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Provisional Peer-Reviewed Toxicity Values for

N,N-Dimethylaniline
(CASRN 121-69-7)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *N,N*-DIMETHYLANILINE (CASRN 121-69-7)

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 Environmental 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 derived values. It is not intended to be a comprehensive treatise on a given chemical or its toxicological nature.

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 use 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 a 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 this toxicity 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.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVS

Questions regarding the content 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

N,N-Dimethylaniline, CASRN 121-69-7, is used as a chemical intermediate, notably in the manufacture of dyes and vanillin (HSDB, 2014). It is also used as a stabilizer, a catalytic hardener for fiberglass, an activator for polyester, and an extraction solvent for refining sulfur dioxide (HSDB, 2014). *N,N*-Dimethylaniline has been found as a synthetic impurity in β-lactam antibiotics (IARC, 1993). It has also been detected in soil and lake and river waters near industrial sources (IARC, 1993). *N,N*-Dimethylaniline is regulated under Sections 8(a) and 8(d) of the Toxic Substances Control Act (TSCA) (40 CFR 712.30 and 716.20 [7/1/99]). It is also listed as a hazardous air pollutant (HAP) under the Clean Air Act as amended in 1990 (CAA, 1990). *N,N*-Dimethylaniline may also be referred to as *N,N*-dimethylbenzeneamine, (dimethylamino)benzene, *N,N*-dimethylaminobenzene, dimethylaniline, dimethylphenylamine, and *N,N*-dimethylphenylamine (IARC, 1993; U.S. EPA, 1987).

N,N-Dimethylaniline is liquid at room temperature. Its low melting point (2.5°C) suggests that it may solidify at colder ambient temperatures. The estimated Henry's law constant of the neutral form of *N,N*-dimethylaniline indicates moderate volatilization from moist soil and water surfaces. Based on the moderate vapor pressure, the neutral form of *N,N*-dimethylaniline is not expected to volatize from dry soils, but if released to the air, *N,N*-dimethylaniline would remain in the vapor phase (HSDB, 2014). *N,N*-Dimethylaniline is expected to exist partially as a cation in the environment: the pKa value of its conjugate acid is 5.15. The cationic form of *N,N*-dimethylaniline is not expected to volatilize from either water or soil (HSDB, 2014). *N,N*-Dimethylaniline's ability to leach from soil to groundwater is dependent on local conditions. In areas with high amounts of organic matter, leaching of *N,N*-dimethylaniline may be inhibited due to the high reactivity of the aromatic amine group; the protonated form of *N,N*-dimethylaniline is expected to bind strongly to soil surfaces (HSDB, 2014). In other areas, *N,N*-dimethylaniline deposited on soil is likely to leach to groundwater or undergo runoff after a rain event, due to its moderate water solubility and relatively low soil absorption coefficient. As a result, removal of *N,N*-dimethylaniline from soil by leaching with water will likely compete with volatilization, depending on the local conditions. The empirical formula for *N,N*-dimethylaniline is $C_8H_{11}N$ (see Figure 1). Some physicochemical properties of *N,N*-dimethylaniline are shown in Table 1.

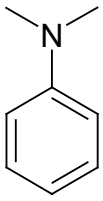

Figure 1. *N,N*-Dimethylaniline Structure

Table 1. Physicochemical Properties of *N,N*-Dimethylaniline (CASRN 121-69-7)

Property (unit)	Value
Physical state	Pale yellow, oily liquid[a]
Boiling point (°C)	193.54[a]
Melting point (°C)	2.50[a]
Density (g/cm^3)	0.956[a]
Vapor pressure (mm Hg at 25°C)	0.70[a]
pH (unitless)	6.46 for a 1% aqueous solution[a]
pKa (at 25°C)	5.15 for conjugate acid[a]
Solubility in water (g/L at 25°C)	1.45[a]
Octanol-water partition constant (log K_{ow})	2.31[a]
Henry's law constant (atm-m^3/mol at 25°C)	5.68×10^{-5} (estimated)[b]
Soil adsorption coefficient (K_{oc}) (mL/g)	79 (estimated)[b]
Relative vapor density (air = 1)	4.17[a]
Molecular weight (g/mol)	121.18[a]

[a]HSDB (2014).
[b]U.S. EPA (2012c).

EPA's Integrated Risk Information System (IRIS) has developed a chronic oral reference dose (RfD) value for *N,N*-dimethylaniline (U.S. EPA, 1987). A summary of this value and other available toxicity values for *N,N*-dimethylaniline from EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for *N,N*-Dimethylaniline (CASRN 121-69-7)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS (RfC)	NV	NA	U.S. EPA (2016)
IRIS (RfD)	2×10^{-3} mg/kg-d	Based on splenomegaly, increased splenic hemosiderosis and hematopoiesis in mice.	U.S. EPA (1987)
HEAST (sRfD)	2×10^{-2} mg/kg-d	Based on effects on the spleen in mice.	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2016)
WHO	NV	NA	WHO (2016)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2016a); Cal/EPA (2016b)
OSHA (PEL)	TWA 5 ppm (25 mg/m^3); [skin]	The "[skin]" designation indicates the potential for dermal absorption.	OSHA (2006); OSHA (2011)
NIOSH (REL)	TWA 5 ppm (25 mg/m^3); STEL 10 ppm (50 mg/m^3); [skin]	The "[skin]" designation indicates the potential for dermal absorption.	NIOSH (2015)
ACGIH (TLV)	TWA 5 ppm (25 mg/m^3) STEL 10 ppm (50 mg/m^3); [skin] notation	Based on potential for methemoglobinemia, anoxia, and resultant neurotoxicity due to structural similarity to aniline.	ACGIH (2015)
ACGIH (BEI for methemoglobin inducers)	Methemoglobin in blood: 1.5% of hemoglobin	Sampling time: during or end of shift.	ACGIH (2006); ACGIH (2015)
Cancer			
IRIS	NV	NA	U.S. EPA (2016)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC (WOE)	Group 3—not classifiable as to its carcinogenicity to humans	Based on limited evidence of carcinogenicity in one study in mice and in one study in rats by gavage.	IARC (1993)

Table 2. Summary of Available Toxicity Values for *N,N*-Dimethylaniline (CASRN 121-69-7)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2016a); Cal/EPA (2016b)
ACGIH (WOE)	A4—not classifiable as a human carcinogen	Based on equivocal oncogenic data from 2-yr gavage studies with rats and mice.	ACGIH (2001); ACGIH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.
[b]Parameters: BEI = biological exposure indices; PEL = permissible exposure level; REL = recommended exposure level; RfC = inhalation reference concentration; RfD = oral reference dose; sRfD = reference dose for subchronic oral exposure; TLV = threshold limit value; WOE = weight of evidence.

NA = not applicable; NV = no value; STEL = short-term exposure limit; TWA = time-weighted average.

Literature searches were conducted on sources published from 1900 through March 2016 for studies relevant to the derivation of provisional toxicity values for *N,N*-dimethylaniline (CASRN 121-69-7). The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for toxicity values or exposure limits: 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 (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant databases for *N,N*-dimethylaniline and include all potentially relevant repeat-dose, short-term-, subchronic-, and chronic-duration studies. Principal studies are identified. The phrases, "statistical significance" and "significant," used throughout the document, indicate a p-value of < 0.05 unless otherwise noted. Chronic-duration oral studies are described below; however, a chronic provisional reference dose (p-RfD) is not derived due to the availability of a chronic oral RfD value for *N,N*-dimethylaniline on EPA's IRIS database (see Table 2).

Table 3A. Summary of Potentially Relevant Noncancer Data for *N,N*-Dimethylaniline (CASRN 121-69-7)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Human								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								
Animal								
1. Oral (mg/kg-d)[b]								
Short-term	5 M/5 F, F344/N rat, gavage (corn oil), 14 d	0, 94, 188, 375, 750, 1,500 ADD: 0, 94, 188, 375, 750, 1,500	Splenomegaly	94	NDr	188 FEL: 750	NTP (1989)	PR
Short-term	5 M/5 F, B6C3F$_1$ mouse, gavage (corn oil), 15 d	0, 94, 188, 375, 750, 1,500 ADD: 0, 94, 188, 375, 750, 1,500	Splenomegaly and splenic pathology (extramedullary hematopoiesis and hemosiderosis)	188	NDr	375 FEL: 750	NTP (1989)	PR
Short-term	5 M/0 F, rat (strain not specified), gavage, 11/15 d (undiluted) or 13/17 d (corn oil)	0, 100, 1,000 ADD: 0, 73.3 (11/15 d), 1,000 (2 d)	Mortality (1,000 mg/kg-d), abnormal RBC morphology, increased spleen weight, splenic congestion	ND	NDr	73.3 FEL: 1,000	Eastman Kodak (1992); Eastman Kodak (1995)	NPR
		0, 10, 100 ADD: 0, 7.7, 76.5 (13/17 d)	Abnormal RBC morphology, increased spleen weight, splenic congestion	7.7	NDr	76.5		

Table 3A. Summary of Potentially Relevant Noncancer Data for *N,N*-Dimethylaniline (CASRN 121-69-7)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Short-term	0 M/10 F, CD-1 mouse, gavage (corn oil), 8 d	0, 365, 725, 1,455, 2,910, 5,815 ADD: 0, 365, 725, 1,455, 2,910, 5,815	High mortality, clinical signs (lethargy, prostration, unkempt appearance)	ND	NDr	FEL: 365	Piccirillo et al. (1983)	NPR
Subchronic	**10 M/10 F; F344/N rat, gavage (corn oil), 5 d/wk, 13 wk**	**0, 31.25, 62.5, 125, 250, 500** **ADD: 0, 22.32, 44.6, 89.3, 179, 357**	**Splenic pathology (extramedullary hematopoiesis and hemosiderosis)**	**ND**	**NDr**	**22.32**	**Abdo et al. (1990); NTP (1989) (Hematology, clinical chemistry, urinalysis, and organ weights not examined or reported)**	**PR, PS**
			Renal pathology (hemosiderosis)	**ND**	**3.1[d]**	**22.32**		
Subchronic	10 M/10 F, $B6C3F_1$ mouse, gavage (corn oil), 5 d/wk, 13 wk	0, 31.25, 62.5, 125, 250, 500 ADD: 0, 22.32, 44.6, 89.3, 179, 357	Splenomegaly (≥22.32 mg/kg-d) and splenic pathology (extramedullary hematopoiesis and hemosiderosis; ≥44.6 mg/kg-d)	ND	5.48 (based on increased spleen hematopoiesis in males)	22.32	Abdo et al. (1990); NTP (1989) (Hematology, clinical chemistry, urinalysis, and organ weights not examined or reported; incidence of all groups and severity of splenomegaly not reported)	PR, IRIS
Chronic	50 M/50 F; F344/N rat, gavage (corn oil), 5 d/wk, 103 wk	0, 3, 30 ADD: 0, 2, 21	Hemosiderosis of the spleen (increased severity)	ND	NDr	2	NTP (1989) (Hematology, clinical chemistry, urinalysis, and organ weights not examined or reported)	PR
Chronic	50 M/50 F, $B6C3F_1$ mouse, gavage (corn oil), 5 d/wk, 103 wk	0, 15, 30 ADD: 0, 11, 21	No significant effects	21	NDr	ND	NTP (1989) (Hematology, clinical chemistry, urinalysis, and organ weights not examined or reported)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for *N,N*-Dimethylaniline (CASRN 121-69-7)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Developmental	0 M/50 F, CD-1 pregnant mouse, gavage (corn oil), GDs 6−13	0, 365 ADD: 0, 365	No significant effects on evaluated maternal or developmental endpoints (number of litters, litter size, offspring survival and body weight)	365	NDr	ND	Hardin et al. (1987); Piccirillo et al. (1983) (Fetal development not examined)	PR
2. Inhalation (mg/m^3)[b]								
Subchronic	Unspecified M/0 F, albino rat, unspecified inhalation, 24 hr/d, 100 d	0, 0.0055, 0.3 HEC: 0, 0.0055, 0.3	Changes in several hematology and clinical chemistry parameters and histopathological lesions in the liver, spleen, brain, and lungs	0.0055	NDr	0.3	Markosyan (1969) (data from this study cannot be considered reliable due to inadequate reporting)	PR (Translated from Russian journal)

[a]Category (treatment/exposure duration, unless otherwise noted): short-term = repeated exposure for >24 hours ≤30 days (U.S. EPA, 2002); long-term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (more than 30 days up to approximately 90 days in typically used laboratory animal species) (U.S. EPA, 2002); chronic = repeated exposure for >10% lifespan for humans (more than approximately 90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: values are presented as adjusted daily dose (ADD, in mg/kg-day) for oral noncancer effects and as human equivalent concentration (HEC, in mg/m^3) for inhalation noncancer effects. The HEC was calculated using the equation for extrarespiratory effects from a Category 3 gas (U.S. EPA, 1994): HEC_{EXRESP} = continuous concentration in mg/m^3 × ratio of animal:human blood-gas partition coefficients (default value of 1 applied).
[c]Notes: IRIS = used by IRIS; NPR = not peer reviewed; PR = peer reviewed; PS = principal study.
[d]Benchmark dose modeling was performed with four data points (minus two highest doses).

ADD = adjusted daily dose; BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; F = female(s); FEL = frank effect level; GD = gestation day; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell.

Table 3B. Summary of Potentially Relevant Cancer Data for *N,N*-Dimethylaniline (CASRN 121-69-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	BMDL/BMCL[a]	Reference (comments)	Notes[b]
Human						
1. Oral (mg/kg-d)						
ND						
2. Inhalation (mg/m^3)						
ND						
Animal						
1. Oral (mg/kg-d)[a]						
Carcinogenicity	**50 M/50 F; F344/N rat, gavage, 5 d/wk, 103 wk**	**0, 3, 30** **HED: 0, 0.5, 5.0**	**Combined incidence of sarcoma and osteosarcoma in males (considered "some evidence of carcinogenicity" by NTP)**	**3.7**	**NTP (1989)**	**PR, PS**
Carcinogenicity	50 M/50 F, B6C3F$_1$ mouse, gavage, 5 d/wk, 103 wk	0, 15, 30 HED: 0, 1.5, 3.0	Squamous cell papillomas of the forestomach in females (considered "equivocal evidence of carcinogenicity" by NTP)	NDr	NTP (1989)	PR
2. Inhalation (mg/m^3)						
ND						

[a]Dosimetry: the units for oral exposures are expressed as human equivalent dose (HED) (mg/kg-day). HED = animal dose as ADD (mg/kg-day) × default dosimetric adjustment factor (DAF) calculated as $(BW_a \div BW_h)^{1/4}$ [0.24 for rats and 0.14 for mice (U.S. EPA, 2011b)].
[b]Notes: PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; F = female(s); HED = human equivalent dose; M = male(s); ND = no data; NDr = not determined; NTP = National Toxicology Program.

HUMAN STUDIES

Oral Exposures

No studies examining possible associations between health effects in humans and oral exposure to *N*,*N*-dimethylaniline have been identified.

Inhalation Exposures

No studies examining possible associations between health effects in humans and repeated inhalation exposure to *N*,*N*-dimethylaniline have been identified.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to *N*,*N*-dimethylaniline were evaluated in five short-term-duration studies (Dow Chemical Co, 1995; Eastman Kodak, 1995, 1992; NTP, 1989; Piccirillo et al., 1983), two subchronic-duration studies (Abdo et al., 1990; NTP, 1989), two chronic-duration studies (NTP, 1989), and a single developmental toxicity study (Hardin et al., 1987; Piccirillo et al., 1983).

Short-Term-Duration Studies

NTP (1989)

Male and female Fischer 344/N rats and B6C3F$_1$ mice (five/sex/group) were administered doses of 0 (vehicle control), 94, 188, 375, 750, or 1,500 mg/kg-day *N*,*N*-dimethylaniline (>98% pure) via gavage in corn oil for 14 consecutive days (rats) or 15 consecutive days (mice). The animals were observed twice daily and weighed on Days 1, 7, 14 (rats), and 15 (mice). Food and water consumption were not reported. Hematology, clinical chemistry, and urinalysis data were not collected in this study. All animals were necropsied; however, organ weights were not measured. Histologic examinations were performed on three male and three female rats from the 94- and 375-mg/kg-day dose groups and on three male and three female mice from the 375-mg/kg-day dose group. Tissues examined include adrenal glands, brain, colon, duodenum, esophagus, gallbladder (mice only), heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, salivary glands, testes or ovaries/uterus, skin, spleen, thymus, and trachea.

All male and female rats that received the 1,500-mg/kg-day dose died during the study, as did four out of five male rats and all five female rats at the 750-mg/kg-day dose level (see Table B-1). As shown in Table B-1, terminal body weights of male rats given 375 and 750 mg/kg-day were 15% and, in the one survivor at 750 mg/kg-day, 47% lower than controls, respectively. Terminal body-weight measurements for female rats were within 10% of control values for all dose groups with survivors (i.e., ≤375 mg/kg-day) (see Table B-1). Clinical signs observed in the 750- and 1,500-mg/kg-day dose groups of male and female rats included cyanosis, lethargy, fine body tremors, diarrhea, and red ocular or nasal discharge. A statistically significant increase in the incidence of splenomegaly was seen in rats given doses ≥188 mg/kg-day (genders combined; see Table B-1). Extramedullary hematopoiesis and increased hemosiderin were observed in the spleens of all three male and three female rats examined at the 375-mg/kg-day dose level (and presumably none of those examined at the 94-mg/kg-day dose level, although that was not explicitly stated). No-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values of 94 and 188 mg/kg-day, respectively, are identified for this study based on the significant increase in the incidence of splenomegaly in rats (combined genders).

In the mouse study, mortality was observed in all male and female mice that received 750 or 1,500 mg/kg-day of *N*,*N*-dimethylaniline (see Table B-2). One male mouse died after receiving 188 mg/kg-day, but this death was determined by the study authors not to be compound related. Terminal body weights of treated male and female mice were within 10% of control values for all dose groups with survivors (i.e., ≤375 mg/kg-day) (see Table B-2). Clinical signs observed in male and female mice included lethargy, excess salivation, and tremors (dose levels were not specified, but the signs were reported as "compound-related"). Splenomegaly was seen in one of five male mice at 188 mg/kg-day, and two of five male and three of five female mice at 375 mg/kg-day (see Table B-2). Congestion and increased extramedullary hematopoiesis or hemosiderin were seen in the spleens of all three male and three female mice examined at the 375-mg/kg-day dose (no histopathology was examined in the 188-mg/kg-day group). NOAEL and LOAEL values of 188 and 375 mg/kg-day, respectively, are identified based on splenomegaly and splenic pathology in male and female mice.

Eastman Kodak (1992); Eastman Kodak (1995)

Male rats (five/group; strain not specified) were administered *N,N*-dimethylaniline (purity not reported) via gavage (undiluted) at 100 or 1,000 mg/kg-day for up to 15 days (2−11 exposures total). Although a group of five control rats (administered water) was reportedly used, no data for these animals were provided. Mortality and clinical signs of toxicity were monitored regularly. Body weights were recorded (presumably prior to study initiation and at study termination). Food consumption was measured (time points not specified). Hematology (red blood cell [RBC] and total and differential white blood cell [WBC] counts, hematocrit [Hct], and hemoglobin [Hb] concentration) and clinical chemistry evaluations (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], lactate dehydrogenase [LDH], blood urea nitrogen [BUN], and glucose) were performed. The animals were subjected to gross pathology examinations. Liver, kidney, and/or spleen weights were recorded. Various tissues (not specified, but likely tissues warranting further examination based on gross observations and including the liver, kidney, spleen, and thymus) were examined microscopically. Quantitative data were not provided; effects were classified by the direction of change (no change, increased, or decreased) and/or severity (slight, moderate, or great).

The rats administered two daily doses of 1,000 mg/kg-day died or were sacrificed moribund within 8 hours of the second treatment. Clinical signs of toxicity included loss of coordination in hindquarters, depression, dark eyes, pale skin, and otherwise poor general appearance. Rats treated at 1,000 mg/kg-day also showed decreased food intake (graded as "great") and decreased body weights (graded as "slight") compared to controls. The one animal subjected to clinical pathology analyses showed hematological effects (slight reductions in Hct, Hb concentration, and RBC count, and abnormal RBC morphology with substantially increased total WBC and granulocyte counts) and clinical chemistry effects (moderately increased AST activity, and greatly increased serum glucose and BUN). In the animals dosed at 1,000 mg/kg-day and sacrificed moribund (three rats), absolute liver and kidney weights were unaffected by treatment; the small increases in relative organ weights were likely an artifact of decreased body weight. Gross pathology revealed brownish-colored blood in the internal organs, and enlarged, dark spleens. Microscopic examinations showed effects in the liver (hypertrophy of hepatic nuclei, in 1/3 animals), kidney (bilateral tubular nephrosis, in 2/3 animals), spleen (congestion with lymphoid follicular hyperplasia, in 3/3 animals), and thymus (necrotic thymiditis, in 2/3 animals).

Rats dosed at 100 mg/kg-day received 11 treatments over 15 days. Gavage doses of 100 mg/kg-day were converted to average daily doses of 73.3 mg/kg-day by multiplying the administered gavage dose by doses/days (11/15). No mortality or clinical signs of toxicity were reported. Food intake was not affected, and body weights were decreased (graded as "slight") in treated rats relative to controls. Clinical pathology changes in 73.3-mg/kg-day rats were limited to abnormal RBC morphology (polychromasia, poikilocytosis, anisocytosis, and macrocytosis) and an increase in LDH activity (graded as "slight"). There were no biologically or statistically significant treatment-related effects on absolute or relative liver and kidney weights; however, absolute and relative spleen weights were increased (graded as "great"). Gross and microscopic pathology findings were also confined to the spleen. Spleens appeared dark and enlarged; microscopic evaluations revealed congestion (possibly hemorrhagic in nature). The results suggest that the duration-adjusted lowest-observed-adverse-effect-level ($LOAEL_{ADJ}$) is 73.3 mg/kg-day for increased spleen weights and corresponding hematological (abnormal RBC morphology) and histopathological (splenic congestion) changes.

In an effort to determine a no-effect level, the same endpoints were evaluated in male rats (five/group) administered *N,N*-dimethylaniline at 10 or 100 mg/kg-day via gavage in corn oil over 17 days (13 total doses). Gavage doses of 10 and 100 mg/kg-day were converted to average daily doses of 7.7 and 76.5 mg/kg-day by multiplying the administered gavage dose by doses/days (13/17). Although a group of control rats was reportedly used, no data for these animals were provided. Mortality, body weights, and food consumption were unaffected by treatment. There were no significant, treatment-related effects in rats treated at 7.7 mg/kg-day. Effects observed at 76.5 mg/kg-day included those seen in the preceding study (abnormal RBC morphology [polychromasia, anisocytosis, poikilocytosis, and Howell-Jolly bodies], increased absolute and relative spleen weight, and gross and microscopic spleen changes [enlarged, dark spleens in 2/5 animals and congestion with lymphoid hyperplasia in 4/5 animals]). Changes in other hematological parameters (increased WBCs, granulocytes, mean corpuscular volume [MCV] and Hb; decreased RBC count, Hct, and Hb concentration) were also observed, but were classified as slight. Whitish tissue on the peritoneum, pericardium, and lung (one lobe), observed grossly in both groups of treated rats, was determined microscopically to be lipoidal connective tissue. These data, while limited and not peer reviewed, provide evidence for a $LOAEL_{ADJ}$ of 76.5 mg/kg-day based on hematological effects (including abnormal RBC morphology), increased spleen weight, and spleen histopathology (congestion with lymphoid hyperplasia). The duration-adjusted no-observed-adverse-effect level ($NOAEL_{ADJ}$) is 7.7 mg/kg-day.

Dow Chemical Co (1995)

Rats (n = 9 in total; strain not specified) were administered *N,N*-dimethylaniline (purity not reported) orally (presumably daily via gavage) at 0.1, 1, 10, 100, 500, or 5,000 mg/kg until death or until 20 doses were given; sacrifices were performed 9−10 days following dosing in the surviving animals. The number of rats per treatment group was 1, 2, 1, 2, 2, and 1 in the 0.1-, 1-, 10-, 100-, 500-, and 5,000-mg/kg groups, respectively. No control group was used. The liver, kidney(s), spleen, adrenal gland, and pancreas from all rats were examined microscopically (other tissues, if examined, were not specified). Hematological analyses (endpoints not specified) were performed on three rats administered 1, 10, and 100 mg/kg after 10 and 20 doses. The study results were described qualitatively; raw data (other than the presence or absence of microscopic lesions with some indication of severity) were not provided. For the purposes of

this review, the severity ratings of (±, +, ++, and +++, given in the study report) were assumed to correspond to minimal, mild or slight, moderate, and marked, respectively.

The incidence of mortality was 0/1, 1/2, 0/1, 0/2, 1/2, and 1/1 at 0.1, 1, 10, 100, 500, and 5,000 mg/kg, respectively. Although the study summary indicates that hematological changes occurred at doses as low as 10 mg/kg, significant changes in blood parameters were only mentioned by the study authors at 100 mg/kg (moderate anemia and slight neutrophilic leukocytosis after 10 doses; anemia in the absence of leukocytosis after 20 doses). Histopathological changes at 1 mg/kg were confined to the spleen, and consisted of minimal to mild congestion and deposition of blood pigments. Higher doses of *N,N*-dimethylaniline induced splenic congestion accompanied by hemosiderosis of the spleen (ranging from minimal to marked at ≥10 mg/kg), tubular nephritis (minimal to moderate at 100 and 500 mg/kg), and hepatic degeneration (minimal to moderate at 500 and 5,000 mg/kg). There were no histopathological changes in the adrenal gland or pancreas at any dose. Owing to the poor quality of the study (based on few numbers of animals per dose group, lack of controls, and inadequate data reporting), no NOAEL or LOAEL can be identified.

Piccirillo et al. (1983)

In a dose-finding study, female virgin CD-1 mice (10/group) were given 0 (vehicle control), 365, 725, 1,455, 2,910, or 5,815 mg/kg-day *N,N*-dimethylaniline by gavage in corn oil for 8 consecutive days (purity assumed by authors to be 100%). Mice were observed for clinical signs of toxicity twice daily during the treatment period and for 8 days following treatment. Body weights and physical examinations were recorded on the first and last days of treatment and on the fourth and eighth day following treatment. Dead mice were necropsied to determine whether the cause of death was gavage error or was compound related. Mortality was observed in all treatment groups, with 100% mortality seen by Day 4 of treatment at doses ≥1,455 mg/kg-day. Doses of 365 and 725 mg/kg-day produced 40 and 70% mortality, respectively, with one death in the lowest-dose group attributed to gavage error. Clinical signs of toxicity included lethargy, tremors, prostration, ataxia, and/or unkempt appearance. Surviving animals from the lowest dose group exhibited lethargy, prostration, and/or unkempt appearance intermittently throughout the treatment period. Body weights for these animals were not significantly different from control values. A frank effect level (FEL) of 365 mg/kg-day is identified based on chemical-related mortality observed in 3/9 mice from the lowest-dose group.

Subchronic-Duration Studies

Abdo et al. (1990); NTP (1989)

Male and female Fischer 344/N rats and B6C3F$_1$ mice (10/sex/group) were exposed to doses of 0 (vehicle control), 31.25, 62.5, 125, 250, or 500 mg/kg-day *N,N*-dimethylaniline (98.2% purity) via gavage in corn oil once daily for 5 consecutive days/week for 13 weeks. These gavage doses were converted to adjusted daily doses (ADDs) of 22.32, 44.6, 89.3, 179, and 357 mg/kg-day by multiplying the administered gavage dose by (5/7) days/week. Animals were observed twice daily for morbidity and mortality. Clinical signs and body weights were recorded weekly. Doses were adjusted weekly for changes in body weights. The study did not report food or water consumption by rats or mice during the 13-week study period. Hematology, clinical chemistry, and urinalysis data were not collected in this study. All animals (those that died during the study and those that survived to study termination) were necropsied and gross lesions were recorded, but organ weights were not measured. Complete histopathological examinations (of >30 tissues) were performed and lesions were graded by severity (i.e., minimal,

mild, moderate, marked, severe). Selected tissues (not specified) were stained to confirm the presence of hemosiderin.

Mortality during the study was observed in one male rat (at 357 mg/kg-day) and three female rats (one each at 44.6, 89.3, and 179 mg/kg-day) (see Table B-3). All of these deaths were attributed to gavage error, as confirmed by the presence of corn oil in the lung. Clinical signs of toxicity were decreased motor activity (noted in all individual rats at doses ≥89.3 mg/kg-day), excessive salivation (doses not reported), and cyanosis (noted in all individual rats at doses ≥179-mg/kg-day). Body weights of male rats exposed to 179 or 357 mg/kg-day were lower than controls throughout the study period. There was a statistically significant decrease in terminal body weights of male rats exposed to 89.3, 179, and 357 mg/kg-day from controls by 7, 15, and 27%, respectively (see Table B-3). Female rats exposed to doses ≥89.3 mg/kg-day also exhibited decreased terminal body weight; however, the observed decreases were <10% of control values (3−5%; see Table B-3). The only gross pathology change noted in this study was splenomegaly, which was observed in all treatment groups of rats (incidence not reported).

Histopathological changes were found in the testis of male rats, and the spleen, liver, kidney, and bone marrow of male and female rats. The incidence and/or severity of lesions increased with increasing dose level. As shown in Table B-4, the severity of extramedullary hematopoiesis and hemosiderosis in the spleen increased with increasing dose in male and female rats. These effects occurred in 90−100% of treated animals in each dose group. Macrophages filled with yellow-brown granular pigment that tested positive for iron (hemosiderin) were prominent in the spleen of male and female rats at all doses (in contrast with controls). Hemosiderosis was also observed in the kidneys, liver, and testes; however, this effect generally occurred with lower incidence and severity and at higher doses, compared to the spleen, where 100% incidence was seen at the lowest dose (see Table B-4). The severity of splenic hematopoiesis and hemosiderosis was mild at the lowest dose and increased to marked and severe, respectively, at the highest dose. The cortical tubular epithelial cells in the kidneys contained abundant hemosiderin at doses ≥44.6 mg/kg-day in male rats and ≥22.32 mg/kg-day in female rats. In the liver, significant numbers of Kupffer cells were enlarged and exhibited hemosiderin in male rats treated with ≥89.3 mg/kg-day *N,N*-dimethylaniline and in female rats receiving doses ≥44.6 mg/kg-day. These cells tended to be localized in the centrilobular region of the liver. Hemosiderin-filled macrophages were present in the testes of male rats treated with 179 or 357 mg/kg-day *N,N*-dimethylaniline, intermingled with interstitial cells between seminiferous tubules. Finally, significantly increased incidence of bone marrow hyperplasia was observed in male and female rats at doses of ≥89.3 mg/kg-day, compared with controls. A LOAEL of 22.32 mg/kg-day is identified based on histopathological effects in the spleen of male and female rats and the kidney of female rats. A NOAEL is not identified because effects occurred at the lowest dose level in treated rats.

In the mouse study, two male mice died at 22.32 mg/kg-day, three died at 44.6 mg/kg-day, one died at 179 mg/kg-day, and one died in the control group (see Table B-5). One female mouse died at 44.6 mg/kg-day. All of these deaths were attributed to gavage error based on the presence of corn oil in the lung. Clinical signs of toxicity include blanching (paling or whitening of skin) and decreased motor activity, which was observed in all treatment groups of male mice and in female mice at ≥89.3 mg/kg-day. No other clinical signs of toxicity were reported. Male mice given *N,N*-dimethylaniline had lower body weights than controls,

beginning at 4 weeks of treatment, and terminal body weights were reduced by 9−12% in each treatment group. Body weight was not significantly affected by treatment in female mice (see Table B-5). The only gross pathology change noted in this study was splenomegaly, which was observed in all mice receiving doses ≥89.3 mg/kg-day *N,N*-dimethylaniline. Splenomegaly was also observed in 4/10 and 7/10 male mice and 4/10 and 8/10 female mice treated with 22.32 and 44.6 mg/kg-day, respectively. Severity of the splenomegaly, organ-weight measures, or incidence of splenomegaly in control mice was not reported.

Histopathologic changes were found in the spleen, liver, and kidney of male and female mice, as noted in Table B-6. As with rats, the incidence and/or severity of lesions increased with increasing dose and effects in the spleen occurred at lower doses than similar effects seen in the liver and kidney. Extramedullary hematopoiesis in the spleen increased statistically significantly in male and female mice compared with control animals at doses ≥44.6 mg/kg-day. Macrophages filled with hemosiderin in the spleen were increased in both sexes of mice at doses ≥44.6 mg/kg-day compared to controls. In the liver of male and female mice treated with ≥89.3 mg/kg-day *N,N*-dimethylaniline, significant numbers of Kupffer cells were enlarged and exhibited hemosiderin. Extramedullary hematopoiesis was observed in the liver of male and female mice at the highest-dose level only (357 mg/kg-day). The cortical tubular epithelial cells in the kidneys contained abundant hemosiderin at doses ≥179 mg/kg-day in female mice, while hemosiderosis occurred only at the highest dose in male mice (357 mg/kg-day). Based on splenomegaly in male and female mice, a LOAEL of 22.32 mg/kg-day is identified. A NOAEL is not identified because effects occurred at the lowest dose in treated mice.

Chronic-Duration/Carcinogenicity studies

NTP (1989)

Groups of male and female F344/N rats or B6C3F$_1$ mice (50/sex/group) were administered *N,N*-dimethylaniline (98.2% purity) via gavage in corn oil at 0, 3, or 30 mg/kg-day (rats) or at 0, 15, or 30 mg/kg-day (mice), 5 days/week for 103 weeks (NTP, 1989). Gavage doses in rats of 3 or 30 mg/kg-day were converted to ADDs of 2 or 21 mg/kg-day by multiplying the administered gavage dose by days/week (5/7). Gavage doses in mice of 15 or 30 mg/kg-day were converted to ADDs of 11 or 21 mg/kg-day by multiplying the administered gavage dose by days/week (5/7). Animals were monitored twice daily for mortality and clinical signs of toxicity. Body weights were recorded at study initiation, weekly for 12 weeks, and once per month thereafter until study termination. No clinical pathology (hematology or clinical chemistry) or urinalysis evaluations were performed. All animals were subjected to necropsy, and complete histopathological examinations (of >30 tissues) were conducted for rats in the control and high-dose groups (and in low-dose animals that died early or with grossly visible lesions). Gross lesions and additional tissues were examined in all low-dose rats including spleen and testes (male rats), kidney, liver, and spleen (female rats), adrenal glands (mice), and liver and spleen (female mice).

The survival of treated rats was not significantly lower than controls; survival in high-dose females was significantly higher than controls after 99 weeks due to a high number of control females killed moribund (survival at study termination [i.e., 104 weeks] was 21/50, 32/50, and 36/50 in control, low-dose, and high-dose female rats, respectively). No explanation was given for the morbidity and mortality observed in the female control rats. No clinical signs of toxicity attributed to treatment were observed. The body weights of rats from all dose groups (including controls) were similar (varied by ≤8% at all measured time points). Nonneoplastic

findings were confined to the spleen and liver (see Table B-7). The incidence of some splenic lesions (hemosiderosis and hematopoiesis) was high in all groups of rats (including controls). However, the severity of these lesions was significantly increased in treated rats of both sexes relative to controls (hemosiderosis at ≥2 mg/kg-day and hematopoiesis at 21 mg/kg-day); the severity of these lesions ranged from minimal to marked (marked lesions [hematopoiesis] reported in female rats at ≥2 mg/kg-day). The incidence of other lesions was significantly increased at 21 mg/kg-day in rats of one sex only (fibrosis and fatty metamorphosis of the spleen in males and chronic focal inflammation of the liver in females). Data with respect to the severity of these effects were not provided by the study authors. A LOAEL of 2 mg/kg-day is identified for increased severity of splenic hemosiderosis in male and female rats. No NOAEL is determined.

Neoplastic findings in male and female rats are shown in Table B-8. The only statistically significant finding was a positive trend for splenic tumors with increasing dose in male rats (based on analyses for sarcoma or combined sarcoma or osteosarcoma, $p = 0.01$ by Cochran-Armitage trend test). The incidence of spleen sarcoma (3/50) or incidence of combined spleen sarcoma or osteosarcoma (4/50) in high-dose males increased compared to the concurrent control group (0/49) ($p = 0.06$ by incidental tumor test and Fisher's exact test), as well as equaled or exceeded the greatest historical incidence of spleen sarcoma in control male rats given corn oil gavage (1/45), and the overall historical incidence for National Toxicology Program (NTP) studies (3/2,081) (no osteosarcomas have been observed) (NTP, 1989). The sarcomas had varied morphology, with characteristics of hemangiosarcomas and osteosarcomas. The NTP concluded that there was *"some evidence of carcinogenic activity"* of *N,N*-dimethylaniline in male rats based on the occurrence of sarcomas or osteosarcomas (combined) of the spleen. Splenic tumors were not increased in treated female rats, and the NTP concluded that there was *"no evidence of carcinogenic activity"* of *N,N*-dimethylaniline in female rats. NTP (1989) also concluded that the carcinogenic responses may have been greater had larger doses been administered to the rats.

The survival of treated mice was not significantly different from controls. No clinical signs of toxicity attributed to treatment were observed. The body weights of treated mice were similar to controls (≥94% of control values at all measured time points). Nonneoplastic findings were confined to the forestomach (focal epithelial hyperplasia) and pituitary gland (chromophobe cell hyperplasia) of female mice; while the incidence of these lesions was slightly increased relative to controls, statistical significance was not achieved (see Table B-9). There were no significant nonneoplastic histopathological findings in male mice. These data identify a NOAEL of 21 mg/kg-day in male and female mice. No LOAEL is determined.

No significantly increased incidences of tumors were observed in male mice. Female mice showed a significantly increased incidence of squamous cell papillomas of the forestomach at 21 mg/kg-day compared to concurrent controls (8/50 vs. 2/50, $p = 0.04$ by incidental tumor test); a statistically significant trend for this tumor type with increasing dose was also seen ($p = 0.02$ by Cochran-Armitage trend test) (see Table B-9). The tumor incidence in high-dose female mice was higher than the overall NTP control incidence of 32/2,047 in corn oil gavage studies, but did not differ markedly from the greatest historical control incidence in female mice in previous studies (8/50 [16%] vs. 5/44 [11%]). No squamous cell carcinomas were identified in high-dose female mice, leading the authors to suggest that the forestomach papillomas might not be progressive. The NTP concluded there was *"equivocal evidence for carcinogenic activity"* of *N,N*-dimethylaniline in female mice based on increased incidence of squamous cell

papillomas of the forestomach, and *"no evidence of carcinogenic activity"* in male mice. NTP (1989) also concluded that the carcinogenic responses may have been greater had larger doses been administered to the mice.

Reproductive/Developmental Studies

Hardin et al. (1987); Piccirillo et al. (1983)

Based on the results of the dose-finding study described above (Piccirillo et al., 1983), time-mated pregnant CD-1 mice (50/group) were given 0 or 365 mg/kg-day *N,N*-dimethylaniline (purity not reported) by gavage in corn oil on Gestation Days (GDs) 6−13 (Hardin et al., 1987; Piccirillo et al., 1983). Mice were permitted to deliver pups, and the total litter weight and number of live born pups were recorded. Offspring were returned to their dams until Postnatal Day (PND) 3 when the number of live pups was counted and the litter weight and dam weights were measured. Females that failed to deliver by GD 22 were sacrificed and uteri were examined grossly. If there was no gross evidence of a failed pregnancy, the uteri were treated with 10% ammonium or sodium sulfide to reveal implantation sites.

Three deaths were recorded among treated dams, but this did not represent a significant increase over controls (0 deaths). Administration of *N,N*-dimethylaniline did not significantly affect maternal-weight gain or the number of viable litters produced. Similarly, no significant effects were seen on the number of live newborns per litter, offspring survival, birth weight, or weight gain per pup. The NOAEL for this study is 365 mg/kg-day. A LOAEL value is not identified because a single dose group was employed and no effects were observed.

Inhalation Exposures

Subchronic-Duration Studies

Markosyan (1969)

In a peer-reviewed study translated to English from Russian, male albino rats (number per group not specified) were exposed to *N,N*-dimethylaniline at reported concentrations of 0, 0.0055, or 0.3 mg/m^3, 24 hours/day, 7 days/week for 100 days and were permitted to recover postexposure (time not specified). No descriptions of the methods used in the experiment (i.e., atmosphere generation, exposure methodology, and/or monitoring data) were provided. The endpoints evaluated included hematological (total RBC, total and differential WBC, and reticulocyte counts; Hb, methemoglobin [MetHb] [by modified cyanohemoglobin method], Hct, mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], mean corpuscular volume, color index, and Heinz bodies in RBCs) and clinical chemistry parameters (total protein, albumin, globulins, and albumin: globulin ratio; SH (sulfhydryl) groups, and pyruvic acid), other specific tests of liver function (bromsulphalein test, concentration of pyruvic acid in the liver, and urinary excretion of coproporphyrins), and rheobase and chronaxie of antagonistic muscles (descriptors of the strength-duration curve for a muscle stimulus). Based on the text and on the time points shown for data presented graphically, at least some of these endpoints (including hematology parameters) were evaluated every 2 weeks. At study termination, the concentration of ascorbic acid (a form of Vitamin C) in the liver, adrenals, spleen, and kidney was measured; relative organ weights (presumably of the same organs) were recorded, and histopathology of "several" organs and tissues (not further specified, but including the brain, spleen, liver, adrenal, and lungs) was performed. Quantitative data pertaining to endpoints other than reticulocyte count and the bromsulphalein test were not shown in the study report.

Mortality, if it occurred, was not reported. No significant effects were reported in rats exposed at 0 or 0.0055 mg/m^3. All of the effects described are for rats exposed to *N,N*-dimethylaniline at 0.3 mg/m^3. Exposure induced anemia as evidenced by decreased Hb levels and RBC counts (data not shown). Anemia was characterized as microcytic and normachromic (likely indicated by decreased MCV with no change in MCH), and moderate poikolocytosis (presence of abnormally shaped RBCs) was noted (data not provided). The level of MetHb (hemoglobin with a compromised ability to bind oxygen) was significantly increased in rats exposed at 0.3 mg/m^3 from 6 weeks (time of maximum decrease in Hb) until study termination. Heinz bodies (RBCs containing denatured Hb) were detected during the second half of the exposure period. Reticulocyte counts were significantly increased, particularly at 6 and 12 weeks (when Hb and RBC counts were decreased and/or MetHb concentration was increased). Based on data presented graphically in the study report, reticulocytes were significantly increased in rats exposed at 0.3 mg/m^3 by about 23% at 6 weeks and 10% at 12 weeks, relative to controls. Total WBC count was decreased in rats exposed at 0.3 mg/m^3; although lymphocytes were increased, segmented neutrophil and eosinophil counts were decreased (data not shown). Clinical pathology results revealed reductions in total protein, albumin, and β- and γ-globulins; the albumin:globulin ratio was increased (data not shown). The level of SH groups in the serum was also decreased, which the study authors suggested might reflect decreased proteinogenic function of the liver. In other specific tests of liver function, exposed rats showed only a slight change with respect to the excretion of bromsulphalein. The retention coefficient for exposed rats was not significantly different from controls. However, the urinary excretion of coproporphyrins was increased, and there was a trend for increasing pyruvic acid in the serum (data not shown).

Evaluations of muscle function in rats exposed to *N,N*-dimethylaniline at 0.3 mg/m^3 showed disturbances to the normal ratios of rheobases and chronaxias (changes not further explained), particularly in the first half of the experiment. At study termination, ascorbic acid (antioxidant) levels tended to be increased in the spleen and decreased in the liver and adrenals of exposed rats (data not shown). Relative spleen and adrenal weights were increased by about 20 and 40%, respectively. No data for absolute organ weights or relative organ weights of other tissues were provided. Histopathology findings were reported for the liver, spleen, brain, and lungs of exposed rats (no incidence or severity data were provided). Rats exposed at 0.3 mg/m^3 showed a high concentration of hemosiderin in the spleen, hepatic trabeculae with cells containing compact nuclei, cellular polymorphisms, moderate dilatation of sinusoids and central veins, and hypertrophy of Kupffer cells in the liver, chromatolysis of the cortical neurons accompanied by decreased tigroid substance and polar rearrangement of Nissl bodies in the brain, and changes to the epithelial cells (marked proliferation, deformation, compact nuclei, desquamation into the lumen) of the bronchial mucosa of the lungs. The study authors indicated that the "majority" of affected endpoints normalized during the recovery period (no additional information was provided). The data provided identify a lowest-observed-adverse-effect concentration (LOAEC) of 0.3 mg/m^3 and a no-observed-adverse-effect concentration (NOAEC) of 0.0055 mg/m^3 based on significant effects on hematology and clinical chemistry parameters and histopathological findings in the liver, spleen, brain, and lungs. However, an independent evaluation of the data from this study was not possible, due to inadequate reporting of the methods and results. No details were provided regarding the test substance purity or the method used to generate the chamber air concentrations, and measured concentrations were not reported

for this study. The study results are presented primarily in a qualitative statement, with no indication of the incidence of occurrence or the magnitude of any effect.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Acute Toxicity

Oral median lethal dose (LD_{50}) values in rodents were 951−1,348 mg/kg (rats), 1,345−1,500 mg/kg (mice), and <2,400 mg/kg (guinea pigs) (Dow Chemical Co, 1995; Eastman Kodak, 1995; Mellon Institute of Industrial Research, 1995; Eastman Kodak, 1992; NTP, 1989). Clinical signs included weakness, rough coats, tremors, prostration, nasal discharge, and cyanosis. Gross and microscopic examinations were not performed.

Median lethal concentration (LC_{50}) values were not established in rats or guinea pigs at nominal concentrations of 2,000−5,000 mg/m^3 (DuPont Haskell Lab, 1995; Mellon Institute of Industrial Research, 1995; DuPont, 1983a; Buffalo Color, 1982; FDRL, 1982a, b; Price et al., 1978). Measured aerosol concentrations, when provided, were substantially lower than nominal concentrations (1,000−2,000 mg/m^3) (Buffalo Color, 1982). Clinical signs of toxicity (such as breathing changes and signs of irritation) were generally transient in nature; no significant gross pathology findings were reported.

In rats (three/group; sex not specified) administered a single gavage dose of *N,N*-dimethylaniline at 500 mg/kg and analyzed 2 and 4 hours after dosing, blood MetHb levels were 34−42% compared to about 1% in controls (Eastman Chemical Company, 1995). No additional details were provided. *N,N*-Dimethylaniline produced methemoglobinemia in two cats (one male/one female) given a dose of 50 mg/kg by gavage as an emulsion in carboxymethylcellulose (BASF, 1996). The MetHb level was increased in blood by 2 hours after dosing and was increased to 70−77% 4 and 6 hours postdosing. The blood MetHb level began to decline 24 hours after exposure. Hb binding was measured 24 hours after gavage dosing with 70 mg/kg *N,N*-dimethylaniline in three female Wistar rats. The Hb binding index (HBI) for *N,N*-dimethylaniline was approximately half the HBI reported for aniline-HCl (Birner and Neumann, 1988).

Blood from male CFE rats (two/group) administered 250 mg/kg *N,N*-dimethylaniline via intramuscular injection was subsequently analyzed for MetHb formation (Mellon Institute of Industrial Research, 1995). MetHb as the percentage of total Hb was about 4−10% 1 hour after treatment and 10−12% 4 hours after treatment in *N,N*-dimethylaniline-treated rats compared to 13−22% 1, 2, and 4 hours after treatment in positive controls (treated with aniline). No negative control group was used. No further information was provided.

Other Routes

New Zealand white (NZW) rabbits (two/sex/group) administered *N,N*-dimethylaniline (undiluted; approximately 7 mg/kg) to the skin under occluded conditions for 24 hours and evaluated immediately after exposure showed increased MetHb levels (4.6 times higher than baseline levels); although some recovery occurred, levels remained 2.2 times higher than pretest levels 5 days postexposure (Bio Dynamics, 1982). There were no significant effects on Hb, Hct, or RBC counts. Rabbits (two/sex/group) administered 2 mL of the test substance at 0.03 or 6 g/L (approximately 0.02 and 4 mg/kg) under the same conditions showed no significant changes in hematological parameters.

DuPont (1983b) reported that undiluted *N,N*-dimethylaniline was moderately irritating to the skin of albino guinea pigs (two males) following application of 0.1 g to shaved skin after 24 and 48 hours.

Genotoxicity

N,N-Dimethylaniline has been tested in a number of in vitro and in vivo genotoxicity assays (see Table 4). *N,N*-Dimethylaniline did not induce reverse mutations in *Salmonella typhimurium* (Taningher et al., 1993; NTP, 1989; Mortelmans et al., 1986; Mori et al., 1980). Forward mutations were increased in mouse lymphoma L5178Y cells (NTP, 1989). *N,N*-Dimethylaniline induced sister chromatid exchanges (SCEs) and chromosomal aberrations (CAs) in Chinese hamster ovary (CHO) cells in the presence of S9 mix (Loveday et al., 1989). In the absence of S9 mix, negative results were obtained for SCEs and only a weak positive result was obtained for CAs at the highest dose tested. In addition, *N,N*-dimethylaniline increased micronuclei in metabolically active Chinese hamster V79 cells (Taningher et al., 1993). Deoxyribonucleic acid (DNA) repair was not induced in cultured rat hepatocytes following exposure to *N,N*-dimethylaniline (Yoshimi et al., 1988). In in vivo studies, *N,N*-dimethylaniline was weakly positive for DNA damage of liver nuclei in male BALB/c mice and Sprague-Dawley (S-D) rats following intraperitoneal (i.p.) administration; however, this compound did not produce DNA damage in liver nuclei assessed by the alkaline elution assay following exposure by gavage (Taningher et al., 1993).

Metabolism/Toxicokinetic Studies

N,N-Dimethylaniline is readily absorbed through the skin but limited information is available on the absorption through oral and inhalation routes (ACGIH, 2001). The metabolism of *N,N*-dimethylaniline has been well studied in in vitro test systems from several species, including adult and fetal human tissues [reviewed by NTP (1989); IARC (1993)]. The primary metabolic reactions identified in vitro include *N*-oxidation, catalyzed by flavin-containing monooxygenases (Ziegler, 1980; Rane, 1974; Gold and Ziegler, 1973), as well as *N*-demethylation and ring hydroxylation, catalyzed by CYP450 enzymes (MacDonald et al., 1989; Pandey et al., 1989; Hamill and Cooper, 1984; Gooderham and Gorrod, 1981; Hlavica and Hulsmann, 1979; Devereux and Fouts, 1974). *N*-Demethylation may also be catalyzed by peroxidative mechanisms mediated by human term placental lipoxygenase enzymes (Hover and Kulkarni, 2000). Demethylation of the parent compound and the *N,N*-dimethylaniline *N*-oxide metabolite results in the formation of *N*-methylaniline and formaldehyde (Kitada et al., 1974). Aryl ring hydroxylation by CYP450 is a minor pathway resulting in formation of *N,N*-dimethyl-4-aminophenol and its nonenzymatic decomposition product, *N*-methyl-4-aminophenol (Gooderham and Gorrod, 1981). The *N*-methylaniline metabolite may undergo further *N*-demethylation to produce aniline followed by subsequent ring- and *N*-hydroxylation to produce 4-aminophenol and phenylhydroxylamine, respectively. The liver is the primary site of *N,N*-dimethylaniline metabolism, but oxidative metabolism has also been shown to occur in the rat and rabbit lung (Ohmiya and Mehendale, 1983).

N,N-Dimethylaniline metabolism and urinary excretion were evaluated in mongrel dogs following a single intravenous (i.v.) injection of 40 mg/kg (undiluted) (Kiese and Renner, 1974). Urine was collected over a 48-hour period, and urinary metabolites were measured after deconjugation with glucuronidase and sulfatase enzymes. Metabolites included *N*-methylaniline, 2- and 4-aminophenol, *N*-methyl-2-aminophenol, *N*-methyl-4-aminophenol, *N,N*-dimethyl-2-aminophenol, and *N,N*-dimethyl-4-aminophenol. *N,N*-dimethylaniline-*N*-oxide

was not detected in blood or urine. Aniline was found in the blood 2 hours after injection, but not the urine. Subsequent metabolism of aniline results in the production of 2- and 4-aminophenol, which may be why aniline was not detected in urine. Fecal excretion was not evaluated in any of the available studies.

Table 4. Summary of *N,N*-Dimethylaniline (CASRN 121-69-7) Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results Without Activation[a]	Results With Activation[a]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* strains TA98, TA100	0−1 µmol	−	−	NA	Mori et al. (1980)
Mutation	*S. typhimurium* strains TA98, TA100, TA1535, TA1537	0, 3, 10, 33, 100, 333, 1,000 µg/plate	−	−	Toxicity was observed at 1,000 µg/plate.	NTP (1989); Mortelmans et al. (1986)
Mutation	*S. typhimurium* strains TA97, TA98, TA100	0, 1, 2.5, 5, 10, 40, 70, 100 µg/plate	−	−	Toxicity was observed at 100 µg/plate.	Taningher et al. (1993)
Genotoxicity studies in mammalian cells—in vitro						
Mutation	Mouse lymphoma L5178Y cells	0, 200, 300, 400, 500, 600, 800 µg/mL (−S9) 0, 10, 20, 30, 40, 50, 60 µg/mL (+S9)	+	+	In the absence of metabolic activation, statistically significant toxicity was observed at concentrations producing a positive response (400−600 µg/mL, 100% lethality at 600 and 800 µg/mL). In the presence of metabolic activation, the relative mutant fraction was increased at concentrations ≥20 µg/mL. Toxicity was observed at concentrations of ≥50 µg/mL in the presence of metabolic activation.	NTP (1989)
SCE	CHO cells	0, 30, 100, 300 µg/mL (−S9) 0, 10, 30, 100, 101, 302, 1,010 µg/mL (+S9)	−	+	The lowest concentration producing a positive response in the presence of metabolic activation was 30 µg/mL.	Loveday et al. (1989); NTP (1989)
Chromosome aberrations	CHO cells	0, 83, 415, 830 µg/mL (−S9) 0, 83, 415, 505, 755, 830, 1,010 µg/mL (+S9)	±	+	Weak positive result in the absence of S9 was seen at the highest concentration only (830 µg/mL). Positive results occurred at all concentrations (≥83 µg/mL) in the presence of S9.	Loveday et al. (1989); NTP (1989)

Table 4. Summary of *N,N*-Dimethylaniline (CASRN 121-69-7) Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results Without Activation[a]	Results With Activation[a]	Comments	References
Micronucleus test	Chinese hamster lung cells (V79)	0, 0.3, 0.9, 1.2 mM	+	NA	Metabolically active cell line. Positive findings seen at concentrations ≥0.9 mM. Mitotic index did not suggest significant cytotoxicity at any concentration.	Taningher et al. (1993)
DNA repair (unscheduled DNA synthesis)	Cultured rat hepatocytes	0, 1, 10, 100, 1,000 µM	−	NA	Metabolically active cells.	Yoshimi et al. (1988)
Genotoxicity studies—in vivo						
DNA damage/strand breaks (alkaline elution test)	Male BALB/c mouse (number/groups not specified); i.p. injection; DNA damage assessed in liver nuclei 2 or 24 hr after treatment	0, 2, 4 mmol/kg (2 hr); 0, 2 mmol/kg (24 hr) 0, 242, 485 mg/kg (2 hr); 0, 242 mg/kg (24 hr)	±	±	Weak positive response at 4 mmol/kg for 2 hr and 2 mmol/kg at 24 hr.	Taningher et al. (1993)
DNA damage/strand breaks (alkaline elution test)	Male S-D rat (number/groups not specified); i.p. injection; DNA damage assessed in liver nuclei 2 or 24 hr after treatment	0, 4, 8 mmol/kg (2 hr); 0, 4 mmol/kg (24 hr) 0, 485, 969 mg/kg (2 hr); 0, 485 mg/kg (24 hr)	±	±	Weak positive response at 4 and 8 mmol/kg for 2 hr. No change was observed 24 hr after injection of 4 mmol/kg.	Taningher et al. (1993)
DNA damage/strand breaks (alkaline elution test)	Male S-D rat (number/groups not specified); gavage; DNA damage assessed in liver nuclei 6 and 24 hr after treatment	0, 8 mmol/kg 0, 969 mg/kg	−	−	No statistically significant changes in DNA elution rate.	Taningher et al. (1993)

[a]+ = positive; ± = weakly positive; − = negative.

CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; i.p. = intraperitoneal; NA = not applicable; SCE = sister chromatid exchange; S-D = Sprague-Dawley.

Mode of Action for Noncancer Effects

Mechanistic studies described above (i.e., "Acute Toxicity" and "Other Routes" sections) demonstrate methemoglobinemia and Hb binding following *N,N*-dimethylaniline treatment (BASF, 1996; Eastman Chemical Company, 1995; Mellon Institute of Industrial Research, 1995; Birner and Neumann, 1988; Bio Dynamics, 1982). Oxidation of the heme iron in Hb leading to the production of MetHb may lead to the noncancer effects of *N,N*-dimethylaniline (e.g., splenomegaly and spleen histopathology). A similar hematological mechanism has been proposed for aniline. Toxicokinetic studies demonstrate that aniline is a metabolite of *N,N*-dimethylaniline, and both compounds have several common metabolites (e.g., 4-aminophenol, phenylhydroxylamine). Mode-of-action (MOA) information pertaining to the splenic toxicity of aniline was reviewed by Bus and Popp (1987). Possible key events leading to the toxicity of aniline were suggested to include: (1) accumulation of the parent compound or metabolites carried to the spleen by RBCs; (2) covalent binding to erythrocyte and splenic macromolecules; and (3) deposition of erythrocyte debris resulting in hemosiderin accumulation, vascular congestion, and hemorrhage. Other studies have suggested that the splenotoxicity of aniline is due to oxidative stress and lipid peroxidation (Khan et al., 1998). Some of these key events may also apply to the splenic toxicity of *N,N*-dimethylaniline; however, evidence to support these key events following exposure to *N,N*-dimethylaniline is limited. Hemosiderin accumulation was observed in rats exposed to *N,N*-dimethylaniline for 13 weeks or 2 years (Abdo et al., 1990; NTP, 1989). Extramedullary hematopoiesis was also observed in these studies. A review that focused on this effect suggested that extramedullary hematopoiesis may be related to specific changes in the stem cell microenvironment, including bone marrow failure, myelostimulation, tissue inflammation, injury, and repair, and abnormal cytokine production (Johns and Christopher, 2012). There are no mechanistic studies available for *N,N*-dimethylaniline that evaluate these possible key events; thus, uncertainty remains on the MOA leading to toxic effects in the spleen following *N,N*-dimethylaniline exposure.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer references values, respectively.

Table 5. Summary of Noncancer Reference Values for *N,N*-Dimethylaniline (CASRN 121-69-7)

Toxicity Type (units)	Species/Sex	Critical Effect	*p*-Reference Value	POD Method	POD (HED)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	F344/N Rat/M and F	Extramedullary hematopoiesis and hemosiderosis of the spleen	2×10^{-3}	LOAEL	5.3	3,000	Abdo et al. (1990); NTP (1989)
Chronic p-RfD (mg/kg-d)	Oral RfD value is available on IRIS (U.S. EPA, 1987)						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

F = female(s); HED = human equivalent dose; IRIS = Integrated Risk Information System; LOAEL = lowest-observed-adverse-effect level; M = male(s); NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 6. Summary of Cancer Reference Values for *N,N*-Dimethylaniline (CASRN 121-69-7)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	Rat/male	Splenic sarcoma or osteosarcoma	2.7×10^{-2}	NTP (1989)
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

The database of oral studies in experimental animals includes five short-term-duration studies (Dow Chemical Co, 1995; Eastman Kodak, 1995, 1992; NTP, 1989; Piccirillo et al., 1983), two subchronic-duration studies (Abdo et al., 1990; NTP, 1989), two chronic-duration studies (NTP, 1989), and one developmental toxicity study (Hardin et al., 1987; Piccirillo et al., 1983). A subchronic p-RfD is derived based on the available studies.

A chronic p-RfD is not derived because there is an oral RfD value on EPA's IRIS database (U.S. EPA, 1987).

Derivation of Subchronic Provisional Oral Reference Dose

The subchronic-duration study in adult rats exposed via gavage to *N,N*-dimethylaniline is considered the principal study for the derivation of the subchronic p-RfD (Abdo et al., 1990; NTP, 1989). The critical effects from this study include extramedullary hematopoiesis and hemosiderosis of the spleen.

The subchronic studies conducted by Abdo et al. (1990) and NTP (1989) report administration of *N,N*-dimethylaniline by gavage to F344/N rats and $B6C3F_1$ mice (10/sex/dose) for 13 weeks. These studies are included in a peer-reviewed technical report conducted

according to Good Laboratory Practice (GLP) standards. They are well-conducted studies with adequate reporting and consideration for appropriate study design, methods, and conduct. However, uncertainty remains due to the lack of comprehensive endpoint evaluation; hematology, clinical chemistry, urinalysis, and organ-weight measurements were not performed or reported. The short-term-duration gavage studies in rats and mice were not selected as principal studies due to the brief exposure duration (8−15 days). A chronic-duration rat study (NTP, 1989) demonstrated spleen effects at 10-fold lower doses than the subchronic-duration study; however, this study was not selected as a principal study for the subchronic p-RfD derivation due to the near-lifetime exposure duration (i.e., 103 weeks). No maternal or offspring effects were observed in mice given 365 mg/kg-day *N,N*-dimethylaniline via gavage on GDs 6−13 (Hardin et al., 1987; Piccirillo et al., 1983). This dose is higher than the dose producing spleen effects in adults.

The subchronic-duration study in rats reported statistically significant increases in extramedullary hematopoiesis in the spleen and hemosiderosis in the spleen and kidney following administration of all treatment doses. Extramedullary hematopoiesis is the formation and development of blood cells outside the medullary spaces of the bone marrow and in adult animals indicates a molecular change in patterns of hematopoiesis to reactivation of embryonic sites of hematopoiesis (e.g., spleen) (Johns and Christopher, 2012). An increase in hemosiderosis is a result of abnormal tissue deposition of iron pigment. Both events may be related to aberrant RBC destruction by intravascular hemolysis and increased erythrophagocytosis, where excessive deposition of damaged RBCs may result in splenomegaly and associated tissue dysfunction.

A $LOAEL_{ADJ}$ of 22.32 mg/kg-day is established based on histopathological lesions of the spleen in rats with no NOAEL identified. A $LOAEL_{ADJ}$ of 44.6 mg/kg-day and $NOAEL_{ADJ}$ of 22.32 mg/kg-day were established in mice based on similar splenic lesions (see Table 7). The increased hematopoiesis and hemosiderosis of the spleen and kidney occurred at lower doses compared to liver and testes, and at lower doses than other observed effects, such as bone marrow hyperplasia in rats (Abdo et al., 1990; NTP, 1989). The effects in the spleen were observed at the lowest doses tested across short-term, subchronic, and chronic exposure durations (see Table 3A).

Table 7. Potential Subchronic PODs in Male and Female F344/N Rats and B6C3F$_1$ Mice Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) for 13 Weeks[a]

Endpoint	Sex	$NOAEL_{ADJ}$[b] (mg/kg-d)	$LOAEL_{ADJ}$[b] (mg/kg-d)	BMD (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)	POD (HED)[c,d] (mg/kg-d)
Rats						
Kidney hemosiderosis	F	ND	22.32	5.14	3.11[e]	0.75
Liver hemosiderosis	F	22.32	44.6	21.8	11.3	2.71
Bone marrow hyperplasia	M	44.6	89.3	33.1	19.7	4.73
Liver hemosiderosis	M	44.6	89.3	33.1	19.7	4.73
Kidney hemosiderosis	M	22.32	44.6	38.0	21.6	5.18
Spleen hematopoiesis	**M**	**ND**	**22.32**	**NA**	**NA**	**5.357**
Spleen hemosiderosis	**M**	**ND**	**22.32**	**NA**	**NA**	**5.357**
Spleen hematopoiesis	**F**	**ND**	**22.32**	**NA**	**NA**	**5.357**
Spleen hemosiderosis	**F**	**ND**	**22.32**	**NA**	**NA**	**5.357**
Bone marrow hyperplasia	F	44.6	89.3	No fit	No fit	10.7
Mice						
Spleen hematopoiesis	M	22.32	44.6	18.0	5.48	0.767
Spleen hemosiderosis	M	44.6	89.3	23.8	12.5	1.75
Spleen hemosiderosis	F	22.32	44.6	36.5	21.4	3.00
Spleen hematopoiesis	F	22.32	44.6	36.5	21.4	3.00
Decreased terminal body weight	M	ND	22.32[f]	No fit	No fit	3.125
Liver hemosiderosis	M	44.6	89.3	No fit	No fit	6.24
Liver hematopoiesis	M	179	357	347	172	24.1

[a]NTP (1989).
[b]Represented as average daily dose (ADD = dose × 5/7 days/week).
[c]POD (HED) = ADD × DAF. DAF = 0.24 for rats; DAF = 0.14 for mice.
[d]PODs do not consider UF application.
[e]BMD modeling was performed with four data points (minus two highest doses).
[f]Change was >10% compared to control values.

ADJ = duration adjusted; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; F = female; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; M = male; NA = not applicable (not amenable to BMDS); ND = no data (LOAEL occurs at lowest dose level tested); NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor.

Potential points of departure (PODs) from both subchronic-duration studies were modeled using the EPA's Benchmark Dose Software (BMDS, Version 2.6) (see Table 7). Appendix C presents the details of the modeling procedure. Benchmark dose (BMD) modeling could not be performed for effects in the spleen of rats because the incidence was 100% at the

lowest dose in all cases and the severity data were reported as mean severity score without an indication of variance (standard deviation [SD] or standard error of the mean).

In EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite, but not for portal-of-entry effects.

A validated human physiologically based toxicokinetic model for *N,N*-dimethylaniline is not available for use in extrapolating doses from animals to humans. Furthermore, spleen lesions are not a portal-of-entry effect. Therefore, scaling by $BW^{3/4}$ is relevant for deriving human equivalent doses (HEDs) for this effect.

Following U.S. EPA (2011b) guidance, the POD for spleen lesions in adult rats is converted to an HED through application of a dosimetric adjustment factor (DAF)[1] derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where:

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a BW_a of 0.25 kg for rats and 0.025 kg for mice, and a BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAFs are 0.24 and 0.14 for rats and mice, respectively. Each POD candidate is multiplied by the appropriate species-specific DAF to obtain the POD (HED) (see Table 7).[2]

The lowest point of departure human equivalent dose (POD [HED]) following subchronic-duration treatment of *N,N*-dimethylaniline appears to be increased kidney hemosiderosis in female rats with a POD (HED) of 0.75 mg/kg-day (10% benchmark dose lower confidence limit [$BMDL_{10}$] = 3.1 mg/kg-day). However, because no NOAEL or BMDL was identified for effects in the spleen of rats, there is uncertainty if other nonsplenic PODs (in rats and mice) would be protective for splenic effects. In addition, there is more support for

[1]As described in detail in *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), rate-related processes scale across species in a manner related to both the direct ($BW^{1/1}$) and allometric scaling ($BW^{3/4}$) aspects such that $BW^{3/4} \div BW^{1/1} = BW^{-1/4}$, converted to a $DAF = BW_a^{1/4} \div BW_h^{1/4}$.

[2]For example, LOAEL (HED) = 22.32 mg/kg-day × DAF = 22.32 mg/kg-day × 0.24 = 5.357 mg/kg-day.

increased toxicity of the spleen being selected as the critical effect, including greater severity of observed lesions, consistency in lesion development across sexes and species, and coherence with other adverse *N,N*-dimethylaniline-induced events (i.e., methemoglobinemia, splenomegaly). The severity of the histopathological responses reported in the spleen (i.e., mild) were greater than that reported for the kidney (i.e., minimal) and an increase in splenic lesions was observed in both male and female rats and mice. Based on the available data, **the LOAEL (HED) for spleen lesions in male and female rats (5.357 mg/kg-day) is selected as the POD for derivation of the subchronic p-RfD.**

The subchronic p-RfD for *N,N*-dimethylaniline, based on a LOAEL (HED) of 5.357 mg/kg-day for spleen lesions, is derived as follows:

$$\begin{aligned}\textbf{Subchronic p-RfD} &= \text{LOAEL (HED)} \div UF_C \\ &= 5.357 \text{ mg/kg-day} \div 3{,}000 \\ &= \mathbf{2 \times 10^{-3} \text{ mg/kg-day}}\end{aligned}$$

The composite uncertainty factor (UF_C) for the subchronic p-RfD for *N,N*-dimethylaniline is 3,000, as summarized in Table 8.

Table 8. Uncertainty Factors for the Subchronic p-RfD for *N,N*-Dimethylaniline (CASRN 121-69-7)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following oral *N,N*-dimethylaniline treatment. The toxicokinetic uncertainty has been accounted for by calculating a HED through application of a DAF as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The available subchronic- and chronic-duration oral toxicity studies and the developmental toxicity screening study for *N,N*-dimethylaniline are not comprehensive. No oral reproductive studies are available for *N,N*-dimethylaniline.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess toxicokinetic and toxicodynamic variability of *N,N*-dimethylaniline in humans.
UF_L	10	A UF_L of 10 is applied for LOAEL-to-NOAEL extrapolation because the POD is a LOAEL.
UF_S	1	A UF_S of 1 is applied because the principal study is a subchronic-duration study (13 wk) (Abdo et al., 1990; NTP, 1989).
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure.

The confidence in the subchronic p-RfD for *N,N*-dimethylaniline is low as described in Table 9.

Table 9. Confidence Descriptors for the Subchronic p-RfD for *N,N*-Dimethylaniline (CASRN 121-69-7)

Confidence Categories	Designation	Discussion
Confidence in study	L	Confidence in the principal study is low. Despite being a peer-reviewed study that used five dose groups in both sexes of two species, a comprehensive evaluation of potential effects was not conducted (hematology, clinical chemistry, and organ-weight measurements were not performed). In addition, a NOAEL dose was not identified because spleen lesions occurred in every animal at all dose levels.
Confidence in database	L	There is low confidence in the database. The available subchronic- and chronic-duration oral toxicity studies for *N,N*-dimethylaniline are not comprehensive. The single developmental toxicity screening study available is not comprehensive (no internal examination of fetal development). No oral reproductive studies are available for *N,N*-dimethylaniline.
Confidence in subchronic p-RfD[a]	L	The overall confidence in the subchronic p-RfD is low.

[a]The overall confidence cannot be greater than the lowest entry in the table.

L = low; NOAEL = no-observed-adverse-effect level; p-RfD = provisional oral reference dose.

Derivation of Chronic Provisional Oral Reference Dose

A chronic p-RfD is not derived because an oral RfD is available on EPA's IRIS database (U.S. EPA, 1987).

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Human and animal data are inadequate to derive subchronic or chronic provisional reference concentrations (p-RfCs). A subchronic-duration inhalation study is available for *N,N*-dimethylaniline (Markosyan, 1969). This study exposed male albino rats (number not specified) to nominal concentrations of 0, 0.0055, or 0.3 mg/m^3 *N,N*-dimethylaniline in air continuously for 100 days. Effects were reported in the blood, spleen, liver, brain, and lung at the high-exposure concentration; however, the study report does not provide adequate details to allow for a thorough review of the methods and results. No details were provided regarding the method used to generate the chamber air concentrations, and measured concentrations were not reported for this study. The study results are presented primarily in a qualitative statement, with no indication of the incidence of occurrence or the magnitude of any effect. As a result of the uncertainties in the available inhalation data for *N,N*-dimethylaniline, subchronic and chronic p-RfCs are not derived.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTORS

The cancer weight-of-evidence (WOE) descriptors for *N,N*-dimethylaniline are presented in Table 10.

Table 10. Cancer Weight-of-Evidence Descriptors for *N,N*-Dimethylaniline (CASRN 121-69-7)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	There are no human data to support this.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no sufficient animal studies to support this.
"Suggestive Evidence of Carcinogenic Potential"	**Selected**	**Oral**	**There are sufficient animal studies to support this selection.**
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Inhalation**	**No carcinogenicity studies are available that evaluated inhalation exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

NA = not applicable; NS = not selected.

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is *"Suggestive Evidence of Carcinogenic Potential"* for *N,N*-dimethylaniline by an oral route of exposure and *"Inadequate Information to Assess Carcinogenic Potential"* by inhalation (see Table 10). These descriptors are based on (1) suggestive evidence of carcinogenicity in orally treated male rats and (2) a lack of carcinogenicity studies in animals exposed by inhalation.

No human studies are available to assess the potential for carcinogenesis following exposure to *N,N*-dimethylaniline. Carcinogenesis studies of *N,N*-dimethylaniline were conducted in F344/N rats and B6C3F$_1$ mice treated via gavage for 103 weeks (NTP, 1989). A review of the study findings indicated that both rats and mice could have tolerated a higher dose of *N,N*-dimethylaniline, suggesting that the carcinogenic responses may have been greater had larger doses been administered in these studies. Nevertheless, the NTP concluded that there was *"Some Evidence of Carcinogenic Activity"* in male rats based on the increased incidence of sarcomas or osteosarcomas (combined) in the spleen (no evidence of carcinogenicity in female rats). The splenic sarcomas were described as anaplastic neoplasms with histologic characteristics of fibrosarcomas, osteosarcomas, or hemangiosarcomas. The sarcomas observed in the spleen were varied in morphology, but there was no evidence to suggest they were derived from other tissues (e.g., bone). The osteosarcoma observed in the spleen may have differentiated from a splenic sarcoma because sarcomas, which are mesenchymal origin, can undergo osteoblastic differentiation toward osteosarcomas (Mutsaers and Walkley, 2014). In fact, one splenic sarcoma observed following *N,N*-dimethylaniline treatment had a focus of minimal osteoid production that the NTP proposed as evidence of early differentiation toward osteosarcoma. Because there is no evidence to suggest the *N,N*-dimethylaniline-induced sarcomas or osteosarcomas are derived from different tissues, it is appropriate to combine the incidence of these neoplasms. The combined incidence of tumors in the high-dose group (21 mg/kg-day) increased compared to the concurrent control group ($p = 0.06$ by incidental tumor test and Fisher's exact test), and a statistically significant dose-response trend was

observed (p = 0.01 by Cochran-Armitage trend test) (see Tables 11 and B-8). The site and sex differences associated with these neoplasms are consistent with those induced by aniline and other structurally analogous chemicals (NTP, 1989). In addition, the incidence of splenic sarcoma in high-dose males (3/50) exceeded the greatest historical incidence of splenic sarcoma in control male rats given corn oil gavage (1/45), as well as equaled the overall historical incidence for males in NTP corn oil gavage studies (3/2,081) (NTP, 1989).

Table 11. Incidence of Splenic Sarcoma or Osteosarcoma in Male F344/N Rats Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage 5 Days/Week for 2 Years[a]

	Adjusted Daily Dose (HED) (mg/kg-d)		
Endpoint	**0 (Control)**	**2 (0.5)**	**21 (5.0)**
Splenic sarcoma or osteosarcoma	0/49* (0%)	0/49 (0%)	4/50 (8%)

[a]NTP (1989).
*Trend test $p \leq 0.05$ (life table test, incidental tumor test, and Cochran-Armitage trend test performed by study authors).

The NTP concluded that there was *"equivocal evidence of carcinogenic activity"* in female mice based on increased incidence of squamous cell papillomas of the forestomach (no evidence of carcinogenicity in male mice). Female mice showed a statistically significant increase in the incidence of this tumor in the high-dose group compared to concurrent controls (p = 0.04), and a statistically significant dose-response trend was observed (p = 0.02) (see Table B-9). However, these tumors were not considered for deriving a provisional oral slope factor (p-OSF) for several reasons. Forestomach papillomas are considered a portal-of-entry effect in gavage treated animals. Portal-of-entry effects would be expected to occur in both sexes because direct toxicity would not be impacted by sex-related differences in toxicokinetics. No increase in forestomach tumors was observed in male mice. Additionally, the tumor incidence in high-dose female mice did not differ markedly from the greatest historical control incidence in female mice given corn oil gavage (8/50 vs. 5/44). The historical incidence for this tumor type in female mice given corn oil gavage in NTP studies varied from 0/50 to 5/44 with an overall incidence of 32/2,047. Finally, no squamous cell carcinomas were identified in high-dose female mice, suggesting that the observed forestomach papillomas might not be progressive. In the diagnosis of papillomas, the NTP noted uncertainty whether "these proliferative lesions are true neoplasms or merely an advanced stage of hyperplasia" (NTP, 1989).

As stated in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), an example of supporting data to conclude that there is *"Suggestive Evidence of Carcinogenic Potential"* includes "a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor *'Likely to Be Carcinogenic to Humans.'*" Based on this example from the U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) and the data available from the study in male rats, there is *"Suggestive Evidence of Carcinogenic Potential"* for *N,N*-dimethylaniline.

MODE OF ACTION

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) define MOA for carcinogenicity "as a sequence of key events and processes, starting with the interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation." Examples of some of the possible modes of carcinogenic action for any given chemical include "mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression." The available studies of *N,N*-dimethylaniline provide evidence for some key events leading to tumor formation in the spleen, with both genotoxic and nongenotoxic events being plausible.

Although not mutagenic in bacteria (Taningher et al., 1993; NTP, 1989; Mortelmans et al., 1986; Mori et al., 1980), *N,N*-dimethylaniline is both mutagenic and clastogenic in mammalian cells (Taningher et al., 1993; Loveday et al., 1989; NTP, 1989) (see Table 4). Genotoxicity appears to be primarily due to one or more of the compound's metabolites (Taningher et al., 1993; Loveday et al., 1989; NTP, 1989), although likely not by direct damage to DNA (Taningher et al., 1993; Yoshimi et al., 1988). These results suggest that a genotoxic MOA is plausible for *N,N*-dimethylaniline-induced tumors.

As described above, toxicokinetic and mechanistic evidence suggests that *N,N*-dimethylaniline may act through a similar hematological mechanism as aniline, a major metabolite of *N,N*-dimethylaniline. Genotoxicity studies of aniline and aniline metabolites reviewed by Bomhard and Herbold (2005) suggest that the carcinogenic activity of aniline may not be due to genotoxicity; however, the evidence is not consistent for all endpoints. MOA information reviewed by Bus and Popp (1987) suggest the following possible key events for aniline carcinogenicity: (1) accumulation of the parent compound or metabolites carried to the spleen by RBCs; (2) covalent binding to erythrocyte and splenic macromolecules; (3) deposition of erythrocyte debris (e.g., iron) resulting in hemosiderin accumulation, vascular congestion, and hemorrhage; and (4) hyperplasia and fibrosis leading to formation of splenic tumors (i.e., fibrosarcomas). Some of these key events may also apply to the splenic toxicity of *N,N*-dimethylaniline; however, evidence to support these key events following exposure to *N,N*-dimethylaniline is limited. Hemosiderin accumulation, fibrosis, sarcoma, and osteosarcoma were observed in the spleens of male rats given *N,N*-dimethylaniline orally for 2 years (NTP, 1989). Still, mechanistic studies that evaluate these possible key events following exposure to *N,N*-dimethylaniline are limited; thus, uncertainty remains on the principal MOA leading to splenic tumors following *N,N*-dimethylaniline exposure.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor

A p-OSF for *N,N*-dimethylaniline is derived from the combined incidence of splenic sarcoma or osteosarcoma in male rats from the NTP (1989) study (see Table 11 for incidence data).

As noted in Table 10, the EPA concluded that there is *"Suggestive Evidence of Carcinogenic Potential"* for *N,N*-dimethylaniline by an oral route of exposure. The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) state: "When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the

magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. In each case, the rationale for the quantitative analysis is explained, considering the uncertainty in the data and the suggestive nature of the weight of evidence. These analyses generally would not be considered Agency consensus estimates."

Prior to dose-response modeling, doses administered to the animals in the studies by NTP (1989) were converted to HEDs according to the equation below:

$$\text{Dose (HED)} = \text{Dose} \times (BW_a \div BW_h)^{1/4}$$

where:

Dose = average daily animal dose of *N,N*-dimethylaniline
BW_a = reference animal body weight[3]
BW_h = 70 kg, reference human body weight (U.S. EPA, 1988)

Using a BW_a of 0.25 kg for rats and a BW_h of 70 kg for humans, the resulting default DAF is 0.24 (U.S. EPA, 2011b, 2005).[4]

Multistage-cancer models in the EPA BMDS (Version 2.6) were fit to the tumor incidence data shown in Table 11, and modeling results are summarized in Appendix C. The benchmark response (BMR) used was 10% extra risk. Calculated POD (HED) doses were used for modeling. The 1- and 2-degree multistage-cancer models provided adequate fit to this data set. The 2-degree model had the lower Akaike's information criterion (AIC) and was selected. The dose associated with 10% extra risk (BMD_{10}) and its 95% lower confidence limit ($BMDL_{10}$) are 5.6 and 3.7 mg/kg-day, respectively (see Table C-1 in Appendix C).

The MOA by which *N,N*-dimethylaniline induces splenic tumors is not known; both genotoxic and nongenotoxic contributions are plausible. In the absence of definitive information, a linear approach is used to obtain the slope from the POD.

Using the linear approach, a **p-OSF of 2.7 × 10^{-2} (mg/kg-day)$^{-1}$** is derived for *N,N*-dimethylaniline from the $BMDL_{10}$ (HED) of 3.7 mg/kg-day for splenic tumors in male rats treated by gavage for 2 years, as follows:

p-OSF = BMR ÷ $BMDL_{10}$ (HED)
= 0.1 ÷ 3.7 mg/kg-day
= **2.7 × 10^{-2} (mg/kg-day)$^{-1}$**

Derivation of Provisional Inhalation Unit Risk

The absence of data identified on the carcinogenicity of *N,N*-dimethylaniline following inhalation exposure precludes the derivation of a quantitative estimate (i.e., p-IUR) for inhalation exposure.

[3]Time-weighted body weight was not reported by the study authors or calculable from reported study data. Default animal body weights (0.25 kg for rats and 0.025 kg for mice) were used in calculating HED values.
[4]For example, POD (HED) = 21 mg/kg-day × 0.24 = 5.2 mg/kg-day.

APPENDIX A. SCREENING PROVISIONAL VALUES

No provisional screening values are identified for *N,N*-dimethylaniline.

APPENDIX B. DATA TABLES

Table B-1. Survival and Body Weights in Male and Female F344/N Rats Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage for 14 Days[a]

Endpoint	Exposure Group (mg/kg-d)					
	0 (control)	94	188	375	750	1,500
Survival[b]						
Males	5/5	5/5	5/5	5/5	1/5	0/5
Females	5/5	5/5	5/5	5/5	0/5	0/5
Mean Body Weight (g)[c]						
Males						
Terminal body weight	199 ± 6	194 ± 7 (−3%)	187 ± 4 (−6%)	169 ± 6* (−15%)	105 (−47%)	ND
Body-weight gain	73 ± 5	64 ± 2 (−12%)	61 ± 3 (−16%)	47 ± 2* (−36%)	−16 (−122%)	ND
Females						
Terminal body weight	135 ± 2	129 ± 3 (−4%)	127 ± 2* (−6%)	131 ± 5 (−3%)	ND	ND
Body-weight gain	32 ± 2	32 ± 2 (0%)	30 ± 2 (−6%)	26 ± 3 (−19%)	ND	ND
Splenomegaly[d]						
Males and females combined	0/10	3/10	9/10*	10/10*	1/1	ND

[a]NTP (1989).
[b]Number surviving/number initially in group (deaths occurred on Days 3, 4, and 6).
[c]Values expressed as group mean body weight ± standard error of the mean (% change compared with control); % change control = [(treatment mean − control mean) ÷ control mean] × 100.
[d]Number with splenomegaly/number examined.
*Statistically significantly different from controls at $p < 0.05$, as calculated for this review (unpaired *t*-test for body weight; Fisher's exact test for splenomegaly).

ND = no data reported due to 100% mortality.

Table B-2. Survival and Body Weights in Male and Female B6C3F$_1$ Mice Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage for 15 Days[a]

Endpoint	Exposure Group (mg/kg-d)					
	0 (control)	94	188	375	750	1,500
Survival[b]						
Males	5/5	5/5	4/5	5/5	0/5	0/5
Females	5/5	5/5	5/5	5/5	0/5	0/5
Mean Body Weight (g)[c]						
Males						
Terminal body weight	26.0 ± 0.6	28.1 ± 1.3 (+8%)	26.6 ± 0.5 (+2%)	28.6 ± 0.7 (+10%)	ND	ND
Body-weight gain	0.8 ± 0.2	2.1 ± 0.4* (+162%)	2.1 ± 0.7 (+162%)	2.1 ± 0.4* (+162%)	ND	ND
Females						
Terminal body weight	21.1 ± 0.3	21.3 ± 0.6 (+1%)	21.3 ± 0.7 (+1%)	22.8 ± 0.6* (+8%)	ND	ND
Body-weight gain	1.3 ± 0.4	1.5 ± 0.3 (+15%)	1.6 ± 0.3 (+23%)	2.4 ± 0.6 (+85%)	ND	ND
Splenomegaly[d]						
Males	0/5	0/5	1/5	2/5	ND	ND
Females	0/5	0/5	0/5	3/5	ND	ND

[a]NTP (1989).
[b]Number surviving/number initially in group (deaths occurred on Days 3, 4, 6, 9, and 12).
[c]Values expressed as group mean body weight ± standard error of the mean (% change compared with control); % change control = [(treatment mean − control mean) ÷ control mean] × 100.
[d]Number with splenomegaly/number examined.
*Statistically significantly different from controls at $p < 0.05$, as calculated for this review (unpaired *t*-test).

ND = no data reported due to 100% mortality.

Table B-3. Survival and Body Weight of Male and Female F344/N Rats Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage 5 Days/Week for 13 Weeks[a]

Endpoint	Average Daily Dose (mg/kg-d)					
	0 (control)	22.32	44.6	89.3	179	357
Survival[b]						
Males	10/10	10/10	10/10	10/10	10/10	9/10
Females	10/10	10/10	9/10	9/10	9/10	10/10
Mean Body Weights (g)[c]						
Males						
Terminal body weight	345 ± 5	331 ± 8 (−4%)	332 ± 5 (−4%)	321 ± 5* (−7%)	292 ± 5* (−15%)	251 ± 9* (−27%)
Body-weight gain	223 ± 6	208 ± 7 (−7%)	204 ± 3* (−9%)	194 ± 4* (−13%)	168 ± 3* (−25%)	130 ± 8* (−42%)
Females						
Terminal body weight	193 ± 2	190 ± 2 (−2%)	188 ± 2 (−3%)	187 ± 2* (−3%)	185 ± 2* (−4%)	183 ± 4* (−5%)
Body-weight gain	90 ± 3	92 ± 2 (+2%)	91 ± 2 (+1%)	88 ± 2 (−2%)	86 ± 2 (−4%)	84 ± 4 (−7%)

[a]Abdo et al. (1990); NTP (1989).
[b]Number surviving/number initially in group (deaths occurred during Weeks 2, 3, and 7).
[c]Values expressed as group mean body weight ± standard error of the mean (% change compared with control); % change control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from controls at $p < 0.05$, as calculated for this review (unpaired *t*-test).

Table B-4. Selected Histopathologic Findings in Male and Female F344/N Rats Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage 5 Days/Week for 13 Weeks[a]

Endpoint	Average Daily Dose (mg/kg-d)					
	0 (control)	22.32	44.6	89.3	179	357
Males						
Spleen						
Hematopoiesis	0/10	10/10* (2.3)[b]	10/10* (2.0)	10/10* (2.8)	10/10* (3.5)	9/9* (4.0)
Hemosiderosis	0/10	10/10* (2.3)	10/10* (2.7)	10/10* (2.9)	10/10* (3.8)	9/9* (4.8)
Liver						
Hemosiderosis	0/10	0/10	2/10 (1.5)	9/10* (1.3)	10/10* (2.5)	9/9* (3.2)
Kidney						
Hemosiderosis	0/10	0/10	7/10* (1.1)	10/10* (2.0)	10/10* (3.7)	9/9* (4.2)
Testis						
Hemosiderosis	0/10	Not examined	Not examined	0/10	10/10* (1.0)	9/9* (1.0)
Bone marrow						
Hyperplasia	0/10	0/10	2/10 (1.0)	9/10* (1.3)	10/10* (2.1)	8/8* (3.0)
Females						
Spleen						
Hematopoiesis	2/10 (2.0)	10/10* (2.1)	10/10* (2.4)	10/10* (2.9)	10/10* (2.9)	10/10* (3.9)
Hemosiderosis	0/10	10/10* (2.0)	9/10* (3.0)	9/10* (3.2)	9/10* (3.1)	10/10* (4.0)
Liver						
Hemosiderosis	0/10	0/10	6/10* (1.0)	9/10* (1.6)	9/10* (2.1)	10/10* (3.5)
Kidney						
Hemosiderosis	1/10 (1.0)	6/10* (1.0)	9/10* (1.3)	9/10* (2.1)	9/10* (3.6)	9/10* (3.6)
Bone marrow						
Hyperplasia	0/10	0/10	1/10 (1.0)	9/10* (1.4)	8/10* (2.1)	9/10* (1.9)

[a]Abdo et al. (1990); NTP (1989).
[b]Number with histopathological lesion/number examined; mean severity score in parentheses: Grade 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe.
*Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test).

Table B-5. Survival and Mean Body Weights of Male and Female B6C3F$_1$ Mice Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage 5 Days/Week for 13 Weeks[a]

Endpoint	Average Daily Dose (mg/kg-d)					
	0 (control)	22.32	44.6	89.3	179	357
Survival[b]						
Males	9/10	8/10	7/10	10/10	9/10	10/10
Females	10/10	10/10	9/10	10/10	10/10	10/10
Mean Body Weights (g)[c]						
Males						
Terminal body weight	38.6 ± 1.0	34.8 ± 0.5* (−10%)	35.1 ± 0.9* (−9%)	33.9 ± 1.0* (−12%)	34.9 ± 1.5 (−10%)	35.3 ± 0.7* (−9%)
Body-weight gain	8.3 ± 0.8	5.5 ± 1.0* (−34%)	5.4 ± 0.4* (−35%)	5.1 ± 0.9* (−39%)	7.6 ± 1.0 (−8%)	4.9 ± 0.8* (−41%)
Females						
Terminal body weight	28.4 ± 1.2	26.4 ± 0.5 (−7%)	26.7 ± 0.9 (−6%)	25.9 ± 0.7 (−9%)	28.0 ± 0.6 (−1%)	27.8 ± 0.7 (−2%)
Body-weight gain	5.0 ± 0.7	1.7 ± 0.3* (−66%)	3.5 ± 0.8 (−30%)	2.7 ± 0.4* (−46%)	3.9 ± 0.5 (−22%)	4.5 ± 0.5 (−10%)

[a]Abdo et al. (1990); NTP (1989).
[b]Number surviving/number initially in group (deaths occurred during Weeks 1, 2, 3, 8, 10, and 12).
[c]Values expressed as group mean body weight ± standard error of the mean (% change compared with control); % change control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from controls at $p < 0.05$, as calculated for this review (unpaired *t*-test).

Table B-6. Selected Histopathologic Findings in Male and Female B6C3F$_1$ Mice Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage 5 Days/Week for 13 Weeks[a]

Endpoint[b]	Average Daily Dose (mg/kg-d)					
	0 (control)	22.32	44.6	89.3	179	357
Males						
Spleen						
Hematopoiesis	1/10 (1.0)[b]	1/10 (2.0)	6/9* (1.4)	9/10* (1.9)	10/10* (2.2)	10/10* (3.9)
Hemosiderosis	1/10 (3.0)	0/10	5/9 (2.0)	9/10* (2.0)	9/10* (2.9)	10/10* (4.6)
Liver						
Hematopoiesis	1/10 (1.0)	0/10	0/10	0/9	0/10	6/10* (2.3)
Hemosiderosis	1/10 (1.0)	1/10 (1.0)	0/10	9/9* (1.1)	9/10* (3.1)	9/10* (3.7)
Kidney						
Hemosiderosis	0/10	0/10	0/3	Not examined	0/10	8/10* (2.6)
Females						
Spleen						
Hematopoiesis	0/10	0/10	8/10* (1.9)	10/10* (1.8)	10/10* (2.4)	10/10* (3.9)
Hemosiderosis	0/10	0/10	8/10* (2.1)	10/10* (2.0)	10/10* (2.9)	10/10* (5.0)
Liver						
Hematopoiesis	0/10	Not examined	0/10	0/10	0/10	8/10* (2.1)
Hemosiderosis	1/10 (1.0)	Not examined	0/10	10/10* (1.0)	10/10* (3.2)	10/10* (3.3)
Kidney						
Hemosiderosis	0/10	Not examined	Not examined	0/10	10/10* (1.2)	10/10* (2.8)

[a]Abdo et al. (1990); NTP (1989).
[b]Number of animals with histopathological lesion/number of animals examined; mean severity in parenthesis: Grade 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe.
*Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test).

Table B-7. Selected Nonneoplastic Lesions in Male and Female F344/N Rats Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage 5 Days/Week for 2 Years[a]

Endpoint	Average Daily Dose (mg/kg-d)		
	0 (control)	2	21
Males			
Spleen			
Hematopoiesis	44/49[b]	48/49	50/50
Normal	5/49	1/49	0/50
Minimal	41/49	38/49	29/50
Mild	2/49	7/49	19/50*
Moderate	0/49	3/49	2/50
Marked	1/49	0/49	0/50
Mean severity score[c]	1.00 ± 0.09	1.24 ± 0.09	1.46 ± 0.08**
Hemosiderosis	43/49	47/49	49/50
Normal	6/49	2/49	1/50
Minimal	39/49	17/49*	13/50*
Mild	4/49	29/49*	25/50*
Moderate	0/49	1/49	11/50*
Marked	0/49	0/49	0/50
Mean severity score	0.96 ± 0.06	1.59 ± 0.09**	1.92 ± 0.11**
Fibrosis	5/49	2/49	22/50**
Fatty metamorphosis	0/49	1/49	10/50**

Table B-7. Selected Nonneoplastic Lesions in Male and Female F344/N Rats Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage 5 Days/Week for 2 Years[a]

Endpoint	Average Daily Dose (mg/kg-d)		
	0 (control)	2	21
Females			
Liver			
Chronic focal inflammation	17/50	20/50	30/50*
Spleen			
Hematopoiesis	47/50	48/49	49/49
Normal	3/50	1/49	0/49
Minimal	25/50	16/49	9/49*
Mild	22/50	30/49	38/49*
Moderate	0/50	1/49	1/49
Marked	0/50	1/49	1/49
Mean severity score	1.38 ± 0.09	1.69 ± 0.09	1.88 ± 0.08**
Hemosiderosis	47/50	48/49	49/49
Normal	3/50	1/49	0/49
Minimal	10/50	5/49	1/49*
Mild	37/50	29/49	20/49*
Moderate	0/50	14/49*	28/49*
Marked	0/50	0/49	0/49
Mean severity score	1.68 ± 0.08	2.14 ± 0.10**	2.55 ± 0.08**
Fibrosis	2/50	0/49	2/49
Fatty metamorphosis	0/50	1/49	0/49

[a]NTP (1989).
[b]Number with histological lesion/number examined.
[c]Mean ± standard error of the mean; 0 = normal; 1 = minimal; 2 = mild; 3 = moderate; 4 = marked.
*Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test).
**$p < 0.01$ (statistics reported by study authors; Mann-Whitney U test for severity data; incidental tumor test for incidence data).

Table B-8. Selected Neoplastic Lesions in Male and Female F344/N Rats Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage 5 Days/Week for 2 Years[a]

Endpoint	Average Daily Dose (mg/kg-d)		
	0 (control)	2	21
Males			
Splenic sarcoma	0/49* (0%)	0/49 (0%)	3/50 (6%)
Splenic osteosarcoma	0/49 (0%)	0/49 (0%)	1/50 (2%)
Splenic sarcoma or osteosarcoma	0/49* (0%)	0/49 (0%)	4/50 (8%)
Females			
Splenic sarcoma	1/50 (2%)	0/49 (0%)	0/49 (0%)

[a]NTP (1989).
*Trend test $p \leq 0.05$ (life table test, incidental tumor test, and Cochran-Armitage trend test performed by study authors).

Table B-9. Selected Histopathological Lesions in Female B6C3F$_1$ Mice Exposed to *N,N*-Dimethylaniline (CASRN 121-69-7) by Gavage 5 Days/Week for 2 Years[a]

Endpoint	Average Daily Dose (mg/kg-d)		
	0 (control)	11	21
Nonneoplastic effects			
Forestomach epithelial hyperplasia	8/50 (16%)	11/19 (58%)[b]	13/50 (26%)
Pituitary gland; chromophobe cell hyperplasia	10/45 (22%)	2/14 (14%)[c]	16/44 (36%)
Neoplastic effects			
Forestomach squamous cell papilloma[d]	2/50* (4%)	2/19 (4%)[b]	8/50* (16%)

[a]NTP (1989).
[b]Nineteen forestomachs were examined microscopically at the low dose for this endpoint.
[c]Incomplete sampling of tissues.
[d]Historical incidence of squamous cell papillomas or carcinomas (combined) at study laboratory (mean ± SD): 7/141 (5% ± 6%); historical incidence in NTP studies: 32/2,047 (2% ± 3%).
*$p \leq 0.05$; indicated next to control incidence for dose-response trend (incidental tumor test and Cochran-Armitage trend test) and treatment group incidence for pair wise comparison to control (incidental tumor test) (statistics reported by study authors).

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING OF NONCANCER ENDPOINTS

As discussed in the body of the report in the "Derivation of Subchronic Provisional Oral Reference Dose" section, the endpoints selected for benchmark dose (BMD) modeling were: (1) incidence of kidney, liver, and spleen hemosiderosis in male and female rats; (2) incidence of spleen hematopoiesis in male and female rats; (3) incidence of bone marrow hyperplasia in male and female rats; (4) incidence of spleen hemosiderosis and hematopoiesis in male and female mice; (5) terminal body weight in male mice; (6) incidence of liver hemosiderosis in male and female mice; and (7) splenomegaly in male and female mice (Abdo et al., 1990; NTP, 1989). The animal doses in the study, converted to adjusted daily doses (ADDs) of *N,N*-dimethylaniline, were used in the BMD modeling; the data are shown in Tables B-4, B-5, and B-6.

Modeling Procedure for Dichotomous Noncancer Data

BMD modeling of dichotomous noncancer data was conducted with the EPA's Benchmark Dose Software (BMDS, Version 2.5). For these data, the Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, and Weibull dichotomous models available within the software were fit using a benchmark response (BMR) of 10% extra risk. The multistage model is run for all polynomial degrees up to $n - 1$, where n is the number of dose groups including control. Adequacy of model fit was judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), scaled residuals at the data point (except the control) closest to the predefined benchmark response (absolute value <2.0), and visual inspection of the model fit. In the cases where no best model was found to fit to the data, a reduced data set without the high-dose group was further attempted for modeling and the result was present along with that of the full data set. Among all of the models providing adequate fit, the benchmark dose lower confidence limit (BMDL) from the model with the lowest Akaike's information criterion (AIC) was selected as a potential point of departure (POD) when BMDL values were sufficiently close. Otherwise, the lowest BMDL was selected as a potential POD.

Modeling Procedure for Continuous Noncancer Data

BMD modeling of continuous noncancer data was conducted with the EPA's BMDS (Version 2.5). For these data, all continuous models available within the software were fit using a BMR of 10% extra risk or 1 standard deviation (SD). Adequacy of model fit was judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of the scaled residuals at the data point (except the control) closest to the predefined benchmark response (absolute value <2.0), and visual inspection of the model fit. In addition to these three criteria for judging the adequacy of model fit, a determination was made as to whether the variance across dose groups was homogeneous. If a homogeneous variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2), the final BMD results were estimated from the homogeneous variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model did not adequately fit the data (i.e., Test 3; $p < 0.1$), the data set was considered unsuitable for BMD modeling. In the cases where no best model was found to fit to the data, a reduced data set without the high-dose group was further attempted for modeling and the result was present along with that of the full data set. Among all of the models providing adequate fit, the BMDL from the model with the

lowest AIC was selected as a POD when BMDL values were sufficiently close. Otherwise, the lowest BMDL was selected as a potential POD.

MODELING OF CANCER ENDPOINTS

As discussed in the body of the report in the "Derivation of Provisional Oral Slope Factor" section, the tumor type selected for BMD modeling was splenic sarcomas or osteosarcomas in male rats administered *N,N*-dimethylaniline via gavage 5 days/week for 103 weeks (NTP, 1989). The tumor incidences and associated human equivalent doses (HEDs) used in the modeling are shown in Tables 11 and B-8.

Modeling Procedure for Cancer Incidence Data

The model-fitting procedure for dichotomous cancer incidence data is as follows. The multistage-cancer model in the EPA's BMDS (Version 2.6) is fit to the incidence data using the extra risk option. The multistage-cancer model is run for all polynomial degrees up to $n - 1$ (where n is the number of dose groups including control). An adequate model fit is judged by three criteria: (1) goodness-of-fit p-value ($p > 0.1$), (2) visual inspection of the dose-response curve, and (3) scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the BMDL from the best fitting multistage-cancer model as judged by the goodness-of-fit p-value, is selected as the POD. In accordance with U.S. EPA (2012b) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated.

Model Predictions for Splenic Sarcomas or Osteosarcomas in Male F344/N Rats

Modeling was performed according to the procedure outlined above using BMDS for combined incidence of splenic sarcoma or osteosarcoma in male F344/N rats based on the POD (HEDs), and Table C-1 summarizes the results. Both the 1- and 2-degree multistage-cancer models provided adequate fit to this data set. The 2-degree model had the lower AIC and was selected. The dose associated with 10% extra risk (BMD_{10}) and its 95% lower confidence limit ($BMDL_{10}$) are 5.64914 and 3.69334 mg/kg-day, respectively.

Table C-1. BMD Modeling Results for Splenic Sarcoma or Osteosarcoma in Male F344/N Rats Exposed to *N,N*-Dimethylaniline by Gavage 5 Days/Week for 2 Years[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual for Dose Group	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Multistage-cancer (1-degree)[c]	2	0.41	0.8147	0.194	30.655	6.96361	3.37669
Multistage-cancer (2-degree)[c,d]	2	0.04	0.9798	0.02	29.9582	5.64914	3.69334

[a]NTP (1989).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Selected model. All models provided adequate fit to the data (selected model with the lowest AIC).

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degrees of freedom.

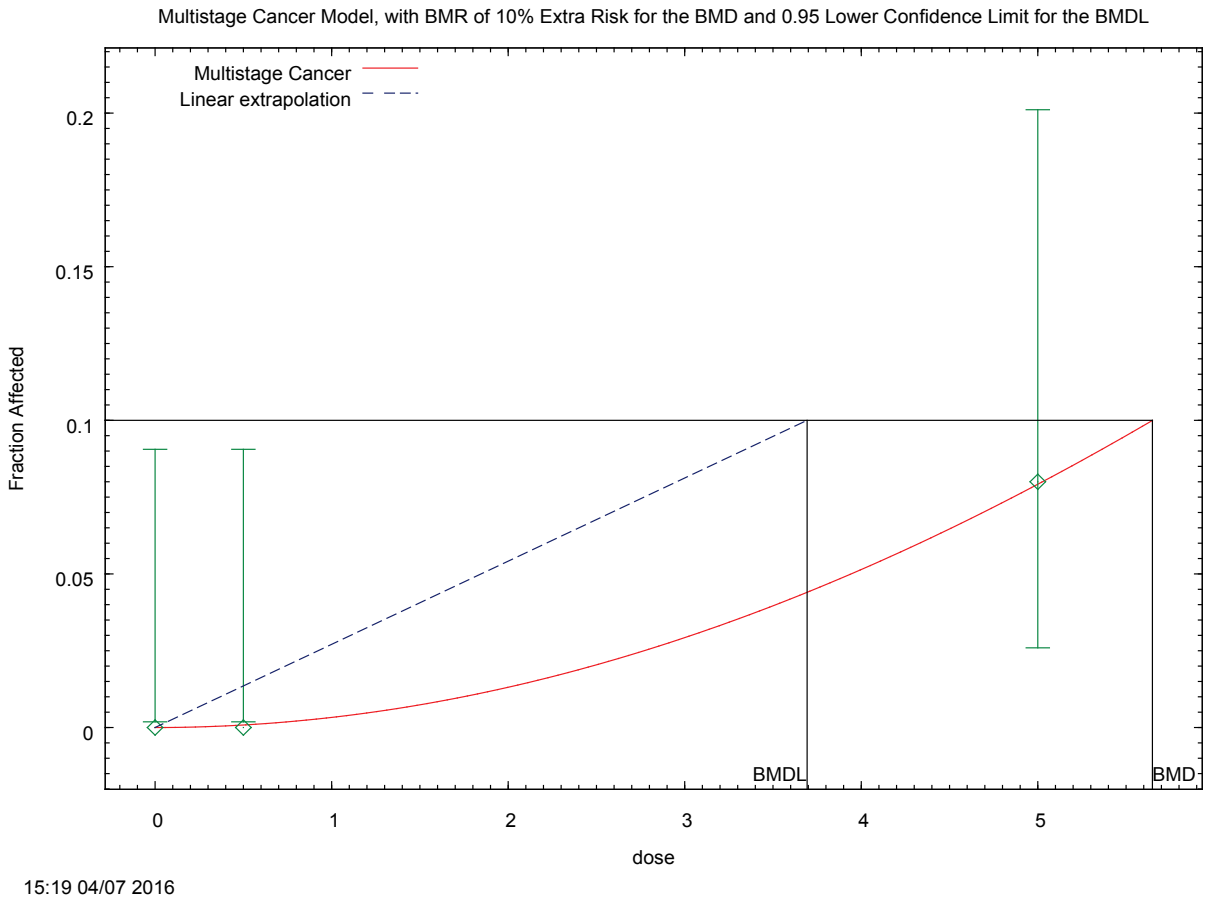

Figure C-1. Multistage-Cancer 1-Degree BMD Model for Increased Splenic Sarcoma or Osteosarcoma in Male Rats Administered *N,N*-Dimethylaniline Via Gavage 5 Days/Week for 103 weeks (NTP, 1989)

Text Output for Multistage-Cancer 1-Degree BMD Model for Increased Splenic Sarcoma or Osteosarcoma in Male Rats (NTP, 1989)

```
 ======================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File: C:/Users/bowens/BMDS2601/Data/msc_Dichotomous cancer_Opt.(d)
        Gnuplot Plotting File:  C:/Users/bowens/BMDS2601/Data/msc_Dichotomous
cancer_Opt.plt
                                          Thu Apr 07 15:21:08 2016
 ======================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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

   The parameter betas are restricted to be positive
```

```
   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 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) =    0.0174093


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
        Beta(1)        0.0151301       0.00756688         0.000299339
0.029961

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


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -13.9385         3
   Fitted model        -14.3275         1      0.778028      2          0.6777
  Reduced model        -18.3891         1       8.90131      2         0.01167

           AIC:          30.655


                                Goodness  of  Fit
                                                        Scaled
```

Dose	Est._Prob.	Expected	Observed	Size	Residual
0.0000	0.0000	0.000	0.000	49.000	0.000
0.5000	0.0075	0.369	0.000	49.000	-0.610
5.0000	0.0729	3.643	4.000	50.000	0.194

Chi^2 = 0.41 d.f. = 2 P-value = 0.8147

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 6.96361

BMDL = 3.37669

BMDU = 18.0513

Taken together, (3.37669, 18.0513) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.0296148

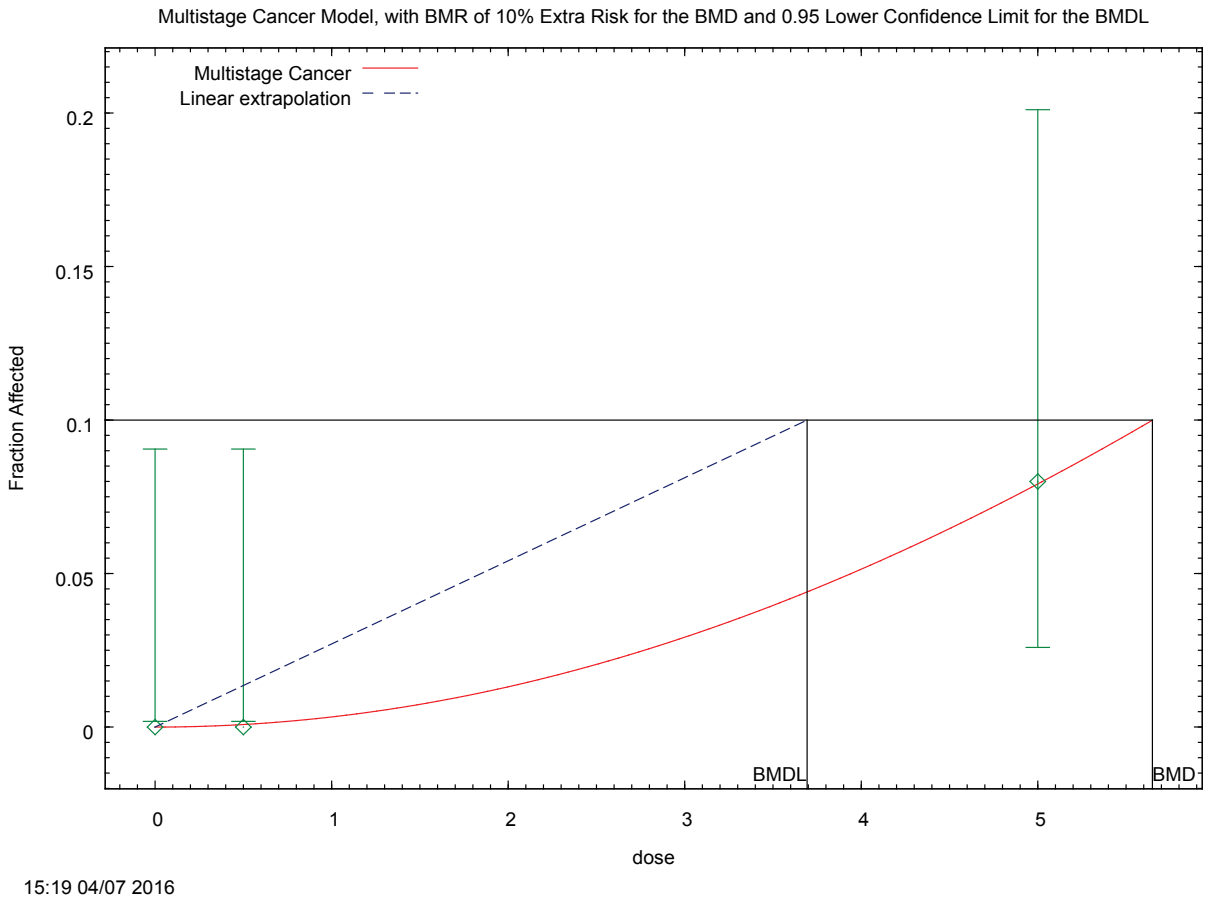

Figure C-2. Multistage-Cancer 2-Degree BMD Model for Increased Splenic Sarcoma or Osteosarcoma in Male Rats Administered *N,N*-Dimethylaniline Via Gavage 5 Days/Week for 103 Weeks (NTP, 1989)

Text Output for Multistage-Cancer 2-Degree BMD Model for Increased Splenic Sarcoma or Osteosarcoma in Male Rats (NTP, 1989)

```
 ======================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File: C:/Users/bowens/BMDS2601/Data/msc_Dichotomous cancer_Opt.(d)
        Gnuplot Plotting File:  C:/Users/bowens/BMDS2601/Data/msc_Dichotomous
cancer_Opt.plt
                                              Thu Apr 07 15:19:04 2016
 ======================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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

   The parameter betas are restricted to be positive
```

```
   Dependent variable = Effect
   Independent variable = Dose

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


 Maximum number of iterations = 500
 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) =   0.00335177


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(2)

   Beta(2)            1



                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
        Beta(1)                0              NA
        Beta(2)       0.00330151       0.00165123        6.51713e-005
0.00653786

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



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -13.9385         3
   Fitted model         -13.9791         1     0.0812992      2          0.9602
  Reduced model         -18.3891         1       8.90131      2         0.01167

           AIC:          29.9582


                               Goodness  of  Fit
```

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	49.000	0.000
0.5000	0.0008	0.040	0.000	49.000	-0.201
5.0000	0.0792	3.961	4.000	50.000	0.020

Chi^2 = 0.04 d.f. = 2 P-value = 0.9798

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 5.64914

BMDL = 3.69334

BMDU = 15.5498

Taken together, (3.69334, 15.5498) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.0270758

APPENDIX D. REFERENCES

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