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United States
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Provisional Peer-Reviewed Toxicity Values for

2-Nitropropane
(CASRN 79-46-9)

U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

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Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
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To the memory of Dr. Jon Brice Reid (1937−2019)

TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
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
CPHEA	Center for Public Health and Environmental Assessment
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
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
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	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum 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_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

[1]Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 2-NITROPROPANE (CASRN 79-46-9)

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 at least two Center for Public Health and Environmental Assessment (CPHEA) scientists and an independent external peer review by at least three scientific experts.

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

Currently available PPRTV assessments can be accessed on the U.S. EPA's PPRTV website at https://www.epa.gov/pprtv. PPRTV assessments are eligible to be updated on a 5-year cycle to incorporate new data or methodologies that might impact the toxicity values or characterization of potential for adverse human-health effects and are revised as appropriate. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. Environmental Protection Agency (EPA) Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

DISCLAIMERS

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

Other U.S. 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 U.S. EPA Office of Research and Development's (ORD's) CPHEA.

INTRODUCTION

2-Nitropropane, CASRN 79-46-9, belongs to the nitroalkanes class of compounds. It is used mainly as an industrial solvent in inks, paints, adhesives, varnishes, polymers, and synthetic material or as a chemical intermediate (O'Neil, 2013; Markofsky, 2012). 2-Nitropropane is listed on the U.S. Environmental Protection Agency (U.S. EPA) Toxic Substances Control Act (TSCA) public inventory (U.S. EPA, 2018b), is registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2018), and was assessed under the U.S. EPA High Production Volume (HPV)/Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS) Programme (OECD, 2010).

Commercial production of 2-nitropropane is achieved by high-temperature vapor-phase nitration of propane (Markofsky, 2012). The process uses nitric acid as the nitrating agent through a NO_2 radical reaction at 350−450°C and 0.8−1.2 MPa. The reaction product from this process is a nitroalkane mixture, rich in nitropropanes. It is washed, dried, and purified by distillation to obtain individual nitroalkanes.

The empirical formula for 2-nitropropane is $C_3H_7NO_2$, and its structure is shown in Figure 1. Table 1 summarizes the physicochemical properties of 2-nitropropane. 2-Nitropropane is a colorless, oily liquid at room temperature. Reported vapor pressures for 2-nitropropane indicate that it will exist almost entirely as a vapor at atmospheric temperature and pressure. The estimated half-life of vapor-phase 2-nitropropane in air by reaction with photochemically produced hydroxyl radicals is 95 days. The vapor pressure and calculated Henry's law constant for 2-nitropropane indicate that it may volatilize from either dry or moist surfaces. The high water solubility and low soil adsorption coefficients for 2-nitropropane indicate that it may leach to groundwater or undergo runoff after a rain event. Based on screening tests, 2-nitropropane may undergo limited biodegradation in the environment. Under aqueous conditions, 2-nitropropane may exist partially in the anion form based on the measured pKa of 7.68 (HSDB, 2006). The rate of hydrolysis of 2-nitropropane is negligible (U.S. EPA, 2011c).

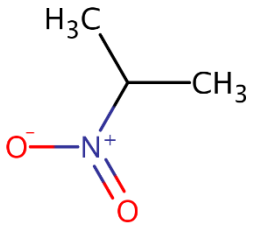

Figure 1. 2-Nitropropane (CASRN 79-46-9) Structure

Table 1. Physicochemical Properties of 2-Nitropropane (CASRN 79-46-9)

Property (unit)	Value
Physical state	Liquid
Boiling point (°C)	120[a]
Melting point (°C)	−92.1[a]
Density (g/cm^3)	0.990[a]
Vapor pressure (mm Hg)	17.2[a]
pH (unitless)	6.2, 0.01 M in water at 25°C[c]
pKa (unitless)	7.68[b]
Solubility in water (mol/L)	0.208[a]
Octanol-water partition constant (log K_{ow})	1.14[a]
Henry's law constant (atm-m^3/mol)	4.77×10^{-5} (predicted average)
Soil adsorption coefficient K_{oc} (L/kg)	0.11 (Texas sandy silt loam soil)[b], 3.8 (Mississippi sandy loam soil)[b]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	2.60×10^{-13}[b]
Atmospheric half-life (d)	95 (calculated based on its measured OH rate constant)[b]
Relative vapor density (air = 1)	3.06[b]
Molecular weight (g/mol)	89.094[a]
Flash point (°C)	26.0[a]

[a]Data were extracted from the U.S. EPA CompTox Chemicals Dashboard (2-Nitropropane, CASRN 79-46-9. https://comptox.epa.gov/dashboard/DTXSID6020981. Accessed 06 May 2019). All values are experimental averages unless otherwise specified.
[b]HSDB (2006) unless otherwise specified; all values are measured unless noted otherwise.
[c]Markofsky (2012).

A summary of available toxicity values for 2-nitropropane from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for 2-Nitropropane (CASRN 79-46-9)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS (RfC)	0.02 mg/m^3	Based on liver focal vacuolization and nodules in a chronic-duration inhalation study in rats.	U.S. EPA (2002a)
HEAST (sRfC)	0.02 mg/m^3	The chronic inhalation RfC was adopted as the subchronic inhalation RfC. Based on liver lesions in a chronic-duration, intermittent, inhalation exposure study in rats.	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2018)
IPCS	NV	NA	IPCS (2018)
CalEPA	NV	NA	CalEPA (2016); CalEPA (2018a); CalEPA (2018b)
ACGIH (TLV-TWA)	10 ppm	Based on liver damage.	ACGIH (2016)
OSHA (PEL-TWA)	25 ppm (91 mg/m^3)	8-hr TWA for general industry, construction, and shipyard employment.	OSHA (2017a); OSHA (2017b); OSHA (2017c)
NIOSH (IDLH)	100 ppm	Based on acute inhalation toxicity data in animals. This may be a conservative value due to the lack of relevant acute toxicity data for workers exposed to concentrations >45 ppm.	NIOSH (1994)
Cancer			
IRIS	NV	NA	U.S. EPA (2018a)
HEAST (IUR)	0.0027 (µg/m^3)$^{-1}$	Based on liver tumors in a chronic-duration, intermittent, inhalation exposure study in rats.	U.S. EPA (2011a); U.S. EPA (1985)
HEAST/HEEP (ISF)	9.4 (mg/kg/d)$^{-1}$		
CAG (WOE)	Group B2: probably carcinogenic to humans	Based on sufficient evidence from animal studies and inadequate evidence from human studies.	U.S. EPA (1988a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP (WOE)	Reasonably anticipated to be a human carcinogen	Based on sufficient evidence of carcinogenicity from studies in experimental animals.	NTP (2016)
IARC (WOE)	Group 2B: possibly carcinogenic to humans	Based on inadequate evidence for carcinogenicity in humans and sufficient evidence in experimental animals.	IARC (1999); IARC (2018)
CalEPA (WOE)	Listed as causing cancer under Proposition 65	NA	CalEPA (2011); CalEPA (2018a); CalEPA (2018b)

Table 2. Summary of Available Toxicity Values for 2-Nitropropane (CASRN 79-46-9)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
ACGIH (WOE)	A3: confirmed animal carcinogen with unknown relevance to humans	NA	ACGIH (2017)
NIOSH (WOE)	Potential occupational carcinogen	NA	NIOSH (2016)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CAG = Carcinogen Assessment Group; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA= Occupational Safety and Health Administration.
[b]Parameters: IDLH = immediately dangerous to life or health concentrations; ISF = inhalation slope factor; IUR = inhalation unit risk; PEL = permissible exposure level; RfC = reference concentration; sRfC = subchronic reference concentration; TLV = threshold limit value; TWA = time-weighted average; WOE = weight of evidence.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in October 2017 and updated in September 2018 for studies relevant to the derivation of provisional toxicity values for 2-nitropropane (CASRN 79-46-9). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA ChemView, U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), Japan Existing Chemical Data Base (JECDB), National Institute for Occupational Safety and Health (NIOSH), National Pesticide Information Retrieval System (NPIRS), National Toxicology Program (NTP), OECD Existing Chemicals Database, OECD SIDS High Production Volume Chemicals via International Programme on Chemical Safety (IPCS) INCHEM, Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer databases, respectively, for 2-nitropropane, and include all potentially relevant repeat dose short-term-, subchronic-, and chronic-duration studies, as well as reproductive and developmental toxicity studies. Principal studies are identified in bold. The phrase "statistical significance," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for 2-Nitropropane (CASRN 79-46-9)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Human							
In an unpublished retrospective mortality study, no evidence of increased mortality or cancer mortality (when evaluated as observed/expected deaths) was observed in male or female workers exposed to 2-nitropropane at a plant in Louisiana (Miller and Temple, 1980). These results were further confirmed in a follow-up mortality study using the same cohort (Parekh and Wilbur, 1982). In an occupational health survey, no increases in effects in the pulmonary, hepatic, renal, cardiovascular, hematological, or integumentary systems were observed in workers exposed to 2-nitropropane at an industrial food plant (Crawford et al., 1985; TOMA, 1980). Case reports of acute hepatic failure in workers exposed to high concentrations of 2-nitropropane are discussed in the "Other Data" section below.							
Animal							
1. Oral (mg/kg-d)							
Short-term	**5 M, Crl:CD (SD), rat, gavage in water, 14 or 28 d** **Reported doses: 0, 5, 20, or 40 mg/kg-d**	**0, 5, 20, 40**	**Increased relative liver weight and minimal to mild hepatocyte hypertrophy at 28 d. At the high dose, these changes were increased and accompanied by additional gross and microscopic lesions and serum chemistry changes indicative of hepatic effects.**	**5**	**20**	**Kawakami et al. (2015)** **(only clinical signs, body weight, and hepatic endpoints were evaluated)**	**PR, PS**
Short-term	4 M, F344, rat, gavage in corn oil, 1, 3, 7, 14, or 28 d Reported doses: 0 or 40 mg/kg-d	0, 40	Increased absolute liver weight and glycogen accumulation in hepatocytes at 28 d.	NDr	40	Nakayama et al. (2006) (only mortality, body weight, and hepatic endpoints were evaluated)	PR
Short-term	5 M, F344, rat, gavage in distilled water containing 0.1% Tween 20, 2 wk (dosed a total of six times) Reported doses: 0, 60, or 110 (time-weighted average) mg/kg-d	0, 26, 47.1	Mild hepatic lesions (hepatocyte swelling), decreased serum triglycerides and liver glycogen content, increased markers of oxidative stress, and increased cell proliferation in liver. At the high dose, liver effects were increased and included severe swelling of hepatocytes, degenerative changes, and single-cell necrosis.	NDr	26	Sai et al. (1998) (only hepatic endpoints were evaluated)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for 2-Nitropropane (CASRN 79-46-9)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Short-term	8−13 M, Wistar, rat, oral in canola oil, 3 d/wk, 2 wk Reported doses: 0 or 120 mg/kg-d	0, 51.4	Elevated serum ALT, AST, LDH, and urea; decreased hepatic catalase activity.	NDr	51.4	Wilhelm et al. (2009) (only hepatic and renal endpoints were evaluated)	PR
Chronic	22−29 M, S-D, rat, gavage in Emulphor EL-620, 3 d/wk, 16 wk Reported doses: 0 or 90 mg/kg-d	0, 39	Death of "several" treated rats during the exposure phase of the study and "significantly lower" body weights throughout the study (no further details reported).	NDr	39 (FEL)	Fiala et al. (1987b) (data reporting was limited)	PR
2. Inhalation (mg/m^3)							
Subchronic-Duration Studies							
Subchronic	10 M/10 F, LE, rat, whole-body exposure, 7 hr/d, 5 d/wk, 2 mo Reported nominal concentrations: 0 or 200 ppm	0, 129	Hepatocellular vacuolization in the liver of male rats.	NDr	129	Coulston et al. (1978)	NPR
Chronic-Duration Studies with Interim Sacrifices							
Short-term	10 M, S-D, rat, whole-body exposure, 7 hr/d, 5 d/wk, 10 d Reported analytical concentrations: 0, 27, or 207 ppm	0, 20, 157	Decreased body weight, elevated relative liver weight, elevated serum ALT, and increased hepatic pericholangitis.	20	157	Lewis et al. (1979); Ulrich et al. (1977) (interim sacrifice)	PR
Subchronic	**10 M, S-D, rat, whole-body exposure, 7 hr/d, 5 d/wk, 1 or 3 mo Reported analytical concentrations: 0, 27, or 207 ppm**	**0, 20, 157**	**Increased absolute liver weight. Decreased body weight, as well as increased relative liver weight, serum ALT, and non-neoplastic liver lesions (focal hepatocyte hypertrophy, focal hepatocyte hyperplasia, and basophilic foci) were observed at 157 mg/m^3.**	**NDr**	**20**	**Lewis et al. (1979); Ulrich et al. (1977) (interim sacrifices)**	**PR, PS**

Table 3A. Summary of Potentially Relevant Noncancer Data for 2-Nitropropane (CASRN 79-46-9)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Chronic	10 M, S-D, rat, whole-body exposure, 7 hr/d, 5 d/wk, 6 mo Reported analytical concentrations: 0, 27, or 207 ppm	0, 20, 157	Decreased body weight, elevated serum ALT, and elevated absolute and relative liver weights. Elevated absolute and relative lung weights and slight edema were also reported (HEC = 581 mg/m^3 for pulmonary effects).	20	157	Lewis et al. (1979); Ulrich et al. (1977)	PR
Short-term	10 M/10 F, S-D, rat, whole-body exposure, 7 hr/d, 5 d/wk, 10 d Reported analytical concentrations: 0 or 196 ppm	0, 127	Elevated serum ALT and microscopic liver changes, including single cell necrosis, basophilic hepatocytes, mitotic cells, and bile duct proliferation, in males.	NDr	127	Coulston et al. (1978) (interim sacrifice)	NPR
Subchronic	10 M/10 F, S-D, rat, whole-body exposure, 7 hr/d, 5 d/wk, 1 or 3 mo Reported analytical concentrations: 0 or 196 ppm	0, 127	Decreased body weight in males, elevated relative liver weights in males and females, increased serum ALT in males, and microscopic liver changes in males.	NDr	127	Coulston et al. (1978) (interim sacrifices)	NPR
Chronic	10 M/10 F, S-D, rat, whole-body exposure, 7 hr/d, 5 d/wk, 6 mo Reported analytical concentrations: 0 or 196 ppm	0, 127	Elevated relative liver weights in males and females, increased serum ALT and AST in males, and microscopic liver changes in males and females.	NDr	127	Coulston et al. (1978)	NPR
Subchronic	10 M/10 F, S-D, rat, whole-body exposure, 7 hr/d, 5 d/wk, 1 or 3 mo Reported analytical concentrations: 0 or 25.1 ppm	0, 16.2	No adverse effects.	16.2	NDr	Griffin et al. (1981); Griffin et al. (1980) (interim sacrifices; histological data combined for main study group plus interim sacrifices and recovery groups)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for 2-Nitropropane (CASRN 79-46-9)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Chronic	10 M/10 F, S-D, rat, whole-body exposure, 7 hr/d, 5 d/wk, 6−22 mo Reported analytical concentrations: 0 or 25.1 ppm	0, 16.2	Increased absolute and relative liver weight in males; increased incidences of focal vacuolization of hepatocytes and hepatocellular nodules in the liver of male rats; liver congestion in male and female rats.	NDr	16.2	Griffin et al. (1981); Griffin et al. (1980) (histological data combined for main study group plus interim sacrifices and recovery groups)	PR, IRIS
Subchronic	10 M/10 F, S-D, rat, whole-body exposure, 7 hr/d, 5 d/wk, 1 or 3 mo Reported analytical concentrations: 0 or 100 ppm	0, 65.0	Increased absolute and relative liver weights at 3 mo in males.	NDr	65.0	Griffin et al. (1979) (interim sacrifices; histopathology not reported)	NPR
Chronic	95−105 M/95−105 F, S-D, rat, whole-body exposure, 7 hr/d, 5 d/wk, 6−18 mo Reported analytical concentrations: 0 or 100 ppm	0, 65.0	Decreased body weights, renal calcification, elevated ALT, and elevated liver weights in male rats and hepatic lesions in male and female rats.	NDr	65.0	Griffin et al. (1979)	NPR
Subchronic	5 M, NZW, rabbit, whole-body exposure, 7 hr/d, 5 d/wk, 1 or 3 mo Reported analytical concentrations: 0, 27, or 207 ppm	0, 20, 157	No adverse effects.	157	NDr	Lewis et al. (1979); Ulrich et al. (1977) (interim sacrifices)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for 2-Nitropropane (CASRN 79-46-9)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Chronic	5 M, NZW, rabbit, whole-body exposure, 7 hr/d, 5 d/wk, 6 mo Reported analytical concentrations: 0, 27, or 207 ppm	0, 20, 157	No adverse effects.	157	NDr	Lewis et al. (1979); Ulrich et al. (1977)	PR

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002b).
[b]Dosimetry: Doses are presented as ADDs (mg/kg-day) for oral noncancer effects and as HECs (in mg/m^3) for inhalation noncancer effects. Inhalation exposures reported in ppm were converted to mg/m^3 using the molecular weight of 89.09 mol/g and assuming standard temperature and air pressure for Lewis et al. (1979)/Ulrich et al. (1977), yielding a conversion factor of 1 ppm = 3.6 mg/m^3. For the other inhalation studies, conversion to mg/m^3 was calculated using the study author's conversions due to lower barometric pressure at the altitude of the testing facility (1,350 m), yielding a conversion factor of 1 ppm = 3.1 mg/m^3. Once converted to mg/m^3, it is current practice that HECs are calculated differently for systemic (ER) and pulmonary effects. 2-Nitropropane has characteristics of a highly reactive, Category 1 gas that often results in portal-of-entry effects in the PU region as well as less reactive Category 3 gas for ER effects. As HEC equations for a Category 2 gas are currently unavailable, the HECs are calculated using both Category 1 and Category 3 gas equations. The HEC for ER effects is calculated by treating 2-nitropropane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 since the rat blood-air partition coefficient of 183 [and rabbit value of 170; AFOSR (1992)] is greater than the human blood-air partition coefficient of 154 as indicated by Gargas et al. (1989). The HEC for pulmonary effects is calculated by treating 2-nitropropane as a Category 1 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{PU} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × $RGDR_{PU}$, where $RGDR_{PU}$ is calculated as per U.S. EPA (1994) using default human V_E and human and animal respiratory tissue surface area values and animal V_E calculated from study (if available) or reference body weight values.
[c]Notes: IRIS = used by IRIS U.S. EPA (2002a); NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ER = extrarespiratory; F = female(s); FEL = frank effect level; HEC = human equivalent concentration; IRIS = Integrated Risk Information System; LDH = lactate dehydrogenase; LE = Long-Evans; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; NZW = New Zealand White; PU = pulmonary; RGDR = regional gas dose ratio; S-D = Sprague-Dawley; V_E = minute volume.

Table 3B. Summary of Potentially Relevant Cancer Data for 2-Nitropropane (CASRN 79-46-9)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[a]	Critical Effects	Reference (comments)	Notes[b]
Human					
Carcinogenicity (occupational)	1,334 M/147 F, workers employed in a 2-nitropropane production plant in Louisiana from 1955−1981, average duration of employment not reported	Generally, <91	No excess of cancer mortality in exposed workers.	Parekh and Wilbur (1982); Miller and Temple (1980)	NPR
Animal					
1. Oral (mg/kg-d)					
Carcinogenicity	22−29 M, S-D, rat, gavage in Emulphor EL-620, 3 d/wk, 16 wk Reported doses: 0 or 90 mg/kg-d	0, 9.8	Significant increase in the incidence of hepatocarcinomas in exposed male rats (22/22 treated vs. 0/29 control).	Fiala et al. (1987b)	PR
2. Inhalation (mg/m^3)					
Carcinogenicity	**10 M, S-D, rat, 7 hr/d, 5 d/wk, 6 mo** **Reported analytical concentrations: 0, 27, or 207 ppm**	**0, 20, 157**	**Significant increases in the incidences of hepatocellular carcinomas and neoplastic nodules at 157 mg/m^3 (10/10, vs. 0/10 at 20 mg/m^3 and 0/10 in controls).**	**Lewis et al. (1979); Ulrich et al. (1977)**	**PR, PS**
Carcinogenicity	10−20 M/10 F, S-D, rat, 7 hr/d, 5 d/wk, 6 mo Reported analytical concentrations: 0 or 196 ppm	0, 127	Hepatic nodules with features indicative of "malignant transformation" after 6 mo exposure in males. Hepatic tumors with metastasis in 9/10 males exposed for 6 mo and observed for an additional 6 mo.	Coulston et al. (1978)	NPR
Carcinogenicity	125 M/125 F, S-D, rat, 7 hr/d, 5 d/wk, up to 22 mo Reported analytical concentrations: 0 or 25.1 ppm	0, 16.2	No evidence of carcinogenicity.	Griffin et al. (1981); Griffin et al. (1980)	PR
Carcinogenicity	95−105 M/95−105 F, S-D, rat, 7 hr/d, 5 d/wk, 6−18 mo Reported analytical concentrations: 0 or 100 ppm	0, 65.0	Significant increase in the incidence of hepatocarcinomas in exposed male rats sacrificed at 18 mo (7/23 vs. 0/63 controls). No hepatocellular carcinomas in females.	Griffin et al. (1979)	NPR

Table 3B. Summary of Potentially Relevant Cancer Data for 2-Nitropropane (CASRN 79-46-9)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[a]	Critical Effects	Reference (comments)	Notes[b]
Carcinogenicity	5 M, NZW, rabbit, 7 hr/d, 5 d/wk, 6 mo Reported analytical concentrations: 0, 27, or 207 ppm	0, 20, 157	No evidence of carcinogenicity.	Lewis et al. (1979); Ulrich et al. (1977)	PR

[a]Dosimetry: Oral exposures are expressed as HEDs (mg/kg-day); HEDs are calculated using DAFs, as recommended by U.S. EPA (2011b): HED = ADD (mg/kg-day) × DAF. The DAF is calculated as follows: DAF = $(BW_a \div BW_h)^{1/4}$, where DAF = dosimetric adjustment factor, BW_a = animal body weight, and BW_h = human body weight, using study (if available) or reference body weight values for BW_a and the reference value of 70 kg for BW_h. Inhalation exposure units are expressed as HECs (mg/m^3). Inhalation exposures reported in ppm were converted to mg/m^3 using the molecular weight of 89.09 mol/g and assuming standard temperature and air pressure for Lewis et al. (1979)/Ulrich et al. (1977), yielding a conversion factor of 1 ppm = 3.6 mg/m^3. For the other inhalation studies, conversion to mg/m^3 was calculated using the study author's conversions due to lower barometric pressure at the altitude of the testing facility (1,350 m), yielding a conversion factor of 1 ppm = 3.1 mg/m^3. Once converted to mg/m^3, the HEC for ER effects was calculated by treating 2-nitropropane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 since the rat blood-air partition coefficient of 183 [and rabbit value of 170; AFOSR (1992)] is greater than the human blood-air partition coefficient of 154 as indicated by Gargas et al. (1989).

[b]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; BW = body weight; DAF = dosimetric adjustment factor; ER = extrarespiratory; F = female(s); HEC = human equivalent concentration; HED = human equivalent dose; M = male(s); NZW = New Zealand White; S-D = Sprague-Dawley.

HUMAN STUDIES

Parekh and Wilbur (1982); Miller and Temple (1980)

In an unpublished retrospective mortality study, Miller and Temple (1980) evaluated mortality patterns in a cohort of 1,334 male workers and 147 female workers employed between January 1955 and July 1977 at a plant in Louisiana that manufactured 2-nitropropane. Workers were divided into three 2-nitropropane exposure groups based on job title: direct exposure (*n* = 372; laboratory, research, production, warehouse), indirect exposure (*n* = 366; machine shop, electric shop, general maintenance, instrument shop, shipping, engineering, technical service, process development), and no exposure (*n* = 743; other workers, e.g., office staff). Standard mortality ratios (SMRs) were calculated based on U.S. mortality rates.

Historical exposure data showed periodic exposure levels over the OSHA standard of 25 ppm (91 mg/m^3) between 1962−1977; however, no formalized exposure data were recorded. Levels from 580−1,640 ppm (2,110−5,980 mg/m^3) were reported during the filling phase of the drumming operation. Personal air sampling between January and June of 1977 found that 141/144 (97.9%) of the time-weighted air samples were 0.2−10 ppm (0.7−36 mg/m^3), 1/144 was 10−25 ppm (36−91 mg/m^3), and 2/144 were 25−100 ppm (91−364 mg/m^3). The two samples in the highest exposure bin were in proximity of a spill. It was not reported whether personal air monitoring was conducted in the direct exposure group only or in the direct and indirect exposure groups.

The study authors indicated that incidents of exposures above the OSHA standard of 91 mg/m^3 coincided with drumming operators who reported occasional nausea and headache; however, incidence data for these complaints were not reported. It is not clear whether these complaints were ever made at exposures <91 mg/m^3. No evidence of increased mortality or cancer mortality (when evaluated as observed/expected deaths) was associated with exposure to 2-nitropropane (see Table B-1). Overall SMRs for white males, black males, and females for all causes of mortality were 85, 67, and 279, respectively (no confidence intervals [CIs] were reported). Similarly, SMRs for all cancer mortalities for white males, black males, and females were 72, 67, and 500, respectively (no CIs were reported). While the female data suggested a potential increase in mortality in this cohort, these findings were driven by four cases of cancer at four different sites (buccal cavity, respiratory, breast, and "residual cancer") in this small cohort of women. When broken down into exposure groups, three of four female cancer cases were from the "unexposed" group, indicating that the observed findings are not related to 2-nitropropane exposure (see Table B-1).

Parekh and Wilbur (1982) conducted a follow-up mortality study on this cohort, including workers employed through the end of 1981. The follow-up cohort comprised 1,390 male workers and 189 female workers, including 400 employees with direct exposure, 206 with indirect exposure, and 773 with no exposure. Findings in the follow-up were comparable/similar to the initial study. Overall SMRs for white males, black males, and females for all causes of mortality were 79, 58, and 183, respectively, and SMRs for all cancer mortalities for white males, black males, and females were 70, 54, and 301, respectively (no CIs were reported). As with the initial cohort, female findings were driven by the same four cases of cancer, three of which were in the unexposed group.

Together, these data suggest that occupational exposure below the OSHA standard of 91 mg/m^3 is not associated with increased mortality or cancer mortality, compared with the

general population. However, these results should be interpreted with caution due to study limitations, including small cohort sizes, inadequate exposure reporting per group, unreported duration of exposure, and lack of control for confounding factors.

Crawford et al. (1985); TOMA (1980)

In an occupational health survey, employee health examinations were conducted in 18 workers with potential exposure to 2-nitropropane during solvent extraction of triglycerides in an industrial food plant and 28 coworkers from the same facility that were not expected to have exposure (primarily operating and maintenance personnel). Initial health exams were conducted in 1979, with follow-up exams in 1982. Workers were 96% male, aged 45−64 years, and had been working for the company for 16−35 years. Health examinations included self-reported personal health, electrocardiogram, chest X-ray, pulmonary function tests, clinical chemistry, hematology, urinalysis, and a physical exam by an occupational physician.

Air sampling was conducted in March, June, and August of 1981, with measurements at specific locations (Area 1, Area 2, Area 3) throughout the plant where process operators routinely monitored the process. Job descriptions for the different areas were not reported. In addition, 2−5 personal air monitoring samples were measured at each evaluation. The study authors did not indicate the job titles of individuals who were selected for personal air monitoring or whether those individuals were in the "potentially exposed" group. During "routine production," the mean air level of 2-nitropropane was 36 ± 10 ppm (130 ± 36 mg/m^3) in Area 1 (range 23−58 ppm [84−210 mg/m^3]), 55 ± 23 ppm (200 ± 84 mg/m^3) in Area 2 (range 29−100 ppm [110−364 mg/m^3]), 56 ± 15 ppm (200 ± 55 mg/m^3) in Area 3 (range 35−75 ppm [130−270 mg/m^3]), and 2.3 ± 2.1 ppm (8.4 ± 7.7 mg/m^3) for personal air monitoring (range 0−5.4 ppm [0−20 mg/m^3]). When the "old way" of production (steam blow-down) was used in August of 1981, the reported air levels were 130, 120, 120, and 15 ppm (474, 437, 437, and 55 mg/m^3) in Area 1, Area 2, Area 3, and personal monitoring, respectively. This "old way" is no longer used in production, but the test was conducted to estimate potential prior exposure levels.

Additional personal air samples were measured on five occasions, beginning in November of 1981 and ending in May of 1983. Personal air samples were taken over at least two operating shifts, with 2−4 samples/shift (5−8 samples/date). The study authors did not indicate the job titles of individuals who were selected for personal air monitoring or whether those individuals were in the "potentially exposed" group. Overall, the mean personal monitoring level of 2-nitropropane was 12 ± 15 ppm (44 ± 55 mg/m^3), with a range of 0−73 ppm (0−270 mg/m^3). The lowest mean level was reported in May of 1983 (0.9 ± 1.7 ppm [3.3 ± 6.2 mg/m^3]), and the highest mean level was reported in February of 1983 (24 ± 28 ppm [87 ± 102 mg/m^3]). There was no discussion regarding the potential reason for the large fluctuations in observed exposure levels.

When all workers in the cohort were grouped together, no increases in adverse health effects in the pulmonary, hepatic, renal, cardiovascular, hematological, or integumentary systems were observed, compared with national population rates. The study authors also reported no significant differences between the 18 employees with potential exposure and the 28 coworkers who were not expected to be exposed; however, the authors provided no data for these comparisons.

This study has numerous limitations that preclude clear conclusions regarding potential health effects of occupational exposure to 2-nitropropane. A critical limitation is the inadequate reporting of separate exposure and outcome data for the "exposed" versus the "unexposed" group. Additional limitations include small sample size, lack of details on work environment or personal protective equipment, lack of discussion regarding factors contributing to large fluctuations in personal exposure levels, and lack of discussion of other potential routes of exposure (e.g., dermal).

Case reports of acute hepatic failure in workers exposed to high concentrations of 2-nitropropane are discussed in the "Other Data" section below.

ANIMAL STUDIES

Oral Exposures

Short-Term-Duration Studies

Kawakami et al. (2015)

Male Crl:CD (SD) rats were administered 2-nitropropane (98.1% purity) at doses of 0, 5, 20, or 40 mg/kg-day via gavage in water daily for 14 or 28 days (5/group per time point) (Kawakami et al., 2015). Mortality, clinical signs, and body weight were monitored. Animals were sacrificed 24 hours after the final dose. Blood was collected at sacrifice to determine serum aspartate aminotransferase (AST), alanine transaminase (ALT), cholinesterase (ChE), and γ-glutamyl transferase (GGT). The livers were removed, weighed, and examined for histopathological changes. Dose-response relationships were analyzed using Dunnett's test.

All animals survived until scheduled sacrifice, and no clinical signs of toxicity were observed. Body weights were similar between control and exposed animals (see Table B-2). The relative liver weight was significantly elevated by 14−24% after exposure to doses ≥20 mg/kg-day for 28 days; no significant exposure-related (i.e., when compared to control animals) changes were observed at 14 days of exposure (see Table B-2). Significant changes in serum chemistry were observed at 40 mg/kg-day, including a 21% increase in AST at 14 days, 83 and 169% increases in ChE at 14 and 28 days, respectively, and 33 and 225% increases in GGT at 14 and 28 days, respectively (see Table B-3). At necropsy, pale livers were observed at 40 mg/kg-day after 14 days and at ≥20 mg/kg-day after 28 days (see Table B-4). Histopathological changes were only observed after exposure for 28 days, including minimal-to-mild diffuse hepatocyte hypertrophy at ≥20 mg/kg-day and minimal basophilic foci and anisokaryosis of hepatocytes at 40 mg/kg-day (see Table B-4).

A no-observed-adverse-effect level (NOAEL) of 5 mg/kg-day and a lowest-observed-adverse-effect level (LOAEL) of 20 mg/kg-day are identified from this study based on significantly elevated relative liver weight and hepatocyte hypertrophy after 28 days of exposure. The liver was the only organ examined for pathology. At the high dose of 40 mg/kg-day, both relative liver weight and hepatocyte hypertrophy were increased and accompanied by additional gross and microscopic lesions and serum chemistry changes indicative of hepatic effects.

Nakayama et al. (2006)

Male F344 rats were administered 2-nitropropane (>97% purity) at doses of 0 or 40 mg/kg-day via gavage in corn oil daily for 1, 3, 7, 14, or 28 days (4/group per time point). Mortality and body weight were monitored. Animals were sacrificed 24 hours after the final

dose. Blood was collected at sacrifice to determine serum AST, ALT, and alkaline phosphatase (ALP). The livers were removed, weighed, and examined for histopathological changes. Body weight, liver weight, and serum chemistry data were evaluated statistically using an unreported method.

Only findings at 28 days were provided by the study authors. No mortalities were reported. Body weights were comparable at 28 days between the exposed and control groups. Absolute liver weights were significantly increased by 18% in exposed rats, compared with control (see Table B-5); relative liver weights were not calculated. Serum liver enzyme levels were comparable between exposed and control rats (see Table B-5).

The only dose administered (40 mg/kg-day) is identified as a LOAEL for this study based on elevated absolute liver weight and glycogen accumulation in hepatocytes after 28 days of exposure. No NOAEL is identified.

Sai et al. (1998)

Male F344 rats were administered 2-nitropropane (purity not reported) via gavage in distilled water containing 0.1% Tween 20 over a 2-week period. Exposure groups (5/group) included a vehicle control, a low-dose group (dosed a total of six times at 60 mg/kg-day), and a high-dose group (dosed twice at 90 mg/kg-day and four times at 120 mg/kg-day; time-weighted average [TWA] of 110 mg/kg-day). Adjusted daily doses (ADDs) to account for intermittent exposure (6/14 days) are calculated to be 26 and 47.1 mg/kg-day for the low- and high-dose groups, respectively. Additional groups were given green tea infusion for 1 week prior to 2-nitropropane and throughout 2-nitropropane exposure to evaluate potential protective effects of antioxidants. To evaluate cell proliferation, rats were intraperitoneally injected with 20 mg/kg 5-bromo-2′-deoxyuridine (BrdU) twice daily for 2 days prior to terminal sacrifice and once 2 hours prior to sacrifice. Terminal sacrifice was 4 hours after the final 2-nitropropane administration. At sacrifice, blood was collected to determine serum AST and triglyceride levels. The liver was removed and divided into sections for biochemical analysis of thiobarbituric acid reactive substances (TBARS), 8-hydroxydeoxyguanosine (8-OHdG), and glycogen content; analysis of cell proliferation (BrdU staining); and histopathology. Statistical analysis of continuous data sets was conducted using Student's *t*-test.

Significant changes noted in this study were increases in serum AST in the high-dose group (1.4-fold), and dose-related decreases in serum triglycerides (−58 and −85%) and liver glycogen (−45 and −62%) and increases in lipid peroxidation (1.6- and 3.4-fold as TBARS), deoxyribonucleic acid (DNA) oxidation (1.8- and 2.9-fold as 8-OHdG) and cell proliferation (2.5- and 5.7-fold as BrdU) in the liver in the low- and high-dose groups, respectively, relative to controls. Histopathological changes in the livers of exposed animals included slight swelling of hepatocytes without degeneration in the low-dose group and severe swelling of hepatocytes, degenerative changes, and single cell necrosis in the high-dose group (incidence data not reported by study authors). The study authors noted that green tea infusions inhibited 2-nitropropane hepatic toxicity.

A LOAEL of 26 mg/kg-day is identified in this study based on mild histopathological changes in the liver accompanied by signs of oxidative stress and increased cell proliferation. Liver effects were also increased at the high dose. No NOAEL is identified.

Wilhelm et al. (2009)

Male Wistar rats (8−13/group) were administered oral doses of 2-nitropropane (purity not specified) at doses of 0 or 120 mg/kg-day in canola oil three days per week for 2 weeks. The ADD to account for intermittent exposure (3 days/week) is calculated to be 51.4 mg/kg-day. This experiment was conducted twice to evaluate whether administrating the antioxidants diphenyl diselenide ($[PhSe]_2$) or *m*-trifluoromethyl-diphenyl diselenide ($[F_3CPhSe]_2$) was protective; the antioxidants were administered orally on alternating days with 2-nitropropane in additional rat groups. The rats were sacrificed 36 hours after the final exposure. Blood was collected for serum chemistry (AST, ALT, GGT, urea, creatinine). Liver and kidney samples were homogenized for determining ascorbic acid levels and catalase activity. No additional endpoints were evaluated. Statistical tests were conducted with a two-way analysis of variance (ANOVA) followed by Duncan's multiple range test when appropriate.

Plasma ALT, AST, GGT, and urea levels were significantly elevated by up to 2.7-, 1.7-, 5-, and 1.4-fold, respectively, in exposed rats from both experiments, compared with respective controls (see Table B-6). No exposure-related changes were observed in serum creatinine. Hepatic catalase activity was significantly decreased by 39−57% in exposed rats from both experiments, compared with respective controls (see Table B-6). Renal catalase activity and renal and hepatic ascorbic acid levels was not altered in the liver of dosed rats. Treatment with $(PhSe)_2$ or $(F_3CPhSe)_2$ decreased or ameliorated observed hepatic effects associated with exposure to 2-nitropropane.

The only administered dose (51.4 mg/kg-day) is identified as a LOAEL based on elevated serum ALT, AST, GGT, and urea and decreased hepatic catalase activity, and no NOAEL is identified.

Chronic-Duration/Carcinogenicity Studies

Fiala et al. (1987b)

In a short communication, Fiala et al. (1987b) reported carcinogenic effects in male Sprague-Dawley (S-D) rats administered 2-nitropropane (purity not reported) at doses of 0 or 1 mmol/kg-day (0 or 90 mg/kg-day) via gavage in Emulphor EL-620 vehicle 3 days/week for 16 weeks followed (in controls only) by 1 day/week for an additional 10 weeks. Due to "several" deaths in the treated group, 2-nitropropane treatment was discontinued after 16 weeks, and rats were held for 61 weeks without further exposure. The control animals continued receiving vehicle treatments 1 day per week for 10 weeks (this group was also serving as a control for additional chemicals) and were held for 51 weeks without vehicle exposure. Survival and body weight were monitored (no further details provided). All surviving rats were sacrificed during the 77th week after the first treatment. Gross necropsy was conducted on all terminal sacrifice animals, as well as animals sacrificed moribund. Histopathology was performed for neoplastic lesions; details of examination or tissues examined were not reported. The initial number of rats in each group was not reported; the "effective" numbers of rats for tumor analysis (not further defined) were 29 in the control group and 22 in the treated group. The study authors reported statistical analysis of tumor incidence; however, the statistical methods were not reported.

Reporting of non-neoplastic findings was limited to death in "several" treated rats during the exposure phase of the study and "significantly lower" body weights throughout the study (quantitative data for these endpoints were not reported). Based on these reported findings, the

only administered dose of 90 mg/kg-day is a frank effect level (FEL). Adjusted for intermittent exposure (3 days/week), the administered dose of 90 mg/kg-day is equivalent to an ADD of 39 mg/kg-day.

With respect to carcinogenicity endpoints observed, all surviving treated rats developed hepatocarcinomas (22/22), and metastasis to the lung was observed in 4/22 treated rats; these tumors were not observed in any control rats (0/29). Benign liver tumors were observed in 4/22 treated rats and 1/29 control rats. Observed tumors in other systems in the treated rats were comparable to control (see Table B-7). Despite study limitations (small animal numbers, limited reporting), this study shows that 2-nitropropane is a liver carcinogen by oral exposure in rats. The administered dose of 90 mg/kg-day corresponds to a human equivalent dose (HED) of 9.8 mg/kg-day.[2]

Inhalation Exposures

Subchronic-Duration Studies

Coulston et al. (1978)

In an unpublished report, groups of Long-Evans rats (10/sex/group) were exposed to 2-nitropropane (purity not reported) at nominal concentrations of 0 or 200 ppm for 7 hours/day, 5 days/week for 2 months via whole-body exposure. Analytical concentrations for this study were not reported. Based on the altitude of the Holloman Air Force Base testing facility (1,350 m), the study authors indicated that the nominal test concentration of 200 ppm is equivalent to 620 mg/m^3 due to barometric pressure of approximately 650 mm Hg (as opposed to 760 mm Hg at sea level). Food and water were removed from the cages during the exposure periods to avoid accidental oral exposure due to absorption of the compound into food and/or water. At sacrifice, the following tissues were examined microscopically (based on reported results): liver, lung, kidney, thyroid, lymph nodes, spleen, pancreas, and central nervous system tissues. Statistical analysis was not conducted by the study authors. No other endpoints were reported.

The only exposure-related lesion observed was hepatocellular vacuolization in exposed males (10/10) compared with controls (0/10). Vacuolization was not observed in control or exposed females. Incidences of lesions in other examined organs were comparable between exposed and control animals.

The only exposure level of 620 mg/m^3 is identified as a LOAEL based on hepatocellular vacuolization in the liver of male rats. The nominal concentration of 620 mg/m^3 was converted into a human equivalent concentration (HEC) value of 129 mg/m^3 for extrarespiratory effects.[3]

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[2]The ADD dose was calculated as follows: 90 mg/kg-day × 3 days ÷ 7 days = 39 mg/kg-day. The ADD was converted into an HED of 9.8 mg/kg-day using a DAF of 0.25 (HED = ADD × DAF). The DAF was calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$), where DAF = dosimetric adjustment factor, BW_a = animal body weight, and BW_h = human body weight. Quantitative body weight data were not reported; therefore, reference body weights recommended by the U.S. EPA (1988b) were used to calculate the DAF: 70 kg for humans and 0.267 kg for male S-D rats in a subchronic-duration study.

[3]HEC calculated by treating 2-nitropropane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air partition coefficient of 183 is greater than the human blood-air partition coefficient of 154 as indicated by Gargas et al. (1989).

Chronic-Duration/Carcinogenicity Studies with Interim Sacrifices

The chronic-duration inhalation studies also conducted interim sacrifices constituting short-term or subchronic duration exposures. The results from these interim sacrifices are discussed together in the text under the heading of "Chronic-Duration/Carcinogenic Studies with Interim Sacrifices" below, and are provided under short-term, subchronic, and chronic headings in Table 3A for clarity.

Lewis et al. (1979); Ulrich et al. (1977)

Male S-D rats (50/group) were exposed to 2-nitropropane (94.45% purity) at nominal concentrations of 0, 25, or 200 ppm for 7 hours/day, 5 days/week for up to 6 months via whole-body exposure. Interim sacrifices (10 rats/group) were conducted at 2 days, 10 days, 1 month, and 3 months. Results were reported in a published study by Lewis et al. (1979); additional data are also available in an unpublished study by Ulrich et al. (1977). Reported analytical concentrations (mean ± SD) were 27 ± 3 ppm (98 ± 10 mg/m^3) and 207 ± 15 ppm (754 ± 55 mg/m^3). In the absence of information on altitude of the testing facility for this study, inhalation exposures reported in ppm were converted to mg/m^3 assuming standard temperature and air pressure, yielding a conversion factor of 1 ppm = 3.6 mg/m^3. Mortality and body weight were monitored. At sacrifice, blood was collected for hematology (hemoglobin, erythrocyte count, prothrombin time, methemoglobin) and serum chemistry (ALT, ornithine carbamoyl transferase [OCT], T4), and all animals underwent a complete necropsy. The liver, kidney, lungs plus trachea, brain, and thyroid were removed and weighed. Brain and lung edema was evaluated using classical wet and dry weight techniques. The following tissues were examined microscopically: adrenals, bronchi, cerebellum, cerebral hemispheres, eyes, kidneys, liver, lung, spleen, thyroid, and trachea. Data were evaluated by parametric methods with Bartlett's test for homogeneity of variance (rejection level set at $p = 0.01$) followed by one-way ANOVA with the rejection level set at $p = 0.10$. When significant differences were indicated, data were further analyzed by Student's *t*-test with the significance level set at $p = 0.05$.

No exposure-related changes in survival were reported. Body weights were significantly decreased by 11−36% in rats exposed to 754 mg/m^3 for ≥2 days, compared with controls; greater decreases were observed at earlier time points (see Table B-15). Body weights in rats exposed to 98 mg/m^3 were comparable to controls. Sporadic changes were observed in some hematological parameters, but none of the findings showed a clear concentration- or time-related change. Serum ALT levels were significantly elevated by 22−23% at 10 days to 1 month in rats exposed to 754 mg/m^3; this effect was not observed at 3 months, but serum ALT levels were significantly elevated again at 6 months by almost fivefold (see Table B-16). Serum OCT levels in exposed animals were not significantly different from control at any time point (see Table B-16). Sporadic significant changes in serum T4 levels were reported, including a 21% decrease at 98 mg/m^3 at 2 days and an 83% increase at 754 mg/m^3 at 3 months; however, these findings do not represent clear exposure- or time-related findings (see Table B-16).

Relative liver weights were significantly increased by 24−176% after exposure to 754 mg/m^3 for ≥10 days; absolute liver weights were also significantly increased by 42−144% at 3 and 6 months (see Table B-15). Absolute and relative lung weights were significantly increased by 23 and 37%, respectively, after exposure to 754 mg/m^3 for 6 months; however, absolute and/or relative lung weights were significantly decreased by 20−53% after 2−30 days of exposure (see Table B-17). Lung weight changes at 754 mg/m^3 were accompanied by a small, but significant, 2−5% increase in water content at 1−6 months, indicating mild lung edema

(see Table B-17). Relative brain weight was also significantly elevated by 7−25% in rats exposed to 754 mg/m^3 at all time points (see Table B-18); no evidence of brain edema was reported. Kidney and thyroid weight changes did not show a consistent pattern regarding direction of change, exposure level, or time (see Tables B-15 and B-18).

Liver weight changes at 754 mg/m^3 were accompanied by increased incidence of gross and microscopic hepatic lesions (see Table B-19). Gross necropsy showed an increased incidence of pale livers and surface lesions on the liver in rats exposed to 754 mg/m^3 for 3 months. At 6 months, livers were enlarged and pale and showed numerous masses and lesions in rats exposed to 754 mg/m^3. Non-neoplastic histopathology findings included significantly increased incidence of pericholangitis at 10 days and focal hepatocyte hypertrophy and hyperplasia and basophilic foci at 3 months. Findings at 6 months were limited to neoplastic lesions (discussed below). No hepatic lesions were significantly increased after exposure to 98 mg/m^3. Pulmonary weight changes were associated with increased incidence of gross pulmonary abnormalities in rats exposed to 754 mg/m^3 for 1, 3, or 6 months (quantitative data not reported by study authors); however, the incidence of microscopic pulmonary lesions was comparable between control and exposed groups. Changes in brain weight were not accompanied by evidence of exposure-related brain lesions. Exposure-related lesions were not identified in other evaluated organs.

A NOAEL of 98 mg/m^3 and a LOAEL of 754 mg/m^3 are identified following 6-months of exposure based on decreased body weight, elevated serum ALT, elevated absolute and relative liver weights, and elevated lung weight and edema. Similarly, a LOAEL of 98 mg/m^3 is identified following 3-months of exposure based on increased absolute liver weight and relative kidney weight (≥10%) and no NOAEL could be identified. A LOAEL of 98 mg/m^3 is identified for increased absolute and relative kidney weights (≥10%) following 1 month of exposure. No 1-month NOAEL could be identified. A NOAEL of 98 mg/m^3 and a LOAEL of 754 mg/m^3 are identified for the short-term interim sacrifice at 10 days based on decreased body weight, elevated serum ALT, elevated relative liver weight, and hepatic pericholangitis. The analytical concentrations of 98 and 754 mg/m^3 correspond to HEC values of 20 and 157 mg/m^3, respectively, for extrarespiratory effects.[4]

With respect to carcinogenicity endpoints observed, neoplastic findings at 6 months included hepatocellular carcinoma and neoplastic nodules in all 10 rats exposed to 754 mg/m^3; no neoplastic hepatic lesions were observed in controls or rats exposed to 98 mg/m^3. No exposure-related neoplastic lesions were observed in other organs.

Coulston et al. (1978)

In an unpublished report, the study authors indicated that groups of S-D rats (125/sex/group) were exposed to 2-nitropropane (purity not reported) at nominal concentrations of 0 or 200 ppm for 7 hours/day, 5 days/week for up to 6 months via whole-body exposure. Interim sacrifices (10 rats/sex/group) were conducted at 10 days, 1 month, 3 months, and 6 months. Additionally, a recovery group (10 rats/sex) was removed from exposure after

[4]HEC calculated by treating 2-nitropropane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 since the rat blood-air partition coefficient of 183 is greater than the human blood-air partition coefficient of 154 as indicated by Gargas et al. (1989).

3 months and maintained until terminal sacrifice (6 months). All surviving animals not included in interim sacrifices were sacrificed 6 months after exposure initiation. A separate recovery group (10 rats/sex) was exposed for 6 months and then sacrificed after a 6-month recovery period; only neoplastic findings for this group were reported (10 males, 1 female). Based on reported results, it appears that animal numbers were 40/sex/group in the main study with an additional 20/sex in the recovery groups. The reported analytical concentration in the exposure group (mean ± SD) was 196 ± 12 ppm. Based on the altitude of the Holloman Air Force Base testing facility (1,350 m), the study authors reported that the nominal test concentration of 200 ppm is equivalent to 620 mg/m^3 (conversion factor of 1 ppm = 3.1 mg/m^3) due to barometric pressure of approximately 650 mm Hg (instead of the standard conversion factor of 1 ppm = 3.6 mg/m^3 at 760 mm Hg). Using the appropriate conversion factor for this testing facility, the analytical concentration is equal to 608 ± 37 mg/m^3.

Food and water were removed from the cages during the exposure periods to avoid accidental oral exposure due to absorption of the compound into food and/or water. Body weights were recorded weekly. At sacrifice, blood samples were obtained for clinical chemistry (ALT [reported as glutamic-pyruvic transaminase], OCT, T4, T3 uptake) and hematology (erythrocyte count, leukocyte count, pack cell volume, hemoglobin concentration, methemoglobin concentration, prothrombin time). Blood was also collected under anesthesia after 2 and 5 months of exposure for examination of these parameters. The brain, liver, kidney, lung, and thyroid were removed and weighed. A detailed histopathological exam was conducted on the liver from all animals. The lung, liver, kidney, spleen, thyroid, and central nervous system tissues were examined microscopically. Statistical analysis was conducted for continuous data using an unspecified method. Hepatic lesion incidence was statistically analyzed using methods established by Mainland et al. (1956) as cited by Coulston et al. (1978); no details on this method were provided.

Body weight was decreased by 4−13% in male rats through Week 27; all decreases >10% occurred within the first 6 weeks of exposure (see Table B-26); no exposure-related changes were observed in female rat body weights (see Table B-27). Statistically significant changes in hematological parameters were observed sporadically; however, no clearly time-related pattern or direction of change was observed (see Tables B-28 and B-29). Serum ALT levels were elevated by 20−354% in all evaluated groups of male rats; these findings were statistically significant at 10 days, 3 months, and 6 months (see Table B-30); serum ALT was comparable to control in recovery males exposed for 3 months and maintained unexposed for 3 additional months. Serum AST was also elevated fivefold in male rats at 6 months (not evaluated at other time points) (see Table B-30). Slight, but statistically significant, changes were observed in serum thyroid hormone levels in exposed males, including a 26% decrease in serum T4 at 2 months and 7−8% decreases in serum T3 uptake at 3−6 months (see Table B-30). No exposure-related changes in serum biochemistry were observed in females.

Significant relative organ weight changes are presented in Table B-26 (males) and Table B-27 (females); the study authors did not report absolute organ weights. Relative liver weights were significantly elevated by 28−44% in males at 3 and 6 months and by 25−29% in females at 1, 3, and 6 months. Relative liver weights were comparable to controls in both sexes in the group exposed for 3 months and maintained unexposed for 3 additional months. Relative kidney weights remained within 10% of control at all time points in both sexes; however, the 9% increase observed in exposed males at 3 months was statistically significant. The only other

significant change observed in organ weights was a 19% increase in relative brain weight in males at 10 days; the biological significance of this finding is unclear because it was not observed at later time points. Only liver weight effects were considered exposure-related by the study authors.

Non-neoplastic histopathological findings associated with exposure were limited to the liver and were observed predominately in males at all sacrifices. The study authors concluded that early microscopic changes were indicative of initial "toxic hepatitis," while findings at later time points are suggestive of the early stages of proliferative lesion development. The study authors did not report statistics for lesions incidence; however, a statistical analysis was conducted for this review (Fisher's exact test). Microscopic indicators of liver pathology that were significantly increased at 10 days in males included basophilic foci, single liver cell necrosis, mitotic cells, and bile duct proliferation; however, only the incidence of single liver cell necrosis was still significantly elevated at 30 days (see Table B-31). Findings at 3 months in males included significant increases in cytoplasmic vacuolation, nuclear changes in ≥6 cells, and broken "cell walls" (see Table B-32). After 6 months of exposure, significant increases were observed in the incidence of focal accumulation of macrophages, cytoplasmic inclusions, and hypertrophic and hyperplastic areas and/or nodules (see Table B-32). Significant increases in hypertrophic and hyperplastic areas and/or nodules were also observed in male rats at 6 months and in those that were exposed for 3 months and then maintained unexposed for 3 months (see Table B-32). Significant changes in exposed females were limited to increased glycogen content at 10 days (see Table B-33) and cytoplasmic vacuolation at 6 months (see Table B-34). The biological relevance of the glycogen content finding is unclear, as it was not observed at later time points and was observed at a high incidence in control animals.

The only administered concentration (608 mg/m^3) is considered a LOAEL for the 6-month component of the study based on elevated relative liver weights in males and females, altered liver serum biochemistry in males, and microscopic liver changes in males and females. Based on interim sacrifices at 1 and 3 months, a subchronic LOAEL of 608 mg/m^3 is also identified for decreased body weight in males, elevated relative liver weights in males and females, altered liver serum biochemistry in males, and microscopic liver changes in males. Additionally, based on the interim sacrifice at 10 days, a short-term LOAEL of 608 mg/m^3 is identified for altered liver serum biochemistry and microscopic liver changes in males. The analytical concentration of 608 mg/m^3 corresponds to an HEC value of 127 mg/m^3 for extrarespiratory effects.[5]

With respect to carcinogenicity endpoints observed, nodules in male rats at 6 months were considered to have features indicative of "malignant transformation," but they were not specifically described as tumors. In male rats exposed for 6 months and then maintained unexposed for 6 months, 9/10 had liver tumors with metastasis. Control data were not reported in this recovery group, and it appears that only one female was evaluated (showing multinucleated cell plates, loss of cohesion, and trabecular formation in the liver).

[5]HEC calculated by treating 2-nitropropane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air partition coefficient of 183 is greater than the human blood-air partition coefficient of 154 indicated by Gargas et al. (1989).

Griffin et al. (1981); Griffin et al. (1980)

Griffin et al. (1981) and Griffin et al. (1980) exposed groups of S-D rats (125/sex/group) to 2-nitropropane (95.65% purity) at nominal concentrations of 0 or 25 ppm for 7 hours/day, 5 days/week for up to 22 months via whole-body exposure. Interim sacrifices (10 rats/sex/group) were conducted at 1, 3, 6, and 12 months. Additionally, recovery groups (10 rats/sex/group) were removed from exposure after 3 and 12 months and maintained until terminal sacrifice. All surviving animals were sacrificed 22 months after exposure initiation. Reported analytical concentration in the exposure group (mean ± standard deviation [SD]) was 25.1 ± 1.4 ppm. Based on the altitude of the Holloman Air Force Base testing facility (1,350 m), the study authors reported that the nominal test concentration of 25 ppm is equivalent to 78 mg/m^3 (conversion factor of 1 ppm = 3.1 mg/m^3) due to barometric pressure of approximately 650 mm Hg (instead of the standard conversion factor of 1 ppm = 3.6 mg/m^3 at 760 mm Hg). Using the appropriate conversion factor for this testing facility, the analytical concentration is equal to 77.8 ± 4.3 mg/m^3.

Food and water were removed from the cages during the exposure periods to avoid accidental oral exposure due to absorption of the compound into food and/or water. Rats were observed daily for mortality and clinical signs of toxicity. Body weights were recorded weekly. At sacrifice, blood samples were obtained for clinical chemistry (ALT, ornithine carbamyl transferase [OCT], thyroxine [T4], triiodothyronine [T3] uptake) and hematology (erythrocyte count, leukocyte count, packed cell volume, hemoglobin concentration, methemoglobin concentration, prothrombin time). The brain, liver, and kidney were removed and weighed. A complete set of 33 tissues, along with all grossly observable lesions, was fixed for histological examination. For continuous data sets, Student's *t*-test was used to compare treatment group means with respective control group means. For noncontinuous data sets, Fisher's exact test conducted by the U.S. EPA for the purposes of this PPRTV assessment was used to compare treatment group means with respective control group means.

No exposure-related mortalities or clinical signs were reported. No exposure-related body weight effects were noted in male rats (see Table B-8). In females, body weights were significantly increased by 13−17% in the exposure group at 6, 12, and 22 months, compared with controls (see Table B-9). A significant 8% increase in body weight was also reported at terminal sacrifice for female rats exposed for 3 months, and then maintained unexposed until 22 months. Sporadic, but statistically significant, changes in hepatic clinical chemistry parameters were observed in exposed males; however, changes were <twofold and no clear pattern was observed regarding direction of change or duration of exposure (see Table B-10). No statistically significant changes were observed in hepatic clinical chemistry measures from exposed females, compared with controls, at any time point. Similarly, sporadic statistically significant changes in serum T4 levels were observed in exposed males and females, but there was no discernable pattern, and all exposed values fell within the range of control values measured over the course of the experiment (see Table B-11). No statistically significant changes were observed in T3 uptake percentage among groups. As observed for clinical chemistry, sporadic statistically significant changes in hematological parameters in male and female rats were small in magnitude and/or did not show a discernable pattern regarding direction of change or duration (see Tables B-12 and B-13).

Significant changes in liver weight in exposed male rats, compared with control, included a 12% increase in absolute liver weight and a 20% increase in relative liver weight at 22 months;

relative liver weights were also significantly increased by 17% at 6 months (see Table B-8). In exposed females, significant 17−23% increases in absolute liver weight were observed at 6, 12, and 22 months, compared with controls; however, no exposure-related findings were observed for relative liver weight at any time point (see Table B-9). Absolute kidney weight was significantly increased by 12% in exposed males at 12 months and exposed females at 1 month, compared with control; however, no significant changes in absolute kidney weight were observed at other time points (see Tables B-8 and B-9). Relative kidney weights were not reported. No exposure-related changes in absolute or relative liver or absolute kidney weight were observed in recovery males or females. Absolute brain weights were comparable between exposed and control rats throughout the study; relative brain weights were not reported.

Histopathological lesions, including focal areas of vacuolation in hepatocytes, focal hepatocellular nodules, and liver congestion, were elevated in exposed males, compared with controls (see Table B-14). In females, only the incidence of liver congestion was elevated. The study authors only reported findings for all animals combined (interim sacrifices and all terminal sacrifices, including recovery groups), so information on the timing of lesion development is unknown. Exposure-related lesions were not observed in other tissues or organ systems.

The only exposure level (77.8 mg/m^3) is identified as a chronic LOAEL based on increased relative liver weight and focal vacuolization and nodules in the liver of male rats, as well as liver congestion in male and female rats exposed to 2-nitropropane for interim sacrifices performed between 6–22 months. The analytical concentration of 77.8 mg/m^3 corresponds to an HEC value of 16.2 mg/m^3 for extrarespiratory effects.[6] No chronic NOAEL is identified. For the 1- and 3-month component of the study, however, the only concentration tested of 16.2 mg/m^3 is identified as a subchronic NOAEL based on the lack of consistent effects being observed at later timepoints. Specifically, in female rats, absolute liver and kidney weights were biologically significantly increased after 1 month of exposure but these effects were not observed after 3 months of exposure.

No evidence of exposure-related carcinogenic effects was noted in this study. Tumor incidences in all tissues and organ systems were comparable in control and exposed groups.

Griffin et al. (1979)

In an unpublished report, groups of S-D rats (125/sex/group) were exposed to 2-nitropropane (95.65% purity) at nominal concentrations of 0 or 100 ppm for 7 hours/day, 5 days/week for up to 18 months via whole-body exposure. Interim sacrifices (10−20/sex/group) were conducted at 1, 3, 6, 9, and 12 months. Additionally, recovery groups (10/sex/group) were removed from exposure after 3, 6, or 9 months, and maintained until terminal sacrifice (18 months). All surviving animals not included in interim sacrifices were sacrificed 18 months after exposure initiation. Reported analytical concentration in the exposure group (mean ± SD) was 100 ± 3 ppm. Based on the altitude of the Holloman Air Force Base testing facility (1,350 m), the study authors reported that the nominal test concentration of 100 ppm is equivalent to 312 mg/m^3 (conversion factor of 1 ppm = 3.1 mg/m^3) due to barometric pressure of

[6]HEC calculated by treating 2-nitropropane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air partition coefficient of 183 is greater than the human blood-air partition coefficient of 154 as indicated by Gargas et al. (1989).

approximately 650 mm Hg (instead of the standard conversion factor of 1 ppm = 3.6 mg/m^3 at 760 mm Hg). Using the appropriate conversion factor for this testing facility, the analytical concentration is equal to 312 ± 9 mg/m^3.

Food and water were removed from the cages during the exposure periods to avoid accidental oral exposure due to absorption of the compound into food and/or water. Rats were observed daily for mortality and clinical signs of toxicity. Body weights were recorded weekly. Gross necropsy was conducted on all animals at interim and terminal sacrifice, as well as for any animal that died or was sacrificed moribund during the study. At interim and terminal sacrifices, blood samples were obtained for clinical chemistry (ALT [reported as glutamic-pyruvic transaminase], OCT, T4, T3 uptake) and hematology (erythrocyte count, leukocyte count, packed cell volume, hemoglobin concentration, methemoglobin concentration, prothrombin time). The brain, liver, and kidney were removed and weighed. At terminal sacrifice only, the lung, liver, kidney, lymph node, and any unusual lesions were fixed for histological examination. No statistical tests were reported.

Body weights were decreased by 22% in male rats exposed for 18 months and by 12−25% in male rats exposed for 6 or 9 months, then sacrificed at 18 months (see Table B-20). Body weights in other exposed male groups and in all exposed female rats were within 10% of respective control values throughout exposure (see Tables B-20 and B-21). In male rats, serum ALT was increased 4.5-fold in the group exposed for 18 months, 2.2-fold in the group exposed for 6 months and then sacrificed at 18 months, and 23-fold in the group exposed for 9 months and then sacrificed at 18 months (see Table B-22). While serum ALT values varied greatly among animals, statistical analysis conducted for this review indicated that these increased values in exposed males were significantly different from respective controls in the Lewis et al. (1979) and Ulrich et al. (1977) studies as well (see Table B-16). In females, no exposure-related serum ALT changes were reported. No exposure-related changes were observed in serum OCT, T4, T3 activity, or hematology in either sex.

Absolute liver weights were increased by >10% in all groups of exposed male rats, and relative liver weights were increased by >10% in male rat groups exposed for 3 months or longer, compared with respective controls (see Table B-20). Increases in liver weight were greater following longer exposure, with increases in absolute and relative liver weight up to 242 and 375%, respectively. In females, absolute and relative liver weights were comparable between exposure and control groups throughout the experiment, with weights generally within 10% of control values and no clear time-related pattern or direction of change (see Table B-21). Similarly, absolute kidney weights were generally within 10% of control at all time points in both males and females, with no clear time-related pattern or direction of change (see Table B-23). No exposure-related changes were observed in absolute brain weights. Relative kidney weights and brain weights were not reported by study authors.

The combined incidence of grossly observed hepatic masses (unspecified) and nodules was significantly increased in males exposed for 12 or 18 months, all recovery groups, and animals found dead or sacrificed moribund, compared to respective controls, but not in females (see Table B-24). Histopathological examination of the livers in animals sacrificed at 18 months showed significant increases in hepatocellular carcinoma (discussed in more detail below) and focal necrosis in male rats and vacuolar degeneration and nodular hyperplasia in both male and female rats, compared with controls (see Table B-25). Increased incidence of renal calcification

was also observed in exposed rats at 18 months, although this finding was only statistically significant in males (see Table B-25). No other non-neoplastic lesions were associated with exposure to 2-nitropropane. Animals that died during the study or were sacrificed at other time points were not examined for histopathology.

The only exposure level (312 mg/m^3) is identified as a chronic LOAEL based on decreased body weights, renal calcification, elevated ALT, and elevated absolute and relative liver weights in male rats and degenerative and hyperplastic hepatic lesions in male and female rats. Based on available interim sacrifice data at 1 and 3 months, 312 mg/m^3 is also identified as a subchronic LOAEL based on elevated absolute and/or relative liver weights in males. The analytical concentration of 312 mg/m^3 corresponds to an HEC value of 65.0 mg/m^3 for extrarespiratory effects.[7] No NOAEL is identified.

With respect to carcinogenicity endpoints, hepatocellular carcinoma was observed in 7/23 males examined for histopathology at 18 months, compared with 0/63 control males (see Table B-25). Based on a Fisher's exact test conducted for this review, this finding is significant. Grossly observed hepatic masses/nodules (hyperplastic), found in 11 of 16 exposed males that died or were sacrificed moribund during the study (see Table B-24), potentially included some carcinomas as well, but no histological examination was performed for these animals. Hepatocellular carcinoma was not observed in control or exposed females. Other observed neoplasms in exposed groups were comparable or lower than respective control incidence.

Lewis et al. (1979); Ulrich et al. (1977)

Groups of male New Zealand White rabbits (15/group) were exposed to 2-nitropropane (94.45% purity) at nominal concentrations of 0, 25, or 200 ppm for 7 hours/day, 5 days/week for up to 6 months via whole-body exposure. Interim sacrifices (5 rabbits/group) were conducted at 1 and 3 months. Results were reported in a published study by Lewis et al. (1979); additional data are also available in an unpublished study by Ulrich et al. (1977). Reported analytical concentrations (mean ± SD) were 27 ± 3 ppm (98 ± 10 mg/m^3) and 207 ± 15 ppm (754 ± 55 mg/m^3). In the absence of information on altitude of the testing facility for this study, inhalation exposures reported in ppm were converted to mg/m^3 assuming standard temperature and air pressure, yielding a conversion factor of 1 ppm = 3.6 mg/m^3. Mortality and body weight were monitored. At sacrifice, blood was collected for hematology (hemoglobin, erythrocyte count, prothrombin time, methemoglobin) and serum chemistry (ALT, OCT, T4), and all animals underwent a complete necropsy. The liver, kidney, lungs plus trachea, brain, and thyroid were removed and weighed. Brain and lung edema was evaluated using classical wet and dry weight techniques. The following tissues were examined microscopically: adrenals, bronchi, cerebellum, cerebral hemispheres, eyes, kidneys, liver, lung spleen, thyroid, and trachea. Data were analyzed using nonparametric statistical methods. First, a Kruskal-Wallis one-way ANOVA was conducted. If differences were indicated ($p \geq 0.10$), the Mann-Whitney U test was used.

[7]HEC calculated by treating 2-nitropropane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air partition coefficient of 183 is greater than the human blood-air partition coefficient of 154 as indicated by Gargas et al. (1989).

No exposure-related changes in survival were reported. Body weights were comparable between exposed and control rabbits throughout the experiment (see Table B-35). Sporadic changes were observed in some hematological parameters, but none of the findings showed a clear concentration- or time-related change. Serum ALT and OCT levels were significantly elevated by 73 and 330%, respectively, after exposure to 754 mg/m^3 for 1 month, compared with controls; these effects were not observed at 3 or 6 months in rabbits exposed to 754 mg/m^3 or at any time point in rabbits exposed to 98 mg/m^3 (see Table B-36). Serum T4 levels were elevated by 6−81% after exposure to 754 mg/m^3 for 1−6 months, but findings were only significantly different from controls at 6 months (see Table B-36). However, nonsignificant decreases in serum T4 were observed at all time points after exposure to 98 mg/m^3; therefore, the biological relevance of these findings is unclear. Sporadic, significant changes in organ weight were observed, but findings did not show a consistent pattern regarding direction of change, exposure level, or time (see Tables B-35, B-37, and B-38).

Potentially exposure-related lesions were limited to non-neoplastic findings in the lungs in rabbits exposed to 754 mg/m^3 at 1 month, including alveolar necrosis, focal hemorrhage, and pulmonary edema, each in 3/5 rabbits compared to 0/5 controls (see Table B-39). However, incidences of pulmonary lesions were similar between exposed and control rabbits at 3 and 6 months (see Table B-39). Additionally, quantitative analysis did not show an exposure-related increase in lung edema at any time point (see Table B-37). In contrast to similarly exposed rats (discussed above), no statistically significant increases of microscopic lesions in the liver were observed compared to controls (see Table B-40). No exposure-related lesions were observed in other evaluated organs.

The highest exposure level (754 mg/m^3) is identified as a NOAEL for a lack of adverse findings following exposure for 1, 3, and 6 months. The analytical concentrations of 98 and 754 mg/m^3 correspond to HEC values of 20 and 157 mg/m^3, respectively, for extrarespiratory effects[8] and 16 and 130 mg/m^3, respectively, for pulmonary effects.[8] No exposure-related neoplastic lesions were observed in rabbits.

[8]2-Nitropropane has characteristics of a highly reactive, Category 1 gas that often results in portal-of-entry effects in the PU region as well as less reactive Category 3 gas for ER effects. As HEC equations for a Category 2 gas are currently unavailable, the HECs are calculated using both Category 1 and Category 3 gas equations. The HEC for extrarespiratory effects was calculated by treating 2-nitropropane as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 since the rabbit blood-air partition coefficient of 170 indicated by AFOSR (1992) is greater than the human blood-air partition coefficient of 154 as indicated by Gargas et al. (1989). AFOSR (1992) reported their value as body-air partition coefficient, but it is assumed to be essentially equivalent to a blood-air value, as their body:air value for rats of 180 is almost the same as the Gargas et al. (1989) blood-air value of 183 for that species. HEC values for pulmonary effects were calculated by treating 2-nitropropane as a Category 1 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{PU} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × $RGDR_{PU}$, where $RGDR_{PU}$ for the 27- and 207-ppm groups were calculated to be 0.80 and 0.83, respectively, using Equation 4-28 in U.S. EPA (1994) and minute volume (V_E) values of 1.23 and 1.26 L/minute, respectively [calculated based on TWA body weight of 3.3 and 3.4 kg, respectively, calculated from body weight data estimated from graphically presented data in Ulrich et al. (1977) using GrabIt! software], and the following default values from U.S. EPA (1994): V_E of 13.8 L/minute for humans, SA_{PU} of 59,000 cm^2 for rabbits and 540,000 cm^2 for humans, SA_{TB} of 300 cm^2 for rabbits and 3,200 cm^2 for humans, and SA_{ET} of 30 cm^2 for rabbits and 200 cm^2 for humans.

Reproductive/Developmental Studies

A screening developmental toxicity study by Hardin et al. (1981) reported delayed cardiac development in the offspring of rat dams exposed to 170 mg/kg-day via intraperitoneal (i.p.) injection on Gestation Days (GDs) 1−15. No exposure-related changes in fetal body weight, length, or skeletal or visceral malformations were observed. No maternal toxicity was observed.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Genotoxicity Studies

The genotoxicity of 2-nitropropane has been extensively evaluated in vitro and in vivo. Available studies are summarized below (see Table 4A for more details). Available data indicate that 2-nitropropane is a genotoxic agent. It is an established mutagen, and there is consistent evidence for chromosomal effects and DNA damage in hepatic cells and tissues. There is also some evidence for chromosomal effects and DNA damage in bone marrow cells and lymphocytes.

Table 4A. Summary of 2-Nitropropane Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
Genotoxicity studies—prokaryotic organisms						
Mutation	*Salmonella typhimurium* TA100, TA102	0−80 µmol/plate	− TA100, TA102	+ TA100, TA102	Preincubation assay. There was a significant increase of revertants at 40 µmol/plate with metabolic activation in TA100 and in TA102 at 80 µmol/plate. There was a dose-dependent increase in revertants without metabolic activation, but results were not significant.	Conaway et al. (1991a)
Mutation	*S. typhimurium* TA98, TA100, TA102	0, 1.7, 3.5, 6.9, 13.9, 27.7, 55.4 µmol/plate	+ TA100, TA102 − TA98	+ TA100, TA102 − TA98	Preincubation assay. Neutral 2-nitropropane significantly induced mutations at 55 µmol/plate with and without activation. 2-Nitropropane nitronate (anionic form of 2-nitropropane) also induced mutations at ~4 µmol/plate. No mutations were induced in TA98.	Fiala et al. (1987a)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Mutation	*S. typhimurium* TA98, TA100, and their NR-deficient strains TA98NR and TA100NR	0, 2.1, 4.2, 10.5, 21.0, 31.5 mM	+ TA98, TA100, TA98NR, TA100NR	+ TA98, TA100, TA98NR, TA100NR	Preincubation assay. Cytotoxicity was reported at doses >21 mM (~5 mg/plate). An increased number of revertants occurred at 10.5 mM (2.45 mg/plate) in the TA100 strain (~10-fold) and in the TA98 strain (~12-fold) over control values without metabolic activation; comparable mutagenicity was noted with metabolic activation. 2-Nitropropane was less mutagenic in the NR-deficient strains (4- to 5-fold increases in revertants).	Göggelmann et al. (1988)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0, 1,500, 3,000, 4,500, 5,000, 6,000, 7,500 µg/plate	− TA98, TA100, TA1535, TA1537, TA1538	± TA1535, TA98, TA100 − TA1537, TA1538	Plate incorporation assay. Weakly mutagenic. There was a dose-dependent increase in the number of mutations in strains TA1535, TA98, and TA100 with metabolic activation. Mutation frequencies were 2.18-, 1.9-, and 2.0-times higher in strains TA1535, TA98, and TA100, respectively, compared to controls. The only concentration tested without activation was 5,000 µg/plate	Russell and Krahn (1977)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	0, 33.0, 100, 333, 1,000, 1,666, 3,333, 6,666, 10,000 µg/plate	+ (TA98, A100, TA1535, TA1537)	+ (TA98, A100, TA1535, TA1537)	Preincubation assay. Increased number of revertants.	Haworth et al. (1983)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Mutation	*S. typhimurium* TA92, TA98, TA100, TA1537	0, 0.0037, 0.1, 0.03, 0.011 mL per plate	+ TA92, TA98, TA100, TA1537	+ TA92, TA98, TA100, TA1537	Preincubation assay. Dose-dependent increase in revertants in all 4 test strains. Undiluted 2-nitropropane was inhibitory for strains TA1537, TA98, and TA100.	Hite and Skeggs (1979)
Mutation	*S. typhimurium* TA100, TA102	0, 0.2−16 µmol/plate	+ TA100, TA102	NDr	Preincubation assay. Dose-dependent induction of mutations. 2-Nitropropane induced mutagenicity was also tested over a range of pH levels. The rate of mutagenicity was increased with increased pH. Cytotoxicity was present at highest concentrations.	Kohl et al. (1994)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Without metabolic activation: 0, 0.001, 0.01, 0.1, 1.0, 5.0 µL/plate With metabolic activation: 0, 0.001, 0.01, 0.1, 1.0, 5, 10, 20 µL/plate	−	+ TA98 − TA100, TA1535, TA1537, TA1538	Plate incorporation assay. Slight toxicity was seen in strain TA1537 at 5 µL/plate. Negative results reported for all strains without metabolic activation; negative results for strains TA100, TA1535, TA1537, TA1538 with activation; 2-nitropropane was mutagenic in *S. typhimurium* strain TA98 with metabolic activation at ≥10 µL/plate.	Litton Bionetics (1977b), Litton Bionetics (1977a)
Mutation	*S. typhimurium* TA98, TA100, TA1535	Unspecified (notes highest doses tested are mostly 20−50 mg/plate)	+ TA98, TA100 ± TA1535	+ TA98, TA100 ± TA1535	Plate incorporation assay. Increased number of revertants per mg in TA98 and TA100. Only a slight increase in number of revertants per mg in TA1535.	Löfroth et al. (1986)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Mutation	*S. typhimurium* TA98, TA100, and their NR-deficient strains TA98NR101 and TA100NR3	0, 0.1, 0.33, 1.0, 3.3, 10.0, 20.0 mg/plate	+ TA98, TA100, TA98NR101, TA100NR3	+ TA98, TA100, TA98NR101, TA100NR3	Preincubation assay. There was a dose-dependent increase in the number of revertants. There was an increase in the number of revertants with metabolic activation, but mutagenicity is not dependent on the presence of S9 microsomes. Also, mutagenic in the NR-deficient strains.	Speck et al. (1982)
DNA damage (SOS chromotest)	*S. typhimurium* NM7000 (parent strain), NM7001, NM7002, NM7003 (new strains expressing human SULT 1A1, 1A2, and 1A3, respectively)	1,000, 2,000, 4,000, 10,000 µM	+ NM7002 – NM7000, NM7001, NM7003	NDr	*Umu* assay. DNA damage was induced in NM7002 strain (expressing SULT1A2) at ≥2,000 µM. DNA damage was not induced in other strains.	Oda et al. (2012)
Genotoxicity studies—nonmammalian eukaryotic organisms						
Mutation	*Saccharomyces cerevisiae* D4	Without metabolic activation: 0, 0.001, 0.01, 0.1, 1.0, 5.0 µg/plate With metabolic activation: 0, 0.001, 0.01, 0.1, 1.0, 2.0, 10, 20 µg/plate	–	–	Negative with and without metabolic activation.	Litton Bionetics (1977b)

Table 4A. Summary of 2-Nitropropane Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
Genotoxicity studies in mammalian cells—in vitro						
Mutation	Rat hepatoma H4IIEC3/G$^-$ cells, hprt locus	0.3−10 mM 24 hr	+	NDr	Mutagenicity was estimated by measuring the induction of clones resistant to TG. Cells were pretreated with dexamethasone (an inducer of liver-specific CYP450 forms; results were negative without this pretreatment). Cytotoxicity was only present when treated with dexamethasone. Induced frequency of TG-resistant cells with dexamethasone treatment, but not without.	Roscher et al. (1990)
Mutation	Chinese hamster lung V79 cells, hprt locus	0, 3 mM	+	NDr	Induced mutations at 3 mM. V79 cells capable of reducing and oxidizing 2-nitropropane, but reduced metabolites (acetone oxime) were found not responsible for mutations.	Haas-Jobelius et al. (1991)
Mutation	Gene mutation, Chinese hamster lung V79 cells, hprt locus	0.3−10 mM 3 hr	+	NDr	Mutagenicity was estimated by measuring the induction of clones resistant to TG. Induced frequency of TG-resistant cells with and without dexamethasone treatment. Marginally cytotoxic at all treatment levels.	Roscher et al. (1990)

Table 4A. Summary of 2-Nitropropane Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
CA	Primary human lymphocytes from a healthy female donor	Without S9: 0, 15, 30, 60, 80 mM With S9: 0, 7.5, 15, 30, 60, 80 mM	+	+	CAs were induced in the presence of metabolic activation at 60 and 80 mM, and without activation at 80 mM. CAs included open breaks and gaps in chromatid.	Bauchinger et al. (1987)
CA	Human lymphocytes	0, 30, 60, 80, 111 mM	−	+	CAs were increased at ≥80 mM. CAs were not significantly induced without activation. Highest tolerated dose was 111 mM for cells to undergo mitosis.	Göggelmann et al. (1988)
CA	CHO cells	160−5,000 µg/mL	−	−	2-Nitropropane did not induce CAs with or without metabolic activation.	Galloway et al. (1987)
SCE	Primary human lymphocytes from a healthy female donor	Without S9: 0, 15, 30, 60, 80 mM With S9: 0, 7.5, 15, 30, 60, 80 mM	+	+	SCEs were increased at all doses with metabolic activation and at 80 mM and without activation.	Bauchinger et al. (1987)
SCE	Human lymphocytes	0, 30, 60, 80, 111 mM	NDr	±	SCE could not be scored without S9 mix (no M2 metaphases observed). With S9 mix, weak induction of SCEs was observed. Highest tolerated dose was 111 mM for cells to undergo mitosis.	Göggelmann et al. (1988)
SCE	CHO cells	160−5,000 µg/mL	−	−	2-Nitropropane did not induce SCEs with or without metabolic activation.	Galloway et al. (1987)
MN	Wistar rat primary hepatocytes (male)	0−0.0015 mol/L	+	NDr	Significant dose-dependent increase in micronucleus formation.	Muller-Tegethoff et al. (1995)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
MN	Rat hepatoma cell lines H4IIEC3/G⁻, 2sFou, and C2Rev7	0.3−10 mM 24 hr	−	+	Cells were pretreated with dexamethasone (an inducer of liver-specific CYP450 forms). Frequency of MN was not altered without dexamethasone treatment. With dexamethasone pretreatment, there was an increase in frequency of MN.	Roscher et al. (1990)
MN	Chinese hamster lung V79 cells	0, 2.5, 5 mM	−	NDr	2-Nitropropane did not affect the frequencies of MN or abnormal nuclei at concentrations up to 5 mM and did not affect the mitotic index (data not shown).	Haas-Jobelius et al. (1991)
MN	Chinese hamster lung V79 cells	0.3−10 mM 3 hr	−	NDr	No increase in MN.	Roscher et al. (1990)
MN	V79-hCYP2E1-hSULT1A1 cells (cells express human CYP2E1 and human SULT1A1)	0, 1, 3, 5 mM	+	NDr	MN tests done in the presence of modulators: pentachlorophenol, a specific inhibitor of SULT1A1, or 1-aminobenzotriazole, a specific inhibitor of CYP2E1. Increased frequencies of micronucleated and multinucleated cells in the presence of 1-aminobenzotriazole but not pentachlorophenol. Mild dose-dependent cytotoxicity.	Deng et al. (2011)
UDS	Human primary hepatocytes (4 M, 2 F)	0, 0.01, 0.1, 1.0 mmol	±	NDr	Minimal induction of UDS.	Davies et al. (1993)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
UDS	Human diploid fibroblasts	0−5,000 µg/mL 3 hr	−	NDr	No increase in UDS.	McGregor (1981)
UDS	Wistar rat primary hepatocytes	0, 0.01, 0.1, 1.0 mmol	+	NDr	Marked induction of UDS at 0.1 mmol.	Davies et al. (1993)
UDS	F344 rat primary hepatocytes (M)	10^{-7} to 10^{-3} M/plate	+	NDr	2-Nitropropane was toxic at 10^{-3} M. 2-Nitropropane induced UDS at concentrations of 10^{-5} and 10^{-4} M.	Fiala et al. (1995)
UDS	Rat primary hepatocytes	0, 0.25, 6.25 mM	+	NDr	2-Nitropropane induced UDS.	Kohl et al. (1994)
UDS	BALB/c mouse primary hepatocytes	0, 0.01, 0.1, 1.0 mmol	±	NDr	Minimal induction of UDS.	Davies et al. (1993)
DNA repair synthesis	Human cell lines (W138, NCI-H322, A549, Hep2)	10 mM	−	NDr	No evidence of increased DNA repair synthesis.	Andrae et al. (1988)
DNA repair synthesis	Rat hepatocytes (208F, LLC-WRC 256)	10 mM	+	NDr	Increased DNA repair synthesis.	Andrae et al. (1988)
DNA repair synthesis	Rat hepatocytes	0, 1, 3 mM	+	NDr	Increased DNA repair synthesis.	Haas-Jobelius et al. (1991)
DNA repair synthesis	Rat hepatocytes	1×10^{-6} M	+	NDr	Increased DNA repair synthesis in hepatocytes from adult male F344 rats.	Williams et al. (1982)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
DNA repair synthesis	Rat hepatoma cell line (2sFou)	5, 10 mM	±	NDr	Cells were treated with either 2-nitropropane or propane 2-nitronate (anionic form of 2-nitropropane). 2-Nitropropane was shown to release nitrite into incubation medium at a lesser rate than propane 2-nitronate. 2-Nitropropane was weakly active for the induction of DNA repair synthesis while propane 2-nitronate had a marked induction of DNA repair synthesis, suggesting propane 2-nitronate is oxidized by the liver to produce DNA damage via nitronate formation.	Dalke and Andrae (1992)
DNA repair synthesis	Rat hepatoma cell lines (2sFou, C2Rev7)	0.3−10 mM 24 hr	±	NDr	Weakly induced DNA repair synthesis.	Roscher et al. (1990)
DNA repair synthesis	Mouse 3T3-NIH cells	10 mM	−	NDr	No evidence of increased DNA repair synthesis.	Andrae et al. (1988)
DNA repair synthesis	Chinese hamster lung V79 cells	0, 1, 3, 10 mM	−	NDr	No evidence of increased DNA repair synthesis.	Andrae et al. (1999)
DNA repair synthesis	Chinese hamster lung V79-rPST-IV and V79-rST1C1 cells (cells express rat hepatic SULT1A1 or SULT1C1)	0, 0.3, 1, 3, 10 mM	+	NDr	2- to 4-fold increase in DNA repair synthesis with exposure.	Andrae et al. (1999)
DNA repair synthesis	Chinese hamster cell lines (V79, CHO)	10 mM	−	NDr	No evidence of increased DNA repair synthesis.	Andrae et al. (1988)
DNA repair synthesis	Chinese hamster lung V79 cells	0.3−10 mM 24 hr	−	NDr	No evidence of increased DNA repair synthesis.	Roscher et al. (1990)

Table 4A. Summary of 2-Nitropropane Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
Genotoxicity studies—mammalian species-in vivo						
Dominant lethal mutations	Male CD rats were exposed to 2-nitropropane via inhalation for 5 d (7 hr/d) and mated to unexposed females; endpoints examined included pregnancy frequency, number of corpora lutea and implantation, and frequency of early and late fetal death	0, 25, 200 ppm	+	NA	75% reduction in pregnancy frequency at 200 ppm; decreased frequency of live implantations at 200 ppm.	McGregor (1981)
Mutations (*lacI* assay)	Male C57BL/6 mice were exposed once to 2-nitropropane via i.p. injection in olive oil and sacrificed 14 d later; liver tissue was examined for *lacI* transgene mutations frequency	0, 100 mg/kg	+	NA	2.6-fold increase in mutation frequency of the *lacI* transgene.	Cabelof et al. (2002)
CA (bone marrow)	Male and female CD rats were exposed to 2-nitropropane via inhalation for 1 or 5 d (7 hr/d); bone marrow was evaluated for CAs	0, 25, 200 ppm	−	NA	No significant induction of CAs at 1 or 5 d.	McGregor (1981)
MN (liver)	Male S-D rats (5−8/group) were exposed once to 2-nitropropane via gavage in water; 3 d later, rats were given single oral dose of 4-acetylaminofluorene; liver tissue was evaluated for MN 2 d after 4-acetylaminofluorene exposure using both suspension and coverslip methods	0, 25, 50, 75, 300 mg/kg	+	NA	Suspension method: 2- to 4-fold increase in MN at all doses; significant at all doses except 75 mg/kg. Coverslip method: 1.6- to 4-fold increase in MN at all doses; significant at 50 and 300 mg/kg only.	George et al. (1989)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
MN (liver)	Male Crl:CD (SD) rats were administered 2-nitropropane via gavage in water for 14 or 28 d; rats were sacrificed 24 hr after final dose; liver tissue was evaluated for MN	0, 5, 20, 40 mg/kg-d	+	NA	Significant increases in hepatic MN in both 14- and 28-d treated rats	Kawakami et al. (2015)
MN (bone marrow)	Male S-D rats (number/group not reported) were exposed once to 2-nitropropane via gavage in water; bone marrow was evaluated for MN 24−48 hr after exposure	0, 50, 100, 300 mg/kg (oral)	−	NA	No significant induction of MN at any dose. Decreased survival observed at 300 mg/kg (6/11 died within 24 hr).	George et al. (1989)
MN (bone marrow)	Male Crl:CD (SD) rats were administered 2-nitropropane via gavage in water for 14 or 28 d; rats were sacrificed 24 hr after final dose; bone marrow was evaluated for MN	0, 5, 20, 40 mg/kg-d	−	NA	No significant induction of MN at after 14 or 28 d.	Kawakami et al. (2015)
MN (bone marrow)	Male and female CD-1 mice were orally administered 2 daily doses and sacrificed 6 hr after second dose; bone marrow was evaluated for MN	0, 0.1, 0.2, 0.3 mL/kg-d (0, 100, 200, 300 mg/kg-d)	−	NA	No significant induction of MN at any dose.	Hite and Skeggs (1979)
MN (bone marrow)	Male and female (101/E1 × CeH/E1)F1 mice were exposed once to 2-nitropropane via i.p. injection; mice were sacrificed at intervals 18−120 hr after exposure; bone marrow was evaluated for MN	0, 100, 200, 300 mg/kg	−	NA	No significant induction of MN at any dose.	Kliesch and Adler (1987)
DNA damage (comet assay)	Male Wistar rats were exposed once to 2-nitropropane via i.p. injection in olive oil and sacrificed 24 hr later; bone marrow cells were assessed for DNA damage	0, 100 mg/kg	+	NA	8-fold increase in average tail length, indicating DNA damage.	Deng et al. (1997)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
DNA damage (alkaline elution assay)	Male S-D rats were exposed once to 2-nitropropane via gavage in distilled water; DNA fragmentation was determined in liver, lung, bone marrow, kidney, and brain at intervals of 1−36 hr post exposure (4−9 rats per time point)	0, 0.5, 2, 8 mmol/kg (0, 40, 200, 700 mg/kg)	+ (liver, bone marrow) – (kidney, lung, brain)	NA	Significant increases in DNA fragmentation in liver (2- to 4-fold) and bone marrow (1.2- to 1.3-fold). DNA fragmentation was not induced in kidney, lung, or brain.	Robbiano et al. (1991)
DNA damage (comet assay)	Male wild-type C57BL/6 and β-pol$^{\pm}$ C57BL/6 mice were exposed once to 2-nitropropane via i.p. injection in olive oil and sacrificed 24 hr later; liver tissue was examined for SSB; β-pol (DNA polymerase β) is associated with repair synthesis in short-patch BER	0, 100 mg/kg	+	NA	Number of SSBs increased by 4- to 5-fold; the increase was greater in β-pol$^{\pm}$ C57BL/6 mice. Other indicators of DNA damage included an increase in p53 protein levels; the increase was greater in β-pol$^{\pm}$ C57BL/6 mice.	Cabelof et al. (2002)
DNA damage	Young (4−6 mo) and aged (24−28 mo) mice were exposed to 2-nitropropane via i.p. injection in olive oil; liver tissue was examined for 3'OH-containing DNA strand breaks	0, 100 mg/kg	+ (young) – (aged)	NA	Statistically significant increase (~2-fold) in 3'OH groups in DNA from young mice, compared with control. Slight (~20%), but significant, decrease in 3'OH groups in DNA from aged mice, compared with control.	Cabelof et al. (2006)
DNA repair (BrdU density-shift)	Male and female Wistar rats were exposed once to 2-nitropropane via i.p. injection in olive oil; rats were sacrificed 4 hr later and liver tissue was examined for DNA repair (BrdU incorporation)	0, 20, 40, 60, 80 mg/kg	+	NA	DNA repair increased up to 4-fold in males and 3-fold in females.	Andrae et al. (1988)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
DNA repair (BER)	Male wild-type C57BL/6 and β-pol$^{\pm}$ C57BL/6 mice were exposed once to 2-nitropropane via i.p. injection in olive oil and sacrificed 24 hr later; liver tissue was examined for BER; B-pol (DNA polymerase β) is associated with repair synthesis in short-patch BER	0, 100 mg/kg	+	NA	Number of BERs increased 4- to 5-fold; the increase was greater in β-pol$^{\pm}$ C57BL/6 mice.	Cabelof et al. (2002)
UDS	Male S-D rats were exposed once to 2-nitropropane via gavage in water; UDS was evaluated in bone marrow 14−16 hr after exposure	0, 25, 50, 75, 100 mg/kg	+	NA	2-Nitropropane induced UDS at ≥50 mg/kg.	George et al. (1989)
Oxidative DNA damage	Male S-D rats were exposed once to 2-nitropropane via i.p. injection in Emulphor-620:H_2O (1:4 v/v); rats were sacrificed 4 hr later; liver DNA and RNA was evaluated for 8-OHdG levels	0, 1.12 mmol/kg (100 mg/kg)	+	NA	Significant increases in 8-OHdG in hepatic DNA and RNA. There was also formation of unknown moieties of DX1 (DNA), and RX1 and RX2 (RNA).	Conaway et al. (1991b)
Oxidative DNA damage	Male F344 rats were exposed once to 2-nitropropane via i.p. injection in corn oil; rats were sacrificed 6 hr later; liver DNA was evaluated for 8-OHdG levels	0, 100 mg/kg	+	NA	12-fold increase in 8-OHdG in hepatic DNA. There was also formation of unknown moieties in DNA (DX1).	Dahlhaus and Appel (1993)
Oxidative DNA damage	Male Wistar rats were exposed once to 2-nitropropane via i.p. injection in olive oil and sacrificed 24 hr later; bone marrow cells were assessed for 8-oxodG levels	0, 100 mg/kg	+	NA	5-fold increase in 8-OHdG levels in bone marrow DNA.	Deng et al. (1997)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Oxidative DNA damage	Male S-D rats were exposed once to 2-nitropropane via i.p. injection in Emulphor-620:H_2O (1:4 v/v); rats were sacrificed 6 hr later; liver DNA and RNA were evaluated for 8-OHdG levels	0, 100 mg/kg	+	NA	Significant 3.6- and 11-fold increases in 8-OHdG in hepatic DNA and RNA, respectively, in treated rats. There was also formation of unknown moieties of DX1 (DNA), and RX1 and RX2 (RNA).	Fiala et al. (1989)
Oxidative DNA damage	Male S-D rats were exposed once to 2-nitropropane via i.p. injection in Emulphor-620:H_2O (1:4 v/v); rats were sacrificed 6, 18, or 42 hr later; liver DNA was evaluated for 8-O-dG and 8-A-dG and RNA was evaluated for 8-O-GR and 8-A-GR	0, 1.12 mmol/kg (0, 100 mg/kg)	+	NA	Significant increases in 8-O-dG in liver DNA and 8-O-GR in liver RNA. There were no significant increases in 8-A-GR in RNA or 8-A-dG in DNA. There were small increases in unknown moieties of DX1 (DNA) and (RNA).	Fiala et al. (1993)
Oxidative DNA damage	Male and female S-D rats were exposed once to 2-nitropropane via i.p. injection in Emulphor-620:H_2O (1:4 v/v); rats were sacrificed 6 or 18 hr later; liver and kidney DNA and RNA were evaluated for 8-OHdG and 8-OH-GR levels, respectively	0, 1.12 mmol/kg (0, 100 mg/kg)	+ (liver) – (kidney)	NA	Increased 8-OHdG in liver DNA and 8-OH-GR in liver RNA in males 6 and 18 hr after treatment, and in females 6 hr after treatment. Induced unknown moieties in liver DNA (DX1) and RNA (RX1, RX2); the increases was higher in males than females. No evidence of oxidative DNA or RNA damage in kidneys.	Guo et al. (1990)
Oxidative DNA damage	Male F344 rats were exposed once to 2-nitropropane via i.p. injection in a 0.9% NaCl solution; animals were sacrificed 6 or 15 hr after exposure; liver DNA was evaluated for 8-OHdG levels	0, 100 mg/kg	+	NA	Significant increase in 8-OHdG in liver DNA at both time points.	Hasegawa et al. (1995)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Oxidative DNA damage	Male S-D and F344 rats were exposed once to 2-nitropropane via i.p. injection in Emulphor-620:H_2O (1:4 v/v); rats were sacrificed 6 hr later; liver DNA and RNA were evaluated for 8-OHdG and 8-OH-GR levels, respectively	0, 1.12 mmol/kg (0, 100 mg/kg)	+	NA	Increased 8-OHdG in liver DNA and 8-OH-GR in liver RNA in both rat strains. Induced unknown moieties in liver DNA (DX1) and RNA (RX1, RX2) in both strains.	Hussain et al. (1990)
Oxidative DNA damage	Male F344 rats were exposed to 2-nitropropane via gavage in water for 2 wk (3 d/wk); rats were sacrificed 4 hr after final dose; liver DNA was evaluated for 8-OHdG levels	0, 60, 90/120 mg/kg-d (high-dose was a total of 2 doses of 90 mg/kg-d and 4 doses of 120 mg/kg-d; TWA of 110 mg/kg-d)	+	NA	1.8- to 2.9-fold increase in 8-OHdG levels in treated rats. Pretreatment with antioxidants partially protected DNA from oxidative damage.	Sai et al. (1998)
Oxidative DNA damage	Male F344 rats were exposed once to 2-nitropropane via i.p. injection in Emulphor-620:H_2O (1:4 v/v); rats were sacrificed 18 hr later; liver DNA and RNA were evaluated for 8-A-dG and 8-A-GR levels, respectively	0, 100 mg/kg	+	NA	Increased levels of 8-A-dG in liver DNA and 8-A-GR in liver RNA.	Sodum et al. (1993)
Oxidative DNA damage	Male F344 rats were exposed once to 2-nitropropane via i.p. injection in a 0.9% NaCl solution containing 0.1% Tween 20; animals were sacrificed 6 hr after exposure; liver DNA was evaluated for 8-OHdG levels	0, 100 mg/kg	+	NA	1.7-fold increase in liver DNA 8-OHdG levels. Induced unknown moieties in liver DNA (DX1). Pretreatment with antioxidants partially protected DNA from oxidative damage.	Takagi et al. (1995)

Table 4A. Summary of 2-Nitropropane Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Oxidative DNA damage	Male wild-type C57BL/6 and β-pol$^{\pm}$ C57BL/6 mice were exposed once to 2-nitropropane via i.p. injection in olive oil and sacrificed 24 hr later; liver tissue was examined for 8-OHdG levels; DNA polymerase β is associated with repair synthesis in short-patch BER	0, 100 mg/kg (i.p.)	+	NA	4- to 5-fold increase in 8-OHdG levels in both wild-type and β-pol$^{\pm}$ mice.	Cabelof et al. (2002)
Oxidative DNA damage	Male New Zealand White rabbits were exposed once to 2-nitropropane via i.p. injection in Emulphor-620:H_2O (1:4 v/v); rabbits were sacrificed 6, 18, or 42 hr later; liver DNA was evaluated for 8-O-dG and 8-A-dG and RNA was evaluated for 8-O-GR and 8-A-GR	0, 1.12 mmol/kg (0, 100 mg/kg)	−	NA	No evidence of oxidative DNA or RNA damage.	Fiala et al. (1993)

Table 4A. Summary of 2-Nitropropane Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
Genotoxicity studies—invertebrates-in vivo						
Sex-linked recessive lethal	*Drosophila melanogaster* males were exposed to 2-nitropropane via inhalation for 4.5 hr prior to mating with unexposed females	700 ppm	−	NA	No increase in frequencies of sex-linked recessive lethal mutations.	McGregor (1981)
Sex-linked recessive lethal	*Drosophila* sp. males were exposed to 2-nitropropane via feeding (72 hr) or single injection prior to mating with unexposed females	Feeding: 0, 1,000 ppm; Injection: 0, 5,000 ppm	−	NA	No increase in frequencies of sex-linked recessive lethal mutations.	Zimmering et al. (1985)
Mitotic recombination (white/white$^+$ eye mosaic bioassay)	*Drosophila* sp. larvae were exposed to 2-nitropropane via feeding for 15 min	0, 5 mM	−	NA	No evidence of increased mitotic recombination.	Vogel and Nivard (1993)

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

8-OHdG = 8-hydroxydeoxyguanosine; 8-A-dG = 8-aminodeoxyguanosine; 8-A-GR = 8-aminoguanosine; 8-O-dG = 8-oxydeoxyguanosine; 8-O-GR = 8-oxyguanosine; 8-OH-GR = 8-hydroxyguanosine; 8-oxodG = 8-oxo-7,8-dihydro-2′-deoxyguanosine; BER = base excision repair; BrdU = bromodeoxyuridine; CA = chromosomal aberration; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; F = female(s); i.p. = intraperitoneal; M = male(s); MN = micronuclei; NA = not applicable; NaCl = sodium chloride; NDr = not determined; NR = nitroreductase; RNA = ribonucleic acid; SCE = sister chromatid exchange; S-D = Sprague-Dawley; SSB = single stranded break; TG = 6-thioguanine; TWA = time-weighted average; UDS = unscheduled DNA synthesis.

Mutagenicity

2-Nitropropane is mutagenic in bacterial and mammalian cells in vitro. It is a well-established mutagen in various *Salmonella typhimurium* strains both with and without metabolic activation (Kohl et al., 1994; Conaway et al., 1991a; Göggelmann et al., 1988; Fiala et al., 1987a; Löfroth et al., 1986; Haworth et al., 1983; Speck et al., 1982; Hite and Skeggs, 1979; Litton Bionetics, 1977a, b; Russell and Krahn, 1977). 2-Nitropropane is also mutagenic in Chinese hamster lung V79 cells and rat hepatoma H4IIEC3/G-cells (Haas-Jobelius et al., 1991; Roscher et al., 1990). It is often used as a positive control in mutagenicity assays or to test efficacy of potential antimutagens (Nikolic et al., 2012; Stajkovic et al., 2007; Deng et al., 1998; Weisburger et al., 1996; Adachi et al., 1993; Sakai and Uchida, 1992); these positive control studies were not included in Table 4A. However, 2-nitropropane was not mutagenic to *Saccharomyces cerevisiae* D4 strain with or without metabolic activation (Litton Bionetics, 1977b).

In vivo, 2-nitropropane has been associated with dominant lethal mutation in rats following inhalation exposure to 200 ppm for 5 days (7 hours/day) (McGregor, 1981) and *lacI* mutations in mouse liver tissue following a single i.p. injection exposure (Cabelof et al., 2002). 2-Nitropropane was not associated with sex-linked recessive lethal mutations or mitotic recombination in *Drosophila* species (Vogel and Nivard, 1993; Zimmering et al., 1985; McGregor, 1981).

Clastogenicity

2-Nitropropane is capable of inducing clastogenic effects in vitro in human and rat cells, and data suggest that reactive metabolite(s) may contribute to these findings. Increased frequency of chromosomal aberrations (CAs) and sister chromatid exchanges (SCEs) have been reported with and without metabolic activation in primary human lymphocytes in one study (Bauchinger et al., 1987), but only with external activation in another (Göggelmann et al., 1988). Micronuclei (MN) were induced in rat hepatocytes without external metabolic activation and in rat hepatoma cells pretreated with the cytochrome P450 (CYP450) inducer, dexamethasone (Muller-Tegethoff et al., 1995; Roscher et al., 1990). 2-Nitropropane did not cause CAs or SCEs in Chinese hamster ovary (CHO) cells with or without metabolic activation (Galloway et al., 1987). Similarly, 2-nitropropane did not cause MN in Chinese hamster V79 cells without external metabolic activation; these cells were not tested with metabolic activation because they have the intrinsic capability of reducing and oxidizing 2-nitropropane (Haas-Jobelius et al., 1991; Roscher et al., 1990). However, MN were observed in Chinese hamster V79 cells transfected to express human CYP2E1 and SULT1A1 (Deng et al., 2011).

In vivo, 2-nitropropane is clastogenic to liver tissue, inducing hepatic MN in rats following single oral exposure to doses ≥25 mg/kg (George et al., 1989) or repeated oral exposure to doses ≥5 mg/kg-day (Kawakami et al., 2015). However, MN were not induced in bone marrow under the same conditions in rats (Kawakami et al., 2015; George et al., 1989) or in mice at oral or i.p. doses up to 300 mg/kg-day (Kliesch and Adler, 1987; Hite and Skeggs, 1979). Additionally, CAs were not induced in rat bone marrow following inhalation exposure for 1 or 5 days to concentrations up to 200 ppm (7 hours/day) (McGregor, 1981).

DNA Damage and Repair

DNA damage was observed following in vitro exposure to 2-nitropropane in a *S. typhimurium* strain transfected with the human sulfotransferase SULT1A2; DNA damage was not observed in the parent strain (no human SULT) or strains expressing SULT1A1 or 1A3 (Oda et al., 2012). Unscheduled DNA synthesis (UDS) was weakly induced in human primary hepatocytes

exposed to 2-nitropropane in vitro without external metabolic activation (Davies et al., 1993). However, UDS was not induced in human diploid fibroblasts exposed to 2-nitropropane without metabolic activation (McGregor, 1981), and DNA repair synthesis was not induced in several human cell lines (W138, NCI-H322, A549, Hep2) in the absence of metabolic activation (Andrae et al., 1988). In rat hepatocytes, UDS and DNA repair synthesis were consistently observed in rat hepatocytes exposed to 2-nitropropane in vitro without external metabolic activation (Fiala et al., 1995; Kohl et al., 1994; Davies et al., 1993; Haas-Jobelius et al., 1991; Andrae et al., 1988; Williams et al., 1982); weak induction of DNA repair synthesis was also observed in rat hepatoma cell lines without metabolic activation (Dalke and Andrae, 1992; Roscher et al., 1990). In other species, in vitro studies of 2-nitropropane without metabolic activation induced a weak induction of UDS in mouse primary hepatocytes (Davies et al., 1993) but no evidence of increased DNA repair synthesis in mouse 3T3-NIH cells, CHO cells, or Chinese hamster V79 cells (Roscher et al., 1990; Andrae et al., 1988). However, 2-nitropropane induced DNA repair synthesis in V79 cells that were transfected to express rat hepatic SULT1A1 or 1C1 (Andrae et al., 1999).

In vivo studies consistently report evidence of DNA damage and/or repair in hepatic tissue of rats and mice following single oral doses or i.p. injections of 2-nitropropane, including DNA fragmentation (Robbiano et al., 1991), single strand breaks (Cabelof et al., 2006; Cabelof et al., 2002), DNA repair (Cabelof et al., 2002; Andrae et al., 1988), UDS (George et al., 1989), and evidence of oxidative DNA damage (Cabelof et al., 2002; Sai et al., 1998; Hasegawa et al., 1995; Takagi et al., 1995; Dahlhaus and Appel, 1993; Fiala et al., 1993; Sodum et al., 1993; Conaway et al., 1991b; Guo et al., 1990; Hussain et al., 1990; Fiala et al., 1989). DNA damage has also been reported in rat bone marrow (Deng et al., 1997; Robbiano et al., 1991), but not kidney, lung, or brain tissue (Robbiano et al., 1991; Guo et al., 1990). However, there was no evidence of oxidative DNA damage in rabbits exposed once to 2-nitropropane via i.p. injection (Fiala et al., 1993).

Supporting Human Toxicity Studies

Several cases of acute hepatic failure have been reported in workers exposed to high concentrations of 2-nitropropane (and other chemicals) over 1−3 work days without proper personal protective equipment (e.g., respirators, gloves) and/or ventilation; most reported cases were lethal (Harrison et al., 1987; Harrison et al., 1985; NIOSH, 1985; Rondia, 1979; Hine et al., 1978). Signs and symptoms associated with exposure included nausea, vomiting, diarrhea, anorexia, weakness, dizziness, dyspnea, ataxia, chest pain, abdominal pain, jaundice, and scleral icterus. Common laboratory findings included elevated serum enzymes (ALP, ALT, AST, lactate dehydrogenase [LDH]) and hyperbilirubinemia. Additional findings in one or more lethal cases included gastrointestinal bleeding, arrhythmia, cardiac arrest, pulmonary edema, renal failure, lesions in the liver and kidney, and metabolic acidosis (Harrison et al., 1987; Harrison et al., 1985; Hine et al., 1978). Actual exposure levels were not available in these cases; however, serum concentrations of 8.5−13 µg/mL were reported in two workers after exposure to an epoxy resin coating containing 2-nitropropane in an unventilated room over 3 work days (Harrison et al., 1987; Harrison et al., 1985). The worker with the higher serum level died; the second worker survived. Based on reported serum concentrations and pharmacokinetic studies in rats, Harrison et al. (1987) estimated that the workers had exposure levels of ≥600 ppm.

Supporting Animal Toxicity Studies

A number of acute and short-term-duration studies, inadequately reported subchronic-duration animal toxicity studies, and studies via other routes (e.g., injection) were identified. Together, these studies support that the liver is the main target of 2-nitropropane toxicity (see Table 4B for additional details).

Table 4B. Other Studies				
Test[a]	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting evidence—noncancer effects in animals following oral exposure				
Acute (oral)	The LD_{50} was determined in groups of rats. No further details were provided.	2-Nitropropane classified as slightly toxic (LD_{50} value of 500−5,000 mg/kg).	Rat LD_{50} = 500 mg/kg	Kennedy and Graepel (1991)
Acute (oral)	Groups of male Wistar rats (5/group) were given oral doses of 0 or 120 mg/kg of 2-nitropropane in canola oil once, with or without pretreatment with the antioxidant $(NapSe)_2$ (50 mg/kg). Endpoints evaluated included serum chemistry (AST, ALT, creatinine, plasma urea), liver histology, and markers of oxidative stress in the liver (TBARS, NPSH, ascorbic acid, catalase, δ-ALA-D activity).	Significant findings in animals exposed to 2-nitropropane alone included a 2-fold increase in serum AST and ALT, altered markers of oxidative stress (increased TBARS and NPSH, decreased δ-ALA-D activity), and inflammatory cell infiltration in the liver. Pretreatment with $(NapSe)_2$ prevented changes in serum AST and ALT, hepatic TBARS and δ-ALA-D, and liver histology.	The only administered dose of 120 mg/kg is a LOAEL (liver effects) Hepatic alterations appear to be mediated, at least in part, via oxidative stress	Ibrahim et al. (2010)
Acute (oral)	Groups of male Wistar rats (number per group is not specified) were given oral doses of 0 or 120 mg/kg 2-nitropropane in canola oil, with or without pretreatment with the antioxidant, BPD (50 mg/kg). Endpoints evaluated included serum chemistry (AST, ALT, ALP, LDH), liver histology, and markers of lipid peroxidation and oxidative stress in the liver (TBARS, MDA, ascorbic acid, catalase, δ-ALA-D activity, GST, GPx, and GSH reductase).	Significant findings in animals exposed to 2-nitropropane alone included a 1.5- to 2-fold increase in serum ALT, AST, ALP, and LDH; altered markers of lipid peroxidation and oxidative stress (increased TBARS and MDA, decreased δ-ALA-D, GSH, GPx, GR, and GST); and inflammatory cell infiltration in the liver. Pretreatment with BPD offered partial protection against all the liver endpoints tested.	The only administered dose of 120 mg/kg is a LOAEL (liver effects) Hepatic alterations appear to be mediated, at least in part, via oxidative stress	Wilhelm et al. (2011)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Conclusions	References
Acute (oral)	Groups of male Wistar rats (6−8/group) were given oral doses of 0 or 100 mg/kg 2-nitropropane in canola oil, with or without pretreatment with the antioxidant 3-ASP (25 mg/kg). Endpoints evaluated included serum chemistry (AST, ALT), liver histology, and markers of lipid peroxidation and oxidative stress in the liver (TBARS, MDA, ascorbic acid, catalase, δ-ALA-D activity).	Significant findings in animals exposed to 2-nitropropane alone included a 2−3-fold increase in serum AST and ALT, altered markers of lipid peroxidation and oxidative stress (increased TBARS and MDA, decreased δ-ALA-D activity), and histopathological lesions in the liver (inflammatory cells infiltration in the liver and loss of cellular architecture). There was no indication of 2-nitropropane induced liver damage when animals were pretreated with 3-ASP.	The only administered dose of 100 mg/kg is a LOAEL (liver effects) Hepatic alterations appear to be mediated, at least in part, via oxidative stress	Wilhelm et al. (2010)
Acute (oral)	The LD_{50} was determined in groups of mice. No further details were provided.	ND	Mouse LD_{50} (95% CI) = 0.400 (0.352−0.424) mL/kg = 392 (346−416) mg/kg	Hite and Skeggs (1979)
Acute (oral)	The LD_{50} was determined in groups of rabbits exposed via gavage. Animals were observed for 2−3 hr following administration.	ND	Rabbit LD_{50} = 500−750 mg/kg	Machle et al. (1940)
Supporting evidence—noncancer effects in animals following inhalation exposure				
Acute (inhalation)	The ALC, or the concentration at which mortality was first observed following a 5-hr exposure, was determined in rats. No further details were provided.	2-Nitropropane was classified as slightly toxic (ALC value of 500−5,000 ppm).	Rat ALC (5-hr) = 1,513 ppm	Kennedy and Graepel (1991)
Acute (inhalation)	The 6-hr LC_{50} was determined in groups of rats. The highest concentration used was 580 ppm. No further details were provided.	ND	Rat LC_{50} (6-hr): Male: 400 ppm Female: >580 ppm	Lewis et al. (1979)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Conclusions	References
Acute (inhalation)	The 1-, 2.25-, and 4.5-hr ALCs were determined for cat, rat, rabbit, and guinea pig. Endpoints included mortality, clinical signs, body weight, hematology, and gross necropsy.	Clinical signs associated with "high" exposure concentrations in all species included dyspnea, cyanosis, prostration, convulsions, and coma. Cats also showed lacrimation, salivation, and gastric regurgitation prior to death. Slight decreases in weight were observed, with transitory observations in animals that survived. Exposure to ≥2,353 ppm was associated with widespread organ damage. Methemoglobinemia and Heinz bodies were observed in rabbits and cats.	Cat ALC: 1-hr: 2,353 ppm 2.25-hr: 1,148 ppm 4.5-hr: 714 ppm Rat ALC: 1-hr: 3,865 ppm 2.25-hr: 2,633 ppm 4.5-hr: 1,513 ppm Rabbit ALC: 1-hr: 9,523 ppm 2.25-hr: 4,313 ppm 4.5-hr: 2,381 ppm Guinea pig ALC: 1-hr: NDr 2.25-hr: 9,607 ppm 4.5-hr: 4,622 ppm	Treon and Dutra (1952)
Short-term (inhalation)	Lethality was reported in rats exposed to 328 ppm for a total of up to 17 exposures (7 hr/d, 5 d/wk). The number of cats was not reported; no controls were reported. Endpoints included mortality, clinical signs, body weight, hematology, and gross and microscopic necropsy.	All cats died after 3−17 exposures. Dyspnea was observed, and cats did not gain weight. Heinz bodies and impaired blood clotting were observed. Histopathological changes included parenchymal degeneration and focal necrosis of the liver, slight to moderate toxic degeneration of the heart and kidney, pulmonary edema, intra-alveolar hemorrhage, and interstitial pneumonitis.	The only exposure level (328 ppm) is an apparent FEL; however, the study has numerous limitations, including lack of control group and inadequate study design and data reporting	Treon and Dutra (1952)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Conclusions	References
Short-term (inhalation)	Male S-D rats were exposed to 2-nitropropane vapor concentrations of 0 or 100 ppm (364 mg/m^3), 7 hr/d for up to 4 d. Three animals/group were sacrificed on D 1, 2, and 4. Endpoints evaluated included serum chemistry (ALP, AST), hepatic enzyme activities (GST, GPx, GSH reductase), and hepatic microsomal protein levels (CYP450, cytochrome b_5, UDP-glucuronosyltransferase, MDA).	Significant findings in exposed animals included decreased CYP450 (all collection days), increased UDP-glucuronosyltransferase and total GSH (collection Day 4), and increased GST (all collection days).	Endpoints evaluated were inadequate to identify a NOAEL or LOAEL. The study authors indicated that the effects of 2-nitropropane exposure on microsomal CYP450 indicate that reactive intermediates may be formed	Haas-Jobelius et al. (1992)
Subchronic (inhalation)	In a lethality study, 2 rats, 2 guinea pigs, 3 rabbits, and 1 monkey were exposed to 328 ppm for a total of up to 130 exposures (7 hr/exposure) over the course of 199 d and 2 cats, 1 rat, 4 rabbits, 2 guinea pigs, and 1 monkey were exposed to 83 ppm for a total of 130 exposures (7 hr/exposure) over the course of 191 d. Endpoints included mortality, clinical signs, body weight, and gross and microscopic necropsy. No control animals were reported.	The only reported deaths were 2 rabbits that died on D 95 and 97 of infection unrelated to treatment. The monkey was only exposed for 100 d (no reason given). No signs of intoxication or body weight effects were observed. All tissues were normal.	The exposure level of 328 ppm is an apparent NOAEL for all species; however, the study has numerous limitations, including small animal numbers, lack of control group, and inadequate study design and data reporting	Treon and Dutra (1952)

Table 4B. Other Studies				
Test[a]	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting evidence—noncancer effects in animals following intraperitoneal exposure				
Acute (i.p.)	Groups of male albino Wistar rats (*n* = 6/group) were exposed to 0 or 100 mg/kg of 2-nitropropane via i.p injection in corn oil, with or without administration of the antioxidant $(PhSe)_2$ (10 µmol/kg) 24 hr later. Endpoints evaluated included serum chemistry (plasma urea, creatinine, GGT, AST, ALT), liver weight and histology, and markers of lipid peroxidation and oxidative stress in the liver (superoxide dismutase and catalase activities, ascorbic acid, and TBARS levels) and kidney (MDA).	Significant findings in animals exposed to 2-nitropropane alone included increased serum urea, ALT, AST, and GGT; altered markers of lipid peroxidation and oxidative stress (increased TBARS in both kidney and liver and decreased in catalase activity); and histopathological lesions in the liver (severe swelling, lymphocytic infiltration, and confluent necrosis in the centrilobular zone). Liver weight was not reported. Postexposure treatment with $(PhSe)_2$ led to a decrease in hepatic effects associated with 2-nitropropane exposure.	The only administered dose of 100 mg/kg is a LOAEL (liver effects) Hepatic alterations appear to be mediated, at least in part, via oxidative stress	Borges et al. (2006)
Acute (i.p.)	Groups of male albino Wistar rats (*n* = 6/group) were exposed to 0 or 100 mg/kg of 2-nitropropane via i.p injection in olive oil, with or without administration of the antioxidant $(PhSe)_2$ (10 µmol/kg) 24 hr before 2-nitropropane exposure. Endpoints evaluated included serum chemistry (plasma urea, creatinine, GGT, AST, ALT), plasma AFP (hepatic tumor marker), markers of lipid peroxidation in the liver (TBARS), and gross and microscopic liver histology.	Significant findings in animals exposed to 2-nitropropane alone included increased serum urea, ALT, GGT, and AFP, increased TBARS, and hepatic damage (moderate swelling and degenerative alterations). Pre-exposure treatment with $(PhSe)_2$ resulted in a protective effect against 2-nitropropane induced liver toxicity.	The only administered dose of 100 mg/kg is a LOAEL (liver effects) Hepatic alterations appear to be mediated, at least in part, via oxidative stress	Borges et al. (2005)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Conclusions	References
Acute (i.p.)	Groups of male S-D rats (10/group) were administered 2-nitropropane at doses of 0 or 4 mmol/kg via i.p. injection in olive oil, with or without administration of the antioxidant melatonin (10 mg/kg) 30 min later. All rats were sacrificed at 24 hr; 6/group were used to evaluate hepatic cell proliferation (received injection of thymidine ^{3}H at 22 hr) and 4/group were used for examination of liver and lung histology.	Histopathological changes in treated rats included hepatic lesions (focal necrosis, with diffuse vacuolar degeneration, lymphocytic infiltration, degenerated hepatic cells [apoptosis], congestion of blood vessels) and lung lesions (mucinous degeneration and proliferation of the bronchial epithelium, congestion of vessels and interalveolar capillaries, hemorrhage and edema of the bronchi). Increased cell proliferation was observed in treated rats. Melatonin treatment reduced cell proliferative effects of 2-nitropropane and reversed histopathological changes in liver and lung.	The only administered dose of 4 mmol/kg (356 mg/kg) is a LOAEL (liver and lung effects) Hepatic and pulmonary alterations appear to be mediated, at least in part, via oxidative stress	El-Sokkary (2002)
Acute (i.p.)	Groups of male F344 rats were exposed once to 2-nitropropane at doses of 0 or 100 mg/kg via i.p. injection in a 0.9% NaCl solution containing 0.1% Tween 20, with or without pretreatment with 2% green tea or with concentrated tea extract in their drinking water. Animals were sacrificed 6 or 15 hr following the 2-nitropropane injection. Endpoints evaluated included serum biochemistry (AST, ALT, triglycerides, LDH), hepatic biochemistry (TBARS, glycogen content), and liver histology (15 hr only).	Significant findings in rats exposed to 2-nitropropane alone included increased serum ALT and LDH and decreased triglycerides at 6 hr after dosing. At 15 hr, animals treated with 2-nitropropane alone had decreased TBARS and histopathological changes in the liver (swelling and severe degeneration of hepatocytes). Green tea and concentrated tea extracts had minimal impacts on 2-nitropropane-induced changes.	The only administered dose of 100 mg/kg is a LOAEL (liver effects)	Hasegawa et al. (1995)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Conclusions	References
Acute (i.p.)	Groups of male F344 rats (5−7/group) were exposed once to 2-nitropropane at doses of 0 or 100 mg/kg via i.p. injection in 0.9% NaCl solution containing 0.1% Tween 20, with or without pretreatment with an antioxidant (β-carotene, vitamin E, or ellagic acid). Liver serum biochemistry (ALT, AST) was evaluated.	Significant findings in rats exposed to 2-nitropropane alone included increased serum ALT and AST. Pretreatment with antioxidants did not alter serum ALT and AST findings.	The only administered dose of 100 mg/kg is a LOAEL (liver effects)	Takagi et al. (1995)
Acute (i.p.)	Groups of male Wistar rats (n = 4−5/group) were exposed once to 2-nitropropane at doses of 0 or 50 mg/kg via i.p. injection in olive oil. Groups of animals were sacrificed at 1, 4, and 24 hr after exposure. Endpoints evaluated included serum biochemistry (ALT), liver histology via electron microscopy, hepatic biochemistry (GSH, GST, GPx, and xenobiotic metabolic products), and brain biochemistry (acid proteinase activity in the cerebral homogenate, activities of acetylcholine esterase and 2′,3′-cyclic nucleotide 3′-phosphohydrolase, and RNA and protein content).	Significant hepatic findings in exposed rats included increased serum ALT, histopathological changes (lipid accumulation, centrilobular necrosis, degranulation of RER, proliferation of SER), altered hepatic biochemistry (elevated GSH and GPx, decreased GST), and altered xenobiotic enzymes (decreased CYP450, 7-ethoxycoumarin *O*-deethylase, 7-ethoxyresorufin *O*-deethylase; increased NADPH-cytochrome c reductase, UDP-glucuronosyltransferase, epoxide hydratase). Significant brain findings in exposed rats included increased acetylcholine esterase, decreased 2′,3′-cyclic nucleotide 3′-phosphohydrolase, and decreased acid proteinase.	The only administered dose of 50 mg/kg is a LOAEL (liver effects) Observed findings are indicative of lipid peroxidation	Zitting et al. (1981)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Conclusions	References
Acute (i.p.)	Groups of male and female BALB/c mice (n = 5−12/sex/group per time point) were exposed once to 2-nitropropane at doses of 0, 4.5, 6.7, or 9 mmol/kg via i.p. injection in saline. Mice were sacrificed 24, 48, 72, or 96 hr after dosing. Endpoints included serum biochemistry (SDH, ALT, AST) and liver histology.	Significant serum biochemistry findings in exposed animals included a mild increase in SDH in females at ≥4.5 mmol/kg, increased ALT and AST in females at ≥6.7 mmol/kg, and increased SDH, ALT, and AST in males at 9 mmol/kg. Significant histopathological findings in females were observed at 9 mmol/kg (severe periportal degeneration, apoptosis, necrosis, hemorrhage, mild proliferation of ductal type cells in periportal region). Hepatic lesion incidence in males was comparable to controls.	A NOAEL of 4.5 mmol/kg (400 mg/kg) and a LOAEL of 6.7 mmol/kg (600 mg/kg) are identified (liver effects)	Dayal et al. (1989)
Reproductive/ Developmental (i.p.)	Groups of inseminated female S-D rats (10−15/group) were administered 2-nitropropane at 0 or 170 mg/kg-d in corn oil via i.p. injection on GDs 1−15. Dams were sacrificed on GD 21. Endpoints evaluated included maternal body weight, gross examination of uterine contents and organs, maternal organ weight and histology (brain, heart, lungs, liver, spleen, kidneys, adrenals, ovaries), and fetal endpoints (weight, crown-to-rump length, sex, visceral and skeletal examinations).	A significant increase in delayed fetal development was observed (1- to 2-d delay in heart development; no further information provided). No other fetal endpoints were altered with exposure. No maternal toxicity was observed.	The only administered dose of 170 mg/kg-d is a LOAEL (developmental effects)	Hardin et al. (1981)

Table 4B. Other Studies				
Test[a]	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting evidence—cancer effects in animals following exposure via any route				
Subchronic (oral)	In an initiation-promotion study, 60 male F344/DuCrj rats were given a single i.p. injection for the tumor initiator, DEN (200 mg/kg). 2 wk after initiation, groups of rats (15/group) were orally administered 2-nitropropane in corn oil at doses of 0, 0.8, 4, or 20 mg/kg-d for 6 wk (6 d/wk). Uninitiated rats (6/group) were administered 0 or 20 mg/kg-d for 6 wk (6 d/wk). At the end of the 3rd wk of 2-nitropropane exposure, animals were subject to a partial hepatectomy. Endpoints evaluated included clinical signs, body weights, food consumption, liver weights, and GST-P positive preneoplastic foci.	A significant increase in GST-P positive foci >0.2 mm was observed in rats initiated with DEN and then treated with 20 mg/kg-d of 2-nitropropane, compared to rats initiated with DEN only. In rats exposed only to 2-nitropropane, significant findings include a 19% increase in absolute liver weight, a 13% increase in relative liver weight, and increased incidence of GST-P positive foci <0.2 mm (no foci >0.2 mm were observed).	The only administered dose of 20 mg/kg is a LOAEL (liver effects) 2-Nitropropane is a tumor promotor under the conditions of this assay	Doi et al. (2011)
Short-term (inhalation)	In an initiation-promotion study, groups of weanling S-D rats (6−12/sex/group) were exposed to 2-nitropropane (initiation) at doses of 0, 24, 40, 50, 80, 123, or 200 ppm for 3 wk (6 hr/d, 5 d/wk). 1 wk later, all animals were given oral doses of the promoting agent, Clphen A50, at doses of 10 mg/kg-d for 8 wk (2 d/wk). 1 wk after final exposure, the rats were sacrificed, and livers were removed and evaluated for preneoplastic foci.	The 200-ppm exposure group was discontinued due to high mortality within a few days. No mortality or signs of toxicity at lower concentrations. A dose-related increase in the number of hepatic preneoplastic foci was observed in both male and female rats.	The highest concentration tested (200 ppm) is a FEL 2-Nitropropane was a tumor initiator under the conditions of this study	Denk et al. (1990)

Table 4B. Other Studies

Test[a]	Materials and Methods	Results	Conclusions	References
Short-term (i.p.)	In an initiation-promotion study, groups of male weanling Wistar rats (8/group) were given a total of 6 i.p. injections of 2-nitropropane at doses of 0, 25, 50, or 100 mg/kg-d in 2% Tween 20. Injections were on D 14, 16, 18, 21, 23, and 25 of the experiment. From the 42nd−56th d of the experiment, all rats were exposed the promotor 2-AAF at dietary concentrations of 50 ppm. All rats were exposed to phenobarbital (sodium salt) for an additional 2 wk following 2-AAF exposure. On D 49, all rats were anaesthetized for a 2/3 partial hepatectomy. All rats were sacrificed on D 70 of the experiment and liver tissue was evaluated for GGT- and GST-positive preneoplastic foci.	A dose-related increase in the number of hepatic preneoplastic foci was observed in exposed rats.	2-Nitropropane was a tumor initiator under the conditions of this study	Astorg et al. (1994)

[a]Acute = exposure for ≤24 hours (U.S. EPA, 2002b); short term = repeated exposure for >24 hours ≤30 days (U.S. EPA, 2002b); subchronic = repeated exposure for >30 days ≤10% lifespan (>30 days up to approximately 90 days in typically used laboratory animal species) (U.S. EPA, 2002b) 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, 2002b).

2-AAF = 2-acetylaminofluorene; 3-ASP = 3-alkynyl selenophene; δ-ALA-D = delta-aminolevulinic acid dehydratase; ALC = approximate lethal concentration; AFP = alpha-fetoprotein; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPD = (E)-2-benzylidene-4-phenyl-1,3-diselenole; CI = confidence interval; CYP450 = cytochrome P450; DEN = diethylnitrosamine; FEL = frank effect level; GD = gestation day; GGT = γ-glutamyl transferase; GPx = glutathione peroxidase; GR = glutathione reductase; GSH = glutathione; GST = glutathione-S-transferase; i.p. = intraperitoneal; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; MDA = malondialdehyde; NaCl = sodium chloride; NADPH = reduced form of nicotinamide adenine dinucleotide phosphate; $(NapSe)_2$ = binaphthyl diselenide; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; NPSH = nonprotein thiols; $(PhSe)_2$ = diphenyl diselenide; RER = rough endoplasmic reticulum; RNA = ribonucleic acid; S-D = Sprague-Dawley; SDH = sorbitol dehydrogenase; SER = smooth endoplasmic reticulum; TBARS = thiobarbituric acid reactive substances; UDP-glucuronosyltransferase = uridine 5′-diphospho-glucuronosyltransferase.

Supporting Studies for Noncarcinogenic Effects in Animals

Most supporting animal studies have evaluated hepatic effects in rats after oral or i.p. exposure. Collectively, these studies report elevated serum enzymes (e.g., AST, ALT), altered liver biochemistry indicative of lipid peroxidation and oxidative stress, and hepatic lesions in rats at acute oral doses ≥100 mg/kg (Wilhelm et al., 2011; Ibrahim et al., 2010; Wilhelm et al., 2010) and acute i.p. doses ≥50 mg/kg (Borges et al., 2006; Borges et al., 2005; El-Sokkary, 2002; Hasegawa et al., 1995; Zitting et al., 1981). Most of these studies reported partial or complete amelioration of effects with exposure to antioxidants before, during, or shortly after exposure. In mice, hepatic effects (altered serum chemistry, liver lesions) were only observed after single i.p. doses ≥6.7 mmol/kg (600 mg/kg); adverse effects were not observed at 4.5 mmol/kg [400 mg/kg; Dayal et al. (1989)]. Following inhalation exposure to 364 mg/m^3 for 4 days (7 hours/day), no changes in serum AST or ALT were observed in rats, but altered microsomal enzymes and increased hepatic glutathione (GSH) and glutathione-S-transferase (GST) were observed (Haas-Jobelius et al., 1992).

Acute oral lethality studies with 2-nitropropane reported median lethal dose (LD_{50}) values of 500 mg/kg in rats (Kennedy and Graepel, 1991), 392 mg/kg in mice (Hite and Skeggs, 1979), and 500−750 mg/kg in rabbits (Machle et al., 1940). Acute inhalation studies with 2-nitropropane reported median lethal concentration (LC_{50}) values of 400 ppm in male rats and >580 ppm in female rats (Lewis et al., 1979). Additional studies report the lowest concentration at which mortality was first observed (approximate lethal concentration [ALC]) following inhalation exposure to 2-nitropropane for 1−5 hours; values were 714−2,353 ppm for cats, 1,513−3,865 ppm for rats, 2,381−9,523 ppm for rabbits, and 4,622−9,607 ppm for guinea pigs (Kennedy and Graepel, 1991; Treon and Dutra, 1952). Treon and Dutra (1952) also reported mortality in 100% of cats exposed to 328 ppm for 3−17 exposures (7 hours/day, 5 days/week); similarly exposed rats, guinea pigs, rabbits, and monkeys did not die after a total of 130 exposures. All species survived a total of 130 exposures to 83 ppm (Treon and Dutra, 1952).

Supporting Studies for Carcinogenic Effects in Rats

Initiation-promotion studies in the liver of rats indicated that 2-nitropropane can act as a tumor promotor following oral exposure (Doi et al., 2011) and a tumor initiator in the liver following inhalation or i.p. exposure (Astorg et al., 1994; Denk et al., 1990).

Absorption, Distribution, Metabolism, and Elimination Studies

In the study by Nolan et al. (1982), rats were exposed by inhalation for 6 hours to 20−154 ppm of [^{14}C]-2-nitropropane and the disposition of radioactivity in these animals was followed for 48 hours. These data indicate that at least 40% of the inhaled compound was absorbed. Dermal absorption was very low (<1%) in Rhesus monkeys following exposure for 12 hours in occluded conditions (Norman, 1990). Using human cadaver skin samples, the skin permeability coefficient of 2-nitropropane was estimated to be 1.19 × 10^{-4} cm/hour (Tedesco, 2005). The 10- and 60-minute penetration rates were calculated to be 285.9 and 66.8 µg/cm^2-hour, respectively.

Distribution is rapid following inhalation exposure, with a blood distribution half-life of ~1 hour. Forty-eight hours after inhalation exposure to radiolabeled 2-nitropropane, the highest concentrations were in organs involved with metabolism and elimination, including the lungs, liver, and kidneys (Mueller et al., 1983; Nolan et al., 1982). 2-Nitropropane is initially distributed to the fat, but then is rapidly redistributed to other tissues (Mueller et al., 1983).

Elevated levels of radiolabel have also been identified in adrenal gland, bone marrow, and spleen: the study authors attributed this to incorporation of radiolabeled carbon dioxide in heme and steroid biosynthesis due to the expected metabolism of C1 or C2 fragments or by incorporation of radiolabeled carbon dioxide ($^{14}CO_2$) during the production of oxaloacetate, which introduces it into the Krebs cycle and consequently into heme biosynthesis, or during generation of mevalonate, which is utilized in the biosynthesis of steroids (Mueller et al., 1983).

The main metabolites of 2-nitropropane are carbon dioxide, nitrite/nitrate, acetone, and isopropanol (Sohn and Fiala, 2000; Kohl and Gescher, 1997; Mueller et al., 1983; Ulrich et al., 1977). 2-Nitropropane first undergoes denitrification to form nitrite/nitrate plus acetone and isopropanol, which can be oxidized into CO_2. Nitrogen dioxide and potentially NO-species are released in this process (Smith and Anderson, 2013; Kohl et al., 1995; Bors et al., 1993). Studies have shown that oxidative denitrification of 2-nitropropane into acetone is mediated via CYP450 enzymes, a process that can form reactive intermediates, including 2-hydroxy-2-nitropropane (Smith and Anderson, 2013; Sohn and Fiala, 2000; Ulrich et al., 1977). Isomeric conversion of 2-nitropropane to its aci-tautomer, propane 2-nitronate, increases the rate of denitrification (Kohl and Gescher, 1997). It has also been proposed that 2-nitropropane could undergo reductive metabolism to reactive intermediates, such as 2-nitrosopropane, acetone oxime, isopropyl hydroxylamine, or 2-aminopropane; however, these have only been identified in vitro (Smith and Anderson, 2013; Andrae et al., 1999; Haas-Jobelius et al., 1991; Marker and Kulkarni, 1986). In vitro studies have also shown that sulfotransferases can activate acetone oxime and propane 2-nitronate, leading to generation of NH_2^+ (Kreis et al., 2000; Andrae et al., 1999; Sodum et al., 1994). Following inhalation exposure, the metabolic rate was significantly higher in female rats compared with male rats; metabolic rates in male and female rabbits were similar to those of female rats (AFOSR, 1992).

Elimination in rats following inhalation or i.p. exposure to radiolabeled 2-nitropropane is primarily via exhaled breath as parent compound (4.5%), acetone (10.4%), and CO_2 (38.1%), with the majority being exhaled within the initial 12 hours; minor amounts of radioactivity are eliminated via urine (~6%) and feces (<1%) (Mueller et al., 1983; Nolan et al., 1982). Mueller et al. (1983) identified the following urinary metabolites 6 hours after inhalation exposure: unidentified polar metabolite (60%), isopropanol (18%), and acetone (10%). Twelve percent remained in the urine as unmetabolized 2-nitropropane. At 24 hours, urinary metabolite distribution is 80% unidentified polar metabolite, 8% isopropanol, and 12% acetone (Mueller et al., 1983). Nitrate and nitrite have also been identified in rat urine following i.p. injection (Sohn and Fiala, 2000). Elimination kinetics in rats are dose-dependent, with elimination half-lives of 16 hours at low concentrations and 13.2 hours at high concentrations (Nolan et al., 1982). Similar elimination patterns were observed in chimpanzees following intravenous exposure (Mueller et al., 1983). Following dermal exposure in Rhesus monkeys, 93.4% of the (minimally) absorbed dose was excreted in the urine (Norman, 1990).

Mode-of-Action/Mechanistic Studies

The mechanisms underlying 2-nitropropane liver toxicity and carcinogenicity are unclear; however, researchers have proposed that these effects are secondary to oxidative stress attributed to the generation of reactive intermediates like *N*-nitro compounds and oxygen radicals during the denitrification of 2-nitropropane (Smith and Anderson, 2013; ACGIH, 2001). As discussed in acute and short-term-duration oral studies in Tables 3A and 4B, pre- or cotreatment of rats with antioxidant compounds decreases or prevents hepatic toxicity associated with

2-nitropropane exposure (Wilhelm et al., 2011; Ibrahim et al., 2010; Wilhelm et al., 2010; Wilhelm et al., 2009; Sai et al., 1998). Similar findings have been reported in acute i.p. studies in Table 4B (Borges et al., 2006; Borges et al., 2005; El-Sokkary, 2002; Takagi et al., 1995). Consistent with the proposed mechanism for non-neoplastic effects, there is strong evidence for oxidative DNA damage in the liver (see Table 4A), which has also been shown to be mitigated with pretreatment with antioxidant compounds (Sai et al., 1998; Takagi et al., 1995). These findings support the hypothesis that hepatic toxicity and carcinogenicity is mediated, at least in part, by oxidative stress. However, most of the proposed reactive metabolites are hypothetical and have not been observed in vivo (see "Absorption, Distribution, Metabolism, and Elimination Studies" section above).

Proposed carcinogenic progression following inhalation exposure to 2-nitropropane includes severe cellular damage followed by regenerative hyper-proliferation, which can become autonomous and malignant (Griffin et al., 1980; Griffin et al., 1979; Coulston et al., 1978). Strong evidence for mutagenicity and DNA damage (see Table 4A) could contribute to neoplastic transformation during this regenerative response. The apparent sensitivity of male rats to this process may be due to observed sex and species differences in metabolic rates, namely the fact that female rats and male and female rabbits show more rapid kinetics than male rats (AFOSR, 1992) (see "Absorption, Distribution, Metabolism, and Elimination Studies" section above).

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer references values, respectively, for 2-nitropropane.

Table 5. Summary of Noncancer Reference Values for 2-Nitropropane (CASRN 79-46-9)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Rat/M	Hepatocyte hypertrophy	1×10^{-3}	$BMDL_{10}$	0.34	300	Kawakami et al. (2015)
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	Rat/M	Liver effects (focal hepatocyte hypertrophy, hepatocyte hyperplasia, and hepatocyte basophilic foci)	7×10^{-2}	NOAEL	20	300	Lewis et al. (1979); Ulrich et al. (1977)
Chronic p-RfC (mg/m^3)	Inhalation RfC value of 0.02 mg/m^3 is available on IRIS (U.S. EPA, 2002a).						

BMDL = benchmark dose lower confidence; HEC = human equivalent concentration; HED = human equivalent dose; IRIS = Integrated Risk Information System; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RfC = reference concentration; UF_C = composite uncertainty factor.

Table 6. Summary of Cancer Reference Values for 2-Nitropropane (CASRN 79-46-9)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
Screening p-IUR $(mg/m^3)^{-1}$ (adjusted)	Rat/M	Hepatocellular carcinoma	5.8×10^{-1}	Lewis et al. (1979); Ulrich et al. (1977)

M = male(s); NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

Animal data for 2-nitropropane relevant to provisional reference dose (p-RfD) derivation include a 16-week cancer study in rats with limited reporting on non-neoplastic endpoints (Fiala et al., 1987b), two 14- to 28-day studies in rats that only evaluated clinical signs, body weight, and liver endpoints (Kawakami et al., 2015; Nakayama et al., 2006), two 2-week studies in rats that only evaluated renal and/or liver endpoints (Wilhelm et al., 2009; Sai et al., 1998), three single-exposure-level studies that only evaluated renal and/or liver endpoints (Wilhelm et al.,

2011; Ibrahim et al., 2010; Wilhelm et al., 2010), and acute lethality studies in rats, mice, and rabbits (Kennedy and Graepel, 1991; Hite and Skeggs, 1979; Machle et al., 1940). Although these studies are deemed too limited in scope and/or duration to support derivation of p-RfDs, the 28-day study by Kawakami et al. (2015) provided sufficient data to develop a screening subchronic p-RfD value (see Appendix A).

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional Reference Concentration

The database of potentially relevant studies for deriving a subchronic provisional reference concentration (p-RfC) for 2-nitropropane includes a brief report of a 2-month study in rats (Coulston et al., 1978) and interim sacrifice data from several chronic-duration inhalation studies in rats (Griffin et al., 1979; Lewis et al., 1979; Coulston et al., 1978; Ulrich et al., 1977) and one study in rabbits (Lewis et al., 1979; Ulrich et al., 1977). Collectively, these studies indicate that the liver in the male rat is the most sensitive target of toxicity following subchronic inhalation exposure (7 hours/day, 5 days/week for 1−3 months). Hepatic findings include elevated liver weight in male rats at ≥312 mg/m^3 (HEC = 65.0 mg/m^3) and female rats at ≥608 mg/m^3 (HEC = 127 mg/m^3), and elevated serum enzyme levels and non-neoplastic lesions in male rats at ≥608 mg/m^3 (HEC = 127 mg/m^3). No adverse effects were observed in rabbits following exposure for up to 6 months to concentrations up to 754 mg/m^3 (HEC = 157 mg/m^3).

The liver is also the primary toxicity target following acute, short-term, and chronic inhalation exposure in rats (Griffin et al., 1981; Griffin et al., 1980; Lewis et al., 1979; Coulston et al., 1978; Ulrich et al., 1977) and cats (Treon and Dutra, 1952), and hepatic effects are the basis of the chronic inhalation reference concentration (RfC) in U.S. EPA's IRIS database (U.S. EPA, 2002a). Acute and short-term-duration oral and i.p. injection studies also report hepatic effects in rats (Wilhelm et al., 2011; Ibrahim et al., 2010; Wilhelm et al., 2010; Wilhelm et al., 2009; Borges et al., 2006; Nakayama et al., 2006; Borges et al., 2005; El-Sokkary, 2002; Sai et al., 1998; Hasegawa et al., 1995; Takagi et al., 1995; Zitting et al., 1981) and (at higher doses) mice (Dayal et al., 1989). Case reports of acute hepatic failure in workers exposed to high concentrations of 2-nitropropane support the liver as the primary target of 2-nitropropane toxicity in humans (Harrison et al., 1987; Harrison et al., 1985; NIOSH, 1985; Rondia, 1979; Hine et al., 1978). Altogether, these data indicate that the liver is a primary target organ of toxicity following exposure to 2-nitropropane.

Most of the studies with subchronic data provided no dose-response information because they included only one exposed group plus a control group. These studies identified only LOAELs (HECs) of 65.0 mg/m^3 or more, and no NOAELs were identified. The exception is the published study by Lewis et al. (1979) [and accompanying unpublished report by Ulrich et al. (1977)], which included two dose groups plus a control group. A NOAEL and LOAEL (HEC) of 20 and 157 mg/m^3, respectively, were identified for subchronic effects in this study based on increases in absolute and relative liver weight and increased hepatic lesions (focal hepatocyte hypertrophy, focal hepatocyte hyperplasia, and basophilic foci) in male rats at 3 months. To provide a common basis for comparing potential points of departure (PODs) and critical effects for deriving a subchronic p-RfC for 2-nitropropane, data sets representing the most sensitive liver endpoints from Lewis et al. (1979) and Ulrich et al. (1977) were considered for benchmark dose (BMD) analysis. The data for increased absolute and relative liver weight shown in Table 7 were modeled using all available continuous models in the Benchmark Dose Software (BMDS, Version 2.6), as appropriate. HECs were used as the dose metric, and a benchmark response

(BMR) of 10% relative deviation (RD) from the control mean was run because a 10% change in liver weight is considered biologically significant. On the other hand, the benchmark concentration lower confidence limits (BMCLs) for hepatocyte hypertrophy, hepatocyte hyperplasia, and hepatocyte basophilic foci in male S-D rats exposed to 2-nitropropane for 3 months (Lewis et al., 1979; Ulrich et al., 1977) would be considered unreliable based on the U.S. EPA's *Benchmark Dose Technical Guidance*, which states, "a data set with only the highest dose showing a response would bracket the BMD at the low end but may provide limited information about the shape of the dose-response relationship. In such cases, dose spacing and the proximity of the BMR to the observed response level will influence the uncertainty in the BMD estimate" (U.S. EPA, 2012b). Therefore, the data for hepatic lesions (e.g., hepatocyte hyperplasia) in Table 7 were not BMD modeled.

Table 7. Data for Absolute and Relative Liver Weight and Incidence of Liver Lesions in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 3 Months[a]

Endpoint	Concentration (HEC in mg/m^3)		
	0	20	157
Absolute liver weight (g)[b]	11.8 ± 1.3 (10)	13.0 ± 1.5 (10)	16.7 ± 2.6 (9)
Relative liver weight (% BW)[b]	2.6 ± 0.11 (8)	2.7 ± 0.16 (10)	4.1 ± 0.57 (9)
Focal hepatocyte hypertrophy[c]	0/10	0/10	9/9
Focal hepatocyte hyperplasia[c]	0/10	0/10	4/9
Hepatocyte basophilic foci[c]	0/10	0/10	4/9

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Data reported as mean ± SD (*n*); SD values were calculated from reported SEM values (SD = SEM × √*n*).
[c]Values denote number of animals showing changes/total number of animals examined.

BW = body weight; HEC = human equivalent concentration; S-D = Sprague-Dawley; SD = standard deviation; SEM = standard error of the mean.

Table 8 summarizes the benchmark dose (BMD) modeling results and provides candidate points of departure (PODs) for the modeled endpoints. Details of model fit for each data set are presented in Appendix C.

Table 8. Potential PODs in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 3 Months[a]

Endpoint	NOAEL (HEC) (mg/m^3)	LOAEL (HEC) (mg/m^3)	BMCL (HEC)[b] (mg/m^3)	POD (HEC) (mg/m^3)
Absolute liver weight	NDr	20	29	29 ($BMCL_{10}$)
Relative liver weight	20	157	28	28 ($BMCL_{10}$)
Focal hepatocyte hypertrophy	20	157	NDr	20 (NOAEL)
Focal hepatocyte hyperplasia	20	157	NDr	20 (NOAEL)
Hepatocyte basophilic foci	20	157	NDr	20 (NOAEL)

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Modeling results are described in more detail in Appendix C.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; S-D = Sprague-Dawley.

A NOAEL (HEC) of 20 mg/m^3 is identified as the POD for the hepatic lesions (focal hepatocyte hypertrophy, focal hepatocyte hyperplasia, and basophilic foci) from Lewis et al. (1979) and Ulrich et al. (1977), and is the most health protective subchronic POD identified. Thus, the NOAEL (HEC) of 20 mg/m^3 is chosen as the POD for deriving the subchronic p-RfC.

The subchronic p-RfC is derived by applying a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 10, and a database uncertainty factor [UF_D] of 10) to the selected POD of 20 mg/m^3.

$$\textbf{Subchronic p-RfC} = \text{POD (NOAEL)} \div UF_C$$
$$= 20\ mg/m^3 \div 300$$
$$= \mathbf{7 \times 10^{-2}\ mg/m^3}$$

Table 9 summarizes the uncertainty factors for the subchronic p-RfC for 2-nitropropane.

Table 9. Uncertainty Factors for the Subchronic p-RfC for 2-Nitropropane

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans using toxicokinetic cross-species dosimetric adjustment for extrarespiratory effects from a Category 3 gas, as specified in U.S. EPA (1994) guidelines for deriving RfCs.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The inhalation database for 2-nitropropane includes several subchronic/chronic-duration studies in rats (Griffin et al., 1981; Griffin et al., 1980; Griffin et al., 1979; Lewis et al., 1979; Coulston et al., 1978; Ulrich et al., 1977) and one in rabbits (Lewis et al., 1979; Ulrich et al., 1977) that investigated a wide variety of endpoints and included interim short-term and/or subchronic sacrifices. With the exception of Lewis et al. (1979), however, the studies were unpublished and not peer reviewed, and each included only a single exposure level. Inhalation data in other species are limited to a poorly reported study by Treon and Dutra (1952) with limited endpoint evaluation. There are no reproductive or developmental toxicity studies available by inhalation or oral exposure.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of 2-nitropropane in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL (HEC).
UF_S	1	A UF_S of 1 is applied because the POD was derived from subchronic data.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Confidence in the subchronic p-RfC for 2-nitropropane is low as described in Table 10.

Table 10. Confidence Descriptors for the Subchronic p-RfC for 2-Nitropropane

Confidence Categories	Designation	Discussion
Confidence in study	L	Confidence in the principal study (Lewis et al., 1979; Ulrich et al., 1977) is low. The study examined a wide variety of endpoints and performed interim sacrifices at several time points in rats and rabbits, but only two exposure levels were tested, only males were included for both rats and rabbits, and group sizes were small given that only one sex was tested (10 animals per time point for rats and 5 for rabbits). The published paper included only limited description of study methods and results; much of the data was available only from the unpublished version (Ulrich et al., 1977), which was not peer reviewed.
Confidence in database	L	Confidence in the database is low. The inhalation database for 2-nitropropane includes several subchronic/chronic-duration studies in rats (Griffin et al., 1981; Griffin et al., 1980; Griffin et al., 1979; Lewis et al., 1979; Coulston et al., 1978; Ulrich et al., 1977) and one in rabbits (Lewis et al., 1979; Ulrich et al., 1977) that investigated a wide variety of endpoints and included interim short-term and/or subchronic sacrifices. With the exception of Lewis et al. (1979), however, the studies were unpublished and not peer-reviewed and each included only a single exposure level. Inhalation data in other species are limited to a poorly reported study by Treon and Dutra (1952) with limited endpoint evaluation (cats, rats, rabbits, guinea pigs). No reproductive or developmental toxicity studies are available for inhalation or oral exposure.
Confidence in subchronic p-RfC[a]	L	Overall confidence in the subchronic p-RfC is low.

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

L = low; p-RfC = provisional reference concentration.

Derivation of Chronic Provisional Reference Concentration

A chronic p-RfC value was not derived because an RfC value is available on U.S. EPA's IRIS database (U.S. EPA, 2002a).

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Following *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), 2-nitropropane is *"Likely to be Carcinogenic to Humans"* by oral or inhalation exposure (see Table 11). Available epidemiological studies are not adequate to assess the carcinogenic potential of 2-nitropropane in humans. In animals, 2-nitropropane produced 100% incidence (22/22) of hepatocellular carcinoma in male rats treated by gavage at the only dose tested (90 mg/kg-day) after oral treatment for only 16 weeks (Fiala et al., 1987b). Similarly, in an inhalation study that included multiple concentrations, 2-nitropropane produced hepatocellular carcinoma in all 10 male rats exposed for 6 months at the high concentration of 754 mg/m^3, although no tumors were reported in rats exposed to 98 mg/m^3 (Lewis et al., 1979; Ulrich et al., 1977). Other unpublished inhalation studies reported the development of liver tumors in male rats exposed to 2-nitropropane for ≥6 months at 312−608 mg/m^3 (Griffin et al., 1979; Coulston et al., 1978). These studies also included female rats, which did not develop tumors. Another

study conducted at a concentration of 77.8 mg/m^3 for 22 months found no increase in tumors in male or female rats (Griffin et al., 1981; Griffin et al., 1980). A study in rabbits found no increase in tumors after 6 months at 754 mg/m^3, but small sample sizes limited reliability and interpretability of the study (Lewis et al., 1979; Ulrich et al., 1977). The very high incidence of malignant tumors following oral and inhalation exposure to 2-nitropropane in male rats evident in these studies despite relatively short exposure durations and small group sizes support the conclusion of *"Likely to be Carcinogenic to Humans,"* although tumors have not been found in female rats and adequate studies are not available in other species. This conclusion is also supported by additional evidence demonstrating that 2-nitropropane is genotoxic by exhibiting mutagenicity and producing chromosomal and DNA damage in the liver, which is the site of tumor development (see Table 4A for the list of relevant studies).

Table 11. Cancer WOE Descriptor for 2-Nitropropane

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	No adequate human data are available.
"Likely to Be Carcinogenic to Humans"	**Selected**	**Both**	**2-Nitropropane has been shown to produce very high incidence of malignant liver tumors by oral (90 mg/kg-d) or inhalation (≥312 mg/m^3) exposure in male rats despite relatively short exposure durations and small group sizes in the available studies. Studies performed at concentrations lower than 100 mg/m^3 did not find tumors in male rats and no study found tumors in female rats. No adequate studies in other species were located. The available evidence demonstrates that 2-nitropropane is a mutagen, and produces chromosomal and DNA damage in the liver, which is the site of tumor development.**
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	Evidence of the carcinogenic potential of 2-nitropropane supports a stronger descriptor.
"Inadequate Information to Assess Carcinogenic Potential"	NS	NA	Adequate information is available to assess the carcinogenic potential of 2-nitropropane.
"Not Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.

DNA = deoxyribonucleic acid; NA = not applicable; NS = not selected; WOE = weight of evidence.

MODE-OF-ACTION DISCUSSION

The *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005a) define mode of action (MOA) "…as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation." Examples of possible modes of carcinogenic action for any given chemical include

"mutagenicity, mitogenesis, programmed cell death, cytotoxicity with reparative cell proliferation, and immune suppression."

The available evidence demonstrates that 2-nitropropane is a mutagen, and produces chromosomal and DNA damage in the liver, which is the site of tumor development (see the "Genotoxicity Studies" section for more details). Additionally, it has also been proposed that severe hepatocellular damage by reactive metabolites followed by regenerative hyper-proliferation underlies hepatic tumor development induced by 2-nitropropane (see the "Mode-of-Action/Mechanistic Studies" section above for more details). Therefore, a mixed MOA for 2-nitropropane carcinogenicity is expected; however, available data are inadequate to evaluate which proposed MOA is more plausible. The approach using the Bradford-Hill criteria follows:

Key Events—Available data indicate that 2-nitropropane is a mutagen, both with and without metabolic activation, suggesting a proposed MOA where mutation of critical genes, such as oncogenes, followed by proliferation of initiated cells may occur.

Strength, Consistency, Specificity of Association—The apparent strength and consistency of the available genotoxicity data in bacterial and mammalian cells in vitro with and without metabolic activation demonstrates that 2-nitropropane is mutagenetic (Nikolic et al., 2012; Stajkovic et al., 2007; Cabelof et al., 2002; Deng et al., 1998; Weisburger et al., 1996; Kohl et al., 1994; Adachi et al., 1993; Sakai and Uchida, 1992; Conaway et al., 1991a; Haas-Jobelius et al., 1991; Roscher et al., 1990; Göggelmann et al., 1988; Fiala et al., 1987a; Löfroth et al., 1986; Haworth et al., 1983; Speck et al., 1982; Hite and Skeggs, 1979; Litton Bionetics, 1977a, b), and induced dominant lethal mutations in female rats (McGregor, 1981) and *lacI* mutations in male mouse liver tissue (Cabelof et al., 2002) following in vivo exposure.

Temporal and Dose-Response Concordance—No studies have been located that specifically evaluate both mutagenic events and tumor development. Most available cancer data for 2-nitropropane are reported in animal inhalation studies, which report hepatic tumors in rats following chronic exposure to 364−754 mg/m^3 (Griffin et al., 1979; Lewis et al., 1979; Coulston et al., 1978; Ulrich et al., 1977). In the only inhalation study evaluating mutagenicity, dominant lethal mutations were observed after exposure to 729 mg/m^3. Hepatic tumors have been observed also following oral exposure to 90 mg/kg-day for 16 weeks (only dose tested) (Fiala et al., 1987b). No oral studies evaluated mutagenicity. Based on these findings, mutations may occur at relevant inhalation exposure levels; however, the lack of mutation data in the liver following inhalation exposure precludes adequate evaluation of temporal or dose-response concordance.

Biological Plausibility and Coherence—Supporting evidence for the association between mutagenicity and tumor formation comes from the observation that 2-nitropropane exposure is capable of causing mutations in the liver, which is the site of tumor development (Fiala et al., 1987b; Griffin et al., 1979; Lewis et al., 1979; Coulston et al., 1978; Ulrich et al., 1977). Additionally, it is hypothesized that these carcinogenic effects are secondary to oxidative stress attributed to the generation of reactive intermediates like *N*-nitro and oxygen radicals during the denitrification of 2-nitropropane (Smith and Anderson, 2013; ACGIH, 2001). Evidence from in vitro studies indicates that 2-nitropropane is mutagenic. Furthermore, there is coherence across the evidence from in vivo genotoxicity studies indicating that 2-nitropropane is

mutagenic across species and sexes (e.g., in both sexes of rats and in male mice) (Cabelof et al., 2006; Cabelof et al., 2002; Guo et al., 1990; Hussain et al., 1990).

Because mutagenicity is involved in a plausible mixed MOA, a linear approach is appropriate to extrapolate from the POD in deriving a screening provisional inhalation unit risk (p-IUR) (U.S. EPA, 2005a).

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor

Fiala et al. (1987b) observed a highly significant increase in the incidence of hepatocellular carcinoma in male rats treated with 90 mg/kg-day of 2-nitropropane by gavage 3 times/week for 16 weeks. Study limitations, most notably treatment of a single dose group, precluded developing a provisional oral slope factor (p-OSF) because the data were not amenable to modeling using the Multistage cancer model.

Derivation of Provisional Inhalation Unit Risk

One study in the inhalation database provided dose-response information for tumors induced by 2-nitropropane (Lewis et al., 1979; Ulrich et al., 1977). This study found liver carcinomas in 10/10 high-dose male rats but not in the control or low-dose rats following 6 months of inhalation exposure. Per the U.S. EPA's *Benchmark Dose Technical Guidance*, "a data set with only the highest dose showing a response would bracket the BMD at the low end but may provide limited information about the shape of the dose-response relationship. In such cases, dose spacing and the proximity of the BMR to the observed response level will influence the uncertainty in the BMD estimate" (U.S. EPA, 2012b). Thus, given the uncertainty surrounding BMD modeling of the liver tumor data from the lone inhalation carcinogenicity study, derivation of a p-IUR is precluded, but a screening p-IUR based on the $BMCL_{10}$ for liver tumors is presented in Appendix A.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional reference doses (p-RfDs) for 2-nitropropane. However, information is available for this chemical, which although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the main documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the CPHEA.

DERIVATION OF SCREENING PROVISIONAL REFERENCE DOSES

As discussed in the main body of the report, available oral studies are too limited in scope and/or duration to support derivation of p-RfDs. A screening-level subchronic value can, however, be derived from the 28-day oral study in rats (Kawakami et al., 2015). This study provided dose-response information for several liver endpoints. A no-observed-adverse-effect level (NOAEL) of 5 mg/kg-day and a lowest-observed-adverse-effect level (LOAEL) of 20 mg/kg-day were identified based on increased relative liver weight and increased incidence of hepatocyte hypertrophy. While this is not a comprehensive study, the inhalation database and available acute and short-term-duration oral and intraperitoneal (i.p.) injection studies all identify the liver as the most sensitive target of 2-nitropropane toxicity (see Tables 3A and 4B). To account for the uncertainty associated with basing a reference dose on a 28-day study of limited endpoints, the assessment is considered a screening-level assessment.

Data for the most sensitive endpoints in the 28-day oral study (increased relative liver weight and increased incidence of hepatocyte hypertrophy) were modeled using all available continuous or dichotomous models, as appropriate, in the Benchmark Dose Software (BMDS, Version 2.6). The modeled data are shown in Table A-1. Human equivalent doses (HEDs) in mg/kg-day were used as the dose metric. The administered doses of 0, 5, 20, and 40 mg/kg-day were converted into HEDs of 0, 1, 5.0, and 9.9 mg/kg-day (see Footnote B in Table A-1). For increased relative liver weight, a benchmark response (BMR) of 10% relative deviation (RD) from the control mean was run because a 10% change in liver weight is considered biologically significant. For hepatocellular hypertrophy, a standard BMR for dichotomous data of 10% extra risk was run.

Table A-1. Data for Relative Liver Weight and Hepatocyte Hypertrophy in Male Crl:CD (SD) Rats Administered 2-Nitropropane via Gavage for 28 Days[a]

Parameter	ADD (HED)[b] mg/kg-d			
	0 (0)	5 (1)	20 (5.0)	40 (9.9)
Relative liver weight (10% BW)[c]	2.91 ± 0.09 (5)	2.98 ± 0.23 (5)	3.32 ± 0.2 (5)	3.60 ± 0.19 (5)
Hepatocyte hypertrophy[d]	0/5	0/5	2/5	5/5

[a]Kawakami et al. (2015).
[b]HEDs were calculated using DAFs, as recommended by U.S. EPA (2011b). The DAF is calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$), where DAF = dosimetric adjustment factor, BW_a = animal body weight, and BW_h = human body weight. In the absence of sufficient data to calculate TWA body weights from the rat study, reference body weights recommended by U.S. EPA (1988b) were used to calculate the DAFs: 70 kg for humans and 0.267 kg for male S-D rats in a subchronic-duration study. HED = ADD × DAF.
[c]Data reported as mean ± SD (*n*).
[d]Values denote number of animals showing changes/total number of animals examined

ADD = adjusted daily dose; BW = body weight; DAF = dosimetric adjustment factor; HED = human equivalent dose; SD = standard deviation; S-D = Sprague-Dawley; TWA = time-weighted average.

Table A-2 summarizes the benchmark dose (BMD) modeling results and provides candidate points of departure (PODs) for the modeled endpoints. Details of model fit for each data set are presented in Appendix C.

Table A-2. BMD and BMDL Values from Best Fitting Models for Relative Liver Weight and Hepatocyte Hypertrophy in Male Crl:CD (SD) Rats Administered 2-Nitropropane via Gavage for 28 Days[a]

Endpoint	Best-Fitting Model	BMR	BMD (HED) (mg/kg-d)	BMDL (HED) (mg/kg-d)
Increased relative liver weight	Linear	10% RD from control	BMD_{10} = 4.1	$BMDL_{10}$ = 3.3
Hepatocyte hypertrophy	Multistage 1-degree	10% extra risk	BMD_{10} = 0.64	$BMDL_{10}$ = 0.34

[a]Kawakami et al. (2015).

BMD = benchmark dose; BMDL = benchmark dose lower confidence limit (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; HED = human equivalent dose; RD = relative deviation; SD = standard deviation.

Derivation of Screening Subchronic Provisional Reference Dose

The 10% benchmark dose lower confidence limit ($BMDL_{10}$) (HED) of 0.34 mg/kg-day for increased incidence of hepatocellular hypertrophy in male rats in the 28-day oral study (Kawakami et al., 2015) is the most health protective POD identified and is selected as the POD for deriving the screening subchronic p-RfD.

The screening subchronic p-RfD is derived by applying a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 10, and a database uncertainty factor [UF_D] of 10) to the selected POD of 0.34 mg/kg-day.

Screening Subchronic p-RfD = POD (HED) ÷ UF_C
= 0.34 mg/kg-day ÷ 300
= **1×10^{-3} mg/kg-day**

Table A-3 summarizes the uncertainty factors for the screening subchronic p-RfD for 2-nitropropane.

Table A-3. Uncertainty Factors for the Screening Subchronic p-RfD for 2-Nitropropane

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 2-nitropropane exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 1988b).
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The oral database for 2-nitropropane is limited to short-term-duration and acute studies of limited scope and a cancer bioassay that contains limited information on noncancer endpoints. Although comprehensive oral studies were not identified, inhalation and injection studies provide support for the liver as the critical target for this chemical. No reproductive or developmental toxicity studies are available for oral or inhalation exposure.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of 2-nitropropane in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because the POD was derived from a 28-d study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose with lower confidence limit; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of Screening Chronic Provisional Reference Dose

There are no chronic-duration oral studies on 2-nitropropane. The 28-day study used to derive the screening subchronic p-RfD (Kawakami et al., 2015) is too limited in duration to support derivation of a screening chronic p-RfD. Use of a less-than-subchronic-duration study is inappropriate for deriving chronic toxicity values unless chronic toxicity data are available to indicate that the critical effect observed in the short-term-duration study will not increase in severity or become more sensitive based on dose-response analysis following longer treatment duration. While no longer duration oral data are available, limited inhalation data suggest that sensitivity to hepatic toxicity may increase with exposure durations >6 months. In 6-month studies with interim sacrifices, data show that comparable hepatic effects occur at similar doses

across time points up to 6 months; for example, the hepatic NOAEL (HEC) and LOAEL (HEC) are 20 and 157 mg/m^3, respectively, after 10 days, 1 month, 3 months, or 6 months of exposure in the study by Lewis et al. (1979) and Ulrich et al. (1977). In a longer duration study, Griffin et al. (1981) and Griffin et al. (1980) reported a lower LOAEL (HEC) of 16.2 mg/m^3 for hepatic effects following exposure for up to 22 months, suggesting increased sensitivity to liver effects following 22-month versus 10-day to 6-month exposures. For this reason, no screening chronic p-RfD was derived.

Derivation of Screening Provisional Inhalation Unit Risk

As discussed in the main body of the assessment, only one study in the inhalation database provided dose-response information for tumors induced by 2-nitropropane (Lewis et al., 1979; Ulrich et al., 1977), and based on the dose-spacing of the liver tumor data and tumors in all high-dose treated animals, there is uncertainty in the BMD estimate. Thus, to account for this increased uncertainty, a screening p-IUR is derived. The data for hepatocellular carcinoma are shown in Table A-4.

Table A-4. Data for Hepatocellular Carcinoma in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 6 Months[a]

Endpoint	Concentration (HEC in mg/m^3)		
	0	20	157
Hepatocellular carcinoma[b]	0/10	0/10	10/10

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Values denote number of animals showing changes/total number of animals examined.

HEC = human equivalent concentration; S-D = Sprague-Dawley.

BMD modeling was performed for this data set using the Multistage cancer model in the U.S. EPA BMDS (Version 2.6). The BMR used was 10% extra risk. The HEC in mg/m^3 was used as the dose metric. Modeling results are summarized in Table A-5 (see additional BMD details in Appendix C).

Table A-5. BMD Model Results Based on the Incidence of Hepatocellular Carcinoma in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 6 Months[a]

Tumor Endpoint	Selected Model	BMC_{10} (HEC, mg/m^3)	$BMCL_{10}$ (HEC, mg/m^3)
Hepatocellular carcinoma	Multistage (2-degree)	25	11

[a]Lewis et al. (1979); Ulrich et al. (1977).

BMC = benchmark concentration; BMCL = 95% lower confidence limit on the benchmark concentration (subscripts denote benchmark response: i.e., 10 = concentration associated with 10% extra risk); BMD = benchmark dose; HEC = human equivalent concentration; p-IUR = provisional inhalation unit risk; S-D = Sprague-Dawley.

The Multistage cancer model provided adequate fit to the data set for hepatocellular carcinoma from Lewis et al. (1979) and Ulrich et al. (1977). BMC_{10} and $BMCL_{10}$ values for the best fitting (2-degree) model were 25 and 11 mg/m^3 (HEC), respectively. The $BMCL_{10}$ value of 11 mg/m^3 (HEC) based on hepatocellular carcinoma risk was used as the POD for deriving the screening p-IUR.

The mode of action (MOA) by which 2-nitropropane induces liver tumors is expected to be mixed and includes a mutagenic component. A linear approach is used to calculate the screening p-IUR from the $BMCL_{10}$ (HEC) of 11 mg/m^3 for liver tumors in male rats exposed to 2-nitropropane for 6 months.

Screening p-IUR (unadjusted)	=	BMR ÷ $BMCL_{10}$ (HEC)
	=	0.1 ÷ 11 mg/m^3
	=	**9.1×10^{-3} (mg/m^3)$^{-1}$**

An adjustment was applied to account for the less-than-lifetime observation period (U.S. EPA, 1980). The Lewis et al. (1979) and Ulrich et al. (1977) bioassay was designed to expose rats to 2-nitropropane for only 6 months. Thus, due to the short duration of the study, it cannot be known how an increased duration (i.e., the full 2-year lifetime exposure) might have influenced the tumor incidence in the low-dose treated rats. Therefore, an adjustment factor of $(L \div L_e)^3$ was applied to the unadjusted screening p-IUR, where L = the lifetime of the animal and L_e = the duration of experimental dosing (U.S. EPA, 1980). Using this adjustment, an adjusted screening p-IUR is derived as follows:

Screening p-IUR (adjusted)	=	p-IUR (unadjusted) × $(L \div L_e)^3$
	=	9.1×10^{-3} (mg/m^3)$^{-1}$ × (24 months ÷ 6 months)^3
	=	**5.8×10^{-1} (mg/m^3)$^{-1}$**

It is important to note that the Lewis et al. (1979) and Ulrich et al. (1977) bioassay raises concern for lower exposures and longer durations, but the degree of adjustment is too uncertain for lifetime exposure in this case and is therefore questionable. However, this estimate is more health protective than the estimate without the $(L \div L_e)^3$ adjustment, which is likely to be underestimated. Furthermore, because 2-nitropropane is *"Likely to be Carcinogenic to Humans"* by inhalation exposure (see Table 11), derivation of a screening p-IUR for this chemical is warranted despite the aforementioned uncertainty due to the application of the less-than-lifetime adjustment factor.

A weight-of-evidence (WOE) evaluation has concluded that 2-nitropropane is characterized by a mixed MOA, which includes a mutagenic component. According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), those exposed to carcinogens with a mutagenic MOA are assumed to have increased early-life susceptibility. Data on 2-nitropropane are not sufficient to develop separate risk estimates for childhood exposure. The screening p-IUR of 5.8×10^{-1} (mg/m^3)$^{-1}$ calculated from data from adult exposure does not reflect presumed early-life susceptibility for this chemical, and age-dependent adjustment factors (ADAFs) should be applied to this parameter when assessing cancer risks. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005b). The adjusted screening p-IURs associated with these ADAFs are 5.8×10^{0} (mg/m^3)$^{-1}$ for <2 years, 1.7×10^{0} (mg/m^3)$^{-1}$

for 2 to <16 years, and 5.8×10^{-1} $(mg/m^3)^{-1}$ for 16 years and above. These screening p-IURs are to be combined with age-specific exposure estimates when estimating cancer risks from early life (<16 years of age) exposure to 2-nitropropane. Cancer risks are derived for each age group and summed across age groups to obtain the total risk for the exposure period of interest.

APPENDIX B. DATA TABLES

Table B-1. Observed/Expected Deaths among Workers Employed at a 2-Nitropropane Facility between 1/1/1955−7/1/1977[a]

Parameter[b]	Exposure Group Category[c]		
	Direct + Indirect	Indirect Only	No Exposure
White male workers	*n* = 325	*n* = 331	*n* = 410
All causes of death	11/17.4	29/37.3	54/55.6
All cancer	3/3.2	4/7.3	8/10.2
Lymphatic cancer	0/0.1	0/0.3	2/0.4
Circulatory cancer	5/7.0	15/17.9	26/25.7
External cancer	3/4.0	7/5.3	12/9.4
Residual cancer	0/3.2	3/6.8	8/10.3
Black male workers	*n* = 33	*n* = 28	*n* = 207
All causes of death	0/1.3	0/3.7	27/35.6
All cancer	0/0.2	0/0.7	4/5.1
Lymphatic cancer	0/0.0	0/0.0	2/0.5
Circulatory cancer	0/0.5	0/1.6	12/12.9
External cancer	0/0.2	0/0.6	9/8.4
Residual cancer	0/0.4	0/0.8	2/9.2
Female workers	*n* = 14	*n* = 7	*n* = 126
All causes of death	2/0.4	0/0.1	6/2.4
All cancer	1/0.1	0/0.0	3/0.7
Lymphatic cancer	0/0.0	0/0.0	0/0.1
Circulatory cancer	0/0.1	0/0.0	1/0.5
External cancer	1/0.1	0/0.0	1/0.6
Residual cancer	0/0.1	0/0.1	1/0.6

[a]Miller and Temple (1980).
[b]Data are observed/expected (based on U.S. general population).
[c]Job titles were used to place workers in exposure categories; exposure levels by categories were not reported.

Table B-2. Body and Liver Weight in Male Crl:CD (SD) Rats Administered 2-Nitropropane via Gavage for 14 or 28 Days[a]

Parameter[b, c]	Dose Group, mg/kg-d (ADD)			
	0	5 (5)	20 (20)	40 (40)
Body weight (g)				
14 d	283.5 ± 7.5	295.8 ± 20.2 (+4%)	280.8 ± 18.4 (−1%)	261.6 ± 20.4 (−8%)
28 d	331.8 ± 20.8	332.7 ± 24.6 (+0.3%)	307.9 ± 25.2 (−7%)	305.5 ± 34.0 (−8%)
Relative liver weight (% BW)				
14 d	3.19 ± 0.21	3.17 ± 0.37 (−0.6%)	3.29 ± 0.28 (+3%)	3.54 ± 0.24 (+11%)
28 d	2.91 ± 0.09	2.98 ± 0.23 (+2%)	3.32 ± 0.20* (+14%)	3.60 ± 0.19* (+24%)

[a]Kawakami et al. (2015).
[b]Data are mean ± SD for five rats/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Dunnett's test ($p < 0.05$), as reported by the study authors.

ADD = adjusted daily dose; BW = body weight; SD = standard deviation.

Table B-3. Serum Chemistry in Male Crl:CD (SD) Rats Administered 2-Nitropropane via Gavage for 14 or 28 Days[a]

Parameter[b, c]	Dose Group, mg/kg-d (ADD)			
	0	5 (5)	20 (20)	40 (40)
ALT (IU/L)				
14 d	30.4 ± 3.7	29.1 ± 1.2 (−4%)	25.7 ± 3.3 (−16%)	31.7 ± 4.5 (+4%)
28 d	27.9 ± 1.9	30.1 ± 3.0 (+8%)	25.1 ± 2.2 (−10%)	28.4 ± 5.4 (+2%)
AST (IU/L)				
14 d	76.3 ± 4.6	79.5 ± 9.1 (+4%)	73.5 ± 5.5 (−4%)	92.3 ± 12.9* (+21%)
28 d	79.5 ± 9.9	82.3 ± 2.9 (+4%)	82.6 ± 3.5 (+4%)	93.0 ± 12.3 (+17%)
ChE (IU/L)				
14 d	58 ± 12	55 ± 12 (−5%)	70 ± 16 (+21%)	106 ± 24* (+83%)
28 d	51 ± 11	52 ± 14 (+2%)	76 ± 31 (+49%)	137 ± 27* (+169%)
GGT (IU/L)				
14 d	0.9 ± 0.2	0.8 ± 0.1 (−11%)	0.9 ± 0.2 (0%)	1.2 ± 0.2* (+33%)
28 d	0.4 ± 0.2	0.4 ± 0.2 (0%)	0.7 ± 0.2 (+75%)	1.3 ± 0.7* (+225%)

[a]Kawakami et al. (2015).
[b]Data are mean ± SD for five rats/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Dunnett's test ($p < 0.05$), as reported by the study authors.

ADD = adjusted daily dose; ALT = alanine transaminase; AST = aspartate aminotransferase; ChE = cholinesterase; GGT = γ-glutamyl transferase; SD = standard deviation.

Table B-4. Gross and Microscopic Liver Findings in Male Crl:CD (SD) Rats Administered 2-Nitropropane via Gavage for 14 or 28 Days[a]

Parameter[b]	Dose Group, mg/kg-d (ADD)			
	0	5 (5)	20 (20)	40 (40)
Pale livers				
14 d	0/5 (0%)	0/5 (0%)	0/5 (0%)	5/5 (100%)
28 d	0/5 (0%)	0/5 (0%)	1/5 (20%)	5/5 (100%)
Hypertrophy of hepatocytes, diffuse				
14 d	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)
28 d	0/5 (0%)	0/5 (0%)	2/5 (40%)+	5/5 (100%)++
Focus of altered hepatocyte, basophilic				
14 d	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)
28 d	0/5 (0%)	0/5 (0%)	0/5 (0%)	4/5 (80%)+
Anisokaryosis of hepatocyte				
14 d	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)
28 d	0/5 (0%)	0/5 (0%)	0/5 (0%)	2/5 (40%)+

[a]Kawakami et al. (2015).
[b]Values denote number of animals showing changes ÷ total number of animals examined (% incidence); severity of lesions indicated by + (minimal) and ++ (mild).

ADD = adjusted daily dose.

Table B-5. Body and Liver Weight and Serum Chemistry in Male F344 Orally Administered 2-Nitropropane for 28 Days[a]

Parameter[b, c]	Dose Group, mg/kg-d (ADD)	
	0	40 (40)
Body weight (g)	201.8 ± 4.9	202.5 ± 11.8 (+0.3%)
Absolute liver weight (g)	8.3 ± 0.2	9.8 ± 0.7* (+18%)
AST (units not reported)	63 ± 5.4	64.8 ± 4.8 (+3%)
ALT (units not reported)	48 ± 3.8	43.5 ± 2.9 (−9%)
ALP (units not reported)	1,909 ± 124.2	1,870.3 ± 77.2 (−2%)

[a]Nakayama et al. (2006).
[b]Data are mean ± measure of variance (not defined); n = 4/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control ($p < 0.05$), as reported by the study authors (method not reported).

ADD = adjusted daily dose; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Table B-6. Select Serum Chemistry and Hepatic Enzyme Activity in Male Wistar Rats Orally Administered 2-Nitropropane for 2 Weeks[a]

Parameter[b, c]	Dose Group, mg/kg-d (ADD)	
	0	120 (51.4)
Experiment 1		
Plasma ALT (U/L)	63.4 ± 6.0	169.5 ± 17.0* (+167%)
Plasma AST (U/L)	148.3 ± 24.3	188.2 ± 64.8* (+27%)
Plasma GGT (U/L)	4.8 ± 0.9	24.5 ± 4.2* (+410%)
Plasma urea (mg/dL)	48.5 ± 12.2	60.8 ± 14.0* (+25%)
Hepatic catalase activity (U/mg of protein)	24.3 ± 2.71	10.5 ± 2.62* (−57%)
Experiment 2		
Plasma ALT (U/L)	62.6 ± 8.0	142.5 ± 5.87* (+128%)
Plasma AST (U/L)	151.2 ± 14.3	252.2 ± 34.8* (+67%)
Plasma GGT (U/L)	5.75 ± 0.85	22.6 ± 1.4* (+293%)
Plasma urea (mg/dL)	50.5 ± 1.84	71.2 ± 7.26* (+41%)
Hepatic catalase activity (U/mg of protein)	23.1 ± 3.43	14.0 ± 2.51 (−39%)

[a]Wilhelm et al. (2009).
[b]Data are mean ± SD; n = 8−14/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by two-way ANOVA with Duncan's post hoc multiple range test ($p < 0.05$), as reported by the study authors.

ADD = adjusted daily dose; ALT = alanine aminotransferase; ANOVA = analysis of variance; AST = aspartate aminotransferase; GGT = γ glutamyl transferase; SD = standard deviation.

Table B-7. Incidence of Tumors in Male S-D Rats Administered 2-Nitropropane via Gavage for 16 Weeks[a]

Parameter[b]	Dose Group, mg/kg-d (ADD) [HED]	
	0	90 (39) [9.8]
Liver tumors		
Benign tumors	1/29 (3%)	4/22 (18%)
Malignant hepatocarcinomas	0/29 (0%)	22/22** (100%)
Lung tumors (metastases from liver tumors)	0/29 (0%)	4/22 (18%)
Gastrointestinal system		
Stomach papilloma	0/29 (0%)	1/22 (5%)
Colon adenocarcinoma	0/29 (0%)	1/22 (5%)
Skin tumors	1/29 (3%)	0/22 (5%)

[a]Fiala et al. (1987b).
[b]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
**Significantly different from control ($p < 0.001$), as reported by the study authors (statistical method not specified).

ADD = adjusted daily dose; HED = human equivalent dose; S-D = Sprague-Dawley.

Table B-8. Body Weight and Select Organ Weight Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 22 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	77.8 (16.2)
Body weight (g)		
1 mo	359 ± 30	341 ± 41 (−5%)
3 mo	508 ± 48	488 ± 65 (−4%)
6 mo	593 ± 65	594 ± 69 (+0.2%)
12 mo	618 ± 97	672 ± 60 (+9%)
22 mo	696 ± 121	652 ± 102 (−6%)
Absolute liver weight (g)		
1 mo	14.19 ± 2.01	13.99 ± 2.52 (−1%)
3 mo	18.65 ± 2.55	19.04 ± 2.63 (+2%)
6 mo	19.03 ± 3.98	21.54 ± 3.65 (+13%)
12 mo	16.75 ± 6.64	18.59 ± 2.92 (+11%)
22 mo	17.10 ± 3.05	19.07 ± 3.76** (+12%)
Relative liver weight (% BW)		
1 mo	3.95 ± 0.39	4.08 ± 0.45 (+3%)
3 mo	3.67 ± 0.43	3.93 ± 0.46 (+7%)
6 mo	3.19 ± 0.50	3.73 ± 0.49* (+17%)
12 mo	2.70 ± 0.39	2.78 ± 0.46 (+3%)
22 mo	2.49 ± 0.50	2.98 ± 0.78** (+20%)
Absolute kidney weight (g)		
1 mo	2.59 ± 0.33	2.49 ± 0.37 (−4%)
3 mo	3.23 ± 0.33	3.20 ± 0.39 (−1%)
6 mo	3.35 ± 0.28	3.38 ± 0.40 (+0.9%)
12 mo	3.45 ± 0.40	3.87 ± 0.45* (+12%)
22 mo	4.47 ± 1.13	4.75 ± 1.69 (+6%)

[a]Griffin et al. (1980).
[b]Data are mean ± SD; n = 9−10/group at 1−12 months, and 62−63 for control and 27 for exposed at 22 months.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Student's t-test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Student's t-test ($p < 0.01$), as reported by the study authors.

BW = body weight; ER = extrarespiratory; HEC = human equivalent concentration; SD = standard deviation; S-D = Sprague-Dawley.

Table B-9. Body Weight and Select Organ Weight Data for Female S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 22 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	77.8 (16.2)
Body weight (g)		
1 mo	199 ± 21	211 ± 20 (+6%)
3 mo	283 ± 22	278 ± 24 (−2%)
6 mo	281 ± 15	327 ± 54** (+16%)
12 mo	323 ± 43	377 ± 63** (+17%)
22 mo	408 ± 83	460 ± 104** (+13%)
Absolute liver weight (g)		
1 mo	8.22 ± 1.39	9.09 ± 1.61 (+11%)
3 mo	10.15 ± 1.39	10.12 ± 1.12 (−0.3%)
6 mo	8.92 ± 0.88	10.64 ± 1.65** (+19%)
12 mo	7.93 ± 1.03	9.74 ± 1.44** (+23%)
22 mo	10.73 ± 1.93	12.59 ± 2.70** (+17%)
Relative liver weight (% BW)		
1 mo	4.11 ± 0.39	4.29 ± 0.50 (+4%)
3 mo	3.56 ± 0.41	3.64 ± 0.24 (+2%)
6 mo	3.17 ± 0.21	3.27 ± 0.27 (+3%)
12 mo	2.47 ± 0.23	2.58 ± 0.33 (+5%)
22 mo	2.63 ± 0.40	2.78 ± 0.48 (+6%)
Absolute kidney weight (g)		
1 mo	1.47 ± 0.12	1.65 ± 0.19* (+12%)
3 mo	1.83 ± 0.13	1.84 ± 0.17 (+0.5%)
6 mo	1.69 ± 0.15	1.80 ± 0.21 (+7%)
12 mo	2.17 ± 0.35	2.56 ± 0.56 (+18%)
22 mo	2.71 ± 0.53	2.85 ± 0.48 (+5%)

[a]Griffin et al. (1980).
[b]Data are mean ± SD; n = 9−10/group at 1−12 months, and 44−48 for control and 29 for exposed at 22 months.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Student's t-test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Student's t-test ($p < 0.01$), as reported by the study authors.

BW = body weight; ER = extrarespiratory; HEC = human equivalent concentration; SD = standard deviation; S-D = Sprague-Dawley.

Table B-10. Select Hepatic Clinical Chemistry Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 22 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	77.8 (16.2)
Serum ALT (U/L)		
1 mo	17 ± 3	21 ± 3 (+24%)
3 mo	28 ± 8	24 ± 4 (−14%)
6 mo	38 ± 15	23 ± 10* (−40%)
12 mo	15 ± 12	17 ± 10 (+13%)
22 mo	19 ± 13	20 ± 9 (+5%)
Serum OCT (activity/mL)		
1 mo	0.391 ± 0.020	0.353 ± 0.090 (−10%)
3 mo	0.257 ± 0.090	0.137 ± 0.041** (−47%)
6 mo	0.376 ± 0.084	0.276 ± 0.091* (−27%)
12 mo	0.280 ± 0.090	0.400 ± 0.120* (+43%)
22 mo	0.281 ± 0.114	0.291 ± 0.104 (+4%)

[a]Griffin et al. (1980).
[b]Data are mean ± SD; n = 7−10/group at 1−12 months, and 58−61 for control and 26−27 for exposed at 22 months.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Student's t-test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Student's t-test ($p < 0.01$), as reported by the study authors.

ALT = alanine aminotransferase (glutamic-pyruvic transaminase), ER = extrarespiratory; HEC = human equivalent concentration; OCT = ornithine carbamyl transferase; SD = standard deviation; S-D = Sprague-Dawley.

Table B-11. Select Serum T4 Data for S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 22 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	**77.8 (16.2)**
Males		
Serum T4 (µg/100 mL)		
1 mo	5.7 ± 1.1	4.6 ± 0.8* (−19%)
3 mo	9.7 ± 2.1	8.2 ± 1.5 (−15%)
6 mo	7.6 ± 1.2	7.0 ± 0.6 (−8%)
12 mo	4.8 ± 1.5	4.4 ± 0.8 (−8%)
22 mo	3.4 ± 3.0	3.5 ± 3.7 (+3%)
3-mo exposure; 18-mo recovery[d]	NA	5.2 ± 2.5 (+53%)
12-mo exposure; 10-mo recovery[d]	NA	3.6 ± 3.1 (+6%)
Females		
Serum T4 (µg/100 mL)		
1 mo	4.3 ± 1.2	4.0 ± 1.1 (−7%)
3 mo	7.2 ± 1.6	7.0 ± 2.6 (−3%)
6 mo	6.8 ± 0.7	7.1 ± 0.6 (+4%)
12 mo	3.6 ± 0.6	2.0 ± 0.8** (−44%)
22 mo	1.7 ± 1.8	1.7 ± 2.7 (0%)
3-mo exposure; 18-mo recovery[d]	NA	5.1 ± 2.8** (+200%)
12-mo exposure; 10-mo recovery[d]	NA	4.6 ± 2.0** (+171%)

[a]Griffin et al. (1980).
[b]Data are mean ± SD; n = 7−10/sex/group at 1−12 months; n = 63 for control males, 48 for control females, and 27−28 for exposed at 22 months; n = 9/group in recovery groups.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data for recovery groups compared with control group data at 22 months.
*Significantly different from control by Student's t-test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Student's t-test ($p < 0.01$), as reported by the study authors.

HEC = human equivalent concentration; ER = extrarespiratory; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley; T4 = thyroxine.

Table B-12. Select Hematological Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 22 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	77.8 (16.2)
Methemoglobulin (mg/dL)[d]		
6 mo	38 ± 18	20 ± 13** (−47%)
12 mo	26 ± 11	23 ± 11 (−12%)
22 mo	19 ± 13	18 ± 15 (−5%)
Hb (g/100 mL)		
6 mo	15.5 ± 0.9	16.3 ± 1.2 (+5%)
12 mo	15.7 ± 0.7	16.6 ± 0.7** (+6%)
22 mo	14.9 ± 2.5	15.0 ± 2.8 (+0.7%)
3-mo exposure; 19-mo recovery[e]	NA	15.4 ± 1.5 (+3%)
12-mo exposure; 10-mo recovery[e]	NA	13.8 ± 2.5 (−7%)
Hct (%)		
6 mo	44.6 ± 3.2	44.6 ± 1.8 (0%)
12 mo	45.5 ± 1.4	47.6 ± 2.5* (+5%)
22 mo	41.0 ± 6.8	41.1 ± 7.3 (+0.2%)
3-mo exposure; 19-mo recovery[e]	NA	43.2 ± 3.1 (+5%)
12-mo exposure; 10-mo recovery[e]	NA	39.1 ± 5.4 (−5%)
Erythrocyte count (10^6 cells/mm^3)		
6 mo	5.4 ± 0.8	6.8 ± 1.0** (+26%)
12 mo	7.8 ± 0.6	8.1 ± 0.5 (+4%)
22 mo	5.2 ± 1.5	4.7 ± 1.2 (−10%)
3-mo exposure; 19-mo recovery[e]	NA	7.3 ± 1.0** (+40%)
12-mo exposure; 10-mo recovery[e]	NA	6.4 ± 1.3 (+23%)
Leukocyte count (10^3 cells/mm^3)		
6 mo	4.4 ± 0.7	5.7 ± 0.9** (+30%)
12 mo	4.9 ± 1.9	5.7 ± 1.4 (+16%)
22 mo	5.5 ± 2.6	6.3 ± 4.0 (+15%)
3-mo exposure; 19-mo recovery[e]	NA	4.3 ± 0.4 (−22%)
12-mo exposure; 10-mo recovery[e]	NA	4.7 ± 2.3 (−15%)

[a]Griffin et al. (1980).
[b]Data are mean ± SD; n = 9−10/group at 6 or 12 months; n = 53−54 for controls and 26−27 for exposed at 22 months; n = 6/group in recovery groups. No significant findings were found in any parameter at 1- or 3-month sacrifice (data not shown above).
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Recovery group data for methemoglobin not reported for males.
[e]Data for recovery groups compared with control group data at 22 months.
*Significantly different from control by Student's t-test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Student's t-test ($p < 0.01$), as reported by the study authors.

Hb = hemoglobin; Hct = hematocrit; HEC = human equivalent concentration; ER = extrarespiratory; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley.

Table B-13. Select Hematological Data for Female S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 22 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	77.8 (16.2)
Methemoglobulin (mg/dL)		
6 mo	52 ± 24	38 ± 11 (−27%)
12 mo	26 ± 17	27 ± 21 (+4%)
22 mo	15 ± 13	13 ± 10 (−13%)
3-mo exposure; 19-mo recovery[d]	NA	24 ± 14 (+60%)
12-mo exposure; 10-mo recovery[d]	NA	33 ± 20** (+120%)
Hct (%)		
6 mo	43.2 ± 1.6	45.4 ± 1.8* (+5%)
12 mo	43.9 ± 1.5	45.8 ± 1.2** (+4%)
22 mo	44.7 ± 3.6	45.5 ± 5.3 (+2%)
3-mo exposure; 19-mo recovery[d]	NA	44.0 ± 3.3 (−2%)
12-mo exposure; 10-mo recovery[d]	NA	41.8 ± 9.2 (−7%)
Erythrocyte count (10^6 cells/mm^3)		
6 mo	4.5 ± 0.5	4.9 ± 0.7 (+9%)
12 mo	6.3 ± 0.5	7.3 ± 1.0* (+16%)
22 mo	5.9 ± 1.4	6.2 ± 1.2 (+5%)
3 mo-exposure; 19-mo recovery[d]	NA	6.7 ± 1.8 (+14%)
12-mo exposure; 10-mo recovery[d]	NA	6.5 ± 1.9 (+10%)
Leukocyte count (10^3 cells/mm^3)		
6 mo	3.2 ± 1.0	4.1 ± 1.2 (+28%)
12 mo	2.8 ± 0.8	3.4 ± 1.3 (+21%)
22 mo	3.7 ± 1.6	4.6 ± 2.5 (+24%)
3-mo exposure; 19-mo recovery[d]	NA	5.3 ± 2.6* (+43%)
12-mo exposure; 10-mo recovery[d]	NA	5.1 ± 2.3* (+38%)

[a]Griffin et al. (1980).
[b]Data are mean ± SD; n = 9−10/group at 6 or 12 months; n = 43−44 for controls and 27−28 for exposed at 22 months; n = 9/group in recovery groups. No significant findings were found in any parameter at 1- or 3-month sacrifice (data not shown above).
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data for recovery groups compared with control group data at 22 months.
*Significantly different from control by Student's t-test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Student's t-test ($p < 0.01$), as reported by the study authors.

Hct = hematocrit; HEC = human equivalent concentration; ER = extrarespiratory; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley.

Table B-14. Incidence of Hepatic Lesions in S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 22 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b]	Dose Group, Analytical Concentration in mg/m^3 (HEC in mg/m^3)	
	0	**77.8 (16.2)**
Male		
Focal vacuolization of hepatocytes	22/125 (18%)	58/125* (46%)
Focal areas of hepatocellular nodules	2/125 (2%)	10/125* (8%)
Liver congestion	1/125 (0.8%)	8/125* (6%)
Female		
Focal vacuolization of hepatocytes	18/125 (14%)	19/124 (15%)
Focal areas of hepatocellular nodules	1/125 (0.8%)	3/124 (2%)
Liver congestion	0/125 (0%)	7/124* (6%)

[a]Griffin et al. (1980).
[b]Values denote number of animals showing changes ÷ total number of animals examined (% incidence); all animals from the study were combined for reporting of lesions by study authors; timing of the lesions (interim, terminal, or recovery sacrifice) was not reported.
*Significantly different from control by Fisher's exact test ($p < 0.05$), conducted for this review.

HEC = human equivalent concentration; S-D = Sprague-Dawley.

Table B-15. Body, Liver, and Kidney Weight Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)		
	0	98 (20)	754 (157)
Body weight (g)			
2 d	151 ± 5.2	153 ± 4.0 (+1%)	97 ± 1.7*** (−36%)
10 d	209 ± 11.5	223 ± 6.0 (+7%)	137 ± 8.3*** (−34%)
1 mo	313 ± 10.6	330 ± 5.0 (+5%)	221 ± 6.9*** (−29%)
3 mo	455 ± 14.7	486 ± 15.4 (+7%)	405 ± 16.5* (−11%)
6 mo	579 ± 16.1	579 ± 22.6 (0%)	513 ± 17.0* (−11%)
Absolute liver weight (g)			
2 d	5.9 ± 0.12	5.5 ± 0.13 (−7%)	3.8 ± 0.11*** (−36%)
10 d	7.6 ± 0.16	7.3 ± 0.28 (−4%)	6.3 ± 0.29*** (−17%)
1 mo	9.5 ± 0.35	10.3 ± 0.35 (+8%)	10.0 ± 0.37 (+5%)
3 mo	11.8 ± 0.40	13.0 ± 0.48 (+10%)	16.7 ± 0.85*** (+42%)
6 mo	15.02 ± 0.865	14.42 ± 0.824 (−4%)	36.63 ± 5.787*** (+144%)
Relative liver weight (% BW)			
2 d	4.0 ± 0.13	3.7 ± 0.12 (−8%)	4.0 ± 0.06 (0%)
10 d	3.8 ± 0.32	3.3 ± 0.06 (−13%)	4.7 ± 0.13* (24%)
1 mo	3.0 ± 0.05	3.1 ± 0.08 (+3%)	4.5 ± 0.11*** (+50%)
3 mo	2.6 ± 0.04	2.7 ± 0.05 (+4%)	4.1 ± 0.19*** (+58%)
6 mo	2.6 ± 0.156	2.48 ± 0.056 (−5%)	7.18 ± 1.132*** (+176%)
Absolute kidney weight (g)			
2 d	2.1 ± 0.13	1.8 ± 0.09 (−14%)	1.0 ± 0.02*** (−52%)
10 d	2.3 ± 0.12	1.9 ± 0.13* (−17%)	1.3 ± 0.06*** (−44%)
1 mo	2.5 ± 0.10	2.8 ± 0.08* (+12%)	2.0 ± 0.09*** (−20%)
3 mo	3.4 ± 0.16	3.7 ± 0.15 (+9%)	3.1 ± 0.10 (−9%)
6 mo	3.85 ± 0.187	3.67 ± 0.149 (−5%)	3.7 ± 0.117 (−4%)
Relative kidney weight (% BW)			
2 d	1.4 ± 0.08	1.2 ± 0.09 (−14%)	1.1 ± 0.02*** (−21%)
10 d	1.2 ± 0.12	0.8 ± 0.06* (−33%)	1.0 ± 0.04 (−17%)
1 mo	0.8 ± 0.01	0.9 ± 0.02* (+13%)	0.9 ± 0.03** (+13%)
3 mo	0.7 ± 0.03	0.8 ± 0.02 (+14%)	0.8 ± 0.02 (+14%)
6 mo	0.67 ± 0.036	0.64 ± 0.014 (−5%)	0.72 ± 0.02 (+8%)

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Data are mean ± SEM; n = 8−10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Student's t-test ($p \leq 0.05$), as reported by the study authors.
**Significantly different from control by Student's t-test ($p \leq 0.01$), as reported by the study authors.
***Significantly different from control by Student's t-test ($p \leq 0.005$), as reported by the study authors.

BW = body weight; ER = extrarespiratory; HEC = human equivalent concentration; S-D = Sprague-Dawley; SEM = standard error of the mean.

Table B-16. Clinical Chemistry Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)		
	0	**98 (20)**	**754 (157)**
Serum ALT (U/L)			
2 d	27 ± 1.6	42 ± 12 (+56%)	QNS
10 d	22 ± 0.6	22 ± 0.7 (0%)	27 ± 1.7** (+23%)
1 mo	18 ± 1.7	18 ± 1.1 (0%)	22 ± 1.1* (+22%)
3 mo	46 ± 10.7	24 ± 4.7 (−48%)	26 ± 4.7 (−44%)
6 mo	30 ± 2.7	30 ± 3.2 (0%)	143 ± 46.3* (+377%)
Serum OCT (activity/mL)			
2 d	QNS	QNS	QNS
10 d	469 ± 93.0	502 ± 45.6 (+7%)	QNS
1 mo	600 ± 111.8	678 ± 157.3 (+13%)	398 ± 41.3 (−34%)
3 mo	919 ± 245.5	835 ± 141.2 (−9%)	1,117 ± 203.8 (+22%)
6 mo	1,050 ± 205.1	800 ± 135.1 (−24%)	3,839 ± 1,755.6 (+266%)
Serum T4 (µg/dL)			
2 d	4.4 ± 0.25	3.5 ± 0.33 (−21%)*	QNS
10 d	3.5 ± 0.33	3.1 ± 0.29 (−11%)	3.3 ± 0.25 (−6%)
1 mo	3.8 ± 0.23	4.2 ± 0.42 (+11%)	3.4 ± 0.17 (−11%)
3 mo	1.8 ± 0.12	2.2 ± 0.2 (+22%)	3.3 ± 0.15* (+83%)
6 mo	2.7 ± 0.26	2.3 ± 0.15 (−15%)	3.6 ± 0.38 (+33%)

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Data are mean ± SEM; n = 5−10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Student's t-test ($p \leq 0.05$), as reported by the study authors.
**Significantly different from control by Student's t-test ($p \leq 0.01$), as reported by the study authors.

ALT = alanine aminotransferase (glutamic-pyruvic transaminase); ER = extrarespiratory; HEC = human equivalent concentration; OCT = ornithine carbamyl transferase; QNS = quantity of available material not sufficient for analysis; S-D = Sprague-Dawley; SEM = standard error of the mean; T4 = thyroxine.

Table B-17. Lung Weight and Edema Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC_{PU} in mg/m^3)[d]		
	0	98 (70)	754 (581)
Absolute lung weight (g)			
2 d	1.9 ± 0.15	1.6 ± 0.07 (−16%)	0.9 ± 0.02*** (−53%)
10 d	2.1 ± 0.07	1.7 ± 0.15* (−19%)	1.2 ± 0.06*** (−43%)
1 mo	2.2 ± 0.15	2.3 ± 0.1 (+5%)	1.6 ± 0.08*** (−27%)
3 mo	3.2 ± 0.45	2.9 ± 0.13 (−9%)	2.5 ± 0.07 (−22%)
6 mo	2.92 ± 0.115	2.85 ± 0.14 (−2%)	3.6 ± 0.288* (+23%)
Relative lung weight (% BW)			
2 d	1.2 ± 0.09	1.0 ± 0.07 (−17%)	0.9 ± 0.02*** (−25%)
10 d	1.0 ± 0.10	0.8 ± 0.06 (−20%)	0.8 ± 0.04* (−20%)
1 mo	0.7 ± 0.02	0.7 ± 0.03 (0%)	0.7 ± 0.02 (0%)
3 mo	0.7 ± 0.12	0.6 ± 0.03 (−14%)	0.6 ± 0.02 (−14%)
6 mo	0.51 ± 0.019	0.5 ± 0.025 (−2%)	0.7 ± 0.052*** (+37%)
Lung edema (% water)			
2 d	79.3 ± 0.31	77.3 ± 1.42 (−3%)	78.3 ± 0.36 (−1%)
10 d	80.2 ± 0.31	80.7 ± 0.27 (+0.6%)	78.9 ± 0.29*** (−2%)
1 mo	79.3 ± 0.38	79.7 ± 0.27 (+0.5%)	81.1 ± 0.27*** (+2%)
3 mo	78.7 ± 0.21	79.8 ± 0.3 (+1%)	81.1 ± 0.39*** (+3%)
6 mo	79 ± 0.3	80.6 ± 1.19 (+2%)	82.9 ± 1.61* (+5%)

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Data are mean ± SEM; n = 10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]HEC_{PU} values calculated using 6-month TWA body weight values based on graphically reported body weight data extracted using GrabIt! software.
*Significantly different from control by Student's t-test ($p \leq 0.05$), as reported by the study authors.
**Significantly different from control by Student's t-test ($p \leq 0.01$), as reported by the study authors.
***Significantly different from control by Student's t-test ($p \leq 0.005$), as reported by the study authors.

BW = body weight; HEC = human equivalent concentration; PU = pulmonary; S-D = Sprague-Dawley; SEM = standard error of the mean; TWA = time-weighted average.

Table B-18. Thyroid and Brain Weight Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m³ (HEC$_{ER}$ in mg/m³)		
	0	98 (20)	754 (157)
Absolute thyroid weight (g)			
2 d	0.0153 ± 0.00212	0.0175 ± 0.0019 (+14%)	0.0245 ± 0.00251* (+60%)
10 d	0.0206 ± 0.00186	0.0166 ± 0.0015 (−19%)	0.0231 ± 0.00281 (+12%)
1 mo	0.0232 ± 0.00156	0.0216 ± 0.00137 (−7%)	0.0262 ± 0.0017 (+13%)
3 mo	0.028 ± 0.00219	0.0306 ± 0.00225 (+9%)	0.0233 ± 0.00261 (−17%)
6 mo	0.0225 ± 0.00127	0.0232 ± 0.00291 (+3%)	0.0253 ± 0.00118 (+12%)
Relative thyroid weight (% BW)			
2 d	0.0104 ± 0.00166	0.0117 ± 0.00141 (+13%)	0.0254 ± 0.00272*** (+144%)
10 d	0.0106 ± 0.00162	0.0075 ± 0.00061 (−29%)	0.0181 ± 0.00277* (+71%)
1 mo	0.0075 ± 0.00066	0.0066 ± 0.00042 (−12%)	0.0118 ± 0.00065*** (+57%)
3 mo	0.0062 ± 0.00058	0.0063 ± 0.00047 (+2%)	0.0057 ± 0.00053 (−8%)
6 mo	0.0039 ± 0.00025	0.0042 ± 0.00057 (+8%)	0.0049 ± 0.00019 (+26%)
Absolute brain weight (g)			
2 d	2.1 ± 0.10	1.5 ± 0.06*** (−29%)	1.5 ± 0.04*** (−28%)
10 d	2.0 ± 0.08	1.5 ± 0.13*** (−25%)	1.5 ± 0.06*** (−25%)
1 mo	1.7 ± 0.06	1.8 ± 0.07 (+6%)	1.6 ± 0.06 (−6%)
3 mo	2.2 ± 0.03	2.2 ± 0.05 (0%)	2.3 ± 0.09 (+5%)
6 mo	2.2 ± 0.08	2.2 ± 0.05 (0%)	2.4 ± 0.05 (+9%)
Relative brain weight (% BW)			
2 d	1.4 ± 0.09	1.0 ± 0.05 (−29%)	1.5 ± 0.06*** (+7%)
10 d	0.9 ± 0.05	0.7 ± 0.06* (−22%)	1.1 ± 0.08* (+22%)
1 mo	0.6 ± 0.02	0.5 ± 0.02 (−17%)	0.7 ± 0.04*** (+17%)
3 mo	0.5 ± 0.02	0.4 ± 0.01 (−20%)	0.6 ± 0.03* (+20%)
6 mo	0.4 ± 0.01	0.4 ± 0.01 (0%)	0.5 ± 0.01*** (+25%)

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Data are mean ± SEM; n = 10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Student's t-test ($p \leq 0.05$), as reported by the study authors.
**Significantly different from control by Student's t-test ($p \leq 0.01$), as reported by the study authors.
***Significantly different from control by Student's t-test ($p \leq 0.005$), as reported by the study authors.

BW = body weight; ER = extrarespiratory; HEC = human equivalent concentration; SEM = standard error of the mean; S-D = Sprague-Dawley.

Table B-19. Hepatic Lesions in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b]	Dose Group, Analytical Concentration in mg/m^3 (HEC_{ER} in mg/m^3)		
	0	**98 (20)**	**754 (157)**
Pericholangitis			
2 d	2/10 (20%)	2/10 (20%)	1/10 (10%)
10 d	1/10 (10%)	4/10 (40%)	8/10* (80%)
1 mo	2/10 (20%)	3/10 (30%)	1/10 (10%)
3 mo	1/10 (10%)	1/10 (10%)	0/9 (0%)
6 mo	0/10 (0%)	0/10 (0%)	0/10 (0%)
Focal necrosis			
2 d	0/10 (0%)	3/10 (30%)	0/10 (0%)
10 d	0/10 (0%)	0/10 (0%)	0/10 (0%)
1 mo	0/10 (0%)	0/10 (0%)	0/10 (0%)
3 mo	0/10 (0%)	0/10 (0%)	0/9 (0%)
6 mo	0/10 (0%)	1/10 (10%)	2/10 (20%)
Focal hepatocyte hypertrophy			
3 mo	0/10 (0%)	0/10 (0%)	9/9* (100%)
Basophilic foci			
3 mo	0/10 (0%)	0/10 (0%)	4/9* (44%)
Focal hepatocyte hyperplasia			
3 mo	0/10 (0%)	0/10 (0%)	4/9* (44%)
Clear cell focus			
3 mo	0/10 (0%)	0/10 (0%)	1/9 (11%)
Hepatocellular necrosis			
3 mo	0/10 (0%)	0/10 (0%)	1/9 (11%)
Hepatocellular carcinoma			
6 mo	0/10 (0%)	0/10 (0%)	10/10* (100%)
Neoplastic nodule			
6 mo	0/10 (0%)	0/10 (0%)	10/10* (100%)

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Values denote number of animals showing changes/total number of animals examined (% incidence).
*Significantly different from control by Fisher's exact test ($p < 0.05$), as calculated for this review.

ER = extrarespiratory; HEC = human equivalent concentration; S-D = Sprague-Dawley.

Table B-20. Body and Liver Weight Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 18 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	312 (65.0)
Body weight (g)		
1 mo	326 ± 40	343 ± 31 (+5%)
3 mo	511 ± 53	521 ± 54 (+2%)
6 mo	585 ± 47	605 ± 62 (+3%)
9 mo	650 ± 40	673 ± 111 (+4%)
12 mo	651 ± 63	672 ± 145 (+3%)
18 mo	710 ± 82	553 ± 101* (−22%)
3-mo exposure; 15-mo recovery[d]	NA	721 ± 99 (+2%)
6-mo exposure; 12-mo recovery[d]	NA	626 ± 90* (−12%)
9-mo exposure; 9-mo recovery[d]	NA	534 ± 153* (−25%)
Absolute liver weight (g)		
1 mo	13.61 ± 1.35	15.36 ± 2.27 (+13%)
3 mo	17.73 ± 0.25	21.73 ± 4.14* (+23%)
6 mo	19.38 ± 3.30	23.92 ± 4.22* (+23%)
9 mo	18.92 ± 2.20	28.95 ± 7.93* (+53%)
12 mo	21.35 ± 4.83	41.16 ± 22.52* (+93%)
18 mo	16.89 ± 2.44	52.19 ± 29.05* (+209%)
3-mo exposure; 15-mo recovery[d]	NA	25.37 ± 8.29* (+50%)
6-mo exposure; 12-mo recovery[d]	NA	32.46 ± 16.50* (+92%)
9-mo exposure; 9-mo recovery[d]	NA	57.77 ± 31.81* (+242%)
Relative liver weight (% BW)		
1 mo	4.21 ± 0.55	4.46 ± 0.39 (+6%)
3 mo	3.46 ± 0.25	4.15 ± 0.58* (+20%)
6 mo	3.30 ± 0.35	3.94 ± 0.44* (+19%)
9 mo	2.91 ± 0.25	4.28 ± 0.92* (+47%)
12 mo	3.26 ± 0.53	6.45 ± 4.30* (+98%)
18 mo	2.39 ± 0.34	10.22 ± 6.63* (+328%)
3-mo exposure; 15-mo recovery[d]	NA	3.65 ± 1.51* (+53%)
6-mo exposure; 12-mo recovery[d]	NA	5.26 ± 2.76* (+120%)
9-mo exposure; 9-mo recovery[d]	NA	11.36 ± 6.20* (+375%)

[a]Griffin et al. (1979).
[b]Data are mean ± SD; *n* = 10/group at 1−12 months, 62 for control and 23 for exposed at 18 months, and 7−8/group in recovery groups.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data for recovery groups compared with control group data at 18 months.
*Significantly different from control by two-tailed Student's *t*-test ($p < 0.05$), conducted for this review.

BW = body weight; ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley.

Table B-21. Body and Liver Weight Data for Female S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 18 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	312 (65.0)
Body weight (g)		
1 mo	224 ± 20	214 ± 21 (−5%)
3 mo	292 ± 27	281 ± 22 (−4%)
6 mo	317 ± 49	318 ± 15 (+0.3%)
9 mo	344 ± 35	340 ± 44 (−1%)
12 mo	365 ± 53	379 ± 90 (+4%)
18 mo	435 ± 92	421 ± 77 (−3%)
3-mo exposure; 15-mo recovery[d]	NA	419 ± 61 (−4%)
6-mo exposure; 12-mo recovery[d]	NA	422 ± 111 (−3%)
9-mo exposure; 9-mo recovery[d]	NA	427 ± 58 (−2%)
Absolute liver weight (g)		
1 mo	9 ± 0.91	8.42 ± 1.27 (−6%)
3 mo	8.56 ± 2.91	9.87 ± 0.97 (+15%)
6 mo	10.63 ± 1.3	11.32 ± 1.10 (+7%)
9 mo	11.39 ± 1.46	10.64 ± 1.58 (−7%)
12 mo	11.82 ± 2.15	14.22 ± 2.11 (+20%)
18 mo	10.50 ± 2.18	11.43 ± 1.95 (+9%)
3-mo exposure; 15-mo recovery[d]	NA	10.36 ± 1.52 (−1%)
6-mo exposure; 12-mo recovery[d]	NA	10.77 ± 2.92 (+3%)
9-mo exposure; 9-mo recovery[d]	NA	11.75 ± 3.35 (+12%)
Relative liver weight (% BW)		
1 mo	4.02 ± 0.20	3.93 ± 0.28 (−2%)
3 mo	3.26 ± 0.30	3.51 ± 0.20 (+8%)
6 mo	3.39 ± 0.52	3.55 ± 0.28 (+5%)
9 mo	3.31 ± 0.35	3.13 ± 0.16 (−5%)
12 mo	3.26 ± 0.47	3.50 ± 0.25 (+7%)
18 mo	2.42 ± 0.30	2.73 ± 0.31 (+13%)
3-mo exposure; 15-mo recovery[d]	NA	2.48 ± 0.23 (+3%)
6-mo exposure; 12-mo recovery[d]	NA	2.60 ± 0.54 (+7%)
9-mo exposure; 9-mo recovery[d]	NA	2.73 ± 0.51 (+13%)

[a]Griffin et al. (1979).
[b]Data are mean ± SD; *n* = 8−10/group at 1−12 months, 67 for control and 30 for exposed at 18 months, and 10/group in recovery groups.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data for recovery groups compared with control group data at 18 months.

BW = body weight; ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley.

Table B-22. Select Hepatic Clinical Chemistry Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 18 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	312 (65.0)
Serum ALT (U/L)		
1 mo	16 ± 2	14 ± 2* (−13%)
3 mo	23 ± 11	17 ± 8 (−26%)
6 mo	30 ± 16	18 ± 7* (−40%)
9 mo	29 ± 7	23 ± 7 (−21%)
12 mo	22 ± 7	25 ± 19 (+14%)
18 mo	17 ± 13	78 ± 97* (+359%)
3-mo exposure; 15-mo recovery[d]	NA	17 ± 11 (0%)
6-mo exposure; 12-mo recovery[d]	NA	38 ± 31* (+124%)
9-mo exposure; 9-mo recovery[d]	NA	397 ± 627* (+2,235%)

[a]Griffin et al. (1979).
[b]Data are mean ± SD; *n* = 7−10/group at 1−12 months, 62 for control and 23 for exposed at 18 months, and 7−8/group in recovery groups.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data for recovery groups compared with control group data at 18 months.
*Significantly different from control by Student's *t*-test ($p < 0.05$), as conducted for this review.

ALT = alanine aminotransferase (glutamic-pyruvic transaminase), ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley.

Table B-23. Kidney Weight Data for S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 18 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC_{ER} in mg/m^3)	
	0	312 (65.0)
Absolute kidney weight (g) in males		
1 mo	1.25 ± 0.16	1.29 ± 0.17 (+3%)
3 mo	3.08 ± 0.22	3.22 ± 0.31 (+5%)
6 mo	3.39 ± 0.45	3.98 ± 0.57 (+17%)
9 mo	3.68 ± 0.37	4.19 ± 0.65 (+14%)
12 mo	4.22 ± 1.04	4.02 ± 0.54 (−5%)
18 mo	4.14 ± 0.72	4.43 ± 0.97 (+7%)
3-mo exposure; 15-mo recovery[d]	NA	4.55 ± 0.81 (+10%)
6-mo exposure; 12-mo recovery[d]	NA	4.40 ± 0.78 (+6%)
9-mo exposure; 9-mo recovery[d]	NA	4.48 ± 1.42 (+8%)
Absolute kidney weight (g) in females		
1 mo	0.85 ± 0.08	0.81 ± 0.04 (−5%)
3 mo	1.70 ± 0.15	1.85 ± 0.16 (+9%)
6 mo	2.00 ± 0.16	2.19 ± 0.21 (+10%)
9 mo	2.31 ± 0.28	2.03 ± 0.24 (−12%)
12 mo	2.39 ± 0.29	2.52 ± 0.45 (+5%)
18 mo	2.46 ± 0.73	2.66 ± 0.37 (+8%)
3-mo exposure; 15-mo recovery[d]	NA	2.5 ± 0.33 (+2%)
6-mo exposure; 12-mo recovery[d]	NA	2.58 ± 0.47 (+5%)
9-mo exposure; 9-mo recovery[d]	NA	2.87 ± 0.5 (+17%)

[a]Griffin et al. (1979).
[b]Data are mean ± SD; *n* = 10/group at 1−12 months, 62 for control and 23 for exposed at 18 months, and 7−8/group in recovery groups; relative kidney weights not reported by study authors.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data for recovery groups compared with control group data at 18 months.

ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley.

Table B-24. Time-Course Data for Incidence of Grossly Observed Hepatic Masses and Nodules (Combined) in S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 18 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b]	Dose Group, Analytical Concentration in mg/m^3 (HEC_{ER} in mg/m^3)	
	0	312 (65.0)
Male		
1 mo	0/10 (0%)	0/10 (0%)
3 mo	0/10 (0%)	0/10 (0%)
6 mo	0/10 (0%)	0/10 (0%)
9 mo	0/10 (0%)	6/16 (28%)
12 mo	0/10 (0%)	5/10* (50%)
18 mo	0/62 (0%)	22/23* (96%)
3-mo exposure; 15-mo recovery[c]	NA	6/10* (60%)
6-mo exposure; 12-mo recovery[c]	NA	7/10* (70%)
9-mo exposure; 9-mo recovery[c]	NA	7/10* (70%)
Found dead or sacrificed moribund	0/13 (0%)	11/16* (69%)
Female[d]		
1 mo	0/10 (0%)	0/10 (0%)
3 mo	0/10 (0%)	0/10 (0%)
6 mo	0/10 (0%)	0/10 (0%)
9 mo	0/10 (0%)	1/10 (10%)
12 mo	0/10 (0%)	0/10 (0%)
18 mo	0/68 (0%)	2/30 (7%)
3-mo exposure; 15-mo recovery[c]	NA	0/10 (0%)
6-mo exposure; 12-mo recovery[c]	NA	0/10 (0%)
9-mo exposure; 9-mo recovery[c]	NA	2/10 (20%)
Found dead or sacrificed moribund	0/7 (0%)	0/5 (0%)

[a]Griffin et al. (1979).
[b]Values denote number of animals showing changes ÷ total number of animals examined (% incidence); all hepatic lesions were combined by study authors.
[c]Exposed incidence in recovery group compared with control group at 18 months.
[d]Incidences as reported by the study authors in Table 16 of the Final Report; some incidence data appear to conflict with the incidence data at 18 months found in the Pathology Report (see Table B-16 of the Pathology Report).
*Significantly different from control by Fisher's exact test ($p < 0.05$), conducted for this review.

ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; S-D = Sprague-Dawley.

Table B-25. Incidence of Hepatic and Renal Lesions Identified by Histopathological Examination in S-D Rats Exposed to 2-Nitropropane via Inhalation for 18 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b]	Dose Group, Analytical Concentration in mg/m^3 (HEC_{ER} in mg/m^3)	
	0	**312 (65.0)**
Male		
Hepatic lesions at 18 mo		
Focal necrosis	2/63 (3%)	10/23* (43%)
Nodular hyperplasia	0/63 (0%)	22/23* (96%)
Vacuolar degeneration	7/63 (11%)	15/23* (65%)
Hepatocellular carcinoma	0/63 (0%)	7/23* (30%)
Renal lesions at 18 mo		
Renal calcification	16/63 (25%)	23/23* (100%)
Female		
Hepatic lesions at 18 mo		
Focal necrosis	0/67 (0%)	0/30 (0%)
Nodular hyperplasia	1/67 (1%)	6/30* (20%)
Vacuolar degeneration	2/67 (3%)	11/30* (37%)
Hepatocellular carcinoma	0/67 (0%)	0/30 (0%)
Renal lesions at 18 mo		
Renal calcification	34/67 (51%)	21/30 (70%)

[a]Griffin et al. (1979).
[b]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
*Significantly different from control by Fisher's exact test ($p < 0.05$), conducted for this review.

ER = extrarespiratory; HEC = human equivalent concentration; S-D = Sprague-Dawley.

Table B-26. Body Weight and Select Organ Weight Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	**608 (127)**
Body weight (g)		
0 wk	138 ± 13	131 ± 14 (−5%)
2 wk	256 ± 25	224 ± 25* (−13%)
4 wk	326 ± 31	303 ± 25 (−7%)
6 wk	395 ± 35	351 ± 27* (−11%)
13 wk	522 ± 44	476 ± 49* (−9%)
27 wk	616 ± 69	590 ± 62 (−4%)
Relative liver weight (% BW)		
10 d	3.93 ± 0.59	4.45 ± 0.52 (+13%)
1 mo	4.12 ± 0.34	4.57 ± 0.34 (+11%)
3 mo	3.41 ± 0.32	4.37 ± 0.26** (+28%)
6 mo	3.45 ± 0.30	4.95 ± 1.48** (+44%)
3 mo + 3-mo recovery[d]	NA	4.45 ± 1.16 (+29%)
Relative kidney weight (% BW)		
10 d	0.407 ± 0.024	0.429 ± 0.032 (+5%)
1 mo	0.371 ± 0.019	0.375 ± 0.016 (+1%)
3 mo	0.310 ± 0.011	0.337 ± 0.024** (+9%)
6 mo	0.305 ± 0.027	0.302 ± 0.023 (−1%)
3 mo + 3-mo recovery[d]	NA	0.292 ± 0.014 (−4%)
Relative brain weight (% BW)		
10 d	0.676 ± 0.091	0.807 ± 0.068** (+19%)
1 mo	0.552 ± 0.036	0.571 ± 0.053 (+3%)
3 mo	0.397 ± 0.028	0.411 ± 0.034 (+4%)
6 mo	0.386 ± 0.087	0.395 ± 0.066 (+2%)
3 mo + 3-mo recovery[d]	NA	0.363 ± 0.027 (−6%)

[a]Coulston et al. (1978).
[b]Data are mean ± SD; n = 9−10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data in recovery group compared with control group at 6 months.
*Significantly different from control by Student's t-test ($p < 0.02$), conducted for this review.
**Significantly different from control ($p < 0.01$), as reported by the study authors (unspecified method).

BW = body weight; ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley.

Table B-27. Body Weight and Select Organ Weight Data for Female S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC_{ER} in mg/m^3)	
	0	608 (127)
Body weight (g)		
0 wk	105 ± 11	102 ± NL[d] (−3%)
2 wk	156 ± 16	150 ± NL (−4%)
4 wk	193 ± 19	190 ± NL (−2%)
13 wk	257 ± 26	250 ± NL (−3%)
27 wk	286 ± 32	287 ± NL (+0.3%)
Relative liver weight (% BW)		
10 d	4.30 ± 0.26	4.34 ± 0.35 (+0.9%)
1 mo	3.93 ± 0.29	4.91 ± 0.52** (+25%)
3 mo	3.38 ± 0.28	4.23 ± 0.73** (+25%)
6 mo	3.18 ± 0.32	4.09 ± 0.45** (+29%)
3 mo + 3-mo recovery[e]	NA	3.37 ± 0.25 (+6%)
Relative kidney weight (% BW)		
10 d	0.398 ± 0.026	0.425 ± 0.046 (+7%)
1 mo	0.373 ± 0.029	0.387 ± 0.067 (+4%)
3 mo	0.311 ± 0.035	0.340 ± 0.028 (+9%)
6 mo	0.315 ± 0.023	0.345 ± 0.018 (+10%)
3 mo + 3-mo recovery[e]	NA	0.328 ± 0.028 (+4)
Relative brain weight (% BW)		
10 d	0.989 ± 0.065	1.059 ± 0.09 (+7%)
1 mo	0.872 ± 0.043	0.831 ± 0.04 (−5%)
3 mo	0.719 ± 0.082	0.772 ± 0.07 (+7%)
6 mo	0.678 ± 0.084	0.708 ± 0.08 (+4%)
3 mo + 3-mo recovery[e]	NA	0.644 ± 0.05 (−5%)

[a]Coulston et al. (1978).
[b]Data are mean ± SD; n = 9−10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]SD values for body weight in exposed females was not legible in the available copy of the study report.
[e]Data in recovery group compared with control group at 6 months.
**Significantly different from control ($p < 0.01$), as reported by the study authors (unspecified method).

BW = body weight; HEC = human equivalent concentration; NA = not applicable; NL = not legible; SD = standard deviation; S-D = Sprague-Dawley.

Table B-28. Select Hematological Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	608 (127)
Leukocyte count (10^3 cells/mm^3)		
10 d	7.9 ± 1.1	8.3 ± 1.0 (+5%)
1 mo	7.0 ± 2.1	8.6 ± 1.7 (+23%)
2 mo	12.4 ± 2.5	13.7 ± 1.5 (+11%)
3 mo	6.5 ± 1.4	7.0 ± 1.8 (+8%)
5 mo	10.0 ± 1.3	12.0 ± 1.5** (+20%)
6 mo	9.4 ± 3.4	11.5 ± 6.1 (+22%)
3 mo + 3-mo recovery[d]	NA	7.5 ± 2.9 (−20%)
Packed cell volume (%)		
10 d	42 ± 3	44 ± 2 (+5%)
1 mo	46 ± 3	46 ± 2 (0%)
2 mo	48 ± 1	47 ± 2 (−2%)
3 mo	47 ± 1	45 ± 2** (−4%)
5 mo	46 ± 1	46 ± 1 (0%)
6 mo	43 ± 5	42 ± 6 (−2%)
3 mo + 3-mo recovery[d]	NA	44 ± 2 (+2%)
Prothrombin time (s)		
10 d	10.1 ± 0.4	11.3 ± 0.6** (+12%)
1 mo	12.4 ± 2.1	12.2 ± 1.6 (−2%)
2 mo	15.4 ± 1.7	13.7 ± 2.4 (−11%)
3 mo	12.9 ± 2.7	13.3 ± 2.4 (+3%)
5 mo	21.6 ± 8.0	17.1 ± 3.3 (−21%)
6 mo	24.5 ± 6.8	28.4 ± 9.3 (+16%)
3 mo + 3-mo recovery[d]	NA	35 ± 11.8 (+43%)

[a]Coulston et al. (1978).
[b]Data are mean ± SD; n = 6−10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data in recovery group compared with control group at 6 months.
**Significantly different from control ($p < 0.01$), as reported by the study authors (unspecified method).

ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley.

Table B-29. Select Hematological Data for Female S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	**608 (127)**
Leukocyte count (10^3 cells/mm^3)		
10 d	8.3 ± 1.4	7.3 ± 2.0 (−12%)
1 mo	6.5 ± 2.0	7.3 ± 1.9 (+12%)
2 mo	7.9 ± 2.8	9.8 ± 2.3 (+24%)
3 mo	5.0 ± 1.8	4.4 ± 1.3 (−12%)
5 mo	7.8 ± 2.2	7.7 ± 1.6 (−1%)
6 mo	6.6 ± 6.5	4.5 ± 1.4 (−32%)
3 mo + 3-mo recovery[d]	NA	4.4 ± 2.2 (−33%)
Packed cell volume (%)		
10 d	45 ± 1	44 ± 3 (−2%)
1 mo	46 ± 2	45 ± 2 (−2%)
2 mo	45 ± 2	47 ± 2 (+4%)
3 mo	45 ± 2	44 ± 2 (−2%)
5 mo	45 ± 2	45 ± 2 (0%)
6 mo	45 ± 3	44 ± 3 (−2%)
3 mo + 3-mo recovery[d]	NA	46 ± 2 (+2%)
Prothrombin time (s)		
10 d	12.3 ± 3.8	11.6 ± NA[e] (−6%)
1 mo	11.4 ± 1.8	12.0 ± 0.9 (+5%)
2 mo	13.9 ± 1.8	10.9 ± 1.0** (−22%)
3 mo	15.6 ± 4.1	16.1 ± 7.0 (+3%)
5 mo	37.9 ± 33.6	18.0 ± 5.8 (−53%)
6 mo	21.7 ± 2.5	19.7 ± 4.8 (−10%)
3 mo + 3-mo recovery[d]	NA	23.8 ± 8.0 (+10%)

[a]Coulston et al. (1978).
[b]Data are mean ± SD; n = 4−10/group, unless otherwise noted.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data in recovery group compared with control group at 6 months.
[e]Data reported only for one rat; inadequate for statistical analysis.
**Significantly different from control (p < 0.01), as reported by the study authors (unspecified method).

ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley.

Table B-30. Select Serum Chemistry Data for Male S-D Rats Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	608 (127)
ALT (U/L)		
10 d	20 ± 5	31 ± 4** (+55%)
1 mo	20 ± 4	24 ± 5 (+20%)
2 mo	20 ± 2	25 ± 5 (+25%)
3 mo	20 ± 5	29 ± 5** (+45%)
5 mo	26 ± 8	28 ± 7 (+8%)
6 mo	50 ± 41	227 ± 560 (+354%)
6 mo (redraw[d])	33 ± 13	102 ± 69** (+209%)
3 mo + 3-mo recovery[e]	NA	41 ± 27 (−18%)
AST (U/L)		
6 mo	100 ± 28	507 ± 520** (+407%)**
T4 (µg/100 mL)		
10 d	8.0 ± 1.9	6.2 ± 1.7 (−23%)
1 mo	5.8 ± 0.6	4.6 ± 1.2 (−21%)
2 mo	7.6 ± 1.4	5.6 ± 1.8** (−26%)
3 mo	4.3 ± 0.8	2.9 ± 1.0 (−33%)
5 mo	10.9 ± 3.7	9.8 ± 0.8 (−10%)
6 mo	2.4 ± 1.6	1.4 ± 0.8 (−42%)
3 mo + 3-mo recovery[e]	NA	2.4 ± 0.7 (0%)
T3 uptake (%)		
10 d	63.4 ± 1.2	65 ± 2.6 (+3%)
1 mo	57.3 ± 1.2	56.9 ± 1.6 (−0.7%)
2 mo	61.3 ± 1.2	61.9 ± 1.2 (+1%)
3 mo	62.3 ± 3.4	58.2 ± 1.2** (−7%)
5 mo	62.2 ± 3.6	57.8 ± 1.4** (−7%)
6 mo	63.7 ± 3.5	58.4 ± 3.2** (−8%)
3 mo + 3-mo recovery[e]	NA	61 ± 1.4 (−4%)

[a]Coulston et al. (1978).
[b]Data are mean ± SD; n = 5−10/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Repeat blood drawing from additional 10 control and 10 exposed males.
[e]Data in recovery group compared with control group at 6 months.
**Significantly different from control (p < 0.01), as reported by the study authors (unspecified method).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; SD = standard deviation; S-D = Sprague-Dawley; T3 = triiodothyronine; T4 = thyroxine.

Table B-31. Non-neoplastic Microscopic Changes in Livers of Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 10 or 30 Days (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	608 (127)
Loss of glycogen		
10 d	6/10	7/10
30 d	6/10	7/10
Vacuolation		
10 d	3/10	8/10
30 d	7/10	8/10
Basophilic hepatocytes present		
10 d	0/10	7/10*
30 d	0/10	0/10
Single liver cell necrosis		
10 d	0/10	10/10*
30 d	2/10	9/10*
Mitosis		
10 d	1/10	6/9*
30 d	1/10	6/10
Bile ductile proliferation		
10 d	0/10	6/10*
30 d	0/10	2/10
Focal macrophages		
10 d	1/10	0/10
30 d	0/10	0/10
Broken cell walls		
10 d	0/10	0/10
30 d	2/10	6/10

[a]Coulston et al. (1978).
[b]Values denote number of animals showing changes/total number of animals examined.
[c]Findings reported as absent (0) or doubtful (±) by the study authors were counted as negative findings; findings reported as slight (+), moderate (++), or marked (+++) were counted as positive findings.
*Significantly different from control by 2-tailed Fisher's exact test ($p < 0.05$) conducted for this review.

ER = extrarespiratory; HEC = human equivalent concentration; S-D = Sprague-Dawley.

Table B-32. Microscopic Changes in Livers of Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 3 or 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	608 (127)
Bile duct proliferation		
3 mo	0/10	1/10
6 mo	0/10	4/10
3 mo + 3-mo recovery[d]	NA	2/10
Focal accumulation of macrophages		
3 mo	1/10	1/10
6 mo	0/10	5/10*
3 mo + 3-mo recovery[d]	NA	2/10
2+ necrotic hepatocytes		
3 mo	0/10	0/10
6 mo	0/10	2/10
3 mo + 3-mo recovery[d]	NA	0/10
Basophilic hepatocytes present		
3 mo	1/10	2/10
6 mo	0/10	2/10
3 mo + 3-mo recovery[d]	NA	1/10
Loss of glycogen		
3 mo	7/10	7/10
6 mo	8/10	10/10
3 mo + 3-mo recovery[d]	NA	10/10
Cytoplasmic vacuolation		
3 mo	2/10	10/10*
6 mo	7/10	9/10
3 mo + 3-mo recovery[d]	NA	10/10
6+ nuclear changes		
3 mo	1/10	10/10*
6 mo	0/10	4/10
3 mo + 3-mo recovery[d]	NA	1/10
Cytoplasmic inclusions		
3 mo	0/10	4/10
6 mo	0/10	5/10*
3 mo + 3-mo recovery[d]	NA	2/10
Nuclear inclusions		
3 mo	0/10	0/10
6 mo	0/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10
Clustered cell necrosis		
3 mo	0/10	2/10
6 mo	0/10	4/10
3 mo + 3-mo recovery[d]	NA	1/10
Broken cell walls		
3 mo	0/10	6/10*
6 mo	0/10	1/10
3 mo + 3-mo recovery[d]	NA	1/10

Table B-32. Microscopic Changes in Livers of Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 3 or 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	608 (127)
Hypertrophic areas and/or nodules		
3 mo	NR	NR
6 mo	0/10	10/10*
3 mo + 3-mo recovery[d]	NA	6/10*
Hyperplastic areas and/or nodules		
3 mo	NR	NR
6 mo	0/10	5/10*
3 mo + 3-mo recovery[d]	NA	6/10*

[a]Coulston et al. (1978).
[b]Values denote number of animals showing changes/total number of animals examined.
[c]Findings reported as absent (0) or doubtful (±) by the study authors were counted as negative findings; findings reported as slight (+), moderate (++), or marked (+++) were counted as positive findings.
[d]Incidence in recovery group compared with incidence in 6-month control animals for statistical analysis (conducted for this review).
*Significantly increased from control by 2-tailed Fisher's exact test ($p < 0.05$) conducted for this review.

ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; NR = not reported; S-D = Sprague-Dawley.

Table B-33. Non-neoplastic Microscopic Changes in Livers of Female S-D Rats Exposed to 2-Nitropropane via Inhalation for 10 or 30 Days (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	608 (127)
Loss of glycogen		
10 d	4/10	10/10*
30 d	0/10	0/10
Vacuolation		
10 d	2/10	1/10
30 d	0/10	0/10
Basophilic hepatocytes present		
10 d	0/10	0/10
30 d	0/10	0/10
Single liver cell necrosis		
10 d	0/10	0/10
30 d	0/10	0/10
Mitosis		
10 d	0/10	0/10
30 d	0/10	0/10
Bile ductile proliferation		
10 d	0/10	0/10
30 d	0/10	0/10
Focal macrophages		
10 d	1/10	1/10
30 d	0/10	0/10
Broken cell walls		
10 d	0/10	0/10
30 d	0/10	0/10

[a]Coulston et al. (1978).
[b]Values denote number of animals showing changes/total number of animals examined.
[c]Findings reported as absent (0) or doubtful (±) by the study authors were counted as negative findings; findings reported as slight (+), moderate (++), or marked (+++) were counted as positive findings.
*Significantly increased from control by 2-tailed Fisher's exact test ($p < 0.05$) conducted for this review.

ER = extrarespiratory; HEC = human equivalent concentration; S-D = Sprague-Dawley.

Table B-34. Microscopic Changes in Livers of Female S-D Rats Exposed to 2-Nitropropane via Inhalation for 3 or 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC_{ER} in mg/m^3)	
	0	608 (127)
Bile duct proliferation		
3 mo	0/10	1/10
6 mo	0/10	1/10
3 mo + 3-mo recovery[d]	NA	0/10
Focal accumulation of macrophages		
3 mo	2/10	1/10
6 mo	1/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10
2+ necrotic hepatocytes		
3 mo	0/10	0/10
6 mo	1/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10
Basophilic hepatocytes present		
3 mo	0/10	0/10
6 mo	0/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10
Loss of glycogen		
3 mo	6/10	7/10
6 mo	10/10	3/10
3 mo + 3-mo recovery[d]	NA	4/10
Cytoplasmic vacuolation		
3 mo	0/10	2/10
6 mo	0/10	5/10*
3 mo + 3-mo recovery[d]	NA	1/10
6+ nuclear changes		
3 mo	0/10	2/10
6 mo	0/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10
Cytoplasmic inclusions		
3 mo	0/10	0/10
6 mo	0/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10
Nuclear inclusions		
3 mo	0/10	0/10
6 mo	0/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10
Clustered cell necrosis		
3 mo	0/10	0/10
6 mo	0/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10
Broken cell walls		
3 mo	0/10	0/10
6 mo	0/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10

Table B-34. Microscopic Changes in Livers of Female S-D Rats Exposed to 2-Nitropropane via Inhalation for 3 or 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)	
	0	608 (127)
Hypertrophic areas and/or nodules		
3 mo	NR	NR
6 mo	0/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10
Hyperplastic areas and/or nodules		
3 mo	NR	NR
6 mo	0/10	0/10
3 mo + 3-mo recovery[d]	NA	0/10

[a]Coulston et al. (1978).
[b]Values denote number of animals showing changes/total number of animals examined.
[c]Findings reported as absent (0) or doubtful (±) by the study authors were counted as negative findings; findings reported as slight (+), moderate (++), or marked (+++) were counted as positive findings.
[d]Incidence in recovery group compared with incidence in 6-month control animals for statistical analysis (conducted for this review).
*Significantly increased from control by two-tailed Fisher's exact test ($p < 0.05$) conducted for this review.

ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; NR = not reported; S-D = Sprague-Dawley.

Table B-35. Body, Liver, and Kidney Weight Data for NZW Male Rabbits Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)		
	0	**98 (20)**	**754 (157)**
Body weight (g)			
1 mo	2,846 ± 60.9	2,712 ± 72.1 (−5%)	2,738 ± 122 (−4%)
3 mo	3,634 ± 197.9	3,537 ± 335.4 (−3%)	3,560 ± 55.1 (−2%)
6 mo	4,142 ± 183.0	3,218 ± 758.8 (−22%)	4,012 ± 158.2 (−3%)
Absolute liver weight (g)			
1 mo	80.4 ± 4.59	65.3 ± 3.49 (−18%)	73 ± 6.65 (−9%)
3 mo	89.9 ± 7.99	95.1 ± 8.03 (+6%)	94.5 ± 5.02 (+5%)
6 mo	81.9 ± 7.044	82.26 ± 2.857 (+0.4%)	82.13 ± 5.71 (+0.3%)
Relative liver weight (g)			
1 mo	2.8 ± 0.14	2.4 ± 0.1 (−14%)	2.7 ± 0.14 (−4%)
3 mo	2.5 ± 0.11	2.6 ± 0.26 (+4%)	2.7 ± 0.16 (+8%)
6 mo	NR	NR	NR
Absolute kidney weight (g)			
1 mo	17.8 ± 0.9	18.4 ± 1.01 (+3%)	18.2 ± 1.39 (+2%)
3 mo	21 ± 1.1	22 ± 1.0 (+5%)	21 ± 1.5 (0%)
6 mo	26.77 ± 3.067	22.48 ± 1.454 (−16%)	21.68 ± 0.995 (−19%)
Relative kidney weight (g)			
1 mo	0.6 ± 0.03	0.7 ± 0.04 (+17%)	0.7 ± 0.04 (+17%)
3 mo	1 ± 0	1 ± 0.1 (0%)	1 ± 0 (0%)
6 mo	NR	NR	NR

[a]Ulrich et al. (1977).
[b]Data are mean ± SEM; n = 5/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Mann-Whitney U test ($U \leq 2$; $p \leq 0.05$), as reported by the study authors.

ER = extrarespiratory; HEC = human equivalent concentration; NR = not reported; NZW = New Zealand White; SEM = standard error of the mean.

Table B-36. Clinical Chemistry Data for Male NZW Rabbits Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)		
	0	**98 (20)**	**754 (157)**
Serum ALT (U/L)			
1 mo	30 ± 4	24 ± 3.4 (−20%)	52 ± 2.2* (+73%)
3 mo	42 ± 3.7	43 ± 3.3 (+2%)	39 ± 4.5 (−7%)
6 mo	35 ± 5.3	27 ± 3.2 (−23%)	31 ± 6.7 (−11%)
Serum OCT (activity/mL)			
1 mo	470 ± 114.7	470 ± 139.3 (0%)	2,020 ± 260.6* (+330%)
3 mo	840 ± 277.2	2,400 ± 769.7 (+186%)	2,230 ± 462.0 (+166%)
6 mo	2,940 ± 1,591.5	1,250 ± 148.3 (−58%)	2,110 ± 585.7 (−28%)
Serum T4 (µg/dL)			
1 mo	3.4 ± 0.45	3.3 ± 0.23 (−3%)	3.6 ± 0.17 (+6%)
3 mo	2.2 ± 0.38	1.3 ± 0.38 (−41%)	2.9 ± 0.2 (+32%)
6 mo	2.1 ± 0.28	1.7 ± 0.36 (−19%)	3.8 ± 0.08* (+81%)

[a]Ulrich et al. (1977).
[b]Data are mean ± SEM; n = 5/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Mann-Whitney U test ($U \leq 2$; $p \leq 0.05$), as reported by the study authors.

ALT = alanine aminotransferase (glutamic-pyruvic transaminase); ER = extrarespiratory; HEC = human equivalent concentration; NZW = New Zealand White; OCT = ornithine carbamyl transferase; SEM = standard error of the mean; T4 = thyroxine.

Table B-37. Lung Weight and Edema Data for Male NZW Rabbits Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC_{PU} in mg/m^3)[d]		
	0	**98 (16)**	**754 (130)**
Absolute lung weight (g)			
1 mo	20.1 ± 1.26	16.5 ± 0.90 (−18%)	23.2 ± 2.26 (+15%)
3 mo	25.1 ± 3.08	23.9 ± 1.82 (−5%)	23.0 ± 0.69 (−8%)
6 mo	31.91 ± 3.506	20.91 ± 1.270* (−35%)	27.18 ± 3.278 (−15%)
Relative lung weight (g)			
1 mo	0.7 ± 0.05	0.6 ± 0.03 (−14%)	0.8 ± 0.05 (+14%)
3 mo	0.7 ± 0.07	0.7 ± 0.12 (0%)	0.6 ± 0.02 (−14%)
6 mo	NR	NR	NR
Lung edema (% water)			
1 mo	80.1 ± 0.22	79.4 ± 0.77 (−0.9%)	81.0 ± 1.24 (+1%)
3 mo	83.6 ± 2.40	79.5 ± 2.99 (−5%)	79.9 ± 0.33 (−4%)
6 mo	80.1 ± 0.09	79.8 ± 0.25 (−0.4%)	80.5 ± 0.68 (+0.5%)

[a]Ulrich et al. (1977).
[b]Data are mean ± SEM; *n* = 5/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]HEC_{PU} values calculated using 6-month TWA body weight values based on graphically reported body weight data extracted using GrabIt! software.
*Significantly different from control by Mann-Whitney U test ($U \leq 2$; $p \leq 0.05$), as reported by the study authors.

HEC = human equivalent concentration; NR = not reported; NZW = New Zealand White; PU = pulmonary; SEM = standard error of the mean; TWA = time-weighted average.

Table B-38. Thyroid and Brain Weight Data for Male NZW Rabbits Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b, c]	Dose Group, Analytical Concentration in mg/m^3 (HEC_{ER} in mg/m^3)		
	0	**98 (20)**	**754 (157)**
Absolute thyroid weight (g)			
1 mo	0.217 ± 0.0729	0.117 ± 0.0253 (−46%)	0.249 ± 0.0508 (+15%)
3 mo	0.501 ± 0.0556	0.591 ± 0.0351 (+18%)	0.404 ± 0.0219 (−19%)
6 mo	0.235 ± 0.033	0.316 ± 0.0188 (+35%)	0.3 ± 0.0337 (+28%)
Relative thyroid weight (g)			
1 mo	0.008 ± 0.0027	0.004 ± 0.001 (−50%)	0.010 ± 0.0021(+25%)
3 mo	0.014 ± 0.0014	0.017 ± 0.017 (+21%)	0.011 ± 0.0005 (−21%)
6 mo	NR	NR	NR
Absolute brain weight (g)			
1 mo	8.3 ± 0.34	10.1 ± 0.22* (+22%)	9.1 ± 0.33 (+10%)
3 mo	10.4 ± 0.25	8.7 ± 0.59 (−16%)	10.2 ± 0.19 (−2%)
6 mo	9.6 ± 0.22	9.87 ± 0.678 (+3%)	10.04 ± 0.415 (+5%)
Relative brain weight (g)			
1 mo	0.3 ± 0.01	0.4 ± 0.01* (+33%)	0.3 ± 0.02 (0%)
3 mo	0.3 ± 0.02	0.2 ± 0.03 (−33%)	0.3 ± 0.01 (0%)
6 mo	NR	NR	NR

[a]Ulrich et al. (1977).
[b]Data are mean ± SEM; n = 4−5/group.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Mann-Whitney U test ($U \leq 2$; $p \leq 0.05$), as reported by the study authors.

ER = extrarespiratory; HEC = human equivalent concentration; NR = not reported; NZW = New Zealand White; SEM = standard error of the mean.

Table B-39. Pulmonary Lesions in Male NZW Rabbits Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b]	Dose Group, Analytical Concentration in mg/m^3 (HEC_{PU} in mg/m^3)[c]		
	0	98 (16)[d]	754 (130)
Interstitial pneumonitis			
1 mo	1/5 (20%)	1/4 (25%)	2/5 (40%)
3 mo	1/5 (20%)	2/4 (50%)	2/5 (40%)
6 mo	4/5 (80%)	3/4 (75%)	3/5 (60%)
Alveolar necrosis			
1 mo	0/5 (0%)	0/4 (0%)	3/5 (60%)
3 mo	1/5 (20%)	0/4 (0%)	1/5 (20%)
6 mo	1/5 (20%)	0/4 (0%)	1/5 (20%)
Focal hemorrhage			
1 mo	0/5 (0%)	0/4 (0%)	3/5 (60%)
3 mo	1/5 (20%)	0/4 (0%)	1/5 (20%)
6 mo	1/5 (20%)	1/4 (25%)	2/5 (40%)
Pulmonary edema			
1 mo	0/5 (0%)	0/4 (0%)	3/5 (60%)
3 mo	1/5 (20%)	0/4 (0%)	0/5 (0%)
6 mo	1/5 (20%)	0/4 (0%)	0/5 (0%)
Interstitial edema			
6 mo	0/5 (0%)	0/4 (0%)	2/5 (40%)

[a]Ulrich et al. (1977).
[b]Values denote number of animals showing changes/total number of animals examined (% incidence).
[c]HEC_{PU} values calculated using 6-month TWA body weight values based on graphically reported body weight data extracted using GrabIt! software.
[d]Data are only legible for 4 in this group; it appears that data for the 5th animal is cut off in the study report.

HEC = human equivalent concentration; NZW = New Zealand White; PU = pulmonary; TWA = time-weighted average.

Table B-40. Hepatic Lesions in Male NZW Rabbits Exposed to 2-Nitropropane via Inhalation for up to 6 Months (7 Hours/Day, 5 Days/Week)[a]

Parameter[b]	Dose Group, Analytical Concentration in mg/m^3 (HEC$_{ER}$ in mg/m^3)		
	0	**98 (20)[c]**	**754 (157)**
Liver pericholangitis			
1 mo	1/5 (20%)	2/4 (50%)	3/5 (60%)
3 mo	2/5 (40%)	3/4 (75%)	3/5 (60%)
6 mo	5/5 (100%)	3/4 (75%)	5/5 (100%)
Hepatocyte vacuolation			
3 mo	0/5 (0%)	1/4 (25%)	0/5 (0%)
6 mo	0/5 (0%)	0/4 (0%)	1/5 (20%)
Focal mononuclear cell infiltration			
3 mo	0/5 (0%)	1/4 (25%)	1/5 (20%)
6 mo	0/5 (0%)	0/4 (0%)	0/5 (0%)

[a]Ulrich et al. (1977).
[b]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
[c]Data are only legible for 4 in this group; it appears that data for the 5th animal is cut off in the study report.

ER = extrarespiratory; HEC = human equivalent concentration; NZW = New Zealand White.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE

Dichotomous Noncancer Data

The benchmark dose (BMD) modeling of dichotomous data is conducted with the U.S. EPA's Benchmark Dose Software (BMDS, Version 2.6 was used for this document). For these data, the Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, and Weibull dichotomous models available within the software are fit using a benchmark response (BMR) of 10% extra risk. Alternative BMRs may also be used where appropriate, as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b). In general, the BMR should be near the low end of the observable range of increased risk in the study. BMRs that are too low can result in widely disparate benchmark dose lower confidence limit (BMDL) estimates from different models (high model dependence). Adequacy of model fit is judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals (absolute value < 2.0), and visual inspection of the model fit. Among all models providing adequate fit, the BMDL from the model with the lowest Akaike's information criterion (AIC) is selected as a potential point of departure (POD), if the BMDLs are sufficiently close (<threefold); if the BMDLs are not sufficiently close (>threefold), model dependence is indicated, and the model with the lowest reliable BMDL is selected.

Continuous Noncancer Data

BMD modeling of continuous data is conducted with U.S. EPA's BMDS (Version 2.6) as well. All continuous models available within the software (Exponential, Hill, Linear, Polynomial, and Power models) are fit using a standard reporting BMR of 1 standard deviation (SD) relative risk. Alternate BMRs may also be used (e.g., BMR = 10% relative derivation [RD] for body weight based on a biologically significant weight loss of 10%), as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b). In general, the BMR should be near the low end of the observable range of increased risk in the study. BMRs that are too low can result in widely disparate BMDL estimates from different models (high model dependence). An adequate fit is judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of the scaled residuals near the BMR (absolute value < 2.0), and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination is made as to whether the variance across dose groups is homogeneous. If a homogeneous variance model is deemed appropriate based on the statistical test provided by BMDS (i.e., Test 2), the final BMD results are estimated from a homogeneous variance model. If the test for homogeneity of variance is rejected ($p < 0.1$), the model is run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model does not adequately fit the data (i.e., Test 3; $p < 0.1$), the data set is considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL is selected if the BMDL estimates from different models vary >threefold (indicating model dependence); otherwise, the BMDL from the model with the lowest AIC is selected as a potential POD from which to derive the reference value.

Cancer Data

The model-fitting procedure for dichotomous cancer incidence is as follows. The Multistage cancer model in the U.S. 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 (absolute value < 2.0). Among the models providing adequate fit to the data, the BMDL for the model with the lowest AIC is selected as the POD, if the BMDLs are sufficiently close (<threefold); if the BMDLs are not sufficiently close (>threefold), model dependence is indicated, and the model with the lowest reliable BMDL is selected. In accordance with U.S. EPA (2012b) and U.S. EPA (2005a) guidance, BMD and BMDL values associated with an extra risk of 10% are calculated, which should be within the observable range of increased risk in a cancer bioassay. Modeling is performed for each individual tumor type with at least a statistically significant trend. Where applicable, the MS Combo model is used to evaluate the combined cancer risk of multiple tumor types. MS Combo is run using the incidence data for the individual tumor types and the polydegrees identified in the model runs for the individual tumor types.

Dropping the High Dose

In the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures much higher than the study lowest-observed-adverse-effect level (LOAEL) do not provide reliable information regarding the shape of the response at low doses. Such exposures, however, can have a strong effect on the shape of the fitted model in the low-dose region of the dose-response curve. Thus, if lack of fit is due to characteristics of the dose-response data for high doses, then the *Benchmark Dose Technical Guidance* document allows for data to be adjusted by eliminating the high-dose group (U.S. EPA, 2012b). Because the focus of BMD analysis is on the low-dose regions of the response curve, elimination of the high-dose group may be reasonable for certain data sets.

BMD MODELING TO IDENTIFY POTENTIAL POINTS OF DEPARTURE FOR THE DERIVATION OF A SCREENING SUBSCHRONIC PROVISIONAL REFERENCE DOSE

The data sets for relative liver weights and hepatocyte hypertrophy in male rats exposed to 2-nitropropane via gavage for 28 days (Kawakami et al., 2015) were selected to determine potential PODs for the screening subchronic provisional reference dose (p-RfD), using BMD analysis. Table A-1 in Appendix A shows the data that were modeled. Summaries of modeling approaches and results follow (see Tables C-3 and C-4 and Figures C-1 and C-2 for each data set).

Increased Relative Liver Weight in Male Rats Exposed to 2-Nitropropane via Gavage for 28 Days (Kawakami et al., 2015)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in male S-D rats exposed to 2-nitropropane via gavage for 28 days (see Table A-1). Table C-1 summarizes the BMD modeling results. The constant variance model provided an adequate fit to the variance data. With the constant variance model applied, all models except Exponential 5 and Hill models provided adequate fit to the data. BMDL values for models providing adequate fit were sufficiently close (<threefold difference), so the model with the lowest AIC was selected (Linear; the Polynomial and Power models converged on the Linear model). Figures C-1 shows the fit of the Linear model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ were 4.1 and 3.3 mg/kg-day, respectively.

Table C-1. BMD Modeling Results for Increased Relative Liver Weight in Male Rats Exposed to 2-Nitropropane via Gavage for 28 Days[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED, mg/kg-d)	$BMDL_{10}$ (HED, mg/kg-d)
Exponential 2[c]	0.2603	0.6681	−0.1759	−45.1230	4.4	3.6
Exponential 3[c]	0.2603	0.6681	−0.1759	−45.1230	4.4	3.6
Exponential 4[c]	0.2603	0.7996	−0.1959	−43.8652	3.3	1.7
Exponential 5[c]	0.2603	NA	-1.32×10^{-7}	−41.9297	3.5	1.7
Hill[c]	0.2603	NA	-1.30×10^{-6}	−41.9297	3.5	1.6
Linear[d, *]	**0.2603**	**0.7796**	**−0.162**	**−45.4317**	**4.1**	**3.3**
Polynomial (2-degree)[d]	0.2603	0.7796	−0.162	−45.4317	4.1	3.3
Polynomial (3-degree)[d]	0.2603	0.7796	−0.162	−45.4317	4.1	3.3
Power[c]	0.2603	0.7796	−0.162	−45.4317	4.1	3.3

[a]Kawakami et al. (2015).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Coefficients restricted to be positive.
*Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., RD10 = exposure concentration associated with a 10% relative deviation change in parameter); BMR = benchmark response; HED = human equivalent dose; NA = not applicable (computation failed); RD = relative deviation.

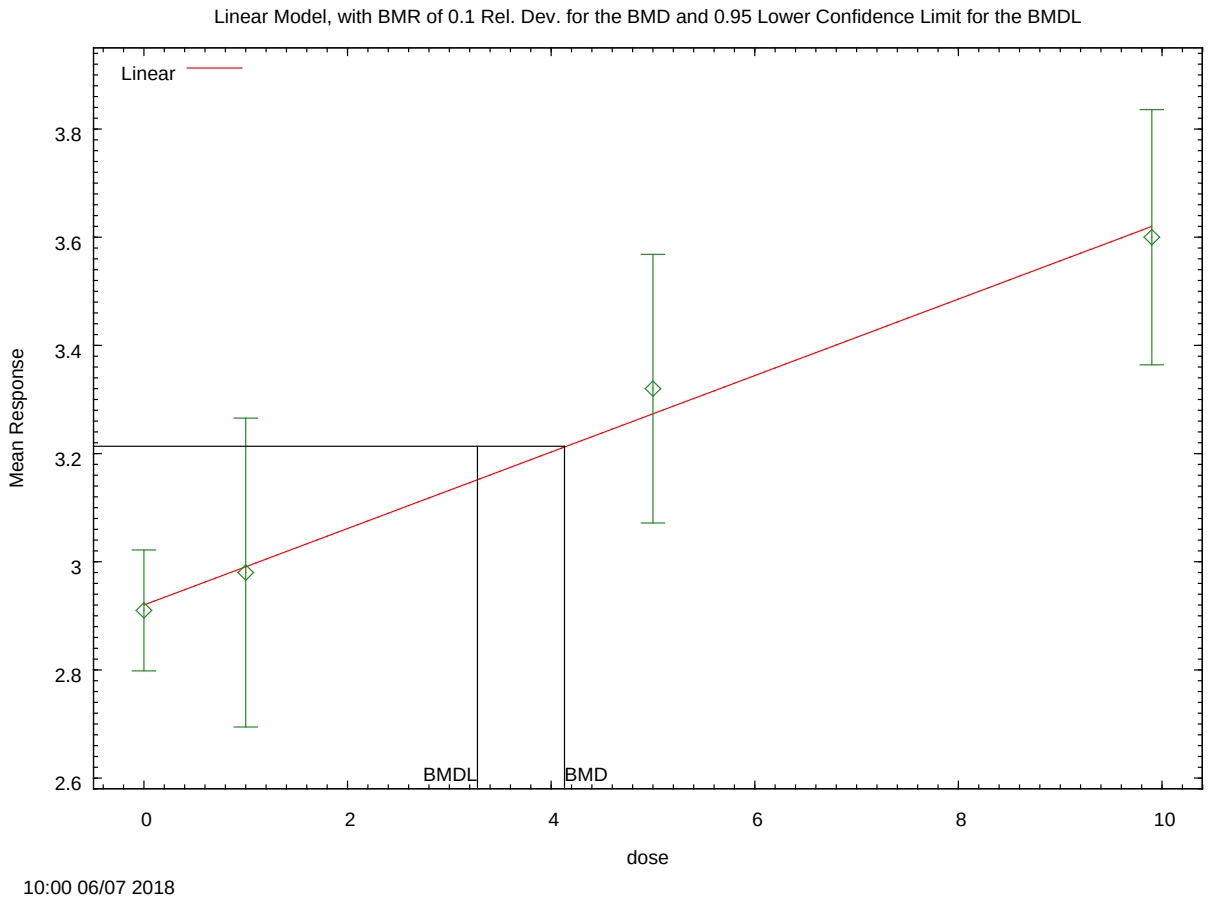

Figure C-1. Fit of Linear Model to Data for Increased Relative Liver Weight in Male Rats Exposed to 2-Nitropropane via Gavage for 28 Days (Kawakami et al., 2015) (BMR = RD 10)

Text Output for Figure C-1:

```
  ================================================================
         Polynomial Model. (Version: 2.20; Date: 10/22/2014)
         Input Data File:
C:/BMDS2601/Data/DataFiles/lin_2NP_kawakami_relLW_Lin-ConstantVariance-BMR10.(d)
         Gnuplot Plotting File:
C:/BMDS2601/Data/DataFiles/lin_2NP_kawakami_relLW_Lin-ConstantVariance-BMR10.plt
                                                Thu Jun 07 10:00:13 2018
 ================================================================

 BMDS Model Run
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   The form of the response function is:

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

   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
```

```
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   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
                          alpha =     0.034275
                            rho =            0   Specified
                         beta_0 =      2.92139
                         beta_1 =    0.0707191

           Asymptotic Correlation Matrix of Parameter Estimates

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

                    alpha       beta_0       beta_1

     alpha              1      -1e-007     1.4e-007

    beta_0       -1e-007            1        -0.71

    beta_1      1.4e-007        -0.71            1

                                Parameter Estimates

                                                                  95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha        0.0281113       0.00888958           0.0106881
0.0455346
         beta_0          2.92139        0.0535396             2.81646
3.02633
         beta_1        0.0707191       0.00961562           0.0518728
0.0895653

     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     5       2.91         2.92         0.09        0.168         -0.152
    1     5       2.98         2.99         0.23        0.168         -0.162
    5     5       3.32         3.27          0.2        0.168            0.6
  9.9     5        3.6         3.62         0.19        0.168         -0.287

 Model Descriptions for likelihoods calculated

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

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

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

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


                       Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1           25.964826            5     -41.929652
             A2           27.970389            8     -39.940778
             A3           25.964826            5     -41.929652
          fitted          25.715827            3     -45.431654
              R           12.620311            2     -21.240623

                     Explanation of Tests

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

                      Tests of Interest

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

   Test 1              30.7002          6          <.0001
   Test 2              4.01113          3          0.2603
   Test 3              4.01113          3          0.2603
   Test 4             0.497998          2          0.7796

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

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

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

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

              Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =     Relative deviation

Confidence level =          0.95

              BMD =        4.13098

             BMDL =        3.27604
```

Increased Incidence of Hepatocyte Hypertrophy in Male Rats Exposed to 2-Nitropropane via Gavage for 28 Days (Kawakami et al., 2015)

The procedure outlined above for dichotomous data was applied to the data for increased incidence of hepatocyte hypertrophy in male S-D rats exposed to 2-nitropropane via gavage for 28 days (see Table A-1). Table C-2 summarizes the BMD modeling results. All models provided adequate fit to the data. BMDLs for models providing adequate fit were not sufficiently close (>threefold), so the model with the lowest BMDL was selected (1-degree Multistage). Figure C-2 shows the fit of the 1-degree Multistage model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ for increased hepatocellular hypertrophy in male rats were 0.64 and 0.34 mg/kg-day.

Table C-2. BMD Modeling Results for Increased Incidence of Hepatocyte Hypertrophy in Male Rats Exposed to 2-Nitropropane via Gavage for 28 Days[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED, mg/kg-d)	$BMDL_{10}$ (HED, mg/kg-d)
Gamma[c]	3	0.01	0.9998	−0.019	8.74717	3.85	1.17
Logistic	2	0	1	0	10.7301	4.61	1.70
LogLogistic[d]	3	0	1	0	8.73019	4.53	1.48
LogProbit[d]	2	0	1	0	10.7301	4.44	1.42
Multistage (1-degree)[e, *]	**3**	**2.64**	**0.4511**	**−0.944**	**13.0787**	**0.64**	**0.34**
Multistage (2-degree)[e]	3	0.71	0.8706	−0.38	9.88838	1.92	0.62
Multistage (3-degree)[e]	3	0.11	0.9907	−0.152	8.92047	2.84	0.71
Probit	2	0	1	0	10.7301	4.25	1.51
Weibull[c]	2	0	1	0	10.7301	4.16	1.08

[a]Kawakami et al. (2015).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
*Selected model.

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

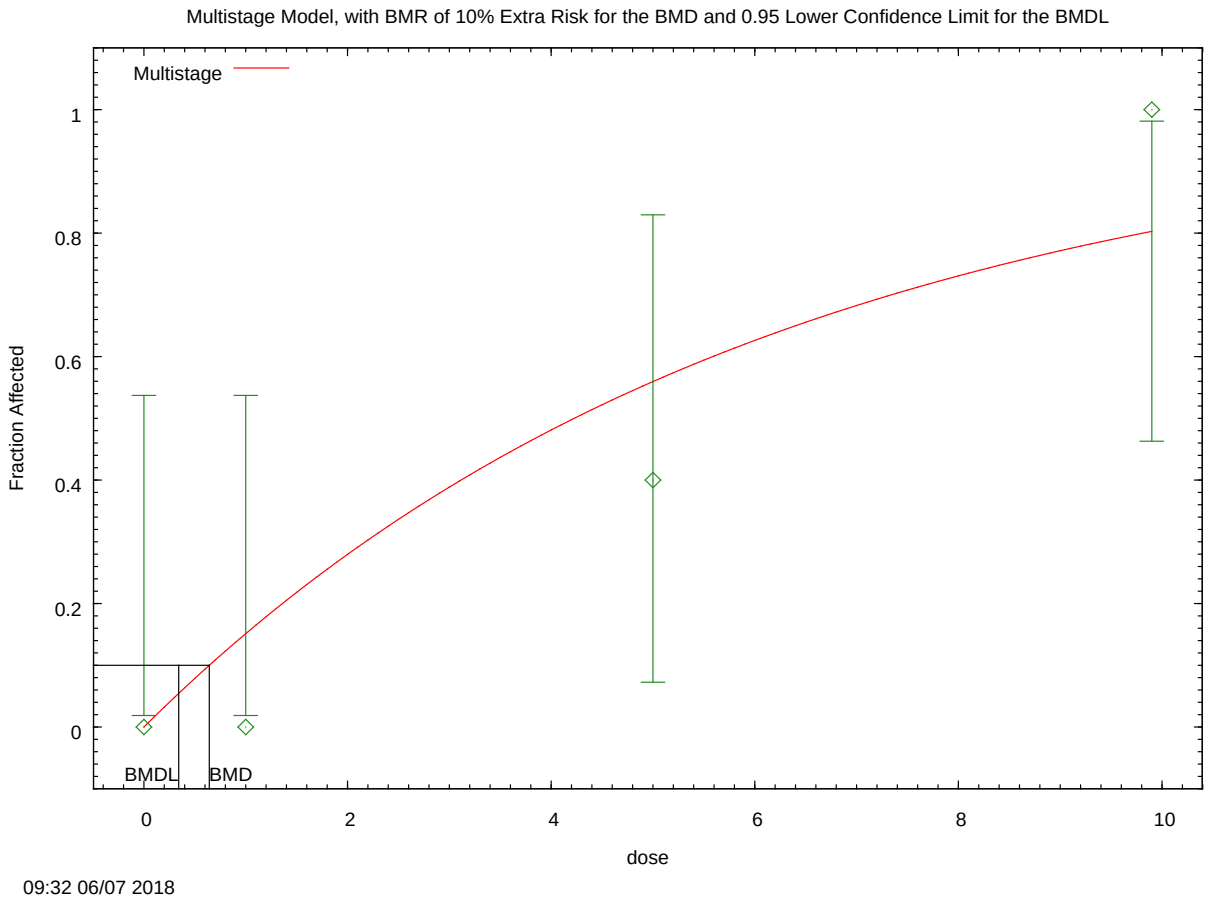

Figure C-2. Fit of 1-Degree Multistage Model to Data for Hepatocyte Hypertrophy in Male Rats Exposed to 2-Nitropropane via Gavage for 28 Days (Kawakami et al., 2015) (BMR = 10% Extra Risk)

Text Output for Figure C-2:

```
 ================================================================
        Multistage Model. (Version: 3.4; Date: 05/02/2014)
        Input Data File:
C:/BMDS2601/Data/DataFiles/mst_2NP_kawakami_hypertrophy_Mst1-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/BMDS2601/Data/DataFiles/mst_2NP_kawakami_hypertrophy_Mst1-BMR10-Restrict.plt
                                          Thu Jun 07 09:32:45 2018
 ================================================================

 BMDS_Model_Run
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   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 = 4
 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) = 9.74386e+018

          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)         0.164132        0.0674432           0.0319463
0.296319

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        -3.36506         4
   Fitted model        -5.53935         1       4.34858      3          0.2262
  Reduced model        -12.9489         1       19.1677      3       0.0002524

          AIC:         13.0787

                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000       5.000        0.000
    1.0000     0.1514         0.757     0.000       5.000       -0.944
    5.0000     0.5599         2.799     2.000       5.000       -0.720
    9.9000     0.8031         4.015     5.000       5.000        1.107

 Chi^2 = 2.64      d.f. = 3        P-value = 0.4511

   Benchmark Dose Computation
```

```
Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.641924

            BMDL =       0.341573

            BMDU =        1.33967

Taken together, (0.341573, 1.33967) is a 90     % two-sided confidence
interval for the BMD
```

BMD MODELING TO IDENTIFY POTENTIAL POINTS OF DEPARTURE FOR THE DERIVATION OF A SUBCHRONIC PROVISIONAL REFERENCE CONCENTRATION

The data sets for increased absolute and relative liver weights for 3 months (Lewis et al., 1979; Ulrich et al., 1977) were modeled to determine potential PODs for the subchronic provisional reference concentration (p-RfC), using BMD analysis. Table 7 in the "Derivation of Inhalation Reference Concentrations" section of the main document shows the data that were modeled. Summaries of modeling approaches and results (see Tables C-3 and C-4 and Figures C-3 and C-4) for each data set follow.

Increased Absolute Liver Weight in Male Rats Exposed to 2-Nitropropane via Inhalation for 3 Months (Lewis et al., 1979; Ulrich et al., 1977)

The procedure outlined above for continuous data was applied to the data for increased absolute liver weight in male Sprague-Dawley (S-D) rats exposed to 2-nitropropane via inhalation for 3 months (see Table 8). Table C-3 summarizes the BMD modeling results. The constant variance model did not provide an adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, all models except the Exponential 4 model provided adequate fit to the data (Exponential 5 and Hill models did not run because the data included too few exposure groups for those models). Benchmark concentration lower confidence limit (BMCL) values for models providing adequate fit were sufficiently close (<threefold difference), so the model with the lowest AIC was selected (Linear; the Polynomial and Power models converged on the Linear model). Figure C-3 shows the fit of the Linear model to the data. Based on HECs, the estimated BMC_{10} and $BMCL_{10}$ for increased absolute liver weights in male rats were 39.39 and 28.70 mg/m^3, respectively.

Table C-3. BMD Modeling Results for Increased Absolute Liver Weight in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 3 Months[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMC	AIC	BMC_{10} (HEC, mg/m^3)	$BMCL_{10}$ (HEC, mg/m^3)
Constant variance						
Linear[c]	0.07045	0.4396	0.576	68.2915	40.68	30.63
Nonconstant variance						
Exponential 2[d]	0.8709	0.2521	0.853	65.7268	45.38	34.90
Exponential 3[d]	0.8709	0.2521	0.853	65.7268	45.38	34.90
Exponential 4[d]	0.8709	NA	0.039	66.4149	20.17	9.15
Linear[c,]*	**0.8709**	**0.3195**	**0.761**	**65.4060**	**39.39**	**28.70**
Polynomial (2-degree)[c]	0.8709	0.3195	0.761	65.4060	39.39	28.70
Power[d]	0.8709	0.3195	0.761	65.4060	39.39	28.70

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Power restricted to ≥1.
*Selected model.

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., RD10 = exposure concentration associated with a 10% relative deviation change in parameter); BMD = benchmark dose; BMR = benchmark response; HEC = human equivalent concentration; NA = not applicable (computation failed); S-D = Sprague-Dawley.

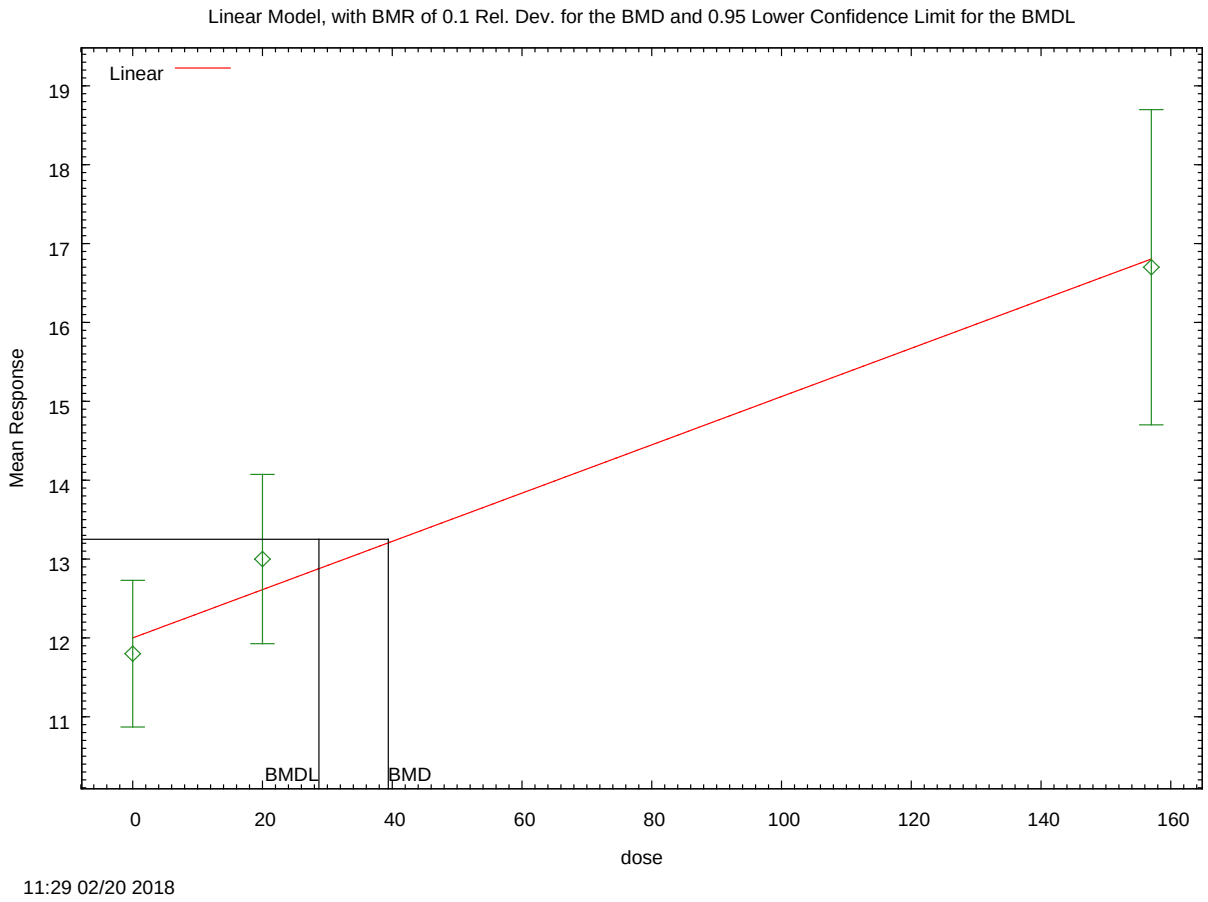

Figure C-3. Fit of Linear Model to Data for Increased Absolute Liver Weight in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 3 Months (Lewis et al., 1979; Ulrich et al., 1977) (BMR = RD 10)

Text Output for Figure C-3:

```
 ================================================================
        Polynomial Model. (Version: 2.20;  Date: 10/22/2014)
        Input Data File:
C:/BMDS2601/Data/DataFiles/lin_2NP_urlich_absLW_Lin-ModelVariance-BMR10.(d)
        Gnuplot Plotting File:
C:/BMDS2601/Data/DataFiles/lin_2NP_urlich_absLW_Lin-ModelVariance-BMR10.plt
                                          Tue Feb 20 11:29:43 2018
 ================================================================
 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

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

   Dependent variable = Mean
   Independent variable = Dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

```
   Total number of dose groups = 3
   Total number of records with missing values = 0
   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
                         lalpha =      1.23659
                            rho =            0
                         beta_0 =      12.0826
                         beta_1 =    0.0296727

           Asymptotic Correlation Matrix of Parameter Estimates

                 lalpha          rho       beta_0       beta_1

    lalpha            1           -1        0.053         -0.1

       rho           -1            1       -0.053          0.1

    beta_0        0.053       -0.053            1        -0.48

    beta_1         -0.1          0.1        -0.48            1

                                Parameter Estimates

                                                      95.0% Wald Confidence Interval
Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
lalpha          -9.0987          4.78625            -18.4796            0.282183
rho           3.86149          1.83111            0.272584             7.4504
beta_0          12.0463         0.323595              11.412             12.6805
beta_1        0.0305787       0.00584009           0.0191324           0.0420251

     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0    10       11.8           12          1.3         1.29         -0.603
   20    10         13         12.7          1.5         1.42          0.761
  157     9       16.7         16.8          2.6         2.47         -0.179

 Model Descriptions for likelihoods calculated

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

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

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

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

                     Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -30.847150           4      69.694299
             A2          -28.194268           6      68.388536
             A3          -28.207463           5      66.414927
```

```
         fitted          -28.702983            4      65.405966
              R          -43.310851            2      90.621702

                    Explanation of Tests

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

                     Tests of Interest

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

   Test 1              30.2332          4          <.0001
   Test 2              5.30576          2         0.07045
   Test 3             0.026391          1          0.8709
   Test 4             0.991039          1          0.3195

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

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

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

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

             Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =     Relative deviation

Confidence level =          0.95

             BMD =        39.3943

            BMDL =        28.6968
```

Increased Relative Liver Weight in Male Rats Exposed to 2-Nitropropane via Inhalation for 3 Months (Lewis et al., 1979; Ulrich et al., 1977)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in male S-D rats exposed to 2-nitropropane via inhalation for 3 months (see Table 8). Table C-4 summarizes the BMD modeling results. The constant variance model did not provide an adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, only the Linear and Exponential 2 models provided adequate fit to the data. BMC values were sufficiently close (<threefold difference), so the model with the lowest AIC was selected (Exponential 2). Figure C-4 shows the fit of the Exponential 2 model to the data. Based on HECs, the BMC_{10} and $BMCL_{10}$ for increased relative liver weight in male rats were 32.94 and 28.06 mg/m^3.

Table C-4. BMD Modeling Results for Relative Liver Weight in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 3 Months[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMC	AIC	BMC_{10} (HEC, mg/m^3)	$BMCL_{10}$ (HEC, mg/m^3)
Constant variance						
Linear[c]	<0.0001	0.5337	−0.442	−26.720	25.93	21.46
Nonconstant variance						
Exponential 2[d, *]	**0.4482**	**0.4473**	**−0.666**	**−49.115**	**32.94**	**28.06**
Exponential 3[d]	0.4482	NA	−0.121	−47.693	40.89	28.56
Exponential 4[d]	0.4482	NA	−1.051	−45.965	28.00	22.79
Linear[c]	0.4482	0.1887	−1.050	−47.965	28.01	22.79
Polynomial (2-degree)[c]	0.4482	NA	−0.121	−47.693	42.18	24.66
Power[d]	0.4482	NA	−0.121	−47.693	39.38	24.66

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Power restricted to ≥1.
*Selected model.

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., RD10 = exposure concentration associated with a 10% relative deviation change in parameter); BMD = benchmark dose; BMR = benchmark response; HEC = human equivalent concentration; NA = not applicable (computation failed); S-D = Sprague-Dawley.

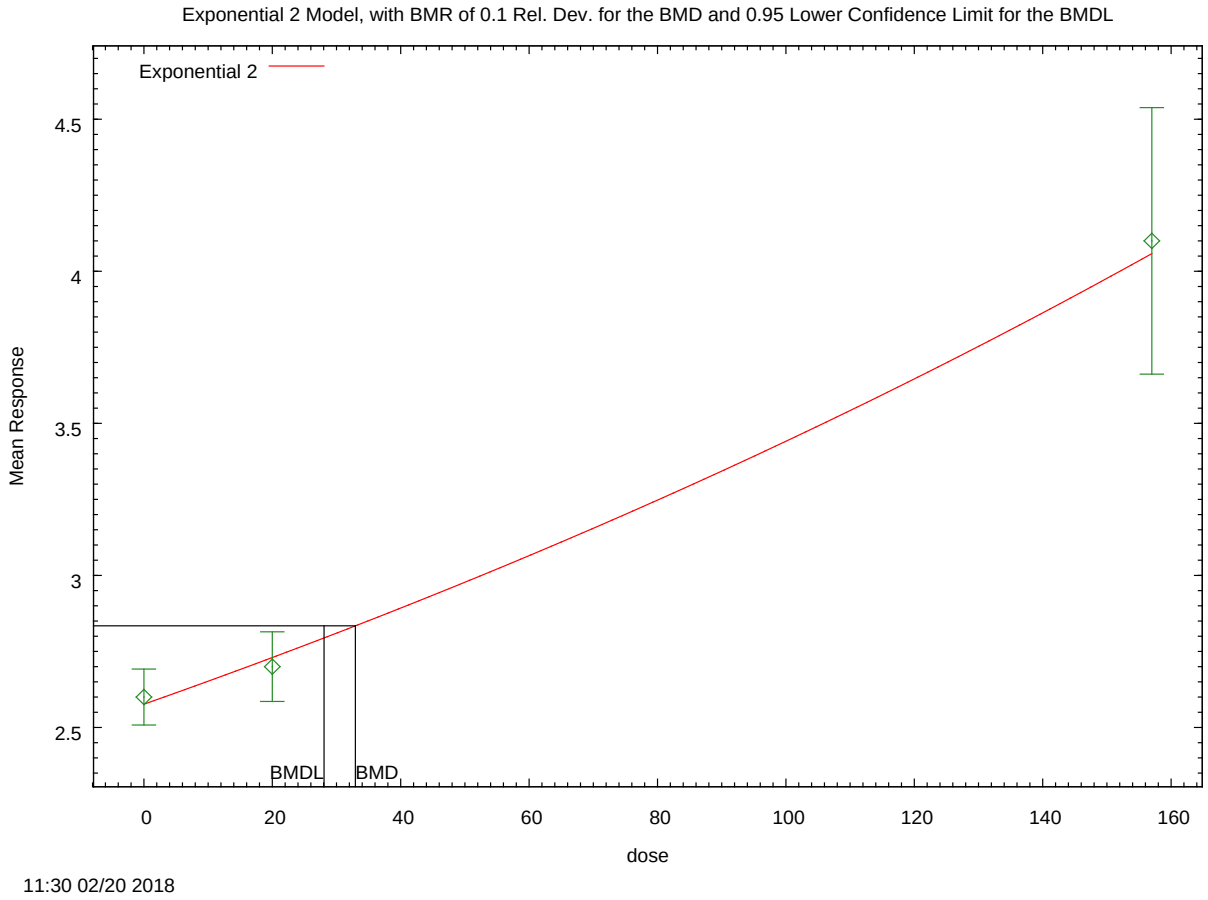

Figure C-4. Fit of Exponential 2 Model to Data for Increased Relative Liver Weight in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 3 Months (Lewis et al., 1979; Ulrich et al., 1977) (BMR = RD 10)

Text Output for Figure C-4:

```
 ================================================================
        Exponential Model. (Version: 1.10;  Date: 01/12/2015)
        Input Data File:
C:/BMDS2601/Data/DataFiles/exp_2NP_urlich_relLW_Exp-ModelVariance-BMR10-Up.(d)
        Gnuplot Plotting File:
                                              Tue Feb 20 11:30:42 2018
 ================================================================

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

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp(sign * b * dose)
      Model 3:     Y[dose] = a * exp(sign * (b * dose)^d)
      Model 4:     Y[dose] = a * [c-(c-1) * exp(-b * dose)]
      Model 5:     Y[dose] = a * [c-(c-1) * exp(-(b * dose)^d)]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.
```

```
   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 3
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

              Initial Parameter Values

              Variable          Model 2
              --------          --------
                lnalpha           -10.629
                    rho           6.75137
                      a           2.57096
                      b        0.00296337
                      c                 0 Specified
                      d                 1 Specified

                 Parameter Estimates

               Variable          Model 2          Std. Err.
               --------          -------          ---------
                lnalpha          -10.6902         0.0806022
                    rho           6.76745           1.65525
                      a           2.57653          0.032442
                      b        0.00289355       0.000307666

  NC = No Convergence

        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0      8          2.6         0.11
     20     10          2.7         0.16
    157      9          4.1         0.57

              Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         2.577       0.1173           0.5656
     20          2.73       0.1427          -0.6655
    157         4.058       0.5458           0.2299

Other models for which likelihoods are calculated:

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

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

```
  Model A3:        Yij = Mu(i) + e(ij)
              Var(e(ij)) = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
              Var(e(ij)) = Sigma^2

                            Likelihoods of Interest

                  Model      Log(likelihood)      DF         AIC
                 -------    -----------------    ----   ------------
                    A1         16.5538            4     -25.10759
                    A2        29.13404            6     -46.26807
                    A3        28.84649            5     -47.69298
                     R       -5.987725            2      15.97545
                     2        28.55773            4     -49.11545

Additive constant for all log-likelihoods =     -24.81.  This constant added to the
above values gives the log-likelihood including the term that does not
depend on the model parameters.

                               Explanation of Tests

Test 1:  Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A2 vs. A1)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does Model 2 fit the data? (A3 vs. 2)

                           Tests of Interest

  Test          -2*log(Likelihood Ratio)       D. F.         p-value
--------        ------------------------      ------     --------------
  Test 1                        70.24           4            < 0.0001
  Test 2                        25.16           2            < 0.0001
  Test 3                       0.5751           1              0.4482
  Test 4                       0.5775           1              0.4473

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

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

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

  The p-value for Test 4 is greater than .1.  Model 2 seems
  to adequately describe the data.

Benchmark Dose Computations:

  Specified Effect = 0.100000

         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      32.9389

              BMDL =      28.0603
```

BMD MODELING TO IDENTIFY POTENTIAL POINTS OF DEPARTURE FOR THE DERIVATION OF A PROVISIONAL INHALATION UNIT RISK

Only one data set provided dose-response information for carcinogenicity of 2-nitropropane (Lewis et al., 1979; Ulrich et al., 1977).

Increased Incidence of Hepatocellular Carcinoma in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 6 Months

The procedure outlined above for dichotomous cancer data was applied to the data for increased incidence of hepatocellular carcinoma in male rats exposed to 2-nitropropane via inhalation 7 hours/day, 5 days/week for 6 months (Lewis et al., 1979; Ulrich et al., 1977). The data are shown in Table A-4 in the cancer derivation section in Appendix A. Table C-5 summarizes the BMD modeling results. The Multistage models provided adequate statistical fit to the data. The $BMCL_{10}$ values were sufficiently close (<threefold), so the model with the lowest AIC was selected (Multistage 2-degree). Figure C-5 shows the fit of the 2-degree Multistage model to the data. Based on HECs, the BMC_{10} and $BMCL_{10}$ for liver carcinoma in male rats were 25.05 and 11.39 mg/m^3, respectively.

Table C-5. BMD Modeling Results for Incidence of Hepatocellular Carcinoma in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 6 Months[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMC	AIC	BMC_{10} (mg/m^3, HEC)	$BMCL_{10}$ (mg/m^3, HEC)
Multistage cancer (1-degree)[c]	2	4.48	0.1067	−1.789	9.95328	7.59	4.09
Multistage cancer (2-degree)[c, *]	**2**	**0.86**	**0.6516**	**−0.833**	**3.66468**	**25.05**	**11.39**

[a]Lewis et al. (1979); Ulrich et al. (1977).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
*Selected model.

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., 10 = concentration associated with 10% extra risk); BMD = benchmark dose; BMR = benchmark response; HEC = human equivalent concentration; S-D = Sprague-Dawley.

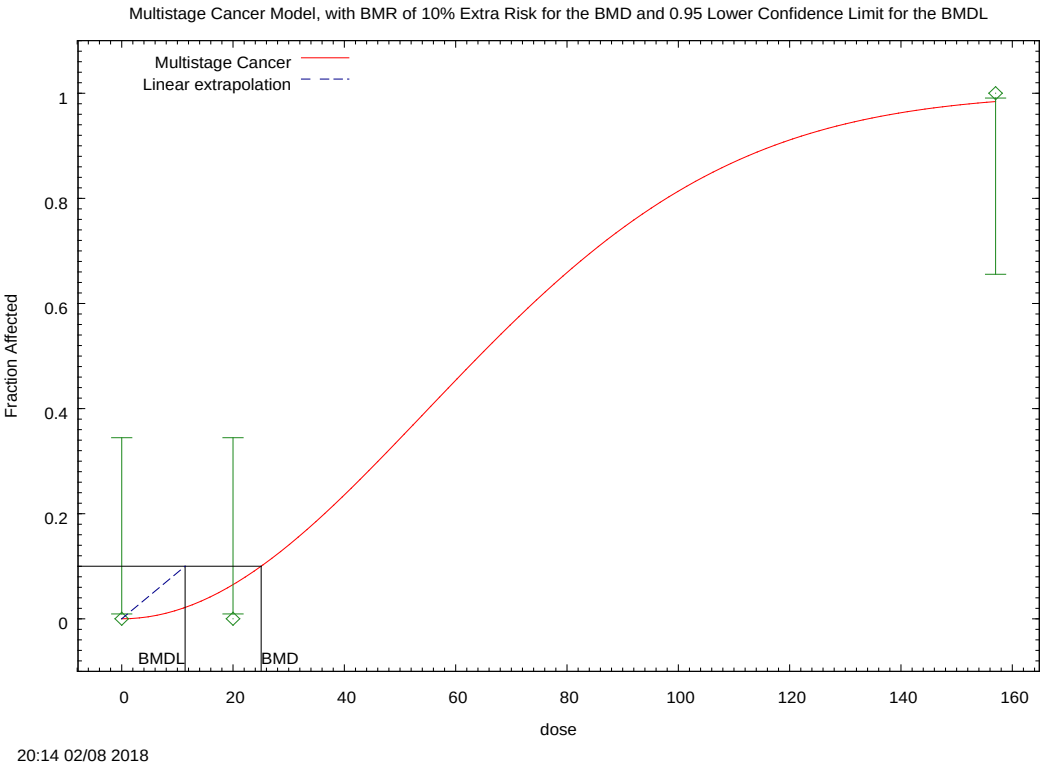

Figure C-5. Fit of the Multistage (2-Degree) Model to Data for Incidence of Hepatocellular Carcinoma in Male S-D Rats Exposed to 2-Nitropropane via Inhalation for 6 Months (Lewis et al., 1979; Ulrich et al., 1977)

Text Output for Figure C-5:

```
 =================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/BMDS2601/Data/DataFiles/msc_2NP_lewis_cancer_Msc2-BMR10.(d)
        Gnuplot Plotting File:
C:/BMDS2601/Data/DataFiles/msc_2NP_lewis_cancer_Msc2-BMR10.plt
                                              Thu Feb 08 20:14:07 2018
 =================================================================
 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) = 4.08933e+015

           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)      0.000167855     9.99192e-005       -2.79832e-005
0.000363693

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              0         3
   Fitted model       -0.832342         1       1.66468      2           0.435
  Reduced model        -19.0954         1       38.1909      2         <.0001

           AIC:         3.66468

                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      10.000        0.000
   20.0000     0.0649         0.649     0.000      10.000       -0.833
  157.0000     0.9840         9.840    10.000      10.000        0.403

 Chi^2 = 0.86      d.f. = 2        P-value = 0.6516


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95
```

```
              BMD =        25.0537

             BMDL =        11.3866

             BMDU =         38.479

Taken together, (11.3866, 38.479 ) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =    0.00878225
```

APPENDIX D. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2001). 2-Nitropropane. In Documentation of the threshold limit values and biological exposure indices. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). (2016). 2-Nitropropane [TLV/BEI]. In 2016 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents & biological exposure indices (pp. 45). Cincinnati, OH. https://www.acgih.org/forms/store/ProductFormPublic/2016-tlvs-and-beis.

ACGIH (American Conference of Governmental Industrial Hygienists). (2017). 2017 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents & biological exposure indices. Cincinnati, OH. http://www.acgih.org/forms/store/ProductFormPublic/2017-tlvs-and-beis.

Adachi, S; Takemoto, K; Hirosue, T; Hosogai, Y. (1993). Spontaneous and 2-nitropropane induced levels of 8-hydroxy-2'-deoxyguanosine in liver DNA of rats fed iron-deficient or manganese- and copper-deficient diets. Carcinogenesis 14: 265-268. http://dx.doi.org/10.1093/carcin/14.2.265.

AFOSR (Air Force Office for Scientific Research). (1992). Toxicokinetics, metabolism, and genotoxicity of nitropropanes in rats and mice. (ADA247681. NTIS/02984215. AFOSR-88-0299). Wright Patterson AFB, OH.

Andrae, U; Homfeldt, H; Vogl, L; Lichtmannegger, J; Summer, KH. (1988). 2-Nitropropane induces DNA repair synthesis in rat hepatocytes in vitro and in vivo. Carcinogenesis 9: 811-815. http://dx.doi.org/10.1093/carcin/9.5.811.

Andrae, U; Kreis, P; Coughtrie, MWH; Pabel, U; Meinl, W; Bartsch, I; Glatt, H. (1999). Activation of propane 2-nitronate to a genotoxicant in V79-derived cell lines engineered for the expression of rat hepatic sulfotransferases. Mutat Res Genet Toxicol Environ Mutagen 439: 191-197. http://dx.doi.org/10.1016/S1383-5718(98)00194-6.

Astorg, P; Bergès, R; Suschetet, M. (1994). Induction of gamma GT- and GST-P positive foci in the liver of rats treated with 2-nitropropane or propane 2-nitronate. Cancer Lett 79: 101-106. http://dx.doi.org/10.1016/0304-3835(94)90069-8.

ATSDR (Agency for Toxic Substances and Disease Registry). (2018). Minimal risk levels (MRLs). June 2018. Atlanta, GA: Agency for Toxic Substances and Disease Registry (ATSDR). Retrieved from http://www.atsdr.cdc.gov/mrls/index.asp

Bauchinger, M; Kulka, U; Schmid, E. (1987). Analysis of cytogenetic effect in human lymphocytes induced by metabolically activated 2-nitropropane. Mutat Res 217: 217-219. http://dx.doi.org/10.1016/0165-7992(87)90032-7.

Borges, LP; Borges, VC; Moro, AV; Nogueira, CW; Rocha, JB; Zeni, G. (2005). Protective effect of diphenyl diselenide on acute liver damage induced by 2-nitropropane in rats. Toxicology 210: 1-8. http://dx.doi.org/10.1016/j.tox.2005.01.002.

Borges, LP; Nogueira, CW; Panatieri, RB; Rocha, JB; Zeni, G. (2006). Acute liver damage induced by 2-nitropropane in rats: effect of diphenyl diselenide on antioxidant defenses. Chem Biol Interact 160: 99-107. http://dx.doi.org/10.1016/j.cbi.2005.12.010.

Bors, W; Michel, C; Dalke, C; Stettmaier, K; Saran, M; Andrae, U. (1993). Radical intermediates during the oxidation of nitropropanes - the formation of no2 from 2-nitropropane, its reactivity with nucleosides, and implications for the genotoxicity of 2-nitropropane. Chem Res Toxicol 6: 302-309.

Cabelof, DC; Raffoul, JJ; Ge, Y; Van Remmen, H; Matherly, LH; Heydari, AR. (2006). Age-related loss of the DNA repair response following exposure to oxidative stress. J Gerontol A Biol Sci Med Sci 61: 427-434.

Cabelof, DC; Raffoul, JJ; Yanamadala, S; Guo, Z; Heydari, AR. (2002). Induction of DNA polymerase beta-dependent base excision repair in response to oxidative stress in vivo. Carcinogenesis 23: 1419-1425.

CalEPA (California Environmental Protection Agency). (2011). Hot spots unit risk and cancer potency values. Appendix A. Sacramento, CA: Office of Environmental Health Hazard Assessment. http://standards.nsf.org/apps/group_public/download.php?document_id=19121.

CalEPA (California Environmental Protection Agency). (2016). All OEHHA acute, 8-hour and chronic reference exposure levels (chRELs) as of June 28 2016. Sacramento, CA: Office of Health Hazard Assessment. Retrieved from http://www.oehha.ca.gov/air/allrels.html

CalEPA (California Environmental Protection Agency). (2018a). Chemicals known to the state to cause cancer or reproductive toxicity May 25, 2018. (Proposition 65 list). Sacramento, CA: Office of Enironmental Health Hazard Assessment. http://oehha.ca.gov/proposition-65/proposition-65-list.

CalEPA (California Environmental Protection Agency). (2018b). OEHHA chemical database. Sacramento, CA: Office of Environmental Health Hazard Assessment. Retrieved from https://oehha.ca.gov/chemicals

Conaway, CC; Hussain, NS; Way, BM; Fiala, ES. (1991a). Evaluation of secondary nitroalkanes, their nitronates, primary nitroalkanes, nitrocarbinols, and other aliphatic nitro-compounds in the ames salmonella assay. Mutat Res 261: 197-207.

Conaway, CC; Nie, G; Hussain, NS; Fiala, ES. (1991b). Comparison of oxidative damage to rat-liver DNA and RNA by primary nitroalkanes, secondary nitroalkanes, cyclopentanone oxime, and related-compounds. Cancer Res 51: 3143-3147.

Coulston, F; Griffin, T; Rosenblum, I; Benitz, KF; Iatropoulos, M. (1978). Initial submission: Chronic inhalation toxicity study with 2-nitropropane in rats (6 month report; final draft) with cover letter dated 081092 and attachments [TSCA Submission]. (OTS054420. 88-920005226. 8EHQ-0892-6580). Albany Medical College. Submitted to the U.S. Environmental Protection Agency by Rohm and Haas Company.

Crawford, GN; Garrison, RP; Mcfee, DR. (1985). Health examination and air monitoring evaluation for workers exposed to 2-nitropropane. AIHA J 46: 45-47. http://dx.doi.org/10.1080/15298668591394365.

Dahlhaus, M; Appel, KE. (1993). N-Nitrosodimethylamine, N-nitrosodiethylamine, and N-nitrosomorpholine fail to generate 8-hydroxy-2-deoxyguanosine in liver DNA of male F344 rats. Mutat Res 285: 295-302. http://dx.doi.org/10.1016/0027-5107(93)90118-Y.

Dalke, C; Andrae, U. (1992). Propane 2-nitronate is more rapidly denitrified and is more genotoxic than 2-nitropropane in cultured rat hepatoma cells. Toxicol Lett 61: 149-157.

Davies, JE; Mynett, K; Gescher, A; Chipman, JK. (1993). DNA modification and repair by 2-nitropropane is extensive in hepatocytes of rats compared to those of humans and mice. Mutat Res 287: 157-164. http://dx.doi.org/10.1016/0027-5107(93)90009-5.

Dayal, R; Gescher, A; Harpur, ES; Pratt, I; Chipman, JK. (1989). Comparison of the hepatotoxicity in mice and the mutagenicity of three nitroalkanes. Fundam Appl Toxicol 13: 341-348. http://dx.doi.org/10.1016/0272-0590(89)90270-4.

Deng, H; Gao, H; Liu, Y. (2011). Biotransformation enzyme-dependent formation of micronucleus and multinuclei in cell line V79-hCYP2E1-hSULT1A1 by 2-nitropropane and N-nitrosodimethylamine. Mutat Res 726: 84-87. http://dx.doi.org/10.1016/j.mrgentox.2011.08.001.

Deng, XS; Tuo, J; Poulsen, HE; Loft, S. (1997). 2-Nitropropane-induced DNA damage in rat bone marrow. Mutat Res 391: 165-169. http://dx.doi.org/10.1016/S1383-5718(97)00064-8.

Deng, XS; Tuo, J; Poulsen, HE; Loft, S. (1998). Prevention of oxidative DNA damage in rats by brussels sprouts. Free Radic Res 28: 323-333. http://dx.doi.org/10.3109/10715769809069284.

Denk, B; Filser, JG; Deml, E; Kessler, W; Shen, J; Oesterle, D. (1990). Dose-dependent emergence of preneoplastic foci in rat livers after exposure to 2-nitropropane. Arch Toxicol 64: 329-331.

Doi, Y; Tamano, S; Kawabe, M; Sano, M; Imai, N; Nakashima, H; Furukawa, F; Hagiwara, A; Otsuka, M; Shirai, T. (2011). Concordance between results of medium-term liver carcinogenesis bioassays and long-term findings for carcinogenic 2-nitropropane and non-carcinogenic 1-nitropropane in F344 rats. J Toxicol Pathol 24: 207-213. http://dx.doi.org/10.1293/tox.24.207.

ECHA (European Chemicals Agency). (2018). Registered Substances: Helsinki, Finland. Retrieved from http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

El-Sokkary, GH. (2002). Inhibition of 2-nitropropane-induced cellular proliferation, DNA synthesis and histopathological changes by melatonin. Neuro Endocrinol Lett 23: 335-340.

Fiala, ES; Conaway, CC; Biles, WT; Johnson, B. (1987a). Enhanced mutagenicity of 2-nitropropane nitronate with respect to 2-nitropropane: possible involvement of free radical species. Mutat Res 179: 15-22.

Fiala, ES; Conaway, CC; Mathis, JE. (1989). Oxidative DNA and RNA damage in the livers of Sprague-Dawley rats treated with the hepatocarcinogen 2-nitropropane. Cancer Res 49: 5518-5522.

Fiala, ES; Czerniak, R; Castonguay, A; Conaway, CC; Rivenson, A. (1987b). Assay of 1-nitropropane, 2-nitropropane, 1-azoxypropane and 2-azoxypropane for carcinogenicity by gavage in Sprague-Dawley rats. Carcinogenesis 8: 1947-1949. http://dx.doi.org/10.1093/carcin/8.12.1947.

Fiala, ES; Nie, G; Sodum, R; Conaway, CC; Sohn, OS. (1993). 2-Nitropropane-induced liver DNA and RNA base modifications: Differences between Sprague-Dawley rats and New Zealand white rabbits. Cancer Lett 74: 9-14.

Fiala, ES; Sodum, RS; Hussain, NS; Rivenson, A; Dolan, L. (1995). Secondary nitroalkanes: induction of DNA repair in rat hepatocytes, activation by aryl sulfotransferase and hepatocarcinogenicity of 2-nitrobutane and 3-nitropentane in male F344 rats. Toxicology 99: 89-97. http://dx.doi.org/10.1016/0300-483X(94)03004-L.

Galloway, SM; Armstrong, MJ; Reuben, C; Colman, S; Brown, B; Cannon, C; Bloom, AD; Nakamura, F; Ahmed, M; Duk, S; Rimpo, J; Margolin, BH; Resnick, MA; Anderson, B; Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells evaluations of 108 chemicals [Review]. Environ Mol Mutagen 10: 1-175. http://dx.doi.org/10.1002/em.2850100502.

Gargas, ML; Burgess, RJ; Voisard, DE; Cason, GH; Andersen, ME. (1989). Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98: 87-99.

George, E; Burlinson, B; Gatehouse, D. (1989). Genotoxicity of 1- and 2-nitropropane in the rat. Carcinogenesis 10: 2329-2334. http://dx.doi.org/10.1093/carcin/10.12.2329.

Göggelmann, W; Bauchinger, M; Kulka, U; Schmid, E. (1988). Genotoxicity of 2-nitropropane and 1-nitropropane in Salmonella typhimurium and human lymphocytes. Mutagenesis 3: 137-140. http://dx.doi.org/10.1093/mutage/3.2.137.

Griffin, T; Davies, D; Groblewski, G; Arias, W; Benitz, KF; Iatropoulos, M. (1979). Letter from International Minerals and Chemical Corporation responding to US EPA letter dated February 5, 1979 concerning 2-nitropropane with attachments [TSCA Submission]. (OTS0200504. 8EHQ-0379-0170). Albany Medical College. Submitted to the U.S. Environmental Protection Agency by International Minerals and Chemical Corporation.

Griffin, TB; Coulston, F; Stein, AA. (1980). Chronic inhalation exposure of rats to vapors of 2-nitropropane at 25 ppm. Ecotoxicol Environ Saf 4: 267-281. http://dx.doi.org/10.1016/0147-6513(80)90029-9.

Griffin, TB; Stein, AA; Coulston, F. (1981). Histologic study of tissues and organs from rats exposed to vapors of 2-nitropropane at 25 ppm. Ecotoxicol Environ Saf 5: 194-201. http://dx.doi.org/10.1016/0147-6513(81)90034-8.

Guo, N; Conaway, CC; Hussain, NS; Fiala, ES. (1990). Sex and organ differences in oxidative DNA and RNA damage due to treatment of Sprague-Dawley rats with acetoxime or 2-nitropropane. Carcinogenesis 11: 1659-1662.

Haas-Jobelius, M; Coulston, F; Korte, F. (1992). Effects of short-term inhalation exposure to 1-nitropropane and 2-nitropropane on rat liver enzymes. Ecotoxicol Environ Saf 23: 253-259.

Haas-Jobelius, M; Ziegler-Skylakakis, K; Andrae, U. (1991). Nitroreduction is not involved in the genotoxicity of 2-nitropropane in cultured mammalian cells. Mutagenesis 6: 87-91. http://dx.doi.org/10.1093/mutage/6.1.87.

Hardin, BD; Bond, GP; Sikov, MR; Andrew, FD; Beliles, RP; Niemeier, RW. (1981). Testing of selected workplace chemicals for teratogenic potential. Scand J Work Environ Health 7: 66-75.

Harrison, R; Letz, G; Pasternak, G; Blanc, P. (1987). Fulminant hepatic failure after occupational exposure to 2-nitropropane. Ann Intern Med 107: 466-468.

Harrison, RJ; Pasternak, G; Blanc, P; Basuk, P; Letz, G. (1985). Leads from the MMWR. Acute hepatic failure after occupational exposure to 2-nitropropane. JAMA 254: 3415-3416.

Hasegawa, R; Chujo, T; Sai-Kato, K; Umemura, T; Tanimura, A; Kurokawa, Y. (1995). Preventive effects of green tea against liver oxidative DNA damage and hepatotoxicity in rats treated with 2-nitropropane. Food Chem Toxicol 33: 961-970. http://dx.doi.org/10.1016/0278-6915(95)00064-9.

Haworth, S; Lawlor, T; Mortelmans, K; Speck, W; Zeiger, E. (1983). Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 5: 3-142. http://dx.doi.org/10.1002/em.2860050703.

Hine, CH; Pasi, A; Stephens, BG. (1978). Fatalities following exposure to 2-nitropropane. J Occup Environ Med 20: 333-337.

Hite, M; Skeggs, H. (1979). Mutagenic evaluation of nitroparaffins in the Salmonella typhimurium/mammalian-microsome test and the micronucleus test. Environ Mutagen 1: 383-389.

HSDB (Hazardous Substances Data Bank). (2006). 2-Nitropropane (CASRN: 79-46-9) [Database]. Bethesda, MD: U.S. National Library of Medicine, Toxicology Data Network (TOXNET). Retrieved from https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm

Hussain, NS; Conaway, CC; Guo, N; Asaad, W; Fiala, ES. (1990). Oxidative DNA and RNA damage in rat liver due to acetoxime: Similarity to effects of 2-nitropropane. Carcinogenesis 11: 1013-1016. http://dx.doi.org/10.1093/carcin/11.6.1013.

IARC (International Agency for Research on Cancer). (1999). 2-Nitropropane [Review]. IARC Monogr Eval Carcinog Risks Hum 71: 1079-1094.

IARC (International Agency for Research on Cancer). (2018). IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php.

Ibrahim, M; Prigol, M; Hassan, W; Nogueira, CW; Rocha, JB. (2010). Protective effect of binaphthyl diselenide, a synthetic organoselenium compound, on 2-nitropropane-induced hepatotoxicity in rats. Cell Biochem Funct 28: 258-265. http://dx.doi.org/10.1002/cbf.1645.

IPCS (International Programme on Chemical Safety). (2018). INCHEM: Chemical safety information from intergovernmental organizations. Geneva, Switzerland: World Health Organization, Canadian Centre for Occupational Health and Safety. Inter-Organization Programme for the Sound Management of Chemicals. Retrieved from http://www.inchem.org/

Kawakami, S; Araki, T; Nakajima, M; Kusuoka, O; Uchida, K; Sato, N; Tanabe, Y; Takahashi, K; Wako, Y; Kawasako, K; Tsurui, K. (2015). Repeated-dose liver micronucleus assay: an investigation with 2-nitropropane, a hepatocarcinogen. Mutat Res Genet Toxicol Environ Mutagen 780-781: 60-63. http://dx.doi.org/10.1016/j.mrgentox.2014.06.005.

Kennedy, GL, Jr; Graepel, GJ. (1991). Acute toxicity in the rat following either oral or inhalation exposure. Toxicol Lett 56: 317-326. http://dx.doi.org/10.1016/0378-4274(91)90160-8.

Kliesch, U; Adler, ID. (1987). Micronucleus test in bone marrow of mice treated with 1-nitropropane, 2-nitropropane and cisplatin. Mutat Res 192: 181-184. http://dx.doi.org/10.1016/0165-7992(87)90053-4.

Kohl, C; Gescher, A. (1997). Denitrification of the genotoxicant 2-nitropropane: relationship to its mechanism of toxicity. Xenobiotica 27: 843-852. http://dx.doi.org/10.1080/004982597240208.

Kohl, C; Morgan, P; Gescher, A. (1995). Metabolism of the genotoxicant 2-nitropropane to a nitric oxide-species. Chem Biol Interact 97: 175-184. http://dx.doi.org/10.1016/0009-2797(95)03614-R.

Kohl, C; Mynett, K; Davies, JE; Gescher, A; Chipman, JK. (1994). Propane 2-nitronate is the major genotoxic form of 2-nitropropane. Mutat Res 321: 65-72. http://dx.doi.org/10.1016/0165-1218(94)90121-X.

Kreis, P; Brandner, S; Coughtrie, MW; Pabel, U; Meinl, W; Glatt, H; Andrae, U. (2000). Human phenol sulfotransferases hP-PST and hM-PST activate propane 2-nitronate to a genotoxicant. Carcinogenesis 21: 295-299. http://dx.doi.org/10.1093/carcin/21.2.295.

Lewis, TR; Ulrich, CE; Busey, WM. (1979). Subchronic inhalation toxicity of nitromethane and 2-nitropropane. J Environ Pathol Toxicol 2: 233-249.

Litton Bionetics. (1977a). Letter from Mobil Oil Corp. to USEPA regarding mutagenicity evaluation of 2-nitropropane with attachments dated 04/26/94 [TSCA Submission]. (OTS0572469. Doc #86940000366). Submitted to the U.S. Environmental Protection Agency by Mobil Oil Corp.

Litton Bionetics. (1977b). Mutagenicity evaluation of 2-nitropropane with cover letter dated 04/26/94 [TSCA Submission]. (OTS0572475. Doc #86940000372). Submitted to the U.S. Environmental Protection Agency by Mobil Oil Corporation.

Löfroth, G; Nilsson, L; Andersen, JR. (1986). Structure-activity relationship of nitroalkane-induced mutagenicity in the Ames Salmonella assay. In Genetic Toxicology of Environmental Chemicals: Proceedings of the Fourth International Conference on Environmental Mutagens, Held in Stockholm, Sweden, June 24-28, 1985. New York, NY: A.R. Liss.

Machle, W; Scott, EW; Treon, J. (1940). The physiological response of animals to some simple mononitroparaffins and to certain derivatives of these compounds. J Ind Hyg Toxicol 22: 315-332.

Marker, EK; Kulkarni, AP. (1986). Cytochrome P-450-mediated denitrification of 2-nitropropane in mouse liver microsomes. J Biochem Mol Toxicol 1: 71-83. http://dx.doi.org/10.1002/jbt.2570010308.

Markofsky, SB. (2012). Nitro-compounds, aliphatic. In B Elvers (Ed.), Ullmann's Encyclopedia of Industrial Chemistry (7th ed.). Hoboken, NJ: WileyVCH Verlag GmbH & Co. http://dx.doi.org/10.1002/14356007.a17_401.pub2.

McGregor, DP. (1981). Tier II mutagenic screening of 13 NIOSH priority compounds including 2-nitropropane, with cover letter dated 05/09/94 [TSCA Submission]. (OTS0557388. Doc #86940000979.). Inveresk Research International. Submitted to the U.S. Environmental Protection Agency by Miles Inc.

Miller, ME; Temple, GW. (1980). Letter from International Minerals and Chemical Corporation to USEPA submitting additional information on 2-nitropropane with attachments. (OTS0200504. Doc #88-8000156. 8EHQ-1280-0170). Albany Medical College. Submitted to the U.S. Environmental Protection Agency by International Minerals and Chemical Corporation.

Mueller, WF; Coulston, F; Korte, F. (1983). Comparative metabolism of 2-nitropropane in rats and chimpanzees. Chemosphere 12: 231-237.

Muller-Tegethoff, K; Kasper, P; Muller, L. (1995). Evaluation studies on the in vitro rat hepatocyte micronucleus assay. Mutat Res 335: 293-307. http://dx.doi.org/10.1016/0165-1161(95)00033-X.

Nakayama, K; Kawano, Y; Kawakami, Y; Moriwaki, N; Sekijima, M; Otsuka, M; Yakabe, Y; Miyaura, H; Saito, K; Sumida, K; Shirai, T. (2006). Differences in gene expression profiles in the liver between carcinogenic and non-carcinogenic isomers of compounds given to rats in a 28-day repeat-dose toxicity study. Toxicol Appl Pharmacol 217: 299-307. http://dx.doi.org/10.1016/j.taap.2006.09.008.

Nikolic, B; Mitic-Culafic, D; Stajkovic-Srbinovic, O; Vukovic-Gacic, B; Knezevic-Vukcevic, J. (2012). Effect of metabolic transformation of monoterpenes on antimutagenic potential in bacterial tests. Arch Biol Sci 64: 885-894. http://dx.doi.org/10.2298/ABS1203885N.

NIOSH (National Institute for Occupational Safety and Health). (1985). FACE report: Construction worker dies as a result of spraying coating material in confined space in California. (NIOSH/00157535). Division of Safety Research, NIOSH, U.S. Department of Health and Human Services. https://www.cdc.gov/niosh/face/In-house/full8533.html.

NIOSH (National Institute for Occupational Safety and Health). (1994). Immediately Dangerous to Life or Health Concentrations (IDLH): 2-Nitropropane. Atlanta, GA: U.S. Department of Health, Education and Welfare, Centers for Disease Control and Prevention. https://www.cdc.gov/niosh/idlh/79469.html.

NIOSH (National Institute for Occupational Safety and Health). (2016). NIOSH pocket guide to chemical hazards: 2-Nitropropane. Atlanta, GA: U.S. Department of Health, Education and Welfare, Centers for Disease Control and Prevention (CDC). https://www.cdc.gov/niosh/npg/npgd0460.html.

Nolan, RJ; Unger, SM; Muller, CJ. (1982). Pharmacokinetics of inhaled [14C]-2-nitropropane in male Sprague-Dawley rats. Ecotoxicol Environ Saf 6: 388-397. http://dx.doi.org/10.1016/0147-6513(82)90054-9.

Norman, S. (1990). Skin absorption and metabolism/toxicokinetic study of 14C-2-nitropropane in female rhesus monkeys with cover letter dated 04/26/94 [TSCA Submission]. (OTS0572461. Doc #86940000358). Coulston International Inc. Submitted to the U.S. Environmental Protection Agency by ANGUS Chemical Company.

NTP (National Toxicology Program). (2016). 14th Report on carcinogens. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html.

O'Neil, MJ. (2013). 2-Nitropropane. In MJ O'Neill; PE Heckelman; PH Dobbelaar; KJ Roman; CM Kenney; LS Karaffa (Eds.), The Merck index (15th ed., pp. 1233). Cambridge, UK: Royal Society of Chemistry.

Oda, Y; Zhang, Y; Buchinger, S; Reifferscheid, G; Yang, M. (2012). Roles of human sulfotransferases in genotoxicity of carcinogens using genetically engineered umu test strains. Environ Mol Mutagen 53: 152-164. http://dx.doi.org/10.1002/em.20696.

OECD (Organisation for Economic Co-operation and Development). (2010). OECD existing chemicals database: 79-46-9. Retrieved from https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?id=A54B4944-2036-44E1-A5B7-6E4B9DD1797E

OSHA (Occupational Safety & Health Administration). (2017a). Air contaminants: Occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. (OSHA Standard 1915.1000). Washington, DC: U.S. Department of Labor. https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286.

OSHA (Occupational Safety & Health Administration). (2017b). Safety and health regulations for construction: Occupational health and environmental controls: Gases, vapors, fumes, dusts, and mists: Appendix A. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10629.

OSHA (Occupational Safety & Health Administration). (2017c). Table Z-1: Limits for air contaminants. Occupational safety and health standards, subpart Z, toxic and hazardous substances. (OSHA standard 1910.1000, 29 CFR). Washington, DC: U.S. Department of Labor. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

Parekh, C; Wilbur, SZ. (1982). Acute toxicity profile, inhalation studies, epidemiological data, and environmental fate studies with cover letter dated 051889 [TSCA Submission]. (OTS0516768. Doc #86-890000233). IMC Chemical Group Inc. Submitted to the U.S. Environmental Protection Agency by Angus Chemical Co.

Robbiano, L; Mattioli, F; Brambilla, G. (1991). DNA fragmentation by 2-nitropropane in rat tissues, and effects of the modulation of biotransformation processes. Cancer Lett 57: 61-66. http://dx.doi.org/10.1016/0304-3835(91)90064-O.

Rondia, D. (1979). 2-Nitropropane: One more death. Vet Hum Toxicol 21: 183-185.
Roscher, E; Ziegler-Skylakakis, K; Andrae, U. (1990). Involvement of different pathways in the genotoxicity of nitropropanes in cultured mammalian cells. Mutagenesis 5: 375-380.
Russell, JF; Krahn, DF. (1977). Mutagenic activity of propane, 2-nitro- in the salmonella/microsome assay with cover letter dated 05/03/94 [TSCA Submission]. (OTSOS72S03. Doc#86940000400). DuPont Haskell Laboratory. Submitted to the U.S. Environmental Protection Agency by Dupont Chem.
Sai, K; Kai, S; Umemura, T; Tanimura, A; Hasegawa, R; Inoue, T; Kurokawa, Y. (1998). Protective effects of green tea on hepatotoxicity, oxidative DNA damage and cell proliferation in the rat liver induced by repeated oral administration of 2-nitropropane. Food Chem Toxicol 36: 1043-1051. http://dx.doi.org/10.1016/S0278-6915(98)00073-8.
Sakai, K; Uchida, R. (1992). Comparative effects of potassium dichromate on the mutagenicity of some nitrohydrocarbons and methylating agents. Bull Environ Contam Toxicol 48: 541-548.
Smith, DJ; Anderson, RC. (2013). Toxicity and metabolism of nitroalkanes and substituted nitroalkanes [Review]. J Agric Food Chem 61: 763-779. http://dx.doi.org/10.1021/jf3039583.
Sodum, RS; Nie, G; Fiala, ES. (1993). 8-Aminoguanine: A base modification produced in rat liver nucleic acids by the hepatocarcinogen 2-nitropropane. Chem Res Toxicol 6: 269-276.
Sodum, RS; Sohn, OS; Nie, G; Fiala, ES. (1994). Activation of the liver carcinogen 2-nitropropane by aryl sulfotransferase. Chem Res Toxicol 7: 344-351. http://dx.doi.org/10.1021/tx00039a011.
Sohn, OS; Fiala, ES. (2000). Analysis of nitrite/nitrate in biological fluids: denitrification of 2-nitropropane in F344 rats. Anal Biochem 279: 202-208. http://dx.doi.org/10.1006/abio.1999.4471.
Speck, WT; Meyer, LW; Zeiger, E; Rosenkranz, HS. (1982). Mutagenicity and DNA-modifying activity of 2-nitropropane. Mutat Res 49: 49-54. http://dx.doi.org/10.1016/0165-7992(82)90119-1.
Stajkovic, O; Beric-Bjedov, T; Mitic-Culafic, D; Stankovic, S; Vukovic-Gacic, B; Simic, D; Knezevic-Vukcevic, J. (2007). Antimutagenic properties of basil (Ocimum basilicum L.) in Salmonella typhimurium TA100. Food Technol Biotechnol 45: 213-217.
Takagi, A; Sai, K; Umemura, T; Hasegawa, R; Kurokawa, Y. (1995). Inhibitory effects of vitamin E and ellagic acid on 8-hydroxydeoxyguanosine formation in liver nuclear DNA of rats treated with 2-nitropropane. Cancer Lett 91: 139-144.
Tedesco, JA. (2005). 2-Nitropropane: In vitro dermal absorption rate testing [TSCA Submission]. E.I. DuPont de Nemours and Company. https://java.epa.gov/oppt_chemical_search/download?filename=79469_dermal absorption_InVitroDermalAbsorptionRateTesting_100505.pdf.
TOMA (Tabershaw Occupational Medicine Associates). (1980). Cross-sectional morbidity study of workers at the [] exposed to 2-nitropropane, with cover letter dated 05/09/94 (sanitized) [TSCA Submission]. (OTS0557389. Doc #86940000980S). Submitted to the U.S. Environmental Protection Agency by Miles, Inc.
Treon, JF; Dutra, FR. (1952). Physiological response of experimental animals to the vapor of 2-nitropropane. AMA Arch Ind Hyg Occup Med 5: 52-61.

U.S. EPA (U.S. Environmental Protection Agency). (1980). Water quality criteria documents; availability Appendix C--Guidelines and methodology used in the preparation of health effects assessment chapters of the consent decree water quality criteria documents. Fed Reg 45: 79347-79357.

U.S. EPA (U.S. Environmental Protection Agency). (1985). Health and environmental effects profile for 2-nitropropane [EPA Report]. (EPA/600/x-85/112). Springfield, VA.

U.S. EPA (U.S. Environmental Protection Agency). (1988a). Evaluation of the potential carcinogenicity of 2-nitropropane. (EPA600891157). Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment.

U.S. EPA (U.S. Environmental Protection Agency). (1988b). Recommendations for and documentation of biological values for use in risk assessment [EPA Report] (pp. 1-395). (EPA/600/6-87/008). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855.

U.S. EPA (U.S. Environmental Protection Agency). (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report]. (EPA/600/8-90/066F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=51174829&CFTOKEN=25006317.

U.S. EPA (U.S. Environmental Protection Agency). (2002a). Integrated Risk Information System (IRIS) chemical assessment summary for 2-nitropropane. Washington, DC: U.S. Environmental Protection Agency, National Center for Environmental Assessment. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0519_summary.pdf.

U.S. EPA (U.S. Environmental Protection Agency). (2002b). A review of the reference dose and reference concentration processes. (EPA/630/P-02/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf.

U.S. EPA (U.S. Environmental Protection Agency). (2005a). Guidelines for carcinogen risk assessment [EPA Report]. (EPA/630/P-03/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.

U.S. EPA (U.S. Environmental Protection Agency). (2005b). Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens [EPA Report]. (EPA/630/R-03/003F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www3.epa.gov/airtoxics/childrens_supplement_final.pdf.

U.S. EPA (U.S. Environmental Protection Agency). (2011a). Health effects assessment summary tables for superfund (HEAST): Nitropropane, 2- (CASRN 79-46-9) [Fact Sheet]. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. https://epa-heast.ornl.gov/heast.php.

U.S. EPA (U.S. Environmental Protection Agency). (2011b). Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose (pp. 1-50). (EPA/100/R-11/0001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor. https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose.

U.S. EPA (U.S. Environmental Protection Agency). (2011c). Screening-level hazard characterization. 2-Nitropropane (CASRN 79-46-9). Hazard Characterization Document [EPA Report]. https://java.epa.gov/oppt_chemical_search/proxy?filename=hazchar/79469_2-Nitropropane_March_2011.pdf.

U.S. EPA (U.S. Environmental Protection Agency). (2012a). 2012 Edition of the drinking water standards and health advisories [EPA Report]. (EPA/822/S-12/001). Washington, DC: U.S. Environmental Protection Agency, Office of Water. https://rais.ornl.gov/documents/2012_drinking_water.pdf.

U.S. EPA (U.S. Environmental Protection Agency). (2012b). Benchmark dose technical guidance. (EPA/100/R-12/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. https://www.epa.gov/risk/benchmark-dose-technical-guidance.

U.S. EPA (U.S. Environmental Protection Agency). (2018a). Integrated risk information system (IRIS) [Database]. Washington, DC: U.S. Environmental Protection Agency, Integrated Risk Information System. Retrieved from http://www.epa.gov/iris/

U.S. EPA (U.S. Environmental Protection Agency). (2018b). The Toxic Substances Control Act's public inventory (TSCA inventory). Retrieved from https://www.epa.gov/tsca-inventory/how-access-tsca-inventory#download

Ulrich, CE; Dorato, MA; Ledbetter, A; Marold, BW; Ward, CO. (1977). Chronic inhalation exposure of rats and rabbits to nitromethane and 2-nitropropane (pp. 210-275). (NIOSH/00080945). Philadelphia, PA: Rohm and Haas.

Vogel, EW; Nivard, MJ. (1993). Performance of 181 chemicals in a Drosophila assay predominantly monitoring interchromosomal mitotic recombination. Mutagenesis 8: 57-81. http://dx.doi.org/10.1093/mutage/8.1.57.

Weisburger, JH; Hara, Y; Dolan, L; Luo, FQ; Pittman, B; Zang, E. (1996). Tea polyphenols as inhibitors of mutagenicity of major classes of carcinogens. Mutat Res Genet Toxicol 371: 57-63. http://dx.doi.org/10.1016/S0165-1218(96)90094-4.

Wilhelm, EA; Jesse, CR; Bortolatto, CF; Nogueira, CW. (2011). (E)-2-benzylidene-4-phenyl-1,3-diselenole has antioxidant and hepatoprotective properties against oxidative damage induced by 2-nitropropane in rats. Fundam Clin Pharmacol 25: 80-90. http://dx.doi.org/10.1111/j.1472-8206.2010.00813.x.

Wilhelm, EA; Jesse, CR; Nogueira, CW; Savegnago, L. (2009). Introduction of trifluoromethyl group into diphenyl diselenide molecule alters its toxicity and protective effect against damage induced by 2-nitropropane in rats. Exp Toxicol Pathol 61: 197-203. http://dx.doi.org/10.1016/j.etp.2008.08.003.

Wilhelm, EA; Jesse, CR; Prigol, M; Alves, D; Schumacher, RF; Nogueira, CW. (2010). 3-Alkynyl selenophene protects against carbon-tetrachloride-induced and 2-nitropropane-induced hepatic damage in rats. Cell Biol Toxicol 26: 569-577. http://dx.doi.org/10.1007/s10565-010-9164-4.

Williams, GM; Laspia, MF; Dunkel, VC. (1982). Reliability of the hepatocyte primary culture/DNA repair test in testing of coded carcinogens and noncarcinogens. Mutat Res 97: 359-370. http://dx.doi.org/10.1016/0165-1161(82)90003-6.

Zimmering, S; Mason, JM; Valencia, R; Woodruff, RC. (1985). Chemical mutagenesis testing in Drosophila. II. Results of 20 coded compounds tested for the National Toxicology Program. Environ Mol Mutagen 7: 87-100.

Zitting, A; Savolainen, H; Nickels, J. (1981). Acute effects of 2-nitropropane on rat liver and brain. Toxicol Lett 9: 237-246. http://dx.doi.org/10.1016/0378-4274(81)90156-9.