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Provisional Peer-Reviewed Toxicity Values for

Nitromethane
(CASRN 75-52-5)

Superfund Health Risk Technical Support Center
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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 confidence limit
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 inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies 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 NITROMETHANE (CASRN 75-52-5)

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

Nitromethane, CAS No. 75-52-5, is a nitroparaffin. Nitromethane is primarily used in rocket and racing fuel as a gasoline additive and is also widely used as an industrial solvent. It can be produced by high-temperature, vapor-phase nitration of propane or methane using nitric acid in a free-radical reaction or by the interaction of sodium nitrite and sodium chloroacetate (HSDB, 2010). A table of physicochemical properties is provided below (see Table 1). The molecular formula for nitromethane is CH_3NO_2 (see Figure 1).

$CH_3—NO_2$

Figure 1. Nitromethane Structure

Table 1. Physicochemical Properties of Nitromethane (CASRN 75-52-5)[a]

Property (unit)	Value
Boiling point (ºC)	101.1
Melting point (ºC)	−28.5
Relative density (g/cm^3 at 20ºC)	1.1371
Vapor pressure (mmHg at 25ºC)	35.8
pH (unitless, 0.01M aqueous solution)	6.12
Solubility in water (mg/L at 25ºC)	1.11×10^5
Relative vapor density (air = 1)	2.11
Molecular weight (g/mol)	61.04

[a]HSDB (2010).

A summary of the available toxicity values for Nitromethane from U.S. EPA and other agencies/organizations is provided below (see Table 2).

Table 2. Summary of Available Toxicity Values for Nitromethane (CASRN 75-52-5)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
Noncancer				
ACGIH	8-hr TLV-TWA = 20 ppm	NA	ACGIH (2008)	NA
ATSDR	NV	NA	ATSDR	7-22-2013
Cal/EPA	NV	NA	Cal/EPA (2012)	NA
NIOSH	NV	NIOSH did submit comments to OSHA regarding its "Proposed Rule on Air Contaminants" (29 CFR 1910, Docket No. H-020) questioning whether the OSHA PEL for nitromethane was "adequate to protect workers from recognized health hazards" (NIOSH, 2011b)	NIOSH (2011a)	NA
OSHA	8-hr PEL-TWA = 100 ppm	NA	OSHA (2006)	NA
IRIS	NV	NA	U.S. EPA	7-22-2013
Drinking water	NV	HEEP declined to derive noncancer toxicity values due to inadequate data on noncancer effects and potential carcinogenic effects of the chemical	U.S. EPA (2011a)	NA
HEAST	NV	NA	U.S. EPA (2011b)	NA
CARA HEEP	NV	NA	U.S. EPA (1994, 1985)	NA
WHO	NV	NA	WHO	7-22-2013
Cancer				
IRIS	NV	NA	U.S. EPA	7-22-2013
HEAST	NV	NA	U.S. EPA (2011b)	NA
IARC	Group 2B, "*Possibly Carcinogenic to Humans"*	Based on sufficient animal carcinogenicity evidence	IARC (2000)	NA
NTP	"*Reasonably Anticipated to be a Human Carcinogen*"	In the key study that supports this classification, increased mammary gland tumors in female rats, increased benign and malignant tumors in the Harderian gland and lung of male and female mice, and liver tumors in female mice were observed (NTP, 1997).	NTP (2011)	NA

Table 2. Summary of Available Toxicity Values for Nitromethane (CASRN 75-52-5)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
Cal/EPA	NSRL = 39 µg/day Cancer Potency = 0.18 mg/kg-day[b]		Cal/EPA (2007)	NA

[a]Sources: American Conference of Governmental Industrial Hygienists (ACGIH); Agency for Toxic Substances and Disease Registry (ATSDR); California Environmental Protection Agency (Cal/EPA); National Institute for Occupational Safety and Health (NIOSH); Occupational Safety and Health Administration (OSHA); Chemical Assessments and Related Activities (CARA); Health and Environmental Effects Profile (HEEP); World Health Organization (WHO); Integrated Risk Information System (IRIS); Health Effects Assessment Summary Tables (HEAST); International Agency for Research on Cancer (IARC); National Toxicology Program (NTP).
[b]This value was derived from NTP (1997) using "Route to Route" extrapolation.

IDLH= immediately dangerous to life or health; NA = not applicable; NSRL = no significant risk level; NV = not available; PEL-TWA = permissible exposure level-time weighted average; REL-TWA = recommended exposure level-time weighted average; TLV-TWA = threshold limit value-time weighted average.

Literature searches were conducted on sources published from 1900 through June 2013, for studies relevant to the derivation of provisional toxicity values for nitromethane, CAS No. 75-52-5. 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 toxicity values: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 3 provides an overview of the relevant database for nitromethane and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. NOAELs, LOAELs, and BMDL/BMCLs are provided in HED/HEC units for comparison except that oral noncancer values are not converted to HEDs and are identified in parentheses as (Adjusted)

rather than HED/HECs. Principal studies are identified in bold. Following the table, important aspects of all the studies in the table are provided in the same order as the table. Reference can be made to details provided in Table 3. The phrase "statistical significance," used throughout the document, indicates a value of <0.05.

Table 3. Summary of Potentially Relevant Data for Nitromethane (CASRN 75-52-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-d)[a]								
Acute[c]	1/0, age 18, oral ingestion, case study, single ingestion	NR	Neurological symptoms	NDr	DU	NDr	Fernandez et al. (2008)	PR
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
2. Inhalation (mg/m^3)[a]								
Acute[c]	ND							
Short-term[d]	1/1, age 23 and 26 yr, inhalation, occupational case study,1–2 mo	25–50 (mean = 32)	Neurological symptoms	NDr	DU	NDr	Page et al. (2001)	PR
Long-term[e]	ND							
Chronic[f]	ND							
Reproductive	ND							
Carcinogenicity	ND							
Animal								
1. Oral (mg/kg-d)[a]								
Subchronic	10/0, albino rat, drinking water, 15 wk	0, 131, 280[g] (Adjusted)	Mortality, reduced body weight, and reduced water consumption	NDr	DU	131 (FEL)	Weatherby (1955)	PR
Chronic	ND							
Developmental	ND							
Reproductive	ND							

Table 3. Summary of Potentially Relevant Data for Nitromethane (CASRN 75-52-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Carcinogenicity	ND							
2. Inhalation (mg/m^3)[a]								
Short-term	5/5, F344 rat, whole body inhalation, 6 hr 12 min/d, 5 d/wk, 16 d (12 exposures)	M: 0, 5.7, 11.2, 22.1, 43.5, 86.1[h] F: 0, 4.5, 8.9, 17.7, 35.3, 69.7	Degeneration of the olfactory epithelium of the nasal turbinates[i]	M: 11.2 F: 8.9	DU	M: 22.1 F: 17.7	NTP (1997)	PR
	5/5, B6C3F$_1$ mouse, whole body inhalation, 6 hr 12 min/d, 5 d/wk, 16 d (12 exposures)	M: 0, 6.6, 13.0, 25.6, 52.1, 103.7[h] F: 0, 5.1, 10.2, 20.2, 40.9, 81.9	Degeneration of the olfactory epithelium of the nasal turbinates[i]	M: 13.0 F: 10.2	DU	M: 25.6 F: 20.2	NTP (1997)	PR
Subchronic	10/10, F344 rat, whole body inhalation, 6 hr 12 min/d, 5 d/wk, 13 wk	M: 0, 6.6, 13.9, 27.1, 53.0, 100.1[h] F: 0, 4.8, 9.7, 19.2, 38.1, 72.1	Degeneration of the olfactory epithelium of the nasal turbinates[i]	M: 13.9 F: 9.7	DU	M: 27.1 F: 19.2	NTP (1997)	PR
	10/0, Sprague-Dawley rat, whole body inhalation, 7 hr/d, 5 d/wk, 3 mo	0, 51, 388[j]	Decreased hematocrit and hemoglobin levels	51	NC[k]	388	Lewis et al. (1979)	PR
	10/10, B6C3F$_1$ mouse, whole body inhalation, 6 hr 12 min/d, 5 d/wk, 13 wk	**M: 0, 7.1, 14.1, 28.0, 55.7, 112.7[h]** **F: 0, 5.9, 12.2, 24.9, 48.0, 93.9**	**Degeneration of the olfactory epithelium and hyaline droplets in the respiratory epithelium of the nasal turbinates[i]**	**5.9 (F)**	**1.31**	**12.2 (F)**	**NTP (1997)**	**PS, PR**

Table 3. Summary of Potentially Relevant Data for Nitromethane (CASRN 75-52-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Subchronic	5/0, New Zealand white rabbit, whole body inhalation, 7 hr/d, 5 d/wk, 3 mo	0, 51, 388[j]	Decreased thyroxin levels	51	NC[g]	388	Lewis et al. (1979)	PR
Chronic	10/0, Sprague-Dawley rat, whole body inhalation, 7 hr/d, 5 d/wk, 6 mo	0, 51, 388[j]	Increased relative thyroid weight	51	NC[k]	388	Lewis et al. (1979)	PR
	50/50, F344 rat, whole body inhalation, 6 hr 12 min/d, 5 d/wk, 103 wk	0, 43, 87, 173[j]	No noncancer effects observed	173	DU	NDr	NTP (1997)	PR
	40/40, Long-Evans rat, whole body inhalation, 7 hr/d, 5 d/wk, 2 yr	0, 45.6, 89.0[l]	No noncancer effects observed	89.0	DU	NDr	Griffin et al. (1996)	PR
	50/50, B6C3F$_1$ mouse, whole body inhalation, 6 hr 12 min/d, 5 d/wk, 103 wk	**M: 0, 22.2, 44.9, 91.6[h]** **F: 0, 21.9, 43.2, 87.9**	**Increased nonneoplastic nasal lesions**	**NDr**	**1.60**	**M: 22.2** **F: 21.9**	**NTP (1997)**	**PS, PR**
	5/0, New Zealand white rabbit, whole body inhalation, 7 hr/d, 5 d/wk, 6 mo	0, 51, 388[j]	Decreased thyroxin levels	NDr	NC[k]	51	Lewis et al. (1979)	PR
Developmental	ND							
Reproductive	ND							
Carcinogenicity	**50/50, F344 rat, whole body inhalation, 6 hr 12 min/d, 5 d/wk, 103 wk**	**0, 43, 87, 173[j]**	**Increased incidence of mammary gland tumors**	**NA**	**NA**	**NA**	**NTP (1997)**	**PS, PR**

Table 3. Summary of Potentially Relevant Data for Nitromethane (CASRN 75-52-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Carcinogenicity	40/40, Long-Evans rat, whole body inhalation, 7 hr/d, 5 d/wk, 2 yr	0, 45.6, 89.0[l]	No cancer effects observed	NA	NA	NA	Griffin et al. (1996b)	PR
	50/50, B6C3F$_1$ mouse, whole body inhalation, 6 hr 12 min/d, 5 d/wk, 103 wk	0, 87, 173, 346[j]	Increased incidence of Harderian gland and liver tumors; BMD based Harderian gland adenomas or carcinomas in males	NA	NA	NA	NTP (1997)	PR

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer and carcinogenic effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous exposure.
[b]Notes: IRIS = utilized by IRIS, date of last update; PS = principal study; PR = peer reviewed; NPR = not peer reviewed; NA = not applicable.
[c]Acute = Exposure for 24 hours or less (U.S. EPA, 2002).
[d]Short-term = Repeated exposure for >24 h ≤30 d (U.S. EPA, 2002).
[e]Long-term = Repeated exposure for >30 d ≤10% lifespan (based on 70 years typical lifespan) (U.S. EPA, 2002).
[f]Chronic = Repeated exposure for ≥10% lifespan (U.S. EPA, 2002).
[g]Daily doses were estimated from digitizing the data in the figure of weekly intakes provided in the study report.
[h]HEC_{RESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × regional gas dose ratio.
[i]Extra-respiratory effects were also observed, but the respiratory effects provided the lowest NOAEL/LOAEL.
[j]HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood:gas partition coefficient.
[k]BMD was not conducted on the data because the effects occurred at concentrations several fold higher than the critical effect in the principal study.
[l]HEC_{EXRESP} = mg/m^3 × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood:gas partition coefficient.

DU = data unsuitable; NA = not applicable; NC = not conducted; ND = no data; NDr = not determinable; NR = not reported.

HUMAN STUDIES

Oral Exposures

The effects of oral exposure of humans to nitromethane have been evaluated in one case study of an acute exposure (Fernandez et al., 2008). An 18-year-old male ingested an undetermined amount of nitromethane fuel. He had generalized tonic-clonic seizures that progressed to partial motor status epilepticus and was also hypertensive. A neurological exam showed him to have mild left dysmetria in finger-to-nose testing, low frequency intention tremor, broad-based gait, and inability to tandem-walk. An MRI revealed bilateral and symmetric lesions in cerebellar white matter, tonsils, uvula, and colliculi. Initial therapy included valproic acid, β-blockers, and clonidine to treat the symptoms. Valproic acid treatment continued. Eight months after exposure there were no abnormalities observed during a clinical exam or in an MRI. There were no other oral studies in humans identified.

Inhalation Exposures

The effects of subchronic inhalation exposure of humans to nitromethane have been evaluated in two case reports on individuals exposed for 1 or 2 months (Page et al., 2001). An investigation was initiated due to severe peripheral neuropathy in two workers in a headlight subassembly plant. OSHA was called in to conduct an industrial hygiene inspection at the plant. In the plant, nitromethane was used to clean off excess glue on the headlights. Nitromethane was sprayed on, and because it was wiped off with a rag without the use of gloves, dermal exposure occurred as well as inhalation exposure. However, in a separate study, Coulston International Inc. (1990) found that very little nitromethane was absorbed dermally in rhesus monkeys. As part of the investigation by Page et al. (2001), the air was sampled for nitromethane and ethyl cyanoacrylate over a 2-day period. Nitromethane was measured in the personal breathing zone of four workers cleaning headlights. Nitromethane levels ranged from 10–20 ppm (25–50 mg/m^3) with a mean of 12.75 ppm (32 mg/m^3) as the 8-hour TWA. A 26-year-old woman who cleaned the headlights with nitromethane began to note weakness in her hands, legs, and feet within a month of beginning the job. She stopped working but felt worse 2 weeks later and was admitted to the hospital. A neurological exam indicated that gastroscoleus and brachioradialis reflexes were absent with weakness more severe distally and in the lower extremities. An MRI did not reveal any abnormalities in the spinal cord. Laboratory tests did not find any abnormalities, but serum immunoelectrophoresis showed an increased gamma component, and a lumbar puncture showed elevated protein levels with a normal cell count. She was eventually diagnosed with severe peripheral neuropathy and had only slight improvement within 8 months. Four to five months later, a 23-year-old male began complaining about foot numbness within 1.5 weeks of beginning work, which progressed over the next few weeks to pain and swelling in both legs and feet. After about 6 weeks of employment as a headlight cleaner, the man was admitted to the hospital. Peripheral neuropathy of the lower extremities with normal testing on the upper extremities was observed. The individual demonstrated diminished lower extremity reflexes, slightly decreased muscle strength on dorsiflexon of both feet, and decreased sensation to pinprick up to the middle of the shin. Laboratory tests for this individual were unremarkable, but symptoms persisted. Follow-up electrodiagnostic studies found progressive denervation and severe axonal peripheral neuropathy. This individual had significant, but not complete, improvement. No other inhalation studies in humans were identified.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure in animals to nitromethane have been evaluated in one subchronic study (Weatherby, 1955).

Subchronic Studies

Weatherby (1955)

Weatherby (1955) exposed young male albino rats (10/treatment group) to 0, 0.1%, 0.25%, 0.5%, 1%, or 2% nitromethane (purity not reported) via drinking water for 15 weeks. There is no indication that the dose formulations were measured for homogeneity, stability, or concentration. It was stated that due to the slight solubility of nitromethane, emulsification with methylcellulose was used. During the first week, animals did not drink the water with concentrations ≥0.5%, and these groups were discontinued. However, several of the exposed animals did die during this time (number not specified), and survivors were sacrificed for microscopic examination of the tissues. The failure in these groups was attributed to refusal of the water. Fluid intake was recorded daily, and the intake of nitromethane was calculated. Intake levels were apparently measured on a per-cage basis, but the study report did not specify how many rats were maintained per cage. The weekly intakes (mg nitromethane/kg-week) were presented in the study report as a figure only and have been estimated by digitizing the data. The weekly intakes divided by seven provide estimated daily intakes of 131 mg/kg-day for the 0.1% group and 280 mg/kg-day for the 0.25% group. Body weights were measured weekly. Body weight and body-weight gain were lower than that of control animals in both nitromethane groups, but this observation did not appear to dose related and may have been a function of reduced fluid intake. Animals were stated to be in moderately good health at study termination. Four of the 131-mg/kg-day animals and three of the 280-mg/kg-day animals died during treatment. Due to destruction by their cage mates, the dead animals were not examined. At study termination, all survivors were sacrificed, and tissues (heart, lungs, liver, spleen, kidney, testes, adrenal gland, and small intestines) were examined microscopically. In the 131-mg/kg-day group, two of the six survivors had large hepatic cells with prominent nuclei. In the 280-mg/kg-day group, two of the seven survivors had Malpighian corpuscles that appeared more prominent than the normal spleens, and six of the survivors had a granular appearance in the cytoplasm of the hepatic cells, less deeply stained hepatocytes, more prominent nuclei, and lymphocytes in the periportal region. One of the 10 surviving controls had large hepatic cells with prominent nuclei. No NOAEL or LOAEL can be determined because the lowest dose was a frank effect level (FEL) due to mortality.

Chronic Studies

There is no suitable information to provide in this regard.

Developmental Studies

There is no suitable information to provide in this regard.

Reproductive Studies

There is no suitable information to provide in this regard.

Carcinogenicity Studies

There is no suitable information to provide in this regard.

Inhalation Exposures

The effects of inhalation exposure of animals to nitromethane have been evaluated in a short-term study in both rats and mice (NTP 1997), two subchronic studies in both rats and mice (NTP, 1997; Lewis, 1979), chronic studies in rats and mice (NTP, 1997; Lewis, 1979) and rats only (Griffin, 1996), and carcinogenicity studies in rats and mice (NTP, 1997) and rats only (Griffin, 1996). All the reports provided information on multiple studies and are individually discussed in this section.

Short-Term Studies

NTP (1997)

In the various substudies conducted by NTP (1997) summarized below, a small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that nitromethane vapor, and not aerosol, was produced. The purity of the chemical was analyzed by gas chromatography and carefully monitored during exposures (details are provided on pages 21-23 of the study report).

For the short-term study, individually housed F344 rats (5/sex/treatment group) were administered nitromethane (purity ≥98%) at concentrations of 0; 94; 188; 375; 750; or 1,500 ppm via whole body inhalation for 6 hours and 12 minutes (12 minutes was the time it took to achieve 90% target concentration) a day, 5 days a week, for 16 days (total of 12 exposures). Chamber concentrations were routinely checked over the course of exposure. Animals were observed twice a day for clinical signs of toxicity. Animals were weighed at study initiation and on Days 8 and 16. At study termination, animals were necropsied, and the heart, right kidney, liver, lungs, right testis, thymus, and thyroid glands were weighed. Histopathology was conducted on respiratory tissues, brain, and sciatic nerve. Typical NTP statistical methods were applied and were appropriate for the data.

All rats survived until study termination. Clinical signs were observed in the high-dose group only and included increased preening, rapid breathing, hyperactivity early in the study, and hypoactivity and loss of coordination near the end of the study in all animals of both sexes. Although there were no statistically significant ($p < 0.05$) effects on body weight in any of the groups, high-dose males had a significantly ($p < 0.05$) lower body-weight gain compared with the controls (see Table B.1). Necropsy body weight was significantly reduced in the high-dose males (see Table B.2). Absolute and relative liver weights were significantly increased and >10% different from controls in female rats at concentrations ≥750 ppm. Relative liver weights were significantly increased in all male treatment groups but were only >10% different from controls at concentrations of 375 and 1,500 ppm (see Table B.2). Relative kidney weight was significantly increased by >10% in high-dose males and females. In all males and all but one female administered ≥375 ppm, there was degeneration of the olfactory epithelium of the nasal turbinates with minimal to mild severity and degeneration of the sciatic nerve with severity (minimal to moderate) increasing with exposure concentration (see Table B.3). Because respiratory and extra-respiratory effects were observed, human equivalent concentrations (HECs) are calculated for both effects. The average of initial and final body weight is used in the calculation of HECs for respiratory effects. The HECs for respiratory effects are 5.7, 11.2, 22.1, 43.5, and 86.1 mg/m^3 in males, respectively, and 4.5, 8.9, 17.7, 35.3, and 69.7 mg/m^3 in females, respectively, after adjusting for duration and multiplying by the regional gas dose ratio (RGDR) for extra-thoracic effects. The RGDR is the ratio of the minute volumes to the applicable surface areas of the lung in the two species respectively (see U.S. EPA 1994b, pages 4-44 through 4-64).

This ratio is used to adjust the observed gas exposure level for interspecies dosimetric differences. The NOAEL for respiratory effects is 11.2 mg/m^3 in males and 8.9 mg/m^3 in females. The LOAEL for respiratory effects is 22.1 mg/m^3 in males and 17.7 mg/m^3 in females based on degeneration of the olfactory epithelium in nasal turbinates. HECs for extra-respiratory effects calculated by adjusting for duration and using the default blood:gas partition coefficient of 1 since chemical-specific information is unavailable (see U.S.EPA 1994b). The corresponding values are 46, 91, 181, 363, and 726 mg/m^3 in both sexes. The NOAEL for systemic effects is 91 mg/m^3, and the LOAEL is 181 mg/m^3 based on degeneration of the sciatic nerve in both sexes.

NTP (1997)

Individually housed male and female B6C3F$_1$ mice (5/sex/treatment group) were administered nitromethane (purity ≥98%) at concentrations of 0; 94; 188; 375; 750; or 1,500 ppm via whole body inhalation for 6 hours and 12 minutes a day, 5 days a week, for 16 days (total of 12 exposures). Chamber concentrations were routinely checked over the course of exposure. Animals were observed twice a day for clinical signs of toxicity. Animals were weighed at study initiation and on Days 8 and 16. At study termination, animals were necropsied, and the heart, right kidney, liver, lungs, right testis, thymus, and thyroid glands were weighed. Histopathology was conducted on respiratory tissues, brain, and sciatic nerve. Typical NTP statistical methods were applied and were appropriate for the data.

All mice survived until study termination. Clinical signs were observed in the high-dose group only and included hypoactivity and tachypnea of both sexes at the end of the study. There were no treatment-related effects on body weight or gross pathology. Absolute liver weight was >10% different from controls at all concentrations in both sexes, but relative liver weights were statistically significant and >10% different from controls at concentrations ≥375 ppm in males and ≥188 ppm in females (see Table B.4). All males and females administered ≥375 ppm had degeneration of the olfactory epithelium of the nasal turbinates with minimal to mild severity. Because respiratory and extra-respiratory effects were observed, HECs are calculated for both effects. The average of initial and final body weight is used for the calculation of HECs for respiratory effects. HECs for respiratory effects are 6.6, 13.0, 25.6, 52.1, and 103.7 mg/m^3 in males, respectively, and 5.1, 10.2, 20.2, 40.9, and 81.9 mg/m^3 in females, respectively, after adjusting for duration and multiplying by the RGDR for extra-thoracic effects. The NOAEL for respiratory effects is 13.0 mg/m^3 in males and 10.2 mg/m^3 in females. The LOAEL for respiratory effects is 25.6 mg/m^3 in males and 20.2 mg/m^3 in females based on degeneration of the olfactory epithelium in nasal turbinates. HECs for extra-respiratory effects calculated by adjusting for duration and using the default blood:gas partition coefficient of 1 (chemical-specific information was unavailable) are 46, 91, 181, 363, and 726 mg/m^3 in both sexes. The NOAEL for systemic effects is 46 mg/m^3, and the LOAEL is 91 mg/m^3 based on increased relative liver weights in females.

Subchronic Studies

NTP (1997)

Individually housed male and female F344 rats (10/sex/treatment group) were administered nitromethane (purity ≥98%) at concentrations of 0; 94; 188; 375; 750; or 1,500 ppm via whole body inhalation for 6 hours and 12 minutes a day, 5 days a week, for 13 weeks. Chamber concentrations were routinely checked over the course of exposure. Animals were observed twice a day for clinical signs of toxicity. Animals were weighed at study

initiation, weekly, and at study termination. Blood was collected on Days 3 and 23 and at study termination for hematology (hematocrit, hemoglobin, erythrocyte counts, nucleated erythrocyte counts, mean cell volume [MCV], mean cell hemoglobin [MCH], mean cell hemoglobin concentration [MCHC], platelet counts, total leukocyte count and differentials, and methemoglobin) and clinical chemistry (blood urea nitrogen [BUN], creatinine, total protein, albumin, globulin, alanine aminotransferase [ALT], alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, bile acid, thyroid-stimulating hormone [TSH], triiodothyronine, and total and free thyroxine concentrations). At study termination, animals were necropsied, and the heart, right kidney, liver, lungs, right testis, thymus, and thyroid glands were weighed. Complete histopathology was conducted on control and high-dose animals. In addition, the following tissues were examined in the lower concentrations until a no-effect level (NOEL) was reached: bone marrow, lung, and nose in both sexes; and cecum, larynx, and testis in male rats. Sperm samples were collected from the 0; 375-; 750-; and 1,500-ppm groups at study termination and evaluated for sperm count and motility. The left cauda, epididymis, and testis were weighed. Vaginal samples were collected for seven consecutive days before study termination and evaluated for the relative frequency of estrous stages and for estrous cycle length. Neurobehavioral tests (forelimb and hindlimb grip strength, tail flick latency, and startle response) were conducted during Week 11. Typical NTP statistical methods were applied and were appropriate for the data.

All rats survived until study termination. Clinical signs included hindlimb paralysis in all high-dose males and females beginning on Day 21, and one male and four females in the 750-ppm group beginning on Day 63. There was a statistically significant decrease in terminal body weight and body-weight gain in high-dose males (see Table B.5). There were several changes in hematology in all treatment groups (see Table B.6). These animals developed microcytic responsive anemia as indicated by mild-to-moderate decreases in hematocrit and hemoglobin and minimal-to-moderate decreases in mean cell volume (see Table B.6). MCH levels were also consistently decreased. The results were dose dependent but were most prominent with concentrations ≥375 ppm. Although the increases in MCHC were less than 5% from the control, the change was consistent. The study authors also reported several changes in erythrocyte morphology related to damage and anemia (e.g., Heinz bodies, schistocytes, polychromasia), but data were not provided. Hyperplasia in the bone marrow was observed at concentrations of 750 and 1,500 ppm, supporting the hematology findings. There were also consistent increases in platelets and methemoglobin mainly at concentrations of 750 and 1,500 ppm. Although there were changes in thyroid hormone levels on Day 23, this was a transient effect in both males and females. Thyroid weight was increased in 1,500-ppm males only, but only the relative weight was statistically significant, which is likely an effect of the lower body weight in this group. There were no other biologically significant changes in organ weights. At concentrations ≥375 ppm, there was degeneration of the olfactory epithelium of the nasal turbinates with minimal-to-mild severity and degeneration of the sciatic nerve and spinal cord with severity increasing with exposure concentration (see Table B.7). Grip strength was only significantly reduced in high-dose males (hind and forelimb) and females (hindlimb) (see Table B.8). There was a statistically significant decrease in absolute left cauda, epididymis, and testis weight in high-dose males. Although this finding may be due to reduced body weight, there also was a 15% decrease in sperm concentration, and sperm motility was significantly decreased with concentrations of 750 and 1,500 ppm (see Table B.9). There were no treatment-related changes in estrous cycle length or stages. Because respiratory and extra-respiratory effects were observed, HECs are calculated for both effects. Because only

initial and final body weights were provided, the average is used to estimate average body weights for the calculation of HECs for respiratory effects. The HECs for respiratory effects are 6.6, 13.9, 27.1, 53.0, and 100.1 mg/m^3 in males, respectively, and 4.8, 9.7, 19.2, 38.1, and 72.1 mg/m^3 in females, respectively, after adjusting for duration and multiplying by the RGDR for extra-thoracic effects. HECs for extra-respiratory effects calculated by adjusting for duration and using the default blood:gas partition coefficient of 1 are 43, 87, 173, 346, and 691 mg/m^3 in both sexes. The NOAEL is 188 ppm, and the LOAEL is 375 ppm based on anemia accompanied by changes in the bone marrow and histopathology of the nasal turbinates, sciatic nerve, and spinal cord. Because the respiratory effects relay a lower HEC value, the study NOAEL is 13.9 mg/m^3 in males and 9.7 mg/m^3 in females, and the LOAEL is 27.1 mg/m^3 in males and 19.2 mg/m^3 in females.

Lewis et al. (1979)

Male Sprague-Dawley rats (10/treatment group) were administered nitromethane (96.5% pure with 1.5% nitroethane and 1.4% 2-nitropropane) at analytical concentrations of 0, 98 ± 5, or 745 ± 34 ppm via whole body inhalation, 7 hours a day, 5 days a week, for 3 months (Lewis et al., 1979a). While Lewis et al. (1979) provided a peer-reviewed publication of the data, the proprietary data were also available for review (Huntingdon Research Center, 1989). Additional groups of 10 animals/concentration group were sacrificed at 2 days, 10 days, and 1 month. Animals were housed in groups of 10 in wire mess stainless-steel cages, which were part of the exposure chamber. Chamber concentrations were measured hourly and recorded twice a day. Animals were observed daily for overt signs of toxicity. Body weights were obtained at regular intervals. At sacrifice, blood was collected for hematology (erythrocyte counts [RBC], hematocrit, hemoglobin, prothrombin time, and methemoglobin) and clinical chemistry (ALT, ornithine carbamyl transferase [OCT], and thyroxin). Animals were necropsied, and select organs (brain, liver, kidneys, lungs, and thyroid) were weighed. Tissue samples were obtained from the brain and lungs. The samples were weighed, dried, and weighed again to determine the percent of water. Adrenals, bronchi, cerebellum, cerebral hemispheres, eyes, kidneys, liver, lung, spleen, thyroid, and trachea were examined histologically. Appropriate statistical methods (Bartlett's test for homogeneity of variance; one-way analysis of variance followed by Student's *t*-test) were conducted on the data.

Not all the data were provided in Lewis et al. (1979). Data in the Huntingdon Research Center (1989) report were not provided in any sort of order, were hard to find (tables were not in order), and, in some cases, were not reported. Both sources were used for evaluation. There were no clinical signs of toxicity noted and no treatment-related effects on mortality. There was no difference in body weight between the low-dose group and controls. However, high-dose rats were stated to have a slower weight gain that was statistically significant from the control beginning around Week 8 (except during Week 13). Body-weight data were only provided in a figure (even in the proprietary data), but the body weights do not appear to differ by more than 10% at any time point during the 3 months. There was a statistically significant decrease in hematocrit and hemoglobin levels in the high-dose group that began after 10 days of treatment (see Table B.10). There were no treatment-related changes in clinical chemistry. Additionally, there were no treatment-related changes in organ weights, lung or brain edema, gross pathology, or organ histopathology. Based on the absence of respiratory toxicity noted, the NOAEL and LOAEL are selected based on extra-respiratory effects. The HECs for extra-respiratory effects adjusted for duration and a blood:gas partition coefficient of 1 are 51 and 388 mg/m^3,

respectively. Therefore, the NOAEL is 51 mg/m^3, and the LOAEL is 388 mg/m^3 based on consistent decreases in hematocrit and hemoglobin levels.

NTP (1997)

The 13-week component of the peer-reviewed mouse study by NTP (1997) is selected as the principal study for the derivation of the subchronic p-RfC. Individually housed male and female B6C3F$_1$ mice (10/sex/treatment group) were administered nitromethane (purity ≥98%) at concentrations of 0; 94; 188; 375; 750; or 1,500 ppm via whole body inhalation for 6 hours and 12 minutes a day, 5 days a week, for 13 weeks. Chamber concentrations were routinely checked over the course of exposure. Animals were observed twice a day for clinical signs of toxicity. Animals were weighed at study initiation, weekly, and at study termination. At study termination, animals were necropsied, and the heart, right kidney, liver, lungs, right testis, and thymus glands were weighed. Complete histopathology was conducted on control and high-dose animals. In addition, tissues of the nose and spleen in both sexes were examined in the lower concentrations until a NOEL was reached. Sperm samples were collected from the 0-; 375-; 750-; and 1,500-ppm groups at study termination and evaluated for sperm count and motility. The left cauda, epididymis, and testis were weighed. Vaginal samples were collected for seven consecutive days before study termination and evaluated for the relative frequency of estrous stages and for estrous cycle length. Typical NTP statistical methods were applied and were appropriate for the data.

All mice survived until study termination. There were no treatment-related clinical signs or changes in body weight. There were statistically significant increases in the absolute and/or relative kidney weight in all treatment groups except in low-dose females (see Table B.11). Although the relative kidney weights in exposed males were >10% relative to controls at all concentrations tested, relative kidney weight changes were not dose dependent and were only >10% in females at the highest concentration tested. Relative liver weights were also significantly increased in males at concentrations ≥375 ppm. However, this response was not dose dependent and was >10% only at concentrations of 750 and 1,500 ppm. Liver weights were unaffected in female mice at any dose. There were no treatment-related changes in male reproductive tissue weight or in sperm concentration, but there was a statistically significant decrease in sperm motility at all concentrations examined (i.e., ≥375 ppm) (see Table B.12). There was a dose-related increase in estrous cycle length at all concentrations examined (see Table B.12). At concentrations ≥375 ppm, there was degeneration of the olfactory epithelium of the nasal turbinates with minimal to moderate severity and hyaline droplets in the respiratory epithelium in all mice (see Table B.13). Female mice also had a statistically significant increase in the incidence of these lesions at 188 ppm. There was a significant increase in extramedullary hematopoiesis in the spleens of high-dose males and females (see Table B.13). Although respiratory and extra-respiratory effects were observed, the NOAEL and LOAEL are based on respiratory effects because they occurred at lower concentrations. Because only initial and final body weights were provided, the average is used to calculate body weights for the calculation of HECs for respiratory effects. The HECs for respiratory effects are 7.1, 14.1, 28.0, 55.7, and 112.7 mg/m^3 in males, respectively, and 5.9, 12.2, 24.9, 48.0, and 93.9 mg/m^3 in females, respectively, after adjusting for duration and multiplying by the RGDR for extra-thoracic effects. The NOAEL is 5.9 mg/m^3 (94 ppm), and the LOAEL is 12.2 mg/m^3 (188 ppm) based on increased histopathology of the nasal turbinates in female mice.

Lewis et al. (1979)

Male New Zealand white rabbits (5/treatment group) were administered nitromethane (96.5% pure with 1.5% nitroethane and 1.4% 2-nitropropane) at analytical concentrations of 0, 98 ± 5, or 745 ± 34 ppm via whole body inhalation, 7 hours a day, 5 days a week, for 3 months (Lewis et al., 1979b). While Lewis et al. (1979) provides a peer-reviewed publication of the data, the proprietary data were also available for review (Huntingdon Research Center, 1989). An additional group of 5 animals/concentration group was sacrificed after 1 month of treatment. Animals were housed individually in wire mess stainless steel cages, which was part of the exposure chamber. Chamber concentrations were measured hourly and recorded twice a day. Animals were observed daily for overt signs of toxicity. Body weights were obtained at regular intervals. At sacrifice, blood was collected for hematology (RBC, hematocrit, hemoglobin, prothrombin time, and methemoglobin) and clinical chemistry (ALT, OCT, and thyroxin). Animals were necropsied, and select organs (brain, liver, kidneys, lungs, and thyroid) were weighed. Tissue samples were obtained from the brain and lungs. The samples were weighed, dried, and weighed again to determine the percent of water. Adrenals, bronchi, cerebellum, cerebral hemispheres, eyes, kidneys, liver, lung, spleen, thyroid, and trachea were examined histologically. A Kruskal-Wallis one-way analysis of variance followed by a Mann-Whitney U test was used on the data due to the small number of animals used.

Not all the data were provided in Lewis et al. (1979). Data in the Huntingdon Research Center (1989) report were not provided in any sort of order, were hard to find (tables were not in order), and, in some cases, were not reported. There were no clinical signs of toxicity noted and no treatment-related effects on mortality or body weight. There was a statistically significant increase in methemoglobin in high-dose rabbits at the 3-month time point only, and a statistically significant decrease in hemoglobin in the high-dose rabbits at the 1-month time point only. There were increases in OCT at both 1 and 3 months (see Table B.14); however, this was not noted at 6 months (see chronic studies below). Thyroxin levels were lower than the control values at both 1 and 3 months but only achieved statistical significance in the high-dose group at 1 month (see Table B.14). Lungs of rabbits at 1 month had focal areas of moderate-to-moderately severe hemorrhage and congestion of the alveolar and alveolar duct walls. This was not stated to occur at 3 months. There were no other treatment-related changes in organ weights, lung or brain edema, gross pathology, or organ histopathology. Based on the absence of respiratory toxicity noted, the NOAEL and LOAEL are selected based on extra-respiratory effects. The HECs for extra-respiratory effects adjusted for duration and a blood:gas partition coefficient of 1 are 51 and 388 mg/m^3, respectively. Therefore, the NOAEL is 51 mg/m^3, and the LOAEL is 388 mg/m^3 based on consistent decreases in thyroxin levels.

Chronic Studies

Lewis et al. (1979)

Male Sprague-Dawley rats (10/treatment group) were administered nitromethane (96.5% pure with 1.5% nitroethane and 1.4% 2-nitropropane) at analytical concentrations of 0, 98 ± 5, or 745 ± 34 ppm via whole body inhalation, 7 hours a day, 5 days a week, for 6 months (Lewis et al., 1979c). While Lewis et al. (1979) provides a peer-reviewed publication of the data, the proprietary data were also available for review (Huntingdon Research Center, 1989). This study was conducted in conjunction with the 3-month subchronic study discussed above, and materials and methods were the same as those previously detailed.

There were no treatment-related effects on mortality. There was no difference in body weight between the low-dose group and the controls. High-dose rats had a slower weight gain, with body weights stated to be statistically significantly different from the control beginning around Week 8 (except during Week 13), but by study termination, body weight was similar to the controls according to the figure in the study report. There was a statistically significant decrease in hematocrit and hemoglobin levels in the high-dose group (see Table B.10). There were no treatment-related changes in clinical chemistry and no treatment-related changes in lung or brain edema, gross pathology, or organ histopathology. The only change in organ weight was a statistically significant increase in absolute and relative thyroid weight in the high-dose group that was dose related (see Table B.15). Based on the absence of respiratory toxicity noted, the NOAEL and LOAEL are selected based on extra-respiratory effects. The HECs for extra-respiratory effects adjusted for duration and a blood:gas partition coefficient of 1 are 51 and 388 mg/m^3, respectively. Therefore, the NOAEL is 51 mg/m^3, and the LOAEL is 388 mg/m^3 based on an increase in relative thyroid weights.

NTP (1997)

Individually housed male and female F344 rats (50/sex/treatment group) were administered nitromethane (purity ≥98%) at concentrations of 0, 94, 188, or 375 ppm via whole body inhalation for 6 hours and 12 minutes a day, 5 days a week, for 103 weeks. Chamber concentrations were routinely checked over the course of exposure. Animals were observed twice a day for clinical signs of toxicity and weighed at study initiation, weekly through Week 12, monthly from Week 15 through Week 91, then every 2 weeks until study termination, and at study termination. At study termination, animals were necropsied. Complete histopathology was conducted on all animals except that spinal cord and sciatic nerve were only examined in control and high-dose animals (15/sex). Typical NTP statistical methods were applied and were appropriate for the data.

There was no treatment-related effect on mortality. Besides tumor masses, there were no clinical signs observed. There were no statistically significant changes in body weight compared with the controls. However, the study authors noted that the high-dose group had a slightly higher body weight than the control beginning around Week 23. The differences were not statistically significant nor did they exceed a 10% difference from controls. The only noncancer effect observed in rats was a slight increase in severity of the nephropathy that occurred in all male rats (2.8, 2.9, 3.1, and 3.2 at 0, 94, 188, and 375 ppm, respectively). Based on the absence of significant noncancer effects, the NOAEL and LOAEL are selected based on extra-respiratory effects. The HECs for extra-respiratory effects adjusted for duration and a blood:gas partition coefficient of 1 are 43, 87, and 173 mg/m^3, respectively. Therefore, the NOAEL is 173 mg/m^3, the highest concentration tested.

Griffin et al. (1996)

Male and female Long-Evans rats (40/sex/treatment group) were administered nitromethane (96.26% pure with 2.79% nitroethane and 0.62% 2-nitropropane) at concentrations of 0, 100, or 200 ppm via whole body inhalation, 7 hours a day, 5 days a week, for 2 years (Griffin et al., 1996). While Griffin et al. (1996) provided a peer-reviewed publication of the study, the proprietary data were also available for review (Coulston International Inc., 1990). Animals were individually housed in stainless-steel cages except during exposure periods when they were placed in exposure chambers. Chamber concentrations were measured 3–4 times per day, with average analytical results of 99.5 ppm (stated by the study authors to be equivalent to

219 mg/m^3) and 199.3 ppm (stated by the study authors to be equivalent to 427 mg/m^3). Animals were observed daily for overt signs of toxicity. Body weights were obtained weekly for the first 6 months and every 2 weeks thereafter. At terminal sacrifice, blood was collected from 10 rats/sex/treatment group for hematology (RBC, leukocyte counts [WBC], MCV, hematocrit, hemoglobin, and platelet counts) and serum clinical chemistry (aspartate aminotransferase [AST], ALT, bilirubin, total protein, BUN, creatinine, sodium, and potassium). Animals were necropsied, and select organs (brain, liver, kidneys, lungs, and heart) were weighed. Thirty-three different tissues/organs were examined histologically in both sexes of rat. Appropriate statistical methods were conducted on the data.

There were no clinical signs of toxicity noted. There were no treatment-related effects on mortality. There were no treatment-related changes in body weight in male rats. Although female rats in both treatment groups had statistically significant lower body weights compared to the controls during the second half of the study, the results were not dose dependent and did not exceed a 10% difference from the control. There were no treatment-related effects on hematology. The only change noted in clinical chemistry was an increase in creatinine in the 200-ppm dose group. However, the increase was associated with the method used (i.e., Jaffe reaction) as nitromethane in the plasma has been found to increase the reaction (De Leacy et al., 1989). There were no treatment-related changes in organ weights, gross pathology, or organ histopathology. Due to the absence of toxicity, the NOAEL and LOAEL are selected based on extra-respiratory effects. The HECs for extra-respiratory effects adjusted for duration and a blood:gas partition coefficient of 1 are 45.6 and 89.0 mg/m^3, respectively. Therefore, the NOAEL is 89.0 mg/m^3, the highest concentration tested.

NTP (1997)

The 2-year component of the peer-reviewed mouse study by NTP (1997) is selected as the principal study for the derivation of the chronic p-RfC. Individually housed male and female B6C3F$_1$ mice (50/sex/treatment group) were administered nitromethane (purity ≥98%) at concentrations of 0, 188, 375, or 750 ppm via whole body inhalation for 6 hours and 12 minutes a day, 5 days a week, for 103 weeks. Chamber concentrations were routinely checked over the course of exposure. Animals were observed twice a day for clinical signs of toxicity. Animals were weighed at study initiation, weekly through Week 12, monthly from Week 15 through Week 91, then every 2 weeks until study termination, and at study termination. At study termination, animals were necropsied. Complete histopathology was conducted on all animals except that spinal cord and sciatic nerve were not examined. Typical NTP statistical methods were applied and were appropriate for the data.

There was no treatment-related effect on mortality. Clinical signs observed included swelling around the eyes and exophthalmos. This was stated to be consistent with Harderian gland neoplasms, which occurred at a greater incidence in treated animals (see carcinogenicity studies below). There were no statistically significant changes in body weight compared with the controls. There were increases in liver lesions in female mice and nasal lesions in both sexes (see Table B.16). The HECs for respiratory effects are 22.2, 44.9, and 91.6 mg/m^3 in males, respectively, and 21.9, 43.2, and 87.9 mg/m^3 in females, respectively, after adjusting for duration and multiplying by the RGDR for extra-respiratory effects. No NOAEL can be determined. The LOAEL is 22.2 mg/m^3 in males and 21.9 mg/m^3 in females based on increased incidence of nasal lesions in both sexes of mice.

Lewis et al. (1979)

Male New Zealand white rabbits (5/treatment group) were administered nitromethane (96.5% pure with 1.5% nitroethane and 1.4% 2-nitropropane) at analytical concentrations of 0, 98 ± 5, or 745 ± 34 ppm via whole body inhalation for 7 hours a day, 5 days a week, for 6 months (Lewis et al., 1979d). While Lewis et al. (1979) provides a peer-reviewed publication of the data, the proprietary data were also available for review (Huntingdon Research Center, 1989). This study was conducted in conjunction with the 3-month subchronic study discussed above, and the materials and methods were the same as those previously detailed.

There were no treatment-related effects on mortality, body weight, hematology, lung or brain edema, gross pathology, or organ histopathology. Thyroxin levels at both concentrations were statistically significantly ($p < 0.05$) lower than the control (see Table B.14). This was accompanied by an increase in absolute and relative thyroid weight that did not achieve statistical significance (see Table B.17). Based on the absence of respiratory toxicity noted, the NOAEL and LOAEL are selected based on extra-respiratory effects. The HECs for extra-respiratory effects adjusted for duration and a blood:gas partition coefficient of 1 are 51 and 388 mg/m^3, respectively. Therefore, the LOAEL is 51 mg/m^3 based on decreases in thyroxin levels, which were accompanied by changes in organ weight. No NOAEL can be determined from the data.

Developmental Studies

There are no developmental studies via oral or inhalation exposure to nitromethane. However, Whitman et al. (1977) intraperitoneally injected 0.5 mL of a 1.5-M solution of nitromethane in saline every third day beginning prior to pregnancy through gestation to albino rats. Few details were provided on the dosing procedure. Controls were similarly treated with saline. No differences were observed in the number of pups (dead or alive), pup body weight, or dam behavior. Pups were maintained with mothers until weaning and behavioral maze tests were conducted when pups were 2.5 months old. Nitromethane-exposed pups had significantly more errors to criterion compared with the control animals.

Reproductive Studies

There are no multigeneration reproductive studies with nitromethane by either oral or inhalation routes of exposure. However, the two 13-week studies by NTP (NTP, 1997) examined some reproductive endpoints after inhalation exposure. In rats (NTP, 1997), there were statistically significant decreases in absolute left cauda, epididymis, and testis weight at 1,500 ppm. Although this may be due to reduced body weight, there was a 15% decrease in sperm concentration in high-dose males, and sperm motility was significantly decreased with concentrations of 750 and 1,500 ppm (see Table B.9; NTP, 1997). Mice also had reduced sperm motility (NTP, 1997), but there was no effect on reproductive tissue weight or sperm concentration (see Table B.12). There were no treatment-related changes in estrous cycle length or estrous stages in female rats (NTP, 1997), but there was a dose-related increase in estrous cycle length at all concentrations examined in female mice (see Table B.12; NTP, 1997).

Carcinogenicity Studies

NTP (1997)

The carcinogenicity component of the chronic peer-reviewed rat study by NTP (1997) is selected as the principal study for the derivation of the p-IUR. Individually housed male and female F344 rats (50/sex/treatment group) were administered nitromethane

(purity ≥98%) at concentrations of 0, 94, 188, or 375 ppm via whole body inhalation for 6 hours and 12 minutes a day, 5 days a week, for 103 weeks. Chamber concentrations were routinely checked over the course of exposure. Animals were observed twice a day for clinical signs of toxicity. Animals were weighed at study initiation, weekly through Week 12, monthly from Week 15 through Week 91, then every 2 weeks until study termination, and at study termination. At study termination, animals were necropsied. Complete histopathology was conducted on all animals except that spinal cord and sciatic nerve were only examined in control and high-dose animals (15/sex). Typical NTP statistical methods were applied and were appropriate for the data.

There was no treatment-related effect on mortality. Besides tumor masses, there were no clinical signs of toxicity observed. There were no statistically significant changes in body weight compared with controls. However, the study authors noted that the high-dose group had a slightly higher body weight than the control beginning around Week 23. The differences were not statistically significant nor did they exceed a 10% difference from the control. There were no treatment-related increases in tumors in male rats. There was an increase in tumors of the mammary gland in females with concentrations of 188 and 375 ppm (see Table B.18). The incidence of mammary gland tumors in the 188- and 375-ppm groups also exceeded the historical control data from inhalation studies. There were concerns raised that the slight increase in body weight in the 375-ppm females was related to the increase in tumors observed in the female rat. However, it was concluded that this was not the case. Based on the increase in body weights, it would be predicted that there would be a 51% incidence of mammary gland tumors, but the incidence was 82%. NTP determined that there was no evidence of carcinogenicity in male rats, but there was clear evidence of carcinogenicity in female rats. The HECs for extra-respiratory carcinogenic effects adjusted for duration and a blood:gas partition coefficient of 1 are 43, 87, and 173 mg/m^3, respectively.

Griffin et al. (1996)

Male and female Long-Evans rats (40/sex/treatment group) were administered nitromethane (96.26% pure with 2.79% nitroethane and 0.62% 2-nitropropane) at concentrations of 0, 100, or 200 ppm via whole body inhalation for 7 hours a day, 5 days a week, for 2 years (Griffin et al., 1996b). While Griffin et al. (1996) provides a peer-reviewed publication of the data, the proprietary data were also available for review (Coulston International Inc., 1990). See the chronic studies discussed above for details on the materials and methods. There was no treatment-related effect on mortality. There were no statistically significant differences in neoplastic lesions. However, two high-dose females had adenocarcinomas of the uterus, which were not observed in either of the other groups. Because the incidence is low and there is no dose response, it is not clear if this is related to treatment. Based on the absence of either systemic or respiratory carcinogenicity, the NOAEL and LOAEL are selected based on extra-respiratory effects. The HECs for extra-respiratory effects adjusted for duration and a blood:gas partition coefficient of 1 are 45.6 and 89.0 mg/m^3, respectively. There is no evidence of carcinogenicity.

NTP (1997)

Individually housed male and female B6C3F$_1$ mice (50/sex/treatment group) were administered nitromethane (purity ≥98%) at concentrations of 0, 188, 375, or 750 ppm via whole body inhalation for 6 hours and 12 minutes a day, 5 days a week, for 103 weeks. Chamber concentrations were routinely checked over the course of exposure. Animals were observed

twice a day for clinical signs of toxicity. Animals were weighed at study initiation, weekly through Week 12, monthly from Week 15 through Week 91, then every 2 weeks until study termination, and at study termination. At study termination, animals were necropsied. Complete histopathology was conducted on all animals except that spinal cord and sciatic nerve were not examined. Typical NTP statistical methods were applied and were appropriate for the data.

There was no treatment-related effect on mortality. Clinical signs observed included swelling around the eyes and exophthalmos. This was stated to be consistent with Harderian gland neoplasms, which occurred at a greater incidence in treated animals. There were no statistically significant changes in body weight compared with controls. There were increases in the incidence of Harderian gland tumors in both sexes, liver tumors in females, and alveolar/bronchiolar carcinomas in males (see Table B.19). Respiratory and systemic tumors developed; therefore, HECs were calculated using both the respiratory and extra-respiratory methods respectively, for respiratory tumors (adjusted for duration and multiplied by a RGDR) and for extra-respiratory tumors (duration-adjusted and multiplied by a blood:gas partition coefficient of 1) (U.S.EPA, 1994b). The HECs for respiratory carcinogenic effects are 359; 727; and 1,484 mg/m^3 in males and 355; 700; and 1,423 mg/m^3 in females, respectively, based on the area of the thoracic region and average body weights provided in the study report. The HECs for extra-respiratory carcinogenic effects are 87, 173, and 346 mg/m^3, respectively. The study authors concluded that there was clear evidence of carcinogenicity in both sexes of mice.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

The genotoxicity of nitromethane has been studied in several in vitro test systems (see Table 4A). Little information on the toxicokinetics of nitromethane is available (Coulston International Inc., 1990; Sakurai et al., 1980) and is presented in Table 4B. Further in-depth details follow Tables 4A and 4B.

Table 4A. Summary of Nitromethane Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium* strains TA1537, TA1535, TA100, TA1538, and/or TA98 with or without S9 metabolic activation	50,000 µg/plate	−	−	Dellarco and Prival (1989) also used flavin mononucleotide in a modified preincubation assay to facilitate nitro reduction and found negative results; some pages of the Haskell Laboratories study illegible; 0.5% stated to be half the 50% survival concentration (Dow Chemical, 1975a)	Dow Chemical (1975a); Haskell Laboratories (2000); Chiu et al. (1978); Löfroth et al., (1986) Mortelmans et al. (1986); Dellarco and Prival (1989); NTP (1997); Gocke et al. (1981a)
Reverse mutation	Preincubation modification of *Salmonella typhimurium* strains TA98, TA100, TA102	200 µmol/plate	−	−	Concentrations ≥500 µmol/plate were cytotoxic and could not be used	Dayal et al. (1989a)
Reverse mutation	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 with or without S9 activation	50 µL/plate	+	+	Mutagenic in TA1535 only	Ong et al. (1980)
SOS repair induction	ND					
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	*Saccharomyces cerevisiae* strain D4 with and without metabolic activation	5%	−	−	5% stated to be half the 50% survival concentration	Dow Chemical (1975b)
Recombination induction	ND					

Table 4A. Summary of Nitromethane Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Chromosomal aberration	The Basc test using *Drosophila melanogaste*r Berlin K (wild type) and Basc strains	125 mM	−	−	2% ethanol used as the solvent	Gocke et al. (1981b)
Chromosomal malsegregation	ND					
Mitotic arrest	ND					
Genotoxicity studies in mammalian cells—in vitro						
Mutation	ND					
Chromosomal aberration	Micronucleus assay of Syrian hamster embryo cells	In DMSO: 6.0 µg/mL In media: 5,000 µg/mL	−	−	Reduction in cell numbers in DMSO at 5.5 and 6.0 µg/mL; no increased frequency in micronuclei	Gibson et al. (1997); Hazelton Washington (1996)
Chromosomal aberration	Transformation assay using Syrian hamster embryo cells	4,000 µg/mL	+	+	Dose-related increase in the number of morphological transformed colonies; cells incubated for 24 hr prior to application of nitromethane; incubation with nitromethane lasted 24 hr	Kerckaert et al. (1996); Brauninger (1995)
Chromosomal aberration	Abs test in Chinese hamster ovary cells with or without S9 metabolic activation	5,000 µg/mL	−	−	No induction of chromosome aberrations	NTP (1997)
Sister chromatid exchange (SCE)	Chinese hamster ovary cells with or without S9 metabolic activation	5,000 µg/mL	−	−	No induction of SCE	NTP (1997)
DNA damage	ND					
DNA adduct	ND					

Table 4A. Summary of Nitromethane Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in mammals—in vivo						
Chromosomal aberration	Subchronic inhalation exposure of male and female mice	1,500 ppm for 13 wk	−	NA	No increased frequency of micronucleated erythrocytes in peripheral blood samples	NTP (1997)
Chromosomal aberration	Micronucleus test on mouse bone marrow	1,830 mg/kg at 0 and 24 hr	−	NA	All treated mice survived; animals sacrificed at 30 hr	Gocke et al. (1981c)
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adduct	ND					
Mouse biochemical or visible specific locus test	ND					
Dominant lethal	ND					
Genotoxicity studies in subcellular systems						
DNA binding	ND					

[a]Lowest effective dose for positive results, highest dose tested for negative results.

[b]+ = positive; ± = equivocal or weakly positive; − = negative; T = cytotoxicity; NA = not applicable; ND = no data; NDr = not determined; NR = not reported; NR/Dr = not reported but determined from data.

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Carcinogenicity other than oral/inhalation	ND			
Other toxicity studies (exposures other than oral or inhalation)	Male and female BALB/c mice, hepatoxicity test via intraperitoneal injection at 4.5, 6.7, or 9.0 mmol/kg; control mice injected with NaCl; animals terminated at 24, 48, 72, or 96 hr after dosing; blood assays for sorbitol dehydrogenase, alanine aminotransferase, and aspartate aminotransferase	No abnormalities found in the enzyme activities for mice dosed with 9 mmol/kg	Not toxic at 9 mmol/kg after 24, 48, 72, or 96 hr	Dayal et al. (1989b)
Short-term studies	Rabbit, acute exposure (80 min) at 8 mg; no information regarding control or study methods provided	No significant effect on blood pressure or respiration	No significant effect on blood pressure or respiration	Machle and Scott (1943)
Metabolism/ toxicokinetic	Two adult female rhesus monkeys; single dermal exposure (300 µL ether/ethanol solution, 5.5% 14C-nitromethane) for 12 h.	No signs of toxicity reported; levels of nitromethane recovered in urine, feces, blood; absorption in skin considered to be low	Not hazardous to human skin	Coulston International Inc. (1990)
	Nitromethane aerobically incubated with liver microsomes isolated from male Sprague-Dawley rat livers treated with phenobarbital or 3-methylcholanthrene	Formaldehyde produced from nitromethane via NADPH-independent reaction; nitromethane did not result in a substrate-binding difference spectrum in the oxidized rat liver microsomal suspension, but peaked at 437 nm, indicating cytochrome P450-NO complex production	Nitrite, formaldehyde, and cyclohexanone are the major reaction products of nitromethane in activated rat liver microsomes in the presence of NADPH and dioxygen; study authors speculated that a special form of cytochrome P450 was necessary to cleave the C–N bond	Sakurai et al. (1980)
Mode of action/ mechanistic	ND			
Immunotoxicity	ND			
Neurotoxicity	ND			

ND = no data.

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

As seen in Table 4A, the majority of the genotoxicity (e.g., clastogenicity, mutagenicity) studies were negative. There was only one study (Ong et al., 1980) using the Ames assay that found a positive result in one strain (TA 1535) of *Salmonella typhimurium*. Negative results were also observed in *Saccharomyces cerevisiae* (Dow Chemical, 1975) and *Drosophila melanogaster* (Gocke et al., 1981). Chromosomal aberrations were not observed in Syrian hamster embryo cells using the micronucleus assay (Gibson et al., 1997; Hazleton Washington, 1996) but were observed as a dose-related increase in morphological-transformed colonies in the transformation assay (Kerkaert et al., 1996; Brauninger, 1995). Chromosomal aberrations were not observed in Chinese hamster ovary cells using either an Abs test or sister chromatid exchange test (NTP, 1997). Chromosomal aberrations were also not observed in mouse bone marrow using the micronucleus test (NTP, 1997; Gocke et al., 1981).

Other Toxicity Studies (Exposures Other Than Oral or Inhalation)

Dayal et al. (1989b) compared the potential hepatotoxicity of 2-nitropropane, nitromethane, and nitroethane following intraperitoneal injection. Biochemical and histopathological effects in male and female BALB/c mice were assessed following intraperitoneal injection of nitromethane at doses 0, 4.5, 6.7, or 9.0 mmol/kg in saline. Animals were sacrificed 24, 48, 72, or 96 hours after dosing, and blood was collected via cardiac puncture. Assays were performed for sorbitol dehydrogenase, alanine aminotransferase, and aspartate aminotransferase enzymes. Livers were investigated for biochemical effects. No liver abnormalities or other toxicity were reported in mice after treatment with 9-mmol/kg nitromethane. Results were not reported for the other doses.

Short-Term Studies

Machle and Scott (1943) examined the blood pressure and respiration of rabbits when exposed to nitromethane and other mononitroparaffins at 8 mg for 80 minutes. Although details of the study were lacking, the study authors reported no significant effect on rabbit blood pressure or respiration.

Metabolism/Toxicokinetic Studies

In a toxicokinetic study, Coulston International Inc. (1990) conducted a skin absorption study on two female rhesus monkeys. Animals were administered a single dose of 5.5% 14C-nitromethane (in a 300-µL ether/ethanol solution) to shaved intact skin on the back for 12 hours. The dosed area was occluded with a plastic foil patch and taped until removal at the end of the 12-hour dosing period. Upon removal of the application patch, the skin was cleaned with acetone and soap to remove any remaining test material. The patch and swab were extracted with ethanol and acetone, respectively, and then the extracts were assayed for radioactivity. Blood, urine, and feces were collected while animals were held in metabolism cages for 72 hours after dosing and assayed for radioactivity. Skin and subcutaneous fat were removed and assayed for radioactivity. Skin samples were examined histologically. No toxicity was reported by the study authors. Feed and water consumption as well as feces and urine output were low during the first 12 hours but returned to normal after animals were returned to their cages. No change in body weight was reported. Skin samples did not reveal any sign of skin damage or irritation. The study authors considered the level of radioactivity detected in blood plasma (37.8 ng/mL and 40.3 ng/mL average maximum per 1 mL blood plasma) and

erythrocytes (40.8 ng/g and 44.3 ng/g maximum) of the two monkeys to be low. Due to the low level of absorption after a high concentration level, study authors concluded that nitromethane is not hazardous to human skin.

Sakurai et al. (1980) investigated the metabolism of nitromethane in liver microsomes isolated from rats pretreated with phenobarbital or 3-methylcholanthrene in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and dioxygen (O_2). Male Sprague-Dawley rats were pretreated with either phenobarbital (80 mg/kg for 3 days) or 3-methylcholanthrene (20 mg/kg for 2 days). The microsomal fraction was then isolated from the livers of the pretreated rats and incubated in the presence of NADPH and dioxygen. The results of the incubation indicated a linear production of nitrite and formaldehyde. Cyclohexanone was also identified as a reaction product of nitromethane. The specific activity (±S.E.M) for denitrification of nitromethane by rat liver microsomal monooxygenases was reported as 0.2 ± 0.1 nmol/mg protein-min. The study authors reported that the addition of nitromethane to oxidized rat liver microsomal suspensions resulted in a peak of 437 nm, which is outside the normal substrate-binding spectrum. Further, the study authors explained the peak as the formation of the cytochrome P450-NO complex. Additionally, the study authors also reported that the oxidized rat liver microsomes produced formaldehyde from nitromethane in an independent NADPH reaction.

Mode-of-Action/Mechanistic Studies

There is insufficient information to determine the mode of action.

Immunotoxicity

There is no suitable information to provide in this regard.

Neurotoxicity

There is no suitable information to provide in this regard.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present a summary of noncancer reference and cancer values, respectively, for nitromethane. IRIS data are indicated in the tables, if available.

Table 5. Summary of Noncancer Reference Values for Nitromethane (CASRN 75-52-5)

Toxicity Type (Units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	NDr						
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	Mouse/F	Hyaline droplets in the respiratory epithelium	4×10^{-3}	$BMCL_{10}$	1.31	300	NTP (1997)
Chronic p-RfC (mg/m^3)	Mouse/F	Hyaline degeneration in the respiratory epithelium	5×10^{-3}	$BMCL_{10}$	1.60	300	NTP (1997)

NDr = not determinable.

Table 6. Summary of Cancer Values for Nitromethane (CASRN 75-52-5)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	NDr			
p-IUR	Rat/F	Combined mammary gland fibroadenoma, adenoma, and carcinoma	8.8×10^{-3} $(mg/m^3)^{-1}$	NTP (1997)

NDr = not determinable.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic and Chronic Provisional RfD (p-RfD)

No subchronic or chronic p-RfD value can be derived because no adequate, well-described studies are available.

Justification

There is a single subchronic oral study available for nitromethane (Weatherby, 1955). The lowest dose administered (i.e., 0.1%) caused mortality in 4 of the 10 animals tested. Due to cannibalism of the dead animals, it was not possible to determine cause of death. Because the lowest dose administered was considered an FEL, it is not possible to use this study to derive a p-RfD.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

There are several studies available for the derivation of the subchronic p-RfC (see Table 7). The study by NTP (1997) in mice is selected as the principal study. This study was peer reviewed and GLP compliant. NTP (1997) examined numerous endpoints in both sexes in

two species (i.e., rats and mice). Details are provided in the "Review of Potentially Relevant Data" section. Among the available and acceptable studies, the NTP (1997) subchronic study in mice represents the lowest POD for developing a subchronic p-RfC. The critical endpoint is hyaline droplets in the respiratory epithelium of the nasal turbinates in female mice. The NTP (1997) studies included histopathologic evaluations of the upper respiratory tract, additionally, histopathological lesions of the nasal tract were observed in rats and mice after 16 days (NTP, 1997) and 13 weeks (1997), with possible progression noted in the 2-year studies (NTP, 1997). The hyaline droplets in the respiratory epithelium are selected as the critical effect because, in addition to being the most sensitive effect in the most sensitive species (mice), it was a lesion of progressing severity. Hyaline droplets of the respiratory epithelium were not noted after 16 days of exposure but were observed after 13 weeks of exposure and progressed to degeneration of the respiratory epithelium after 2 years of exposure. In addition, the severity of the hyaline droplets was stated to increase with concentration, ranging from mild in the lower concentrations to moderate at the highest concentration. Degeneration of the olfactory epithelium also occurred at the same concentrations as hyaline droplets in the respiratory epithelium. Benchmark dose (BMD) analysis has been conducted on both endpoints (hyaline droplets and degenerative lesions) only in mice; these same nasal lesions were also observed in the rats but occurred at greater concentrations. The hyaline droplets in the respiratory epithelium have a lower BMCL. However, this endpoint models better when the highest two concentrations are dropped due to maximal response observed in the top three concentrations. Also occurring at higher nitromethane concentrations was anemia noted by decreased hematocrit and hemoglobin levels as well as other hematological effects, effects to the thyroid (increased thyroid weight and decreased thyroxin levels), and other histological lesions in both species. Relative liver weights were increased in female mice after 16 days of exposure at the same concentration that caused the nasal effects (i.e., 188 ppm). BMD analyses have not been conducted on these endpoints. Histopathology in the 16-day rat and mouse studies and the 13-week rat study was not amenable to BMD analysis due to unsuitable dose-response data.

Table 7. Summary of Relevant Inhalation Subchronic Toxicity Studies for Nitromethane

Reference	Species, #/Sex (M/F)	Exposure (ppm)	Frequency/ Duration	$NOAEL_{ADJ}$[a] (mg/m^3)	$LOAEL_{ADJ}$[b] (mg/m^3)	Critical Endpoint
NTP (1997)	Rat, 5/5	0; 94; 188; 375; 750; 1,500	6.2 hr, 5 d/wk, 16 d	8.9	17.7	Degeneration of the olfactory epithelium of the nasal turbinates in females
NTP (1997)	Mouse, 5/5	0; 94; 188; 375; 750; 1,500	6.2 hr, 5 d/wk, 16 d	10.2	20.2	Degeneration of the olfactory epithelium of the nasal turbinates in females
NTP (1997)	Rat, 10/10	0; 94; 188; 375; 750; 1,500	6.2 hr, 5d/wk, 13 wk	9.7	19.2	Degeneration of the olfactory epithelium of the nasal turbinates in females
NTP (1997)	Mouse, 10/10	0; 94; 188; 375; 750; 1,500	6.2 hr, 5 d/wk, 13 wk	5.9	11.8	Degeneration of the olfactory epithelium and hyaline droplets in the respiratory epithelium of the nasal turbinates in females
Lewis et al. (1979)	Rat, 10/0	0, 98, 745	7 hr/d, 5 d/wk, 3 mo	51	388	Decreased hematocrit and hemoglobin levels
Lewis (1979)	Rabbit, 5/0	0, 98, 745	7 hr/d, 5 d/wk, 3 mo	51	388	Decreased thyroxin levels

[a]$NOAEL_{ADJ}$ is the HEC value for respiratory or extra-respiratory effects; HEC_{resp} = ppm × (molecular weight ÷ 24.45) × (hours exposed per day ÷ 24) × (days dosed ÷ total days) × RGDR; RGDRs were based on average body weights from the study reports and the surface area of the respiratory area affected; HEC_{exresp} = ppm × (molecular weight ÷ 24.45) × (hours exposed per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.

[b]$LOAEL_{ADJ}$ is the HEC value for respiratory or extra-respiratory effects; HEC_{resp} = ppm × (molecular weight ÷ 24.45) × (hours exposed per day ÷ 24) × (days dosed ÷ total days) × RGDR; RGDRs were based on average body weights from the study reports and the surface area of the respiratory area affected; HEC_{exresp} = ppm × (molecular weight ÷ 24.45) × (hours exposed per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.

The following dosimetric adjustments have been made for inhalation with an $EXPOSURE_{ppm}$ for respiratory effects. The RGDR is the ratio of the respiratory minute volumes divided by the surface areas of the extra-thoracic pulmonary region (where the effect occurred) in mice and humans, respectively, and is used in calculating the HEC (U.S. EPA, 1994b). The example shown below is for the second lowest dose.

$(EXPOSURE_{HEC,\ extra\text{-}thoracic})_n$ = ppm × (ppm conversion) × (average daily dose) × RGDR
= ppm × (MW ÷ 24.45) × ([hours exposed ÷ 24 hours] × [days exposed per week ÷ study days per week]) × RGDR
= 188 × (61.04 ÷ 24.45) × (6.2 ÷ 24) × (5 ÷ 7) × 0.136
= 11.8 mg/m^3

Where:

RGDR = $(V_e \div SA)_A \div (V_e \div SA)_H$; V_e = minute volume (m^3/day); SA = surface area of the extra-thoracic region (m^2); calculated using average body weights from the study report
= (0.0408 ÷ 0.0003) ÷ (20 ÷ 0.02)
= 0.136

All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 2.1.2) have been fit to the data on hyaline droplets in the respiratory epithelium in female mice following exposure to nitromethane for 13 weeks (see Table 8). A benchmark response (BMR) of 10% extra risk above the control mean has been used to estimate the BMD (U.S. EPA, 2010).

Table 8. Incidence Data for Female B6C3F$_1$ Mice Treated with Nitromethane for 13 Weeks—Used for BMD Analysis[a]

$(PPM)_n$	$(EXPOSURE_{HEC,\ extra\text{-}thoracic})_n$ (mg/m^3)	Number of Subjects	Response
0	0	10	0
94	5.9	10	2
188	11.8	10	9**
375	24.9	10	10**
750	48.0	10	10**
1500	93.9	10	10**

[a]NTP (1997).

**Statistically significant difference from control ($p \leq 0.01$) using Fisher's exact test as performed by the study authors.

Table 9 summarizes the BMDS model results for the respiratory epithelium hyaline droplet data in female mice. The curve and BMDS output for the selected model only are provided in Appendix C. The BMDS Multistage model with a benchmark concentration lower

bound 95% confidence interval $BMCL_{10HEC,\ extra\text{-}thoracic}$ of 1.31 mg/m^3 is selected. For the models that provided adequate fit (using goodness-of-fit test; $p \geq 0.1$), the Akaike Information Criterion (AIC) values are close, and the BMCLs are within 3-fold of each other; therefore, the model with the lowest AIC is selected. Table 10 summarizes the uncertainty factors applied.

Table 9. Model Predictions for Respiratory Epithelial Hyaline Droplets in Female B6C3F$_1$ Mice[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)	Conclusions
Multistage	**1.00**	**18.556**	**4.431**	**1.31**	**Selected as lowest AIC value for POD with a range of 1.314−3.126**
Weibull	1.00	20.510	4.709	2.14	Not selected
Probit	0.99	20.549	4.755	2.54	Not selected
Logistic	0.96	20.659	4.825	2.73	Not selected
Log-logistic	0.98	20.569	5.078	3.11	Not selected
Log-probit	1.00	20.517	5.121	3.13	Not selected

[a]NTP (1997).
[b]Chi-square *p*-value = *p*-value from chi-square test for lack of fit. Values <0.1 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike Information Criteria; BMC = benchmark concentration; BMCL lower confidence limit (95%) on the benchmark concentration; BMC_{10} = BMC at a response rate of 10% incidence, extra risk.

A POD of 1.31 mg/m^3 is determined by BMD analysis. The subchronic p-RfC for nitromethane, based on a $BMCL_{10HEC,\ extra\text{-}thoracic}$ of 1.31 mg/m^3 in female mice, is derived as follows:

$$\textbf{Subchronic p-RfC} = \textbf{BMCL}_{\textbf{10HEC, extra-thoracic}} \div \textbf{UF}_{\textbf{C}}$$
$$= 1.31\ \text{mg/m}^3 \div 300$$
$$= \mathbf{4 \times 10^{-3}\ mg/m^3}$$

Table 10. Uncertainty Factors for Subchronic p-RfC of Nitromethane

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 studies or developmental studies by this route of exposure.
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 BMCL.
UF_S	1	A UF_S of 1 is applied because a subchronic study was utilized.
UF_C ≤3000	300	Composite uncertainty factor

The confidence of the subchronic p-RfC for nitromethane is medium as explained in Table 11 below.

Table 11. Confidence Descriptors for Subchronic p-RfC for Nitromethane

Confidence Categories	Designation[a]	Discussion
Confidence in study	H	The study by NTP (1997) provided sufficient details, used sufficient numbers of animals, examined both sexes, and examined numerous endpoints including both portal-of-entry and systemic endpoints. In addition, NTP (1997) examined two species (rats and mice) and conducted short-term studies to determine appropriate doses for the subchronic study.
Confidence in database	M	Although there are several short-term, subchronic, chronic, and carcinogenicity studies available, there are no acceptable reproductive or developmental studies available for nitromethane.
Confidence in subchronic p-RfC[b]	M	The overall confidence is medium because the confidence in the database is medium.

[a]L = low; M = medium; H = high.
[b]The overall confidence cannot be greater than lowest entry in the table.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

There are several studies available for the derivation of the chronic p-RfC (see Table 12). The study by NTP (1997) is selected as the principal study for derivation of the chronic p-RfC. This study was peer reviewed and GLP compliant. NTP (1997) examined numerous endpoints in both sexes of two species (i.e., rats and mice). Details are provided in the "Review of Potentially Relevant Data" section. Among the available and acceptable studies, this study represents the lowest POD for developing a chronic p-RfC. The critical effect is hyaline degeneration of the respiratory epithelium of the nasal turbinates in female mice. Only the NTP

(1997) studies included histopathologic evaluations of the upper respiratory tract, but histopathological lesions of the nasal tract were observed in rats and mice after 16 days, 13 weeks, as well as in mice after 2 years (NTP, 1997). As stated previously, the hyaline degeneration of the respiratory epithelium is a progressive lesion with hyaline droplets observed after 13 weeks of exposure in mice. There was also a concentration-related increase in severity of the nasal lesions. Degeneration of the olfactory epithelium also occurred at the same concentration as the hyaline degeneration of the respiratory epithelium. BMD analysis has been conducted on both the degeneration in the olfactory epithelium and the hyaline degeneration in the respiratory epithelium (both in the nasal turbinates) in mice, but hyaline degeneration of the respiratory epithelium is the most sensitive effect. The NTP studies also found signs of anemia including decreased hematocrit and hemoglobin levels and effects on the thyroid (increased thyroid weight and decreased thyroxin levels), but these effects occurred at higher concentrations. Because these effects occurred at higher HECs than the nasal effects observed in the 2-year mouse study, BMD analyses have not been conducted on these endpoints.

Table 12. Summary of Relevant Inhalation Chronic Toxicity Studies for Nitromethane

Reference	Species, #/Sex (M/F)	Exposure (ppm)	Frequency/ Duration	$NOAEL_{ADJ}$[a] (mg/m^3)	$LOAEL_{ADJ}$[b] (mg/m^3)	Critical Endpoint
NTP (1997)	Rat, 50/50	0, 94, 188, 375	6.2 hr, 5 d/wk, 103 wk	173	NDr	No noncancer effects observed, but tumors were observed at 87 mg/m^3
NTP (1997)	Mouse, 50/50	0, 188, 375, 750	6.2 hr, 5 d/wk, 103 wk	NDr	21.9	Increase in nonneoplastic nasal lesions in females
Griffin et al. (1996)	Rat, 40/40	0, 100, 200	7 hr, 5 d/wk, 2 yr	89.0	NDr	No noncancer effects observed
Lewis et al. (1979)	Rat, 10/0	0, 98, 745	7 hr/d, 5 d/wk, 6 mo	51	388	Increase in relative thyroid weight
Lewis et al. (1979)	Rabbit, 5/0	0, 98, 745	7 hr/d, 5 d/wk, 6 mo	NDr	51	Decreased thyroxin levels

[a]$NOAEL_{ADJ}$ is the HEC value for respiratory or extra-respiratory effects; HEC_{resp} = ppm × (molecular weight ÷ 24.45) × (hours exposed per day ÷ 24) × (days dosed ÷ total days) × RGDR; RGDRs were based on average body weights from the study reports and the surface area of the respiratory area affected; HEC_{exresp} = ppm × (molecular weight ÷ 24.45) × (hours exposed per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.

[b]$LOAEL_{ADJ}$ is the HEC value for respiratory or extra-respiratory effects; HEC_{resp} = ppm × (molecular weight ÷ 24.45) × (hours exposed per day ÷ 24) × (days dosed ÷ total days) × RGDR; RGDRs were based on average body weights from the study reports and the surface area of the respiratory area affected; HEC_{exresp} = ppm × (molecular weight ÷ 24.45) × (hours exposed per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.

NDr = not determinable.

Based on its physical properties, nitromethane is a Category 2 gas. This is supported by the observation of both respiratory (direct contact) and extra-respiratory (systemic) effects in the studies that examined endpoints inclusive of both effects. Therefore, dosimetric conversions are based on the endpoint observed and differ for respiratory and extra-respiratory effects. Note that the RGDR used in dosimetric conversions is different from the subchronic-duration derivation because of the difference in average body weights at 13 weeks versus 103 weeks.

The following dosimetric adjustments have been made for inhalation with an $EXPOSURE_{ppm}$ for respiratory effects. The example shown is for the lowest dose.

$(EXPOSURE_{HEC,\ RESP})_n$ = ppm × (ppm conversion) × (average daily dose) × RGDR
= ppm × (MW ÷ 24.45) × ([hours exposed ÷ 24] × [days exposed ÷ study duration]) × RGDR
= 188 × (61.04 ÷ 24.45) × (6.2 ÷ 24) × (5 ÷ 7) × 0.254
= **22.0 mg/m^3**

Where:

RGDR = $(V_e \div SA)_A \div (V_e \div SA)_H$; V_e = minute volume (m^3/day); SA = Surface Area of the extra-thoracic region (m^2); calculated using average body weights from the study report
= (0.0763 ÷ 0.0003) ÷ (20 ÷ 0.02)
= 0.254

The following dosimetric adjustments have been made for inhalation with an $EXPOSURE_{ppm}$ for extra-respiratory effects. Data for calculating a specific blood:gas partition coefficient were not available; therefore, a value of 1 is employed.

$EXPOSURE_{HEC,\ EXRESP}$ = ppm × (ppm conversion) × (average daily dose) × blood:gas partition coefficient
= ppm × (MW ÷ 24.45) × ([hours exposed ÷ 24] × [days exposed ÷ study duration]) × blood:gas partition coefficient
= 188 × (61.04 ÷ 24.45) × (6.2 ÷ 24) × (5 ÷ 7) × 1
= 86.6 mg/m^3

All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 2.1.2) have been fit to the hyaline degeneration of the respiratory epithelium data in female mice following exposure to nitromethane for 2 years (see Table 13). A BMR of 10% extra risk above the control mean is used to estimate the BMD (U.S. EPA, 2010).

Table 13. Incidence Data for Hyaline Degeneration of the Respiratory Epithelium in Female B6C3F$_1$ Mice Treated with Nitromethane for 2 Years—Used for BMDS Analysis[a]

$(PPM)_n$	$(EXPOSURE_{HEC,RESP})$ (mg/m^3)	Number of Subjects	Response
0	0	50	16
188	22.0	49	39**
375	43.9	50	50**
750	87.8	50	50**

[a]NTP (1997).

**Statistically significant difference from control ($p \leq 0.01$) using Fisher's exact test as performed by the study authors.

Table 14 summarizes the BMDS model results for the data in female mice. The curve and BMDS output for the selected model only are provided in Appendix C. The BMDS Multistage model with a $BMCL_{10HEC, RESP}$ of 1.60 mg/m^3 is selected. Following EPA guidance (U.S. EPA, 2012), for the models that provided an adequate fit (using goodness-of-fit test; $p \geq 0.1$), the AIC values are close, but the BMCLs are not within 3-fold of each other; therefore, the model with the lowest BMCL is selected. Table 15 summarizes the uncertainty factors applied.

Table 14. Model Predictions for Hyaline Degeneration of the Respiratory Epithelium in Female B6C3F$_1$ Mice[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)	Conclusion
Multistage	**1.00**	**116.283**	**9.734**	**1.60**	**Selected as lowest BMCL value for POD with a range of 1.602−8.373**
Logistic	0.47	118.672	2.810	2.19	Not selected
Probit	0.66	117.579	2.885	2.33	Not selected
Weibull	1.00	118.276	11.437	2.90	Not selected
Log-probit	1.00	118.276	17.188	6.85	Not selected
Log-logistic	1.00	116.276	18.523	8.37	Not selected

[a]NTP (1997).
[b]Chi-square *p* value = *p*-value from chi-square test for lack of fit. Values <0.1 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike Information Criteria; BMC = benchmark concentration; BMCL lower confidence limit (95%) on the benchmark concentration; BMC_{10} = BMC at a response rate of 10% incidence, extra risk.

The POD in this study is a $BMCL_{10HEC, RESP}$ of 1.60 mg/m^3. The chronic p-RfC for nitromethane, based on a $BMCL_{10HEC, RESP}$ of 1.60 mg/m^3 in female mice, is derived as follows:

Chronic p-RfC = $BMCL_{10HEC, RESP} \div UF_C$
= 1.60 mg/m^3 ÷ 300
= **5×10^{-3} mg/m^3**

Table 15. Uncertainty Factors for Chronic p-RfC of Nitromethane

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 studies or developmental studies by this route of exposure.
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 for using a POD based on a BMCL.
UF_S	1	A UF_S of 1 is applied because a chronic study was utilized.
UF_C ≤3000	300	Composite uncertainty factor

The confidence of the chronic p-RfC for nitromethane is medium as explained in Table 16 below.

Table 16. Confidence Descriptors for Chronic p-RfC for Nitromethane

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	The study by NTP (1997) provided sufficient details, used sufficient numbers of animals, examined both sexes, and examined numerous endpoints including both portal-of-entry and systemic endpoints. In addition, NTP (1997) examined two species (rats and mice) and selected doses based on shorter duration studies. However, the lowest dose tested was a LOAEL.
Confidence in database	M	Although there are several short-term, subchronic, chronic, and carcinogenicity studies available, there are no reproductive or developmental studies available for nitromethane.
Confidence in chronic p-RfC[b]	M	The overall confidence is medium because the confidence in the database is medium.

[a]L = low; M = medium; H = high.
[b]The overall confidence cannot be greater than the lowest entry in table.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 17 identifies the cancer WOE descriptor for nitromethane. As there are statistically significant increases in tumors in more than one species (rats and mice) and in both sexes of mice, the cancer WOE descriptor is *"Likely to Be Carcinogenic to Humans"* (U.S. EPA, 2005*)* for the inhalation route of exposure. Because no carcinogenicity studies on nitromethane via the oral route of exposure have been identified, the cancer WOE descriptor for the oral route is *"Inadequate Information to Assess Carcinogenic Potential"*.

Table 17. Cancer WOE Descriptor for Nitromethane

Possible WOE Descriptor	Designation	Route of entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	No human data has been identified.
"Likely to Be Carcinogenic to Humans"	**Selected**	**Inhalation**	**NTP (1997) determined evidence of carcinogenicity in female F344 rats and both sexes of $B6C3F_1$ mice.**
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	Evidence points more towards likely to be carcinogenic.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Oral**	**No carcinogenicity studies via the oral route of exposure have been identified.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	Animal data indicate this is not true.

NS = not selected; NA = not applicable.

MODE–OF-ACTION DISCUSSION

There are insufficient data to clearly define a mutagenic mode of action. Therefore, a linear approach is applied.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

The lack of oral data on the carcinogenicity of nitromethane precludes the derivation of quantitative estimates for oral (p-OSF) exposure.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

The study in rats by NTP (1997) is selected as the principal study for derivation of the p-IUR. The cancer endpoint is combined mammary gland fibroadenoma, adenoma, and carcinoma in females. While the NTP study in mice provided similar data, the dose response was clearer in rats. This study was peer reviewed, GLP compliant, and otherwise met the standards of study design and performance. Details are provided in the "Review of Potentially Relevant Data" section. Table 18 provides the data that have been applied to the BMDS model.

Among the available, acceptable studies, this study represents the highest IUR from the relevant studies in the database.

The following dosimetric adjustments have been made for inhalation treatment in adjusting exposures for cancer analysis. Since the endpoint (mammary gland tumors) is outside the respiratory tract, the HEC is calculated based upon extra-respiratory effects. Because the rat/human blood gas partition coefficient ratio was not available, the default value of 1 was used (U.S. EPA 1994b). The example shown is the for the low dose.

$$(\text{EXPOSURE}_{\text{HEC, EXRESP}})_n = \text{ppm} \times (\text{ppm conversion}) \times (\text{average daily dose}) \times \text{blood:gas partition coefficients}$$
$$= \text{ppm} \times (\text{MW} \div 24.45) \times ([\text{hours exposed} \div 24] \times [\text{days exposed} \div \text{study duration}]) \times \text{blood:gas partition coefficient})$$
$$= 94 \times (61.04 \div 24.45) \times (6.2 \div 24) \times (5 \div 7) \times 1$$
$$= 43.3 \text{ mg/m}^3$$

Table 18. Incidence Data for Female Sprague-Dawley Rats Treated with Nitromethane for 2 Years—Used for BMD Analysis[a]

$(\text{PPM})_n$	$(\text{EXPOSURE}_{\text{HEC, EXRESP}})_n$ (mg/m^3)	Number of Subjects	Response
0	0	50	21
94	43.3	50	25
188	86.6	50	34**
375	172.8	50	41**

[a]NTP (1997).

**Statistically significant difference from control ($p \leq 0.01$) using Fisher's exact test as performed by study authors.

Table 19 shows the modeling results. Adequate model fit is obtained for the combined mammary gland fibroadenoma, adenoma, and carcinoma data in female rats using the BMDS version 2.1.2 multistage-cancer model (U.S. EPA, 2010). A $\text{BMC}_{10\text{HEC, EXRESP}}$ of 20.4 mg/m^3 and a $\text{BMCL}_{10\text{HEC, EXRESP}}$ of 11.3 mg/m^3 are calculated from BMD modeling with 10% extra risk for combined mammary gland fibroadenoma, adenoma, and carcinoma (see Table 19). The curve and BMDS output for the selected model only is provided in the BMD supplement (see Appendix C); Table C.1 provides the IURs for the various endpoints modeled.

Table 19. Model Predictions for Combined Mammary Gland Fibroadenoma, Adenoma, and Carcinoma in Females Rats[a]

Model	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	$BMC_{10HEC, EXRESP}$ (mg/m^3)	$BMCL_{10HEC, EXRESP}$ (mg/m^3)	Conclusions
Multistage-Cancer	0.49	253.652	20.4	11.3	Lowest BMCL

[a]NTP (1997).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criterion; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; BMC_{10} = BMC at a response rate of 10% incidence, extra risk. HEC = Human Equivalent Concentration; EXRESP = HEC determined using the extra-respiratory method (U.S. EPA, 1994b)

$$\text{p-IUR} = 0.1^{a} \div BMCL_{10HEC, EXRESP}$$
$$= 0.1 \div 11.3\ mg/m^3$$
$$= 8.8 \times 10^{-3}\ (mg/m^3)^{-1}$$

[a]The value 0.1 is the benchmark response/concentration (U.S. EPA 1994b, 2012).

APPENDIX A. PROVISIONAL SCREENING VALUES

No screening values for nitromethane are derived.

APPENDIX B. DATA TABLES

Table B.1. Mean Body Weights of Male and Female F344 Rats After Inhalation Exposure to Nitromethane for 16 Days[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]					
Male		**0**	**94 (46)**	**188 (91)**	**375 (181)**	**750 (363)**	**1500 (726)**
Sample size		5	5	5	5	5	5
Weight[c] (g)	Initial	145 ± 4	147 ± 4 (101)	146 ± 4 (101)	145 ± 3 (100)	144 ± 3 (99)	146 ± 3 (101)
	Final	182 ± 4	189 ± 5 (104)	187 ± 5 (103)	182 ± 6 (100)	177 ± 4 (97)	171 ± 4 (94)
	Change	38 ± 2	43 ± 2 (113)	41 ± 2 (108)	37 ± 3 (97)	34 ± 1 (89)	25 ± 3** (66)
Female		**0**	**94 (46)**	**188 (91)**	**375 (181)**	**750 (363)**	**1500 (726)**
Sample size		5	5	5	5	5	5
Weight[c] (g)	Initial	116 ± 2	116 ± 2 (100)	116 ± 2 (100)	116 ± 2 (100)	117 ± 2 (101)	117 ± 2 (101)
	Final	134 ± 3	135 ± 3 (101)	133 ± 2 (99)	133 ± 2 (99)	132 ± 1 (99)	128 ± 2 (96)
	Change	17 ± 1	18 ± 3 (106)	17 ± 1 (100)	18 ± 2 (106)	15 ± 2 (88)	11 ± 1 (65)

[a]Source: NTP (1997).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Weights expressed as mean ± SE (% of control). Percent change from control in brackets.

**Significantly different from control ($p \leq 0.01$); Williams' or Dunnett's test performed by the study authors.

Table B.2. Liver and Kidney Weights of Male and Female F344 Rats After Inhalation Exposure to Nitromethane for 16 Days[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]					
Male		**0**	**94 (46)**	**188 (91)**	**375 (181)**	**750 (363)**	**1500 (726)**
Sample size		5	5	5	5	5	5
Necropsy body weight[c] (g)		218 ± 3	225 ± 5 (103)	223 ± 6 (102)	215 ± 7 (99)	206 ± 4 (94)	192 ± 4 (88)**
Liver weight[c]	Absolute (g)	8.922 ± 0.201	9.950 ± 0.250 (112)	9.794 ± 0.303 (110)	9.988 ± 0.393 (112)	9.028 ± 0.144 (101)	9.322 ± 0.346 (104)
	Relative (mg/g)	40.98 ± 0.55	44.29 ± 0.71 (108)**	43.87 ± 0.66 (107)**	46.50 ± 0.68 (113)**	43.84 ± 0.63 (107)**	48.49 ± 0.99 (118)**
Right kidney weight[c]	Absolute (g)	0.852 ± 0.014	0.878 ± 0.011 (103)	0.904 ± 0.029 (106)	0.870 ± 0.037 (102)	0.854 ± 0.016 (100)	0.880 ± 0.022 (103)
	Relative (mg/g)	3.91 ± 0.02	3.91 ± 0.08 (100)	4.05 ± 0.05 (104)	4.05 ± 0.07 (104)	4.14 ± 0.02 (106)*	4.58 ± 0.08 (117)**
Female		**0**	**94 (46)**	**188 (91)**	**375 (181)**	**750 (363)**	**1500 (726)**
Sample size		5	5	5	5	5	5
Necropsy body weight[c] (g)		146 ± 2	148 ± 3 (101)	147 ± 2 (101)	146 ± 2 (100)	143 ± 2 (98)	137 ± 3 (94)
Liver weight[c]	Absolute (g)	5.240 ± 0.182	5.472 ± 0.193 (104)	5.578 ± 0.187 (106)	5.750 ± 0.160 (110)*	5.832 ± 0.067 (111)*	6.204 ± 0.118 (118)**
	Relative (mg/g)	35.95 ± 0.86	36.87 ± 0.62 (103)	37.88 ± 0.82 (105)	39.28 ± 1.09 (109)**	40.72 ± 0.22 (113)**	45.30 ± 0.53 (126)**
Right kidney weight[c]	Absolute (g)	0.612 ± 0.022	0.616 ± 0.019 (101)	0.634 ± 0.013 (104)	0.614 ± 0.007 (100)	0.636 ± 0.007 (104)	0.660 ± 0.009 (108)
	Relative (mg/g)	4.20 ± 0.13	4.15 ± 0.05 (99)	4.31 ± 0.08 (103)	4.19 ± 0.04 (100)	4.44 ± 0.06 (106)	4.82 ± 0.10 (115)**

[a]Source: NTP (1997).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Weights expressed as mean ± SE. Percent change from control in brackets.

*Significantly different from control ($p \leq 0.05$); Williams' or Dunnett's test performed by the study authors.
**Significantly different from control ($p \leq 0.01$); Williams' or Dunnett's test performed by the study authors.

Table B.3. Histopathological Findings for Male and Female F344 Rats After Inhalation Exposure to Nitromethane for 16 Days[a]

Parameter	Exposure Group, ppm (HEC, mg/m^3)					
Male	**0**	**94 (5.7)[b]**	**188 (11.2)**	**375 (22.1)**	**750 (43.5)**	**1500 (86.1)**
Nose/Turbinates, degeneration, olfactory epithelium[c]	0/5 (0)	0/5 (0)	0/ 5 (0)	5/5** (100; 1.0)	5/5** (100; 2.0)	5/5** (100; 2.0)
Male	**0**	**94 (46)[d]**	**188 (91)**	**375 (181)**	**750 (363)**	**1500 (726)**
Sciatic nerve degeneration[c]	0/4 (0)	0/5 (0)	0/5 (0)	5/5** (100; 1.0)	5/5** (100; 2.0)	5/5** (100; 3.0)
Female	**0**	**94 (4.5)[b]**	**188 (8.9)**	**375 (17.7)**	**750 (35.3)**	**1500 (69.7)**
Nose/Turbinates, degeneration, olfactory epithelium[c]	0/5 (0)	0/5 (0)	0/ 5 (0)	4/5* (80; 1.0)	5/5** (100; 1.8)	5/5** (100; 2.0)
Female	**0**	**94 (46)[d]**	**188 (91)**	**375 (181)**	**750 (363)**	**1500 (726)**
Sciatic nerve degeneration[c]	0/5 (0)	0/5 (0)	0/5 (0)	5/5** (100; 1.0)	5/5** (100; 2.0)	5/5** (100; 3.0)

[a]Source: NTP (1997).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × RGDR; body weights used to determine the RGDR were calculated as (initial body weight + final body weight) ÷ 2.
[c] Values expressed as number observed with neoplasm/number examined for that neoplasm (% incidence; average severity of lesions 1 = minimal, 2 = mild, 3 = moderate, 4 = marked).
[d]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.

*Significantly different from control ($p \leq 0.05$); Fischer exact test performed by the study authors.
**Significantly different from control ($p \leq 0.01$); Fischer exact test performed by the study authors.

Table B.4. Liver Weights of Male and Female B6C3F$_1$ Mice After Inhalation Exposure to Nitromethane for 16 Days[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]					
Male		**0**	**94 (46)**	**188 (91)**	**375 (181)**	**750 (363)**	**1500 (726)**
Sample size		5	5	5	5	5	5
Necropsy body weight[c] (g)		27.4 ± 0.6	29.0 ± 1.0 (106)	28.9 ± 0.6 (105)	27.7 ± 0.9 (101)	29.2 ± 0.7 (107)	28.6 ± 0.2 (104)
Liver weight[c]	Absolute (g)	1.376 ± 0.044	1.538 ± 0.083 (112)	1.552 ± 0.045 (113)	1.526 ± 0.078 (111)	1.752 ± 0.081 (127)**	1.680 ± 0.053 (122)**
	Relative (mg/g)	50.15 ± 0.67	52.99 ± 2.14 (106)	53.63 ± 0.53 (107)	54.96 ± 1.53 (110)*	59.93 ± 1.38 (120)**	58.72 ± 1.61 (117)**
Female		**0**	**94 (46)**	**188 (91)**	**375 (181)**	**750 (363)**	**1500 (726)**
Sample size		5	5	5	5	5	5
Necropsy body weight[c] (g)		23.3 ± 0.2	23.7 ± 0.3 (102)	23.6 ± 0.3 (101)	23.8 ± 0.4 (102)	24.7 ± 0.4 (106)*	24.0 ± 0.4 (103)
Liver weight[c]	Absolute (g)	1.146 ± 0.020	1.256 ± 0.035 (110)*	1.338 ± 0.037 (117)**	1.364 ± 0.047 (119)**	1.442 ± 0.020 (126)**	1.410 ± 0.044 (123)**
	Relative (mg/g)	49.24 ± 0.96	53.00 ± 1.40 (108)*	56.77 ± 1.15 (115)**	57.28 ± 1.56 (116)**	58.44 ± 1.18 (119)**	58.70 ± 0.90 (119)**

[a]Source: NTP (1997).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Weights expressed as mean ± SE (% of control).

*Significantly different from control ($p \leq 0.05$); Williams' or Dunnett's test performed by the study authors.
**Significantly different from control ($p \leq 0.01$); Williams' or Dunnett's test performed by the study authors.

Table B.5. Mean Body Weights of Male and Female F344 Rats After Inhalation Exposure to Nitromethane for 13 Weeks[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]					
Male		**0**	**94 (43)**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Sample size		10	10	10	10	10	10
Weight[c] (g)	Initial	107 ± 3	105 ± 2 (98)	113 ± 2 (106)	109 ± 3 (102)	106 ± 2 (99)	109 ± 2 (102)
	Final	334 ± 7	323 ± 7 (97)	345 ± 4 (103)	336 ± 5 (101)	327 ± 4 (98)	295 ± 10 (88)**
	Change	228 ± 6	218 ± 7 (96)	232 ± 3 (102)	227 ± 4 (100)	221 ± 5 (97)	185 ± 9 (81)**
Female		**0**	**94 (43)**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Sample size		10	10	10	10	10	10
Weight[c] (g)	Initial	95 ± 1	96 ± 2 (101)	97 ± 2 (102)	95 ± 2 (100)	96 ± 2 (101)	94 ± 2 (99)
	Final	185 ± 5	197 ± 3 (106)	197 ± 3 (106)	198 ± 5 (107)	194 ± 4 (105)	177 ± 4 (96)
	Change	90 ± 3	101 ± 2 (112)	100 ± 2 (111)	103 ± 4 (114)**	97 ± 2 (108)	84 ± 3 (93)

[a]Source: NTP (1997).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Weights expressed as mean ± SE (% of control).

**Significantly different from control ($p \leq 0.01$); Williams' or Dunnett's test performed by study authors.

Table B.6. Select Hematology for Male and Female F344 Rats After Inhalation Exposure to Nitromethane for 13 Weeks[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]					
		0	94 (43)	188 (87)	375 (173)	750 (346)	1500 (691)
Male							
Sample size		10	10	10	10	10	10
Hematocrit[c] (%)	Day 3	36.7 ± 0.5	36.3 ± 0.3 (99)	35.2 ± 0.2 (96)*	33.1 ± 0.3 (90)**	31.7 ± 0.2 (86)**	32.3 ± 0.2 (88)**
	Day 23	40.7 ± 0.3[d]	43.2 ± 0.9 (106)[e]	40.4 ± 0.4 (99)[f]	37.6 ± 0.4 (92)*	34.0 ± 0.4 (84)**	30.3 ± 0.4 (74)**
	Week 13	46.3 ± 0.1	46.6 ± 0.4 (101)	46.1 ± 0.4 (100)	44.6 ± 0.3 (96)**	42.5 ± 0.4 (92)**	39.2 ± 0.4 (85)**
Hemoglobin[c] (g/dL)	Day 3	13.9 ± 0.2	13.5 ± 0.1 (97)	13.3 ± 0.1 (96)*	12.6 ± 0.1 (91)**	12.2 ± 0.1 (88)**	12.4 ± 0.1 (89)**
	Day 23	15.3 ± 0.2[d]	16.1 ± 0.3 (105)[e]	15.0 ± 0.1 (98)[f]	14.3 ± 0.1 (93)*	13.2 ± 0.1 (86)**	11.9 ± 0.1 (78)**
	Week 13	15.3 ± 0.1	15.4 ± 0.1 (101)	15.2 ± 0.1 (99)	14.8 ± 0.1 (97)**	14.3 ± 0.1 (93)**	13.4 ± 0.2 (88)**
Erythrocytes[c] (10^6/μL)	Day 3	7.75 ± 0.10	7.58 ± 0.08 (98)	7.38 ± 0.08 (95)**	7.16 ± 0.07 (92)**	6.97 ± 0.04 (90)**	6.94 ± 0.06 (90)**
	Day 23	8.74 ± 0.06[d]	9.37 ± 0.18 (107)*[e]	9.00 ± 0.07 (103)[f]	9.36 ± 0.09 (107)*	9.10 ± 0.09 (104)	7.77 ± 0.11 (89)
	Week 13	9.12 ± 0.03	9.43 ± 0.06 (103)**	9.53 ± 0.08 (104)**	9.72 ± 0.08 (107)**	10.10 ± 0.09 (111)**	9.41 ± 0.11 (103)**
Nucleated erythrocytes (10^3/μL)	Week 13	0.03 ± 0.02	0.04 ± 0.02 (133)	0.03 ± 0.03 (100)	0.11 ± 0.03 (367)	0.08 ± 0.03 (267)	0.27 ± 0.07 (900)**
MCV[c] (fL)	Day 3	47.2 ± 0.3	47.9 ± 0.3 (101)	47.7 ± 0.4 (101)	46.2 ± 0.1 (98)*	45.5 ± 0.2 (96)**	46.3 ± 0.2 (98)**
	Day 23	46.5 ± 0.3[d]	46.0 ± 0.2 (99)[e]	45.0 ± 0.4 (97)**[f]	40.2 ± 0.3 (86)**	37.5 ± 0.2 (81)**	39.1 ± 0.2 (84)**
	Week 13	50.7 ± 0.2	49.3 ± 0.2 (97)**	48.4 ± 0.2 (95)**	45.8 ± 0.4 (90)**	42.0 ± 0.6 (83)**	41.6 ± 0.3 (82)**
MCH[c] (pg)	Day 3	17.9 ± 0.1	17.8 ± 0.1 (99)	18.1 ± 0.1 (101)	17.6 ± 0.0 (98)*	17.5 ± 0.1 (98)*	17.9 ± 0.1 (100)
	Day 23	17.5 ± 0.02[d]	17.2 ± 0.1 (98)[e]	16.7 ± 0.1 (95)**[f]	15.3 ± 0.1 (87)**	14.5 ± 0.0 (83)**	15.3 ± 0.1 (87)**
	Week 13	16.8 ± 0.0	16.3 ± 0.1 (97)**	16.0 ± 0.0 (95)**	15.2 ± 0.1 (90)**	14.1 ± 0.2 (84)**	14.3 ± 0.1 (85)**
MCHC[c] (g/dL)	Day 3	37.8 ± 0.2	37.3 ± 0.1 (99)	37.8 ± 0.1 (100)	38.1 ± 0.1 (101)*	38.4 ± 0.2 (103)*	38.6 ± 0.1 (102)**
	Day 23	37.5 ± 0.2[d]	37.3 ± 0.1 (99)[e]	37.3 ± 0.2 (99)[f]	38.2 ± 0.3 (102)	38.8 ± 0.2 (103)*	39.3 ± 0.2 (105)**
	Week 13	33.0 ± 0.1	33.0 ± 0.1 (100)	33.0 ± 0.1 (100)	33.2 ± 0.1 (101)	33.6 ± 0.1 (102)**	34.3 ± 0.3 (104)**

Table B.6. Select Hematology for Male and Female F344 Rats After Inhalation Exposure to Nitromethane for 13 Weeks[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]					
		0	**94 (43)**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Platelets[c] (10^3/µL)	Day 3	663.6 ± 15.5	741.9 ± 13.8 (112)**	708.2 ± 13.5 (107)**	732.7 ± 17.8 (110)**	781.2 ± 10.5 (118)**	870.6 ± 16.3 (131)**
	Day 23	643.8 ± 44.1[d]	663.4 ± 8.8 (103)[e]	675.0 ± 16.0 (105)[f]	704.8 ± 19.2 (109)	878.4 ± 22.5 (136)**	1325.2 ± 24.0 (206)**
	Week 13	538.3 ± 7.5	527.8 ± 16.7 (98)	539.2 ± 5.7 (100)	578.7 ± 6.1 (108)**	625.0 ± 9.2 (116)**	817.4 ± 32.9 (152)**
Methemoglobin[c] (g/dL)	Day 3	0.16 ± 0.02[f]	0.14 ± 0.02 (88)[f]	0.19 ± 0.02 (119)[e]	0.34 ± 0.02 (213)**	0.21 ± 0.03 (131)*[g]	0.22 ± 0.02 (138)*[e]
	Day 23	0.08 ± 0.01[d]	0.06 ± 0.01 (75)[e]	0.08 ± 0.01 (100)[f]	0.16 ± 0.06 (200)	0.15 ± 0.01 (188)*	0.28 ± 0.02 (350)**
	Week 13	0.15 ± 0.01	0.17 ± 0.02 (113)	0.17 ± 0.01 (113)*	0.17 ± 0.01 (113)*	0.21 ± 0.01 (140)**	0.41 ± 0.09 (273)**
Female							
Sample size		10	10	10	10	10	10
Hematocrit[c] (%)	Day 3	38.9 ± 0.6	38.7 ± 0.3 (99)	38.1 ± 0.4 (98)	36.7 ± 0.3 (94)**	36.0 ± 0.3 (93)**	36.6 ± 0.4 (94)**
	Day 23	42.6 ± 0.3	40.5 ± 0.9 (95)**	41.1 ± 0.5 (96)*	37.9 ± 0.4 (89)**	35.2 ± 0.3 (83)**	31.7 ± 0.2 (74)**[e]
	Week 13	46.8 ± 0.3	46.6 ± 0.4 (100)	44.7 ± 0.4 (96)**	44.4 ± 0.5 (95)**	40.7 ± 0.4 (87)**	37.8 ± 0.4 (81)**
Hemoglobin[c] (g/dL)	Day 3	14.9 ± 0.2	14.9 ± 0.1 (100)	14.6 ± 0.2 (98)	14.0 ± 0.1 (94)**	13.7 ± 0.1 (92)**	14.1 ± 0.2 (95)**
	Day 23	16.2 ± 0.1	15.4 ± 0.3 (95)**	15.6 ± 0.2 (96)*	14.5 ± 0.1 (90)**	13.5 ± 0.1 (83)**	12.5 ± 0.1 (77)**[e]
	Week 13	16.0 ± 0.1	15.8 ± 0.1 (99)	15.3 ± 0.1 (96)**	15.3 ± 0.1 (96)**	14.1 ± 0.1 (88)**	13.4 ± 0.2 (84)**
Erythrocytes[c] (10^6/µL)	Day 3	8.39 ± 0.15	8.42 ± 0.07 (100)	8.34 ± 0.11 (99)	8.10 ± 0.09 (97)	7.87 ± 0.07 (94)**	8.14 ± 0.11 (97)*
	Day 23	9.03 ± 0.06	8.86 ± 0.18 (98)	9.35 ± 0.09 (104)	9.32 ± 0.09 (103)	9.14 ± 0.09 (101)	8.16 ± 0.06 (90)[e]
	Week 13	8.71 ± 0.05	8.91 ± 0.06 (102)	8.92 ± 0.09 (102)	9.42 ± 0.07 (108)**	9.24 ± 0.07 (106)**	8.51 ± 0.10 (98)
Nucleated erythrocytes[c]	Week 13	0.03 ± 0.01	0.07 ± 0.02 (233)	0.09 ± 0.04 (300)	0.06 ± 0.04 (200)	0.22 ± 0.09 (733)	0.30 ± 0.11 (1000)**
MCV[c] (fL)	Day 3	46.5 ± 0.2	45.8 ± 0.2 (98)*	45.6 ± 0.3 (98)*	45.3 ± 0.2 (97)**	45.7 ± 0.2 (98)**	45.0 ± 0.2 (97)**
	Day 23	47.0 ± 0.0	45.8 ± 0.2 (97)**	43.9 ± 0.2 (93)**	40.6 ± 0.2 (86)**	38.4 ± 0.2 (82)**	38.8 ± 0.2 (83)**[e]
	Week 13	53.9 ± 0.2	52.4 ± 0.2 (97)**	50.1 ± 0.3 (93)**	47.2 ± 0.2 (88)**	44.2 ± 0.5 (82)**	44.4 ± 0.4 (82)**

Table B.6. Select Hematology for Male and Female F344 Rats After Inhalation Exposure to Nitromethane for 13 Weeks[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]					
		0	94 (43)	188 (87)	375 (173)	750 (346)	1500 (691)
MCH[c] (pg)	Day 3	17.7 ± 0.1	17.7 ± 0.1 (100)	17.5 ± 0.1 (99)	17.3 ± 0.1 (98)**	17.4 ± 0.1 (98)**	17.3 ± 0.1 (98)**
	Day 23	18.0 ± 0.1	17.4 ± 0.1 (97)**	16.7 ± 0.1 (93)**	15.6 ± 0.1 (87)**	14.8 ± 0.1 (82)**	15.3 ± 0.1 (85)**[e]
	Week 13	18.3 ± 0.1	17.7 ± 0.1 (97)**	17.1 ± 0.1 (93)**	16.2 ± 0.1 (89)**	15.3 ± 0.1 (84)**	15.7 ± 0.1 (86)**
MCHC[c] (g/dL)	Day 3	38.1 ± 0.1	38.4 ± 0.1 (101)	38.4 ± 0.1 (101)	38.1 ± 0.1 (100)	38.1 ± 0.1 (100)	38.6 ± 0.1 (101)**
	Day 23	38.0 ± 0.2	38.1 ± 0.2 (100)	38.0 ± 0.2 (100)	38.2 ± 0.2 (101)	38.4 ± 0.2 (101)	39.5 ± 0.2 (104)**[e]
	Week 13	34.1 ± 0.2	33.9 ± 0.2 (99)	34.2 ± 0.2 (100)	34.4 ± 0.2 (101)	34.7 ± 0.2 (102)	35.4 ± 0.2 (104)**
Platelets[c] (10^3/µL)	Day 3	669.7 ± 26.8	586.2 ± 15.3 (88)*	609.0 ± 26.4 (91)	657.9 ± 17.9 (98)	668.0 ± 15.8 (100)	624.6 ± 17.6 (93)
	Day 23	649.2 ± 12.7	628.9 ± 14.4 (97)	637.2 ± 12.6 (98)	698.7 ± 14.0 (108)	811.9 ± 14.4 (125)**	1179.0 ± 18.5 (182)**[e]
	Week 13	534.2 ± 7.7	560.6 ± 10.8 (105)	528.4 ± 10.2 (99)	608.8 ± 11.7 (114)**	669.9 ± 10.8 (125)**	765.0 ± 32.6 (143)**
Methemoglobin[c] (g/dL)	Day 3	0.20 ± 0.03	0.27 ± 0.10 (135)	0.17 ± 0.04 (85)	0.10 ± 0.02 (50)*	0.11 ± 0.01 (55)	0.16 ± 0.01 (80)
	Day 23	0.09 ± 0.01	0.10 ± 0.01 (111)[f]	0.12 ± 0.01 (133)*	0.12 ± 0.01 (133)**	0.19 ± 0.01 (211)**	0.35 ± 0.01 (389)**[e]
	Week 13	0.20 ± 0.01	0.20 ± 0.01 (100)	0.20 ± 0.01 (100)	0.21 ± 0.01 (105)	0.25 ± 0.01 (125)**	0.40 ± 0.04 (200)**

[a]Source: NTP (1997).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Results expressed as mean ± SE (% of control).
[d]$n = 6$.
[e]$n = 8$.
[f]$n = 9$.
[g]$n = 7$.

*Significantly different from control ($p \leq 0.05$); Williams' or Dunnett's test performed by study authors.
**Significantly different from control ($p \leq 0.01$); Williams' or Dunnett's test performed by study authors.

Table B.7. Histopathological Findings for Male and Female F344 Rats After Inhalation Exposure to Nitromethane for 13 Weeks[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)					
Male		**0**	**94 (6.6)[b]**	**188 (13.9)**	**375 (27.1)**	**750 (53.0)**	**1500 (100.1)**
Nasal turbinates[c]	Degeneration, olfactory epithelium	0/10 (0)	–[d]	0/ 10 (0)	9/10** (90; 1.0)	10/10** (100; 1.0)	10/10** (100; 1.0)
	Hyaline droplets, respiratory epithelium	0/10 (0)	–[d]	0/10 (0)	0/10 (0)	1/10 (10; 1.0)	8/10 (80; 1.0)**
	Hyperplasia, goblet cell	0/10 (0)	–[d]	0/10 (0)	0/10 (0)	1/10 (10; 1.0)	10/10** (100; 2.0)
Male		**0**	**94 (43)[e]**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Sciatic nerve degeneration[c]		0/10 (0)	–[d]	0/10 (0)	5/10* (50; 1.0)	10/10** (100; 1.2)	10/10** (100; 1.5)
Spinal cord degeneration[c]		0/10 (0)	–[d]	0/10 (0)	9/10** (90; 1.0)	10/10** (100; 1.4)	10/10** (100; 2.0)
Bone marrow hyperplasia[c]		0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	9/10** (90; 1.1)	10/10** (100; 2.0)
Female		**0**	**94 (4.8)[b]**	**188 (9.7)**	**375 (19.2)**	**750 (38.1)**	**1500 (72.1)**
Nasal turbinates[c]	Degeneration, olfactory epithelium	0/10 (0)	0/10 (0)	1/10 (10; 1.0)	10/10** (100; 1.0)	10/10** (100; 1.2)	10/10** (100; 1.8)
	Hyaline droplets, respiratory epithelium	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	4/10* (40; 1.0)	10/10** (100; 1.0)
	Hyperplasia, goblet cell	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	2/10 (20; 1.5)	10/10** (100; 1.7)
Female		**0**	**94 (43)[e]**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Sciatic nerve degeneration[c]		0/10 (0)	–[d]	0/10 (0)	8/10** (80; 1.0)	10/10** (100; 1.1)	10/10** (100; 1.8)
Spinal cord degeneration[c]		0/10 (0)	–[d]	0/10 (0)	2/10 (20; 1.0)	10/10** (100; 1.4)	10/10** (100; 1.9)
Bone marrow hyperplasia[c]		0/10 (0)	0/10 (0)	1/10 (10; 2.0)	6/10** (60; 1.0)	7/10** (70; 1.1)	10/10** (100; 1.7)

[a]Source: NTP (1997).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × RGDR; body weights used to determine the RGDR were calculated as (initial body weight + final body weight) ÷ 2.
[c]Values expressed as number observed with neoplasm/number examined for that neoplasm (% incidence; average severity of lesions 1 = minimal, 2 = mild, 3 = moderate, 4 = marked).
[d]Not examined at this exposure concentration.
[e]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
*Significantly different from control ($p \leq 0.05$); Fischer exact test performed by study authors.
**Significantly different from control ($p \leq 0.01$); Fischer exact test performed by study authors.

Table B.8. Neurological Data for Male and Female F344 Rats After Inhalation Exposure to Nitromethane for 13 Weeks[a]

Parameter[b]	Exposure Group, ppm (HEC, mg/m^3)[c]					
Male	**0**	**94 (43)**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Sample size	10	10	10	10	10	10
Forelimb grip strength (kg)	0.617 ± 0.025	0.554 ± 0.015 (90)	0.583 ± 0.037 (94)	0.592 ± 0.021 (96)	0.568 ± 0.029 (92)	0.471 ± 0.024 (76)**
Hindlimb grip strength (kg)	0.433 ± 0.020	0.399 ± 0.026 (92)	0.407 ± 0.020 (94)	0.378 ± 0.023 (87)	0.382 ± 0.017 (88)	0.213 ± 0.020 (49)**
Female	**0**	**94 (43)**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Sample size	10	10	10	10	10	10
Forelimb grip strength (kg)	0.598 ± 0.020	0.633 ± 0.021 (106)	0.700 ± 0.011 (117)**	0.619 ± 0.029 (104)	0.585 ± 0.019 (98)	0.632 ± 0.018 (106)
Hindlimb grip strength (kg)	0.403 ± 0.018	0.425 ± 0.011 (105)	0.435 ± 0.014 (108)	0.419 ± 0.013 (104)	0.333 ± 0.019 (83)**	0.209 ± 0.015 (52)**

[a]Source: NTP (1997).
[b]Results expressed as mean ± SE (% of control).
[c]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.

**Significantly different from control ($p \leq 0.01$); Williams' or Dunnett's test performed by study authors.

Table B.9. Reproductive Tissue Data for Male F344 Rats After Inhalation Exposure to Nitromethane for 13 Weeks[a]

Parameter[b]	Exposure Group, ppm (HEC, mg/m^3)[c]			
Male	**0**	**375 (173)**	**750 (346)**	**1500 (691)**
Sample size	10	10	10	10
Necropsy body weight (g)	338 ± 7	341 ± 4 (101)	331 ± 4 (98)	299 ± 11 (88)**
Left cauda weight (g)	0.207 ± 0.004	0.210 ± 0.004 (101)	0.204 ± 0.006 (99)	0.177 ± 0.009 (86)**
Left epididymis weight (g)	0.467 ± 0.009	0.468 ± 0.006 (100)	0.444 ± 0.009 (95)	0.412 ± 0.013 (88)**
Left testis weight (g)	1.39 ± 0.03	1.36 ± 0.01 (98)	1.34 ± 0.02 (96)	1.29 ± 0.02 (93)**
Sperm motility (%)	94.57 ± 1.30	92.16 ± 1.90 (97)	87.11 ± 1.88 (92)**	76.43 ± 2.78 (81)**
Sperm concentration (10^6/g cauda epididymal tissue)	449 ± 45	483 ± 24 (108)	434 ± 35 (97)	380 ± 42 (85)

[a]Source: NTP (1997).
[b]Results expressed as mean ± SE (% of control).
[c]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.

**Significantly different from control ($p \leq 0.01$); Williams' or Dunnett's test performed by study authors.

Table B.10. Select Hematology Parameters for Male Sprague-Dawey Rats After Inhalation Exposure to Nitromethane[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]		
		0	**98 (51)**	**745 (388)**
Sample size[c]		10	10	10
Hematocrit[d] (‰)	10 d	41.0 ± 0.5	40.0 ± 0.5 (98)*	39.0 ± 0.9 (95)*
	1 mo	44.0 ± 0.3	43.0 ± 0.4 (98)	42.0 ± 0.4 (95)**
	3 mo	44.0 ± 0.7	44.0 ± 0.7 (100)	41.0 ± 0.3 (93)**
	6 mo	43.0 ± 0.5	43.0 ± 0.7 (100)	40.0 ± 0.8 (93)**
Hemoglobin[d] (%)	10 d	13.9 ± 0.21	13.3 ± 0.17 (96)*	12.9 ± 0.25 (93)**
	1 mo	14.6 ± 0.13	14.9 ± 0.16 (102)	13.7 ± 0.17 (94)**
	3 mo	14.8 ± 0.23	14.6 ± 0.26 (99)	13.0 ± 0.22 (88)**
	6 mo	14.0 ± 0.23	14.6 ± 0.23 (104)	12.3 ± 0.22 (88)**

[a]Source: Lewis et al. (1979) and Huntingdon Research Center (1989).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Sample size was generally 9–10 animals per measurement, but the sample size was not always indicated.
[d]Expressed as mean ± SE (% of control).

*Significantly different from control ($p \leq 0.05$); Student's *t*-test performed by study authors.
**Significantly different from control ($p \leq 0.01$); Student's *t*-test performed by study authors.

Table B.11. Liver and Kidney Weights of Male and Female B6C3F$_1$ Mice After Inhalation Exposure to Nitromethane for 13 Weeks[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]					
Male		**0**	**94 (43)**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Sample size		10	10	10	10	10	10
Necropsy body weight[c] (g)		36.1 ± 0.5	35.9 ± 0.5 (99)	35.5 ± 0.8 (98)	36.3 ± 0.6 (101)	35.2 ± 0.4 (98)	34.7 ± 0.5 (96)
Right kidney weight[c]	Absolute (g)	0.294 ± 0.009	0.329 ± 0.006 (112)**	0.322 ± 0.005 (110)*	0.332 ± 0.007 (113)**	0.339 ± 0.007 (115)**	0.315 ± 0.008 (107)
	Relative (mg/g)	8.15 ± 0.20	9.15 ± 0.11 (112)**	9.10 ± 0.15 (112)**	9.15 ± 0.20 (112)**	9.63 ± 0.20 (118)**	9.08 ± 0.18 (111)**
Liver weight[c]	Absolute (g)	1.633 ± 0.040	1.700 ± 0.023 (104)	1.678 ± 0.031 (103)	1.731 ± 0.027 (106)	1.789 ± 0.029 (110)*	1.724 ± 0.053 (106)
	Relative (mg/g)	45.27 ± 0.89	47.32 ± 0.38 (105)	47.39 ± 0.78 (105)	47.70 ± 0.60 (105)*	50.79 ± 0.72 (112)**	49.62 ± 0.99 (110)**
Female		**0**	**94 (43)**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Sample size		10	10	10	10	10	10
Necropsy body weight[c] (g)		31.1 ± 0.7	31.5 ± 0.7 (101)	32.8 ± 0.7 (105)	34.2 ± 0.8 (110)**	31.5 ± 0.5 (101)	30.4 ± 0.5 (98)
Right kidney weight[c]	Absolute (g)	0.210 ± 0.007	0.221 ± 0.005 (105)	0.228 ± 0.005 (109)*	0.232 ± 0.005 (110)*	0.231 ± 0.006 (110)*	0.230 ± 0.006 (110)
	Relative (mg/g)	6.75 ± 0.18	7.03 ± 0.15 (104)	6.97 ± 0.15 (103)	6.80 ± 0.17 (101)	7.33 ± 0.21 (109)*	7.57 ± 0.15 (112)**
Liver weight[c]	Absolute (g)	1.536 ± 0.033	1.590 ± 0.030 (104)	1.604 ± 0.044 (104)	1.639 ± 0.037 (107)	1.563 ± 0.041 (102)	1.575 ± 0.050 (103)
	Relative (mg/g)	49.49 ± 0.99	50.64 ± 1.15 (102)	48.89 ± 0.72 (99)	47.97 ± 0.95 (97)	49.52 ± 0.76 (100)	51.77 ± 1.25 (105)

[a]Source: NTP (1997).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Weights expressed as mean ± SE (% of control).

*Significantly different from control ($p \leq 0.05$); Williams' or Dunnett's test performed by study authors.
**Significantly different from control ($p \leq 0.01$); Williams' or Dunnett's test performed by study authors.

Table B.12. Reproductive Tissue Data for Male and Female B6C3F$_1$ Mice After Inhalation Exposure to Nitromethane for 13 Weeks[a]

Parameter	Exposure Group, ppm (HEC, mg/m^3)[b]			
Male	**0**	**375 (173)**	**750 (346)**	**1500 (691)**
Sample size	10	10	10	10
Sperm motility (%)[c]	93.50 ± 0.46	85.09 ± 1.21 (91)**	86.47 ± 1.17 (92)**	82.41 ± 1.30 (88)**
Female	**0**	**375 (173)**	**750 (346)**	**1500 (691)**
Sample size	10	10	10	10
Estrous cycle length (days)[c,d]	4.00 ± 0.00	4.33 ± 0.14 (108)*	4.50 ± 0.21 (113)*	4.71 ± 0.26 (118)**

[a]Source: NTP (1997).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Results expressed as mean ± SE (% of control).
[d]Estrous cycle was longer than 12 days or was unclear for at least one mouse in all groups except the 750-ppm group.

*Significantly different from control ($p \leq 0.05$); Shirley's test performed by study authors.
**Significantly different from control ($p \leq 0.01$); Shirley's test performed by study authors.

Table B.13. Histopathological Findings for Male and Female B6C3F$_1$ Mice After Inhalation Exposure to Nitromethane for 13 Weeks[a]

Parameter[b]		Exposure Group, ppm (HEC, mg/m^3)					
Male		**0**	**94 (7.1)[c]**	**188 (14.1)**	**375 (28.0)**	**750 (55.7)**	**1500 (112.7)**
Nasal turbinates	Degeneration, olfactory epithelium	0/10 (0)	0/10 (0)	0/ 10 (0)	10/10** (100; 1.0)	10/10** (100; 1.3)	10/10** (100; 2.0)
	Hyaline droplets, respiratory epithelium	0/10 (0)	0/10 (0)	1/10 (10; 1.0)	10/10** (100; 1.0)	10/10** (100; 1.0)	10/10** (100; 2.0)
Male		**0**	**94 (43)[d]**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Spleen, extramedullary hematopoiesis		0/10 (0)	1/10 (10; 1.0)	0/10 (0)	1/10 (10; 1.0)	2/10 (20; 1.0)	10/10** (100; 1.0)
Female		**0**	**94 (5.9)[c]**	**188 (12.2)**	**375 (24.9)**	**750 (48.0)**	**1500 (93.9)**
Nasal turbinates	Degeneration, olfactory epithelium	0/10 (0)	0/10 (0)	7/10** (70; 1.0)	10/10** (100; 1.0)	10/10** (100; 2.0)	10/10** (100; 3.0)
	Hyaline droplets, respiratory epithelium	0/10 (0)	2/10 (20; 1.0)	9/10** (90; 1.0)	10/10** (100; 2.0)	10/10** (100; 2.0)	10/10** (100; 3.0)
Female		**0**	**94 (43)[d]**	**188 (87)**	**375 (173)**	**750 (346)**	**1500 (691)**
Spleen, extramedullary hematopoiesis		0/10 (0)	0/10 (0)	0/10 (0)	2/10 (20; 1.0)	3/10 (30; 1.0)	9/10** (90; 1.0)

[a]Source: NTP (1997).
[b]Values expressed as number observed with neoplasm/number examined for that neoplasm (% incidence; average severity of lesions 1 = minimal, 2 = mild, 3 = moderate, 4 = marked).
[c]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × RGDR; body weights used were for determining the RGDR were calculated as (initial body weight + final body weight) ÷ 2.
[d]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.

**Significantly different from control ($p \leq 0.01$); Fischer exact test performed by study authors.

Table B.14. Select Clinical Chemistry Parameters for Male New Zealand White Rabbits After Inhalation Exposure to Nitromethane[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]		
		0	98 (51)	745 (388)
Sample size[c]		5	5	5
OCT[d] (Su/mL)	1 mo	470 ± 147.9	788 ± 65.7 (167)*	1790 ± 310.0 (381)*
	3 mo	840 ± 277.2	1363 ± 170.0 (162)	1970 ± 159.4 (235)*
	6 mo	2940 ± 1591.5	1650 ± 352.1 (56)	1110 ± 259.0 (38)
Thyroxin[d] (µg/dL)	1 mo	3.4 ± 0.42	2.8 ± 0.82 (82)	1.9 ± 0.39 (56)*
	3 mo	2.2 ± 0.38	0.8 ± 0.43 (36)	1.4 ± 0.31 (64)
	6 mo	2.1 ± 0.28	1.1 ± 0.33 (52)*	1.0 ± 0.23 (48)*

[a]Source: Lewis et al. (1979) and Huntingdon Research Center (1989).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Sample size per measurement was not specified, but five animals per treatment group were used.
[d]Expressed as mean ± SE (% of control).

*Significantly different from control ($p \leq 0.05$); Mann-Whitney U test performed by the study authors.

Table B.15. Thyroid Weights of Male Sprague-Dawley Rats After Inhalation Exposure to Nitromethane for 6 Months[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]		
		0	98 (51)	745 (388)
Thyroid weight[c]	Sample size	10	10	10
	Absolute (mg)	22.5 ± 1.3	26.7 ± 1.7 (119)	28.3 ± 0.8 (126)**
	Relative (% × 1000)	3.9 ± 0.2	4.4 ± 0.2 (113)	5.3 ± 0.2 (136)**

[a]Source: Lewis et al. (1979).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Values expressed as mean ± SE (% of control).

**Significantly different from control ($p \leq 0.01$); Student's *t*-test performed by the study authors.

Table B.16. Nonneoplastic Lesions in Male and Female B6C3F$_1$ Mice After Inhalation Exposure to Nitromethane for 103 Weeks[a]

Parameter[b]		Exposure Group, ppm (HEC, mg/m^3)			
Males		**0**	**188 (22.2)[c]**	**375 (44.9)**	**750 (91.6)**
Nose	Nasolacrimal duct, Inflammation	2/50 (4) (1.5)	3/49 (6) (1.3)	10/50 (20)* (1.9)	10/50 (20)* (1.9)
	Olfactory epithelium, atrophy, focal	3/50 (6) (1.0)	8/49 (16)* (1.1)	0/50 (0)	0/50 (0)
	Olfactory epithelium, degeneration	0/50 (0)	10/49 (20)** (1.1)	50/50 (100)** (2.5)	50/50 (100)** (3.1)
	Olfactory epithelium, metaplasia	0/50 (0)	1/49 (2) (2.0)	41/50 (82)** (1.8)	49/50 (98)** (2.0)
	Respiratory epithelium, degeneration, hyaline	5/50 (10) (1.0)	5/49 (10) (1.2)	50/50 (100)** (1.9)	50/50 (100)** (2.0)
Females		**0**	**188 (87)[d]**	**375 (173)**	**750 (346)**
Liver	Eosinophilic focus	4/50 (8)	7/49 (14)	11/49 (22)*	15/50 (30)*
Females		**0**	**188 (21.9)[c]**	**375 (43.2)**	**750 (87.9)**
Nose	Nasolacrimal duct, Inflammation	1/50 (2) (2.0)	0/49 (0)	3/50 (6) (1.7)	3/50 (6) (2.0)
	Olfactory epithelium, atrophy, focal	2/50 (4) (1.0)	6/49 (12) (1.0)	0/50 (0)	0/50 (0)
	Olfactory epithelium, degeneration	0/50 (0)	22/49 (45)** (1.1)	50/50 (100)** (2.7)	50/50 (100)** (3.2)
	Olfactory epithelium, metaplasia	0/50 (0)	2/49 (4) (1.0)	46/50 (92)** (1.9)	48/50 (96)** (2.2)
	Respiratory epithelium, degeneration, hyaline	16/50 (32) (1.1)	39/49 (80)** (1.5)	50/50 (100)** (2.0)	50/50 (100)** (2.5)

[a]Source: NTP (1997).
[b]Values expressed as number observed with neoplasm/number examined for that neoplasm (% incidence) (severity when available).
[c]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × RGDR; average body weights from the study were used to determine the RGDR.
[d]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.

*Significantly different from control ($p \leq 0.05$); Logistic regression test performed by the study authors.
**Significantly different from control ($p \leq 0.01$); Logistic regression test performed by the study authors.

Table B.17. Thyroid Weights of Male New Zealand White Rabbits After Inhalation Exposure to Nitromethane for 6 Months[a]

Parameter		Exposure Group, ppm (HEC, mg/m^3)[b]		
		0	98 (51)	745 (388)
Thyroid weight[c]	Sample size	5	5	5
	Absolute (mg)	235 ± 33	265 ± 31 (113)	325 ± 31 (138)
	Relative (% × 1000)	6.0 ± 0.6	7.0 ± 1.0 (117)	8.0 ± 0.7 (133)

[a]Source: Lewis et al. (1979d).
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Values expressed as mean ± SE (% of control).

Table B.18. Mammary Tumors in Female F344 Rats After Inhalation Exposure to Nitromethane for 103 Weeks[a]

Parameter[c]	Exposure Group, ppm (HEC, mg/m^3)[b]			
	0	94 (43)	188 (87)	375 (173)
Fibroadenoma	19/50 (38)	21/50 (42)	33/50 (66)**	36/50 (72)**
Fibroadenoma or adenoma	20/50 (40)	21/50 (42)	33/50 (66)**	36/50 (72)**
Carcinoma	2/50 (4)	7/50 (14)	1/50 (2)	11/50 (22)**
Adenoma or carcinoma	4/50 (8)	7/50 (14)	1/50 (2)	13/50 (26)*
Fibroadenoma, adenoma, or carcinoma	21/50 (42)	25/50 (50)	34/50 (68)**	41/50 (82)**

[a]Source: NTP (1997) .
[b]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[c]Values expressed as number observed with neoplasm/number examined for that neoplasm (% incidence).

*Significantly different from control ($p \leq 0.05$); Fischer exact test performed by the study authors.
**Significantly different from control ($p \leq 0.01$); Fischer exact test performed by the study authors.

Table B.19. Neoplastic Lesions in Male and Female B6C3F$_1$ Mice After Inhalation Exposure to Nitromethane for 103 Weeks[a]

Parameter[b]		Exposure Group, ppm (HEC, mg/m^3)			
Males		**0**	**188 (87)[c]**	**375 (173)**	**750 (346)**
Harderian gland	Adenoma	9/50 (18)	10/50 (20)	19/50 (38)*	32/50 (64)**
	Carcinoma	1/50 (2)	1/50 (2)	6/50 (12)	5/50 (10)
	Adenoma or carcinoma	10/50 (20)	11/50 (22)	25/50 (50)**	37/50 (74)**
Males		**0**	**188 (359)[d]**	**375 (727)**	**750 (1484)**
Lung	Alveolar/bronchiolar adenoma	11/50 (22)	10/50 (20)	9/50 (18)	12/50 (24)
	Alveolar/bronchiolar carcinoma	2/50 (4)	3/50 (6)	3/50 (6)	11/50 (22)**
	Alveolar/bronchiolar adenoma or carcinoma	13/50 (26)	13/50 (26)	12/50 (24)	20/50 (40)
Females		**0**	**188 (87)[b]**	**375 (173)**	**750 (346)**
Harderian gland	Adenoma	5/50 (10)	7/50 (14)	16/50 (32)**	19/50 (38)**
	Carcinoma	1/50 (2)	2/50 (4)	4/50 (8)	3/50 (6)
	Adenoma or carcinoma	6/50 (12)	9/50 (18)	20/50 (40)**	21/50 (42)**
Liver	Hepatocellular adenoma	14/50 (28)	25/49 (51)*	17/49 (35)	35/50 (70)**
	Hepatocellular adenoma, multiple	3/50 (6)	13/49 (27)**	4/49 (8)	13/50 (26)**
	Hepatocellular carcinoma	10/50 (20)	14/49 (29)	8/49 (16)	12/50 (24)
	Hepatocellular adenoma or carcinoma	19/50 (38)	34/49 (69)**	22/49 (45)	40/50 (80)**
Females		**0**	**188 (355)[d]**	**375 (700)**	**750 (1423)**
Lung	Alveolar/bronchiolar adenoma	3/50 (6)	3/50 (6)	2/49 (4)	9/50 (18)
	Alveolar/bronchiolar carcinoma	0/50 (0)	3/50 (6)	5/49 (10)*	3/50 (6)
	Alveolar/bronchiolar adenoma or carcinoma	3/50 (6)	6/50 (12)	6/49 (12)	12/50 (24)*

[a]Source: NTP (1997).
[b]Values expressed as number observed with neoplasm/number examined for that neoplasm (% incidence).
[c]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × blood:gas partition coefficient.
[d]Doses are converted from ppm to mg/m^3 using the following equation: HEC = ppm × (molecular weight ÷ 24.45) × (hours per day ÷ 24) × (days dosed ÷ total days) × $RGDR_{TB+PU}$; average body weights from the study were used to determine the RGDR.

*Significantly different from control ($p \leq 0.05$); Logistic regression test performed by the study authors.
**Significantly different from control ($p \leq 0.01$); Logistic regression test performed by the study authors.

APPENDIX C. BMD OUTPUTS

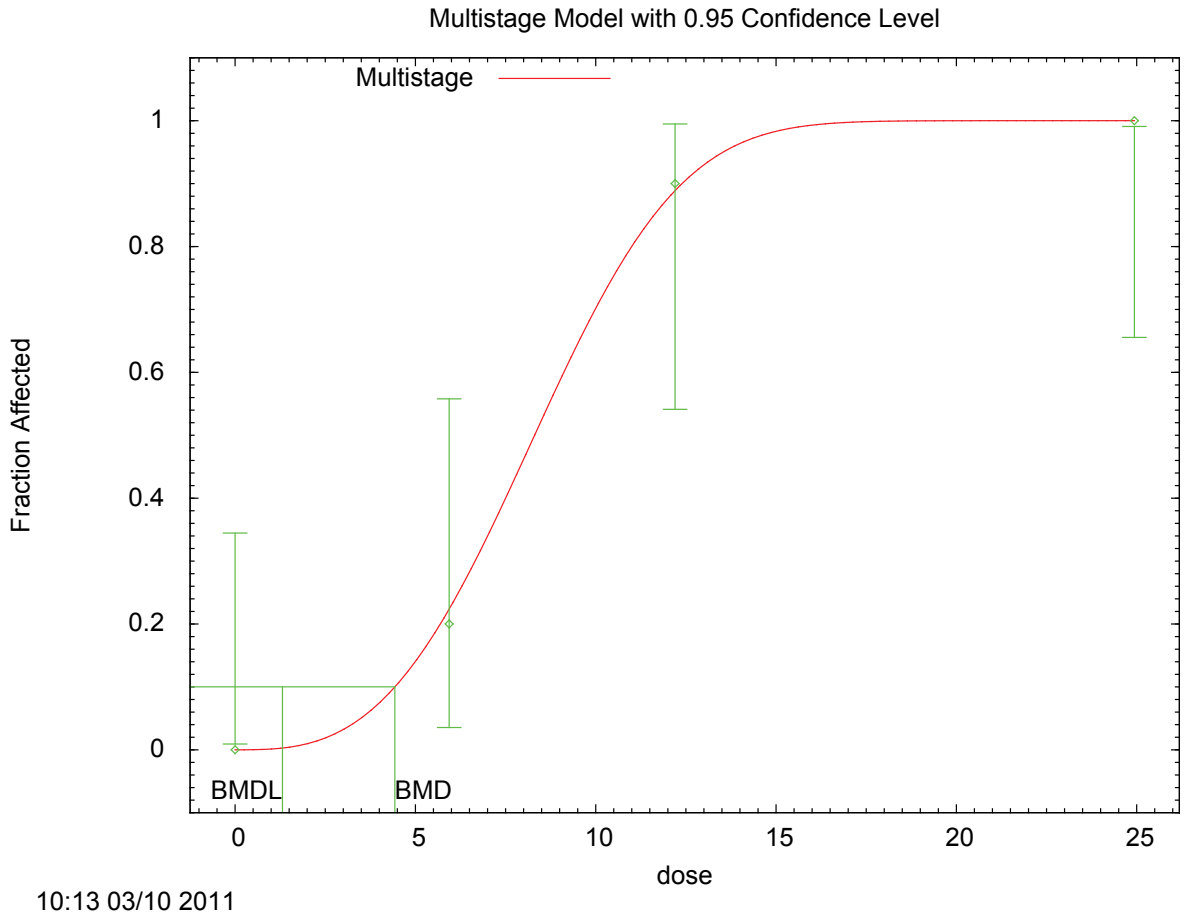

Figure C.1. Multistage BMD Model for Respiratory Epithelium Hyaline Droplets Data (NTP, 1997)

Text Output for Multistage BMD Model for Respiratory Epithelium Hyaline Droplets Data (NTP, 1997)

```
 ======================================================================
        Multistage Model. (Version: 3.2;  Date: 05/26/2010)
        Input Data File:
C:/1/NTP97_13wk_RespEpiHyalDrop_F_mouse_HiDosDrop_Multi3_1.(d)
        Gnuplot Plotting File:
C:/1/NTP97_13wk_RespEpiHyalDrop_F_mouse_HiDosDrop_Multi3_1.plt
                                          Thu Mar 10 10:13:45 2011
 ======================================================================

 [add_notes_here]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:
```

```
   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = DichEff
   Independent variable = Dose

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


 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
                        Beta(2) =            0
                        Beta(3) = 6.66264e+015


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                Beta(3)

   Beta(3)            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0           *                *                  *
        Beta(1)                0           *                *                  *
        Beta(2)                0           *                *                  *
        Beta(3)       0.00121122           *                *                  *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -8.25485         4
   Fitted model        -8.27784         1     0.0459631      3          0.9974
  Reduced model        -27.6759         1        38.842      3         <.0001
```

AIC: 18.5557

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	10	0.000
5.9362	0.2238	2.238	2.000	10	-0.181
12.1994	0.8891	8.891	9.000	10	0.110
24.9367	1.0000	10.000	10.000	10	0.000

Chi^2 = 0.04 d.f. = 3 P-value = 0.9975

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 4.43082

BMDL = 1.31366

BMDU = 5.42422

Taken together, (1.31366, 5.42422) is a 90 % two-sided confidence interval for the BMD

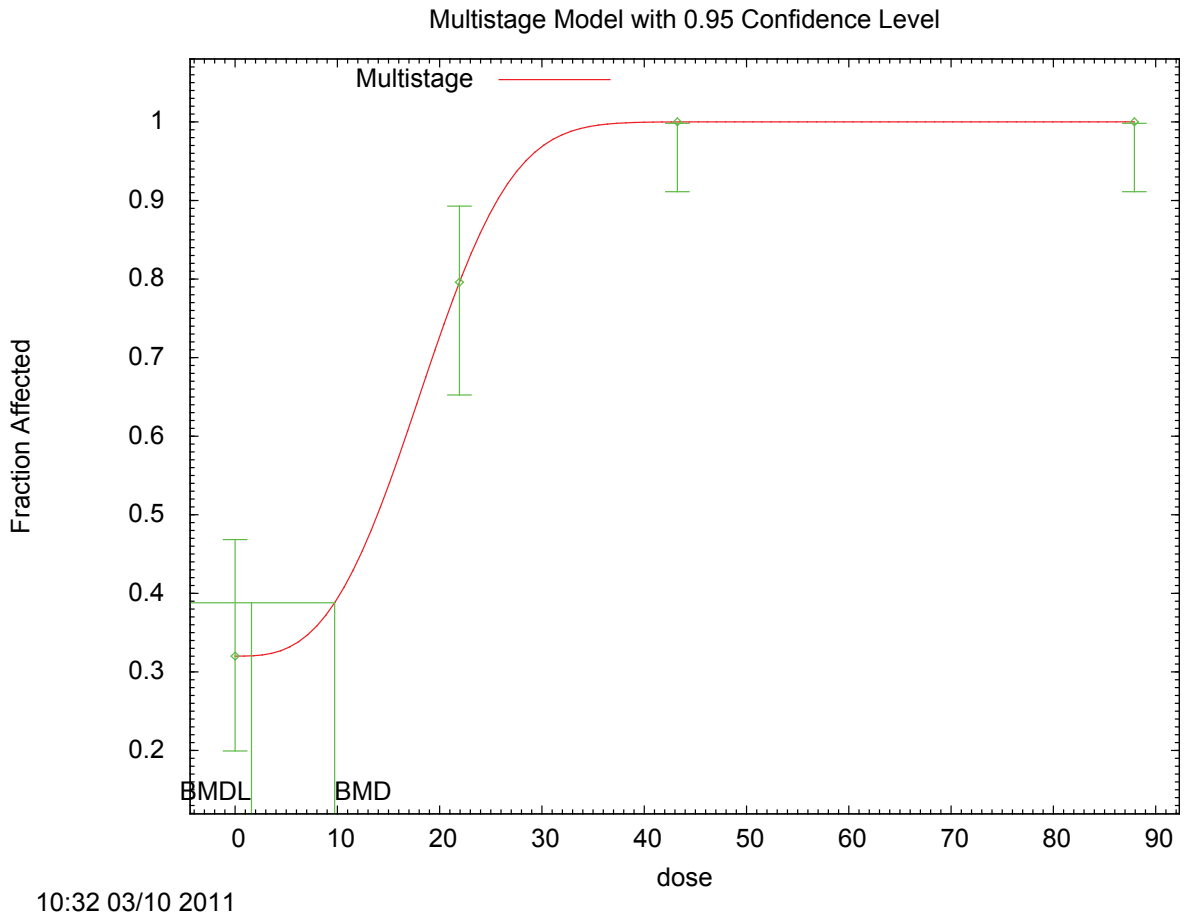

Figure C.2. Multistage BMD Model for Respiratory Epithelium Degeneration Data (NTP, 1997)

Text Output for Multistage BMD Model for Respiratory Epithelium Degeneration Data (NTP, 1997)

```
 ======================================================================
        Multistage Model. (Version: 3.2;  Date: 05/26/2010)
        Input Data File: C:/1/NTP97_103wk_RespEpiDegHyal_F_mouse_Multi3_1.(d)
        Gnuplot Plotting File:  C:/1/NTP97_103wk_RespEpiDegHyal_F_mouse_Multi3_1.plt
                                          Thu Mar 10 10:32:54 2011
 ======================================================================

 [add_notes_here]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive
```

```
   Dependent variable = DichEff
   Independent variable = Dose

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


 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 =            1
                        Beta(1) = 1.29371e+018
                        Beta(2) =            0
                        Beta(3) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

             Background      Beta(3)

Background            1        -0.47

   Beta(3)        -0.47            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background         0.319859           *                *                  *
        Beta(1)                0           *                *                  *
        Beta(2)                0           *                *                  *
        Beta(3)      0.000114246           *                *                  *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -56.1379         4
   Fitted model        -56.1413         2    0.00669167      2          0.9967
  Reduced model        -105.132         1        97.989      3         <.0001

           AIC:         116.283
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.3199	15.993	16.000	50	0.002
21.9354	0.7963	39.020	39.000	49	-0.007
43.2380	0.9999	49.997	50.000	50	0.058
87.9212	1.0000	50.000	50.000	50	0.000

Chi^2 = 0.00 d.f. = 2 P-value = 0.9983

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 9.73372

BMDL = 1.60241

BMDU = 11.3184

Taken together, (1.60241, 11.3184) is a 90 % two-sided confidence interval for the BMD

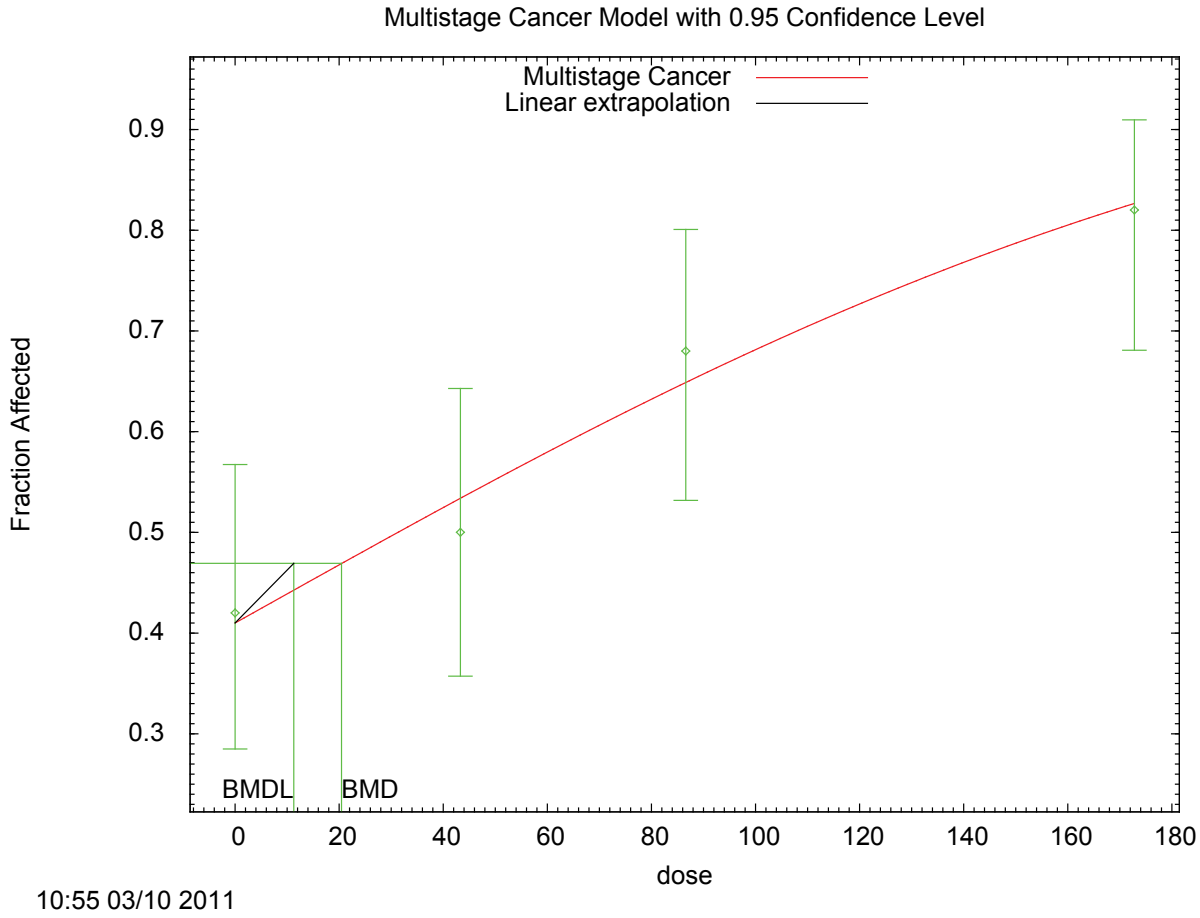

Figure C.3. Multistage Cancer BMD Model for Mammary Fibroadenoma, Adenoma, or Carcinoma Data (NTP, 1997)

Text Output for Multistage-Cancer BMD Model for Mammary Fibroadenoma, Adenoma, or Carcinoma Data (NTP, 1997)

```
 ======================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File:
C:/1/NTP97_103wk_MamFibroadenoORAdenoORCarc_F_rat_MultiCanc3_1.(d)
        Gnuplot Plotting File:
C:/1/NTP97_103wk_MamFibroadenoORAdenoORCarc_F_rat_MultiCanc3_1.plt
                                          Thu Mar 10 10:55:56 2011
 ======================================================================

 [add_notes_here]
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]
```

The parameter betas are restricted to be positive

Dependent variable = DichEff
Independent variable = Dose

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

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 = 0.400606
Beta(1) = 0.00594339
Beta(2) = 6.26236e-006
Beta(3) = 0

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(3)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(1)	Beta(2)
Background	1	-0.67	0.49
Beta(1)	-0.67	1	-0.94
Beta(2)	0.49	-0.94	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.410209	*	*	*
Beta(1)	0.004892	*	*	*
Beta(2)	1.26923e-005	*	*	*
Beta(3)	0	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-123.585	4			
Fitted model	-123.826	3	0.481622	1	0.4877
Reduced model	-134.186	1	21.2027	3	<.0001

AIC: 253.652

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.4102	20.510	21.000	50	0.141
43.3000	0.5340	26.701	25.000	50	-0.482
86.6000	0.6489	32.447	34.000	50	0.460
172.8000	0.8266	41.331	41.000	50	-0.124

Chi^2 = 0.48 d.f. = 1 P-value = 0.4887

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 20.452

BMDL = 11.2764

BMDU = 67.5516

Taken together, (11.2764, 67.5516) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00886811

Table C.1. Multistage Cancer Model Predictions for Tumor Data for Nitromethane[a]

Endpoint	Sex	Species	IUR[d]	Goodness-of-Fit *p*-Value[b]	AIC[c]
Mammary fibroadenoma, adenoma, or carcinoma	F	Rat	0.00886811	0.4887	253.65
Mammary fibroadenoma or adenoma	F	Rat	0.00717979	0.1631	263.41
Mammary fibroadenoma	F	Rat	0.00705667	0.3518	263.95
Hepatocellular adenoma or carcinoma	F	Mouse	0.00338166	0.0008	261.71
Harderian gland adenoma or carcinoma	M	Mouse	0.00283946	0.1674	237.29
Hepatocellular adenoma	F	Mouse	0.00254843	0.0121	263.79
Harderian gland adenoma	M	Mouse	0.00214776	0.4731	235.45
Harderian gland adenoma or carcinoma	F	Mouse	0.00194971	0.2630	225.79
Harderian gland adenoma	F	Mouse	0.00164856	0.4568	207.67
Mammary carcinoma	F	Rat	0.00126694	0.0245	131.45
Harderian gland carcinoma	M	Mouse	0.00055152	0.2574	95.47
Hepatocellular carcinoma	F	Mouse	0.00050530	0.3112	213.71
Harderian gland carcinoma	F	Mouse	0.00038784	0.5942	82.16

[a]NTP (1997).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]AIC = Akaike's Information Criteria.
[d]As calculated by BMDS.

APPENDIX D. REFERENCES

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