ± 20 (100%)
Relative Liver Weight	2532 ± 328	2423 ± 92 (96%)	2470 ± 111 (98%)	2449 ± 198 (97%)
Relative Kidney Weight	629 ± 48	626 ± 39 (99%)	621 ± 41 (99%)	631 ± 46 (100%)
Relative Brain Weight	630 ± 50	612 ± 41 (97%)	614 ± 46 (97%)	619 ± 25 (98%)
Relative Lung Weight	316 ± 19	298 ± 23 (94%)	300 ± 23 (95%)	328 ± 12 (104%)

[a]Gamer et al., 2008c.
[b]Values are mean ± SD and (percentage of control).
[c]*n* = 10 for body weight, measured in grams.
[d]*n* = 10 for organ weight, measured in g/100g bw.

Table B.29. Body Weight and Relative Organ Weight in Female Wistar Rats Administered Diethanolamine by Inhalation for 90 Days[a,b,c,d]

Parameter	Exposure Group mg/m^3 (HEC)			
	0 mg/m^3 (0)	1.5mg/m^3 (0.55)	3 mg/m^3 (1.10)	8 mg/m^3 (2.93)
Body Weight at Termination	220 ± 15	215 ± 12 (98%)	213 ± 10 (97%)	219 ± 12 (100%)
Relative Liver Weight	2624 ± 262	2618 ± 275 (100%)	2556 ± 131 (97%)	2987 ± 291 (114%)*
Relative Kidney Weight	676 ± 44	688 ± 47 (102%)	682 ± 31 (101%)	724 ± 41 (107%)
Relative Brain Weight	886 ± 68	927 ± 57 (105%)	931 ± 46 (105%)	907 ± 43 (102%)
Relative Lung Weight	380 ± 37	399 ± 51 (105%)	404 ± 30 (106%)	425 ± 24 (112%)

[a]Gamer et al., 2008c.
[b]Values are mean ± SD and (percentage of control).
[c]n = 10 for body weight, measured in grams.
[d]n = 10 for organ weight, measured in g/100g bw.

*Statistically significantly different from the control group, $p \leq 0.05$.

Table B.30. Incidence of Changes to the Larynx in Male Wistar Rats Administered Diethanolamine by Inhalation for 90 Days[a,b]

Parameter	Severity	Exposure Group mg/m^3 (HEC)			
		0 (0)[c]	1.5 (1.07)	3.0 (2.15)	8.0 (5.66)
Metaplasia squamous: Level 1	Present	NR	0	3	9
Metaplasia squamous: Level 2	Present	NR	0	0	2
Metaplasia squamous: Level 2: Hyperplasia	Minimal	NR	0	0	0
	Slight	NR	0	0	0
	Moderate	NR	0	0	0
	Marked/Severe	NR	0	0	0
Metaplasia squamous: Level 2: Inflammatory cells	Minimal	NR	1	0	0
	Slight	NR	0	0	2
	Moderate	NR	0	0	1
Metaplasia squamous: Level 2: Chronic Inflammation	Slight	NR	0	0	0
	Moderate	NR	0	0	0
	Marked/Severe	NR	0	0	0

[a]Gamer et al., 2008c.
[b]n = 10/sex.
[c]Incidence in the control group was not reported by the study authors; however, the study authors stated that fields with no entries (see Table 5 in Gamer et al., 2008b) imply no findings.

Table B.31. Incidence of Changes to the Larynx in Female Wistar Rats Administered Diethanolamine by Inhalation for 90 Days[a,b]

Parameter	Severity	Exposure Group mg/m^3 (HEC)			
		0 (0)[c]	1.5 (0.86)	3.0 (1.71)	8.0 (4.61)
Metaplasia squamous: Level 1	Present	NR	0	0	9
Metaplasia squamous: Level 2	Present	NR	0	0	0
Metaplasia squamous: Level 2: Hyperplasia	Minimal	NR	0	0	0
	Slight	NR	0	0	0
	Moderate	NR	0	0	0
	Marked/Severe	NR	0	0	0
Metaplasia squamous: Level 2: Inflammatory cells	Minimal	NR	0	0	1
	Slight	NR	0	0	2
	Moderate	NR	0	0	0
Metaplasia squamous: Level 2: Chronic Inflammation	Slight	NR	0	0	0
	Moderate	NR	0	0	0
	Marked/Severe	NR	0	0	0

[a]Gamer et al., 2008c.
[b]*n* = 10/sex.
[c]Incidence in the control group was not reported by the study authors; however, the study authors stated that fields with no entries (see Table 5 in Gamer et al., 2008b) imply no findings.

APPENDIX C. BMD OUTPUTS

Table C.1. BMD Modeling Output Summary for Hematological and Relative Organ-Weight Changes in Male and Female F334/N Rats Orally Administered Diethanolamine for 13 Weeks[a]

Endpoint	Gender	Continuous Model Type	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value	AIC	Scaled Residual
MCV	Male	Hill	11	6.9	<0.0001	0.2604	24.6869	0.0602
Relative brain weight	Female	Hill	19	10	<0.0001	0.1142	6.3469	0.411
HCT	Male	Hill	20	14	<0.0001	0.5593	77.1213	0.376
MCH	Male	Hill	22	12	<0.0001	0.5642	-37.8055	-0.656
HGB	Male	Hill	23	15	<0.0001	0.7091	-7.91763	0.245
Relative brain weight	Male	Hill	29	17	<0.0001	0.5893	-33.2561	0.36
Necropsy body weight	Male	Hill	29	17	<0.0001	0.8672	381.4234	-0.394
RBC	Male	Hill	31	22	<0.0001	0.1984	-60.5060	0.939
Necropsy body weight	Female	Hill	37	23	<0.0001	0.3043	349.3301	-1.25
Urine lactate	Male	Linear	100	74	0.0004	0.7038	338.9653	-0.407
Reticulocytes	Male	Power	190	150	0.0001	0.7349	-260.903	-0.000
Relative heart weight	Male	Power	200	100	0.0004	0.3296	-87.3291	0.000

[a]NTP, 1992a.

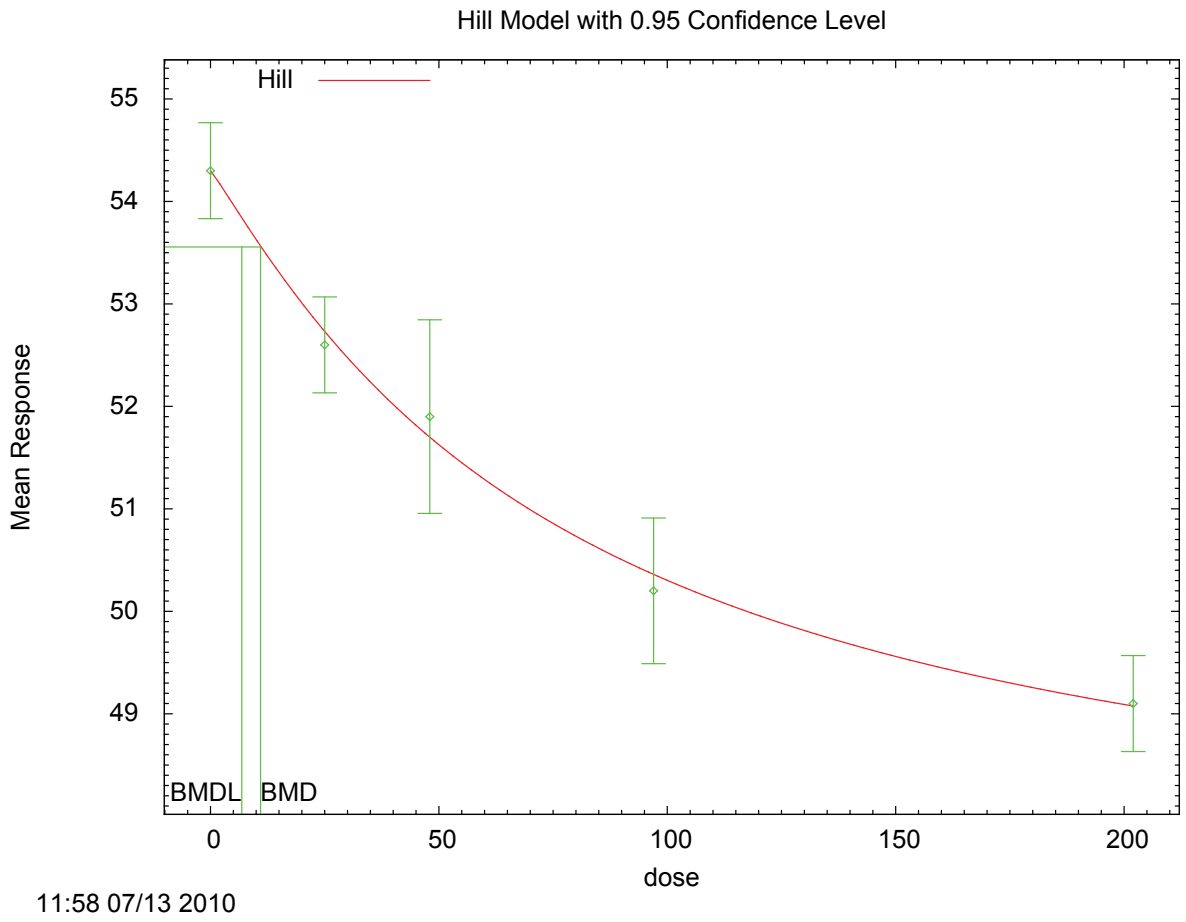

Figure C.1. Continuous-Hill BMD Model for Mean Cell Volume Data (NTP, 1992a)

Text Output for Continuous-Hill BMD Model for Mean Cell Volume Data (NTP, 1992a)

```
================================================================================
        Hill Model. (Version: 2.14;  Date: 06/26/2008)
        Input Data File: C:\1\NTP_1992_MCV_Rats_M_Hill_C.(d)
        Gnuplot Plotting File:  C:\1\NTP_1992_MCV_Rats_M_Hill_C.plt
                                                  Tue Jul 13 11:58:18 2010
================================================================================

Changed SE to SD
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the response function is:

  Y[dose] = intercept + v*dose^n/(k^n + dose^n)


  Dependent variable = Mean
  Independent variable = Dose
  rho is set to 0
  Power parameter restricted to be greater than 1
  A constant variance model is fit
```

Total number of dose groups = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
alpha = 0.58804
rho = 0 Specified
intercept = 54.3
v = -5.2
n = 1.51061
k = 53.7647

Asymptotic Correlation Matrix of Parameter Estimates

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

	alpha	intercept	v	n	k
alpha	1	-1.3e-009	7.8e-008	2.1e-008	-6.3e-008
intercept	-1.3e-009	1	-0.29	-0.3	0.046
v	7.8e-008	-0.29	1	0.95	-0.96
n	2.1e-008	-0.3	0.95	1	-0.91
k	-6.3e-008	0.046	-0.96	-0.91	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
alpha	0.531088	0.118755	0.298333	0.763844
intercept	54.2845	0.259548	53.7758	54.7932
v	-7.11754	2.13185	-11.2959	-2.93919
n	1.09368	0.384682	0.339716	1.84764
k	79.7466	48.3873	-15.0909	174.584

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	8	54.3	54.3	0.56	0.729	0.0602
25	8	52.6	52.7	0.56	0.729	-0.475
48	8	51.9	51.7	1.13	0.729	0.819
97	8	50.2	50.3	0.85	0.729	-0.567
202	8	49.1	49.1	0.56	0.729	0.162

Model Descriptions for likelihoods calculated

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

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

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

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

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-6.710166	6	25.420332
A2	-3.091318	10	26.182636
A3	-6.710166	6	25.420332
fitted	-7.343466	5	24.686931
R	-46.868442	2	97.736884

Explanation of Tests

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

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	87.5542	8	<.0001
Test 2	7.2377	4	0.1238
Test 3	7.2377	4	0.1238
Test 4	1.2666	1	0.2604

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

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

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

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

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 10.9556

BMDL = 6.85376

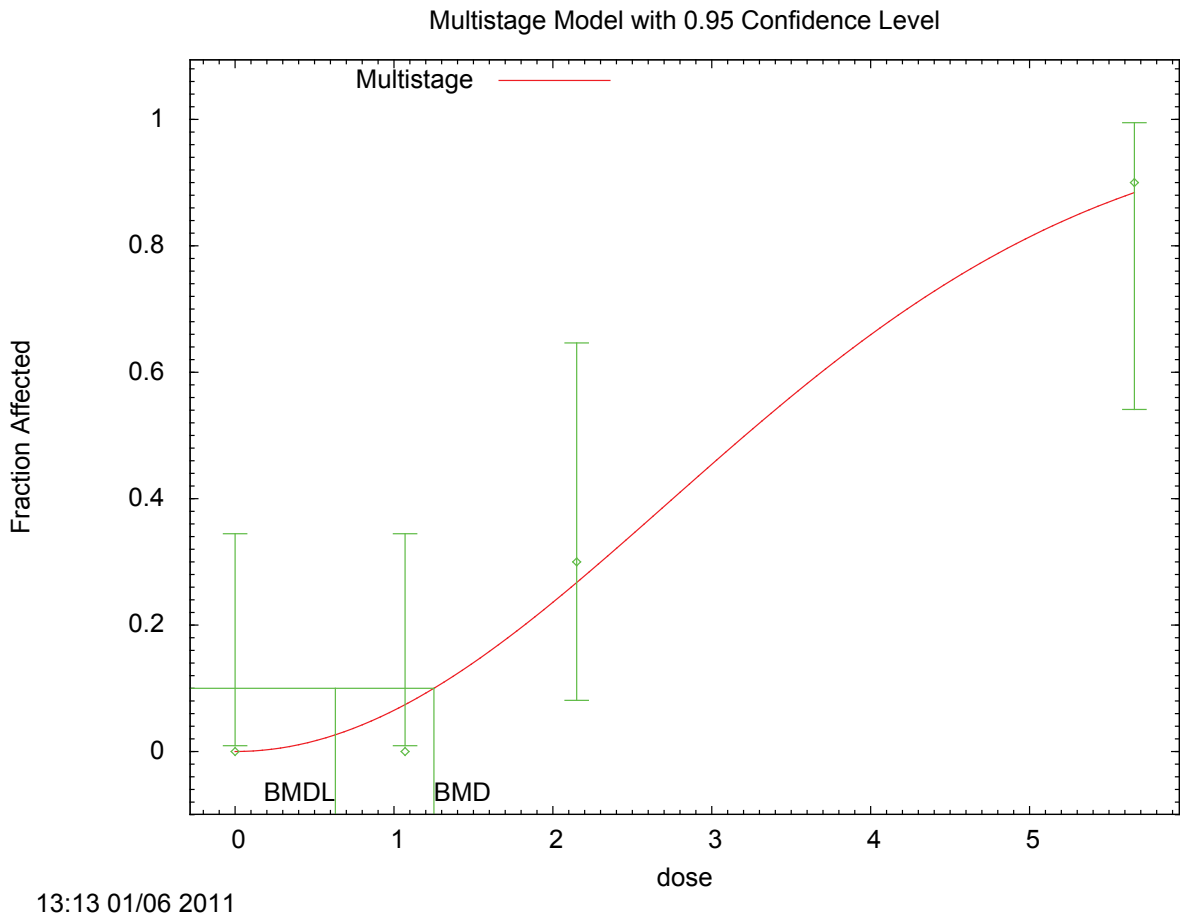

Figure C.2. Dichotomous-Multistage BMD Model for Squamous Metaplasia Data (Gamer et al., 2008c)

Text Output for Dichotomous-Multistage BMD Model for Squamous Metaplasia Data (Gamer et al., 2008c)

```
================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\DEA\mst_DEA2-Malea_dea2-mmulti.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\DEA\mst_DEA2-Malea_dea2-mmulti.plt
                                                Thu Jan 06 13:13:26 2011
================================================================

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

  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
           -beta1*dose^1-beta2*dose^2)]

  The parameter betas are restricted to be positive
```

Dependent variable = Percent
Independent variable = Conc

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

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

Default Initial Parameter Values
Background = 0
Beta(1) = 0.00396146
Beta(2) = 0.0720717

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

Beta(2)

Beta(2) 1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.0672575	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-9.35947	4			
Fitted model	-10.1692	1	1.61951	3	0.655
Reduced model	-24.4346	1	30.1502	3	<.0001

AIC: 22.3385

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0.000	10	0.000
1.0700	0.0741	0.741	0.000	10	-0.895
2.1500	0.2672	2.672	3.000	10	0.234

5.6600 0.8841 8.841 9.000 10 0.157

Chi^2 = 0.88 d.f. = 3 P-value = 0.8302

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.25161

BMDL = 0.631169

BMDU = 1.66582

Taken together, (0.631169, 1.66582) is a 90 % two-sided confidence interval for the BMD

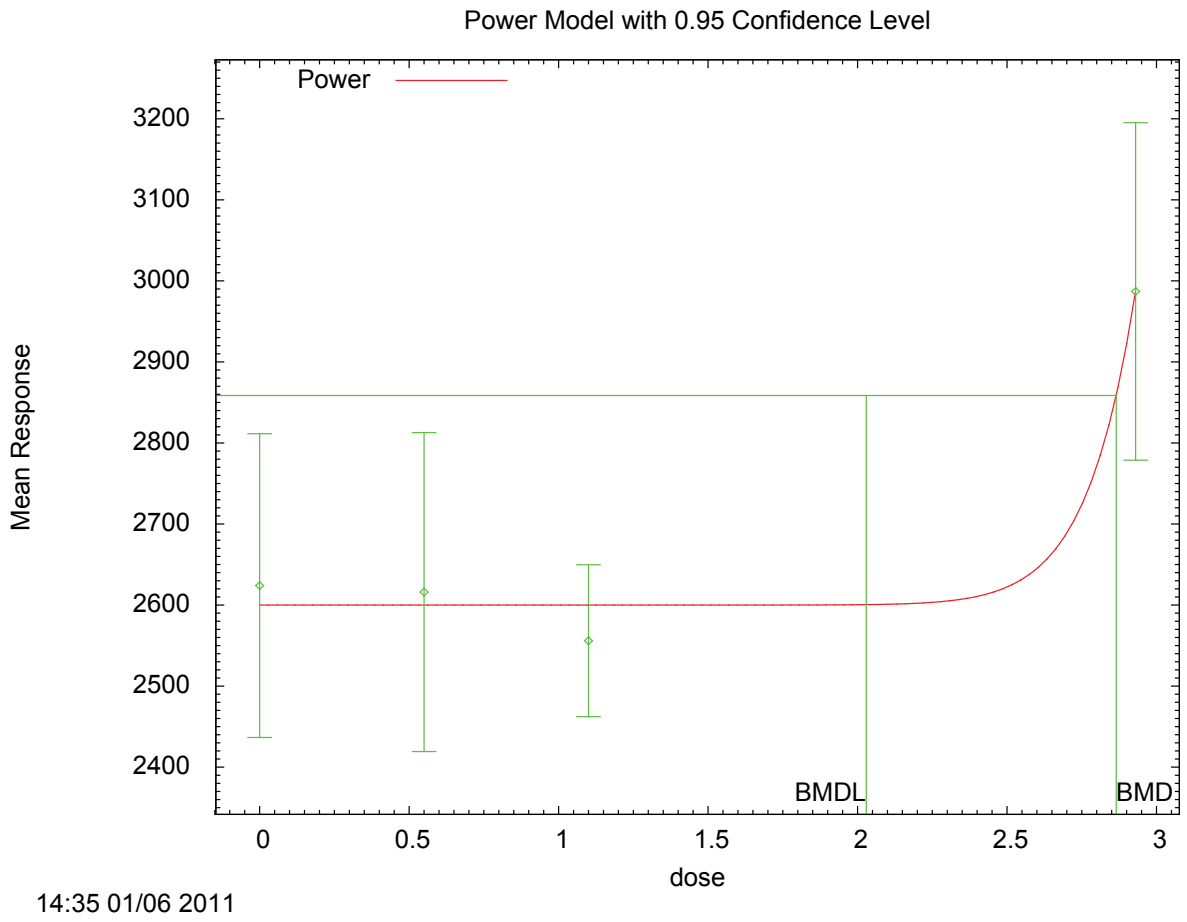

Figure C.3. Continuous Nonconstant Variance Power BMD Model for Relative Liver Weights in Female Rats Data (Gamer et al., 2008c)

Text Output for Continuous Nonconstant Variance Power BMD Model for Relative Liver Weights in Female Rats Data (Gamer et al., 2008c)

```
================================================================================
        Power Model. (Version: 2.15;  Date: 04/07/2008)
        Input Data File: C:\USEPA\BMDS21\Data\pow_dea2-fer_dea2fa-powernv.(d)
        Gnuplot Plotting File:  C:\USEPA\BMDS21\Data\pow_dea2-fer_dea2fa-powernv.plt
                                                    Thu Jan 06 14:35:58 2011
================================================================================

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

  The form of the response function is:

  Y[dose] = control + slope * dose^power


  Dependent variable = Mean
  Independent variable = Conc
```

The power is restricted to be greater than or equal to 1
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
lalpha = 11.0272
rho = 0
control = 2556
slope = 121.39
power = 1.17869

Asymptotic Correlation Matrix of Parameter Estimates

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

	lalpha	rho	control	slope
lalpha	1	-1	-0.094	0.2
rho	-1	1	0.092	-0.2
control	-0.094	0.092	1	-0.42
slope	0.2	-0.2	-0.42	1

Parameter Estimates

			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
lalpha	-13.729	29.8646	-72.2625	44.8044
rho	3.1205	3.78145	-4.291	10.532
control	2598.67	40.5586	2519.17	2678.16
slope	1.53316e-006	3.80046e-007	7.88284e-007	2.27804e-006
power	18	NA		

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

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	2.62e+003	2.6e+003	262	222	0.361
0.55	10	2.62e+003	2.6e+003	275	222	0.247
1.1	10	2.56e+003	2.6e+003	131	222	-0.607
2.93	10	2.99e+003	2.99e+003	291	276	8.17e-009

Model Descriptions for likelihoods calculated

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

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that were specified by the user

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

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-238.437661	5	486.875322
A2	-235.229152	8	486.458303
A3	-237.543402	6	487.086805
fitted	-238.306792	4	484.613584
R	-246.852506	2	497.705012

Explanation of Tests

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

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	23.2467	6	0.0007179
Test 2	6.41702	3	0.09299
Test 3	4.6285	2	0.09884
Test 4	1.52678	2	0.4661

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

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

The p-value for Test 3 is less than .1. You may want to consider a different variance model

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

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Relative risk

Confidence level = 0.95

BMD = 2.86534

BMDL = 2.02919

APPENDIX D. REFERENCES

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