United States
Environmental Protection
Agency

EPA/690/R-16/002F
Final
9-29-2016

Provisional Peer-Reviewed Toxicity Values for

1,2-Dichloropropane
(CASRN 78-87-5)

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

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

J. Phillip Kaiser, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

CONTRIBUTORS

Harlal Choudhury, DVM, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

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

DRAFT DOCUMENT PREPARED BY

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

PRIMARY INTERNAL REVIEWERS

Anuradha Mudipalli, MSc, PhD
National Center for Environmental Assessment, Research Triangle Park, NC

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

This document was externally peer reviewed under contract to:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

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

TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,2-DICHLOROPROPANE (CASRN 78-87-5)

BACKGROUND

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

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

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

DISCLAIMERS

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

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

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

INTRODUCTION

1,2-Dichloropropane, CASRN 78-87-5, also known as propylene dichloride, 1,2-DCP and 1,2-D, is a chemical intermediate for a variety of organic compounds, especially small chlorinated hydrocarbons, such as tetrachloroethylene and carbon tetrachloride (OECD, 2003). 1,2-DCP is a known impurity in 1,3-dichloropropene (1,3-D), which is an EPA registered fumigant (U.S. EPA, 1998). 1,2-DCP was discontinued from direct use as a grain and soil fumigant in the 1980's (OECD, 2003). Additional uses attributed to 1,2-DCP include as a solvent for fats and greases, in dry cleaning fluids, in rubber making and vulcanization, and as a solvent for film production. However, it is likely that many of these additional uses are either outdated or account for only minor use (OECD, 2003). For example, it is known that use of 1,2-DCP as a solvent for film production was phased out in the early 1980's (ATSDR, 1989). In addition, in EPA's 2012 Chemical Data Reporting database, the only reported use for 1,2-DCP was as an intermediate (U.S. EPA, 2012d).

1,2-DCP is a liquid with a high vapor pressure and a high measured Henry's law constant. These indicate that volatilization from both dry and moist surfaces is expected to be an important fate process for 1,2-DCP. Although not susceptible to direct photolysis, 1,2-DCP does react with photochemically generated hydroxy radicals and has an estimated half-life in the troposphere of 25−27 days (OECD, 2003). 1,2-DCP is listed as a hazardous air pollutant under the Clean Air Act, as amended in 1990 (U.S. Congress, 1990). It is not expected to contribute to either global warming or depletion of stratospheric ozone (OECD, 2003). The high water solubility and relatively low soil adsorption coefficient of 1,2-DCP indicate that it is likely to leach to groundwater or undergo runoff after a rain event. As a result, removal from soil by leaching with water is expected to compete with volatilization, depending on the local conditions (wet, dry, etc.). The federal drinking water standard for 1,2-DCP is 5 µg/L (HSDB, 2014). The molecular formula for 1,2-DCP is $C_3H_6Cl_2$ (see Figure 1). Physicochemical properties are provided in Table 1.

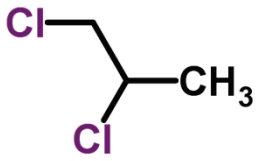

Figure 1. 1,2-Dichloropropane Structure

Table 1. Physicochemical Properties of 1,2-Dichloropropane (CASRN 78-87-5)[a]

Property (unit)	Value
Physical state	Liquid
Boiling point (°C)	96.4
Melting point (°C)	−100.4
Density (g/cm^3 at 25°C)	1.159
Vapor pressure (mm Hg at 25°C)	53.3
pH (unitless)	ND
pKa (unitless)	ND
Solubility in water (mg/L at 25°C)	2,800
Octanol-water partition constant (log K_{ow})	1.98
Henry's law constant (atm-m^3/mol at 25°C)	2.82×10^{-3}
Soil adsorption coefficient K_{oc} (mL/g)	60.7 (estimated)[b]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	4.6×10^{-13} [c]
Atmospheric half-life	25−27 d (estimated for the troposphere)[c]
Relative vapor density (air = 1)	3.9
Molecular weight (g/mol)	112.99

[a]Data were gathered from the HSDB (2014) database unless otherwise specified.
[b]U.S. EPA (2012a).
[c]OECD (2003).

ND = no data.

A summary of available toxicity values for 1,2-DCP from the EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for 1,2-Dichloropropane (CASRN 78-87-5)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS (RfC)	4×10^{-3} mg/m^3	Based on hyperplasia of the nasal mucosa in a rat 13-wk inhalation study	U.S. EPA (2002a)
HEAST (sRfC)	1.3×10^{-2} mg/m^3	Based on hyperplasia of the nasal mucosa in a rat 13-wk inhalation study	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012b)
ATSDR (oral MRL)	0.1 mg/kg-d (acute); 0.07 mg/kg-d (intermediate); 0.09 mg/kg-d (chronic)	Acute: based on neurological effects in a 10-d rat study; Intermediate: based on hematological effects (anemia) in a 13-wk rat study; Chronic: based on liver damage in a 2-yr mouse study	ATSDR (1989); ATSDR (2016)
ATSDR (inhalation MRL)	0.05 ppm (0.23 mg/m^3) (acute); 0.007 ppm (0.032 mg/m^3) (intermediate)	Based on degeneration of the nasal mucosa in a 14-d rat study and a 13-wk rat study	ATSDR (1989); ATSDR (2016)
IPCS	NV	NA	IPCS (2016); WHO (2016)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2016a); Cal/EPA (2016b)
OSHA (PEL)	75 ppm (350 mg/m^3)	8-hr TWA for general industry, construction and shipyard employment	OSHA (2006a); OSHA (2006b); OSHA (2011)
NIOSH (REL)	NV	An REL was not established because 1,2-DCP is a potential occupational carcinogen	NIOSH (1994); NIOSH (2011)
ACGIH (TLV-TWA)	10 ppm (46 mg/m^3)	Based on body weight and nasal pathology observed in rats following a 13 wk inhalation exposure; potential to produce dermal sensitization	ACGIH (2014a); ACGIH (2014b)
Cancer			
IRIS	NV	NA	U.S. EPA (2002a)
HEAST (WOE)	Group B2	B2 indicates sufficient evidence in animals and inadequate or no evidence in humans	U.S. EPA (1987); U.S. EPA (2011a)
HEAST (OSF)	6.8×10^{-2} (mg/kg-d)$^{-1}$	Quantitative estimate of carcinogenic risk from oral exposure based on liver tumors in a mouse gavage study	U.S. EPA (2011a)
DWSHA (WOE)	Group B2	B2 indicates sufficient evidence in animals and inadequate or no evidence in humans	U.S. EPA (2012b)
DWSHA (10^{-4} cancer risk)	0.06 mg/L	Quantitative estimate of carcinogenic risk	U.S. EPA (2012b)
NTP	NV	NA	NTP (2014)

Table 2. Summary of Available Toxicity Values for 1,2-Dichloropropane (CASRN 78-87-5)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
IARC (WOE)	Group 1, carcinogenic to humans	Based on sufficient evidence in humans that exposure to 1,2-DCP causes biliary-tract cancer (cholangiocarcinoma) and sufficient evidence in experimental animals, with malignant lung and hepatocellular tumors observed in exposed mice	Benbrahim-Tallaa et al. (2014); IARC (2015)
Cal/EPA (OSF)	0.036 $(mg/kg\text{-}d)^{-1}$	Hepatocellular adenomas and carcinomas in male mice from a 2-yr gavage study. *Calculated under the Public Health Goals for Drinking Water program using interspecies conversion factor given by the ratio of animal to human body weights raised to the one-fourth power*	Cal/EPA (2016a); Cal/EPA (1999)
Cal/EPA (OSF)	0.072 $(mg/kg\text{-}d)^{-1}$	Hepatocellular adenomas and carcinomas in male mice from a 2-yr gavage study. *Calculated under the Proposition 65 "No Significant Risk Level" (NSRL) program using interspecies conversion factor given by the ratio of animal to human body-weights raised to the one-third power*	Cal/EPA (2004)
ACGIH (WOE)	Category A4, not classifiable as a human carcinogen	Based on negative and equivocal evidence of tumorigenicity in rat and mouse bioassays	ACGIH (2014a); ACGIH (2014b)
NIOSH (WOE)	Ca	Any substance that NIOSH considers to be a potential occupational carcinogen is designated by the notation "Ca"	NIOSH (2011); NIOSH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Research; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; 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: MRL = minimal risk level; OSF = oral slope factor; PEL = permissible exposure level; REL = recommended exposure level; 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 September 2016 for studies relevant to the derivation of provisional toxicity values for 1,2-DCP (CASRN 78-87-5). 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: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, NIOSH, NTP, and OSHA.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant noncancer and cancer databases for 1,2-DCP, respectively, and include all potentially relevant repeated-dose short-term-, subchronic-, and chronic-duration studies. Principal studies are identified. The phrases "statistical significance" and "significant," used throughout the document, indicate a *p*-value of < 0.05, unless otherwise noted.

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,2-Dichloropropane (CASRN 78-87-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Human								
ND								
Animal								
			1. Oral (mg/kg-d)[a]					
Short-term	5 M/0 F, B6C3F$_1$ mice, gavage in corn oil, up to 4 wk	0, 125, 250 ADD: 0, 89.3, 179	Fatty change in the liver, increased absolute and relative liver-weight, increased serum cholesterol, glycerin, and albumin	ND	NDr	89.3	Gi et al. (2015a)	PR
Short-term	5 M/0 F, Syrian hamsters, gavage in corn oil, up to 4 wk	0, 125, 250 ADD: 0, 89.3, 179	Mortality, fatty change in the liver, increased relative liver weight	ND	NDr	89.3 (FEL)	Gi et al. (2015a)	PR
Subchronic[c]	15−16 M/0 F, S-D rat, gavage in corn oil, 5 d/wk, 13 wk	0, 100, 250, 500, 750 ADD: 0, 71.4, 179, 357, 536	Increased serum bilirubin, hemosiderosis and hyperplasia of the spleen, decreased Hct, decreased Hb, increased relative liver, kidney, and spleen weights, mortality	ND	DUB	71.4	Bruckner et al. (1989)	PR
Subchronic	15 M/15 F, F344 rat, gavage in corn oil, 5 d/wk, 13 wk	0, 20, 65, 200 ADD: 0, 14, 46, 143	Decreased body weight in males	46	NDr	143	Dow Chemical Co (1988b)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,2-Dichloropropane (CASRN 78-87-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Subchronic	10 M/10 F, F344/N rat, gavage in corn oil, 5 d/wk, 13 wk	0, 60, 125, 250, 500, 1,000 ADD: 0, 43, 89.3, 179, 357, 714	Increased mortality (50% mortality in males at 357 mg/kg-d; 100% mortality in males and females at 714 mg/kg-d), decreased body weight (M)	179	NA	357 (FEL)	NTP (1986)	PR
Subchronic	10 M/10 F, B6C3F$_1$ mouse, gavage in corn oil, 5 d/wk, 13 wk	0, 30, 60, 125, 250, 500 ADD:0, 21, 43, 89.3, 179, 357	No effects observed	357	NA	ND	NTP (1986)	PR
Chronic[d]	50 M/50 F, F344/N rat, gavage in corn oil, 5 d/wk, 103 wk	0, 62, 125 in males 0, 125, 250 in females ADD: M: 0, 45, 89.3 F: 0, 89.3, 179	Decreased body weight in males and females	45	DUB	89.3	NTP (1986)	PR
Chronic	50 M/50 F, B6C3F$_1$ mouse, gavage in corn oil, 5 d/wk, 103 wk	0, 125, 250 ADD: 0, 89.3, 179	Hepatocytomegaly and hepatic necrosis in males. Increased mortality in females in the high-dose group compared with controls; however, findings are confounded by evidence of infection in 60% of all females that died	89.3	M: 58.5	179	NTP (1986)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,2-Dichloropropane (CASRN 78-87-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Chronic	6−15 M/0 F, hamsters, gavage in corn oil, 5 d/wk, 17 or 19 wk	0, 62.5, 125 ADD: 0, 44.6, 89.3 + N-nitrosobis(2-oxopropyl)amine 0, 89.3 without N-nitrosobis(2-oxopropyl)amine	Decreased body weight at Wk 17	44.6	NDr	89.3	Gi et al. (2015b) (Effects were only observed in hamsters receiving both 1,2-DCP and N-nitrosobis[2-oxopropyl]amine)	PR
Reproductive/ developmental	30 M/30 F, S-D rat, drinking water, 10−12 wk premating plus mating, gestation, and lactation; ~18−21 wk, 2 generations	0, 0.024, 0.1, 0.24% ADD: **F0:** M: 0, 24.8, 82.7, 152 F: 0, 38.8, 127, 254 **F1:** M: 0, 28.3, 109, 213 F: 0, 42.7, 148, 293	F0 M: Decreased body weight at Wk 1 and Wk 10 and decreased platelets F0 maternal: Decreased body weight and anemia F1 offspring: Decreased neonatal weight and survival associated with reduced body weight in dams F1 M: Decreased body weight F1 maternal: Decreased body weight F2 offspring: No effects observed	F0 M: 82.7 F0 maternal: 127 F1 offspring: 127 F1 M: 109 F1 maternal: 148 F2 offspring: 293	NDr NDr NDr NDr NDr NA	F0 M: 152 F0 maternal: 254 F1 offspring: 254 F1 M: 213 F1 maternal: 293 F2 offspring: ND	Dow Chemical Co (1990); Dow Chemical Co (1989b)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,2-Dichloropropane (CASRN 78-87-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Reproductive/ developmental (range-finding)	0 M/10 F, S-D rat, gavage in corn oil, GDs 6−15	0, 50, 125, 250, 500 ADD: 0, 50, 125, 250, 500	Maternal: Increased salivation and perineal staining; decreased maternal body weight Fetal: ND	Maternal: 250 Fetal: ND	NDr	Maternal: 500 Fetal: ND	Dow Chemical Co (1989c)	NPR
Reproductive/ developmental	**0 M/30 F, S-D rat, gavage in corn oil, GDs 6−15**	**0, 10, 30, 125** **ADD: 0, 10, 30, 125**	**Maternal: Transient clinical signs (CNS depression, salivation, lacrimation), decreased maternal body-weight gain** **Fetal: Delayed skeletal ossification of fetal skull**	**Maternal: 30** **Fetal: 30**	**Maternal: NDr** **Fetal: 5.6**	**Maternal: 125** **Fetal: 125**	**Kirk et al. (1995)**	**PR, PS**
Reproductive/ developmental (range-finding)	0 M/7 F, NZW rabbit, gavage in corn oil, GDs 7−19	0, 25, 100, or 250 ADD: 0, 25, 100, or 250	Maternal: Anemia Fetal: ND	Maternal: 25 Fetal: ND	NDr	Maternal: 100 Fetal: ND	Dow Chemical Co (1988d)	NPR
Reproductive/ developmental	0 M/18 F, NZW rabbit, gavage in corn oil, GDs 7−19	0, 15, 50, 150 ADD: 0, 15, 50, 150	Maternal: Anemia, anorexia Fetal: Delays in skeletal ossification of fetal skull	Maternal: 50 Fetal: 50	Maternal: NDr Fetal: 10	Maternal: 150 Fetal: 150	Kirk et al. (1995)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,2-Dichloropropane (CASRN 78-87-5)								
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[a]**	**Critical Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (comments)**	**Notes[b]**
2. Inhalation (mg/m^3)[a]								
Subchronic	10 M/10 F, F344/DuCrj (SPF) rat, 6 hr/d, 5 d/wk, 13 wk	0, 125.3, 250.8, 500.5, 1,000.4, 2,001.3 ppm HEC: M: 0, 13.63, 27.28, 54.42, 108.79, 217.62[e] F: 0, 10.03, 20.09, 40.08, 80.112, 160.26[e]	Nasal lesions (atrophy of the olfactory epithelium and hyperplasia of respiratory epithelium)	ND	DUB	10.03	Umeda et al. (2010) (Other effects include: anemia, increased bilirubin, splenic hemosiderosis and hematopoiesis, bone marrow hematopoiesis, centriloubular swelling in liver [males only], and decreased body weight)	PR
Subchronic	**10 M/10 F, F344 rat, 6 hr/d, 5 d/wk, 13 wk**	**0, 15, 50, 151 ppm** **HEC:** **M: 0, 1.6, 5.4, 16.5[e]** **F: 0, 1.2, 4.0, 12.1[e]**	**Nasal lesions (hyperplasia of respiratory epithelium, degeneration of the olfactory epithelium)**	**1.2**	**F: 0.12**	**4.0**	**Dow Chemical Co (1988a) (Other effects include: decreased body weight in males)**	**NPR, IRIS, PS**

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,2-Dichloropropane (CASRN 78-87-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Subchronic	10 M/10 F, B6D2F$_1$/Crlj (SPF) mouse, 6 hr/d, 5 d/wk, 13 wk	0, 50.0, 100.1, 200.0, 300.2, 399.9 ppm HEC: M: 0, 6.21, 12.43, 24.83, 37.27, 49.66[e] F: 0, 5.14, 10.29, 20.55, 30.86, 41.11[e]	Lesions of the nasal cavity (olfactory epithelium metaplasia, atrophy, and necrosis)	20.55	M: 11.6	30.86	Matsumoto et al. (2013) (Other effects include: decreased body weight in males, increased liver weight, increased relative spleen weight, anemia, increased bilirubin and ALTs [males only], forestomach hyperplasia, pathological changes in liver, bone marrow, spleen, and heart)	PR
Subchronic	10 M/10 F, B6C3F$_1$ mouse, 6 hr/d, 5 d/wk, 13 wk	0, 15, 50, 151 ppm HEC: M: 0, 2.1, 7.3, 22.2[e] F: 0, 1.6, 5.6, 17.1[e]	No effects observed	22.2	NA	ND	Dow Chemical Co (1988a)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,2-Dichloropropane (CASRN 78-87-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Subchronic	7 M/7 F, NZW rabbit, 6 hr/d, 5 d/wk, 13 wk	0, 151, 502, 1,003 ppm HEC: M: 0, 71.0, 236, 471.8[e] F: 0, 66.4, 221, 441.2[e]	No respiratory system effects observed	471.8	ND	ND	Dow Chemical Co (1988a) (Other effects include: bone marrow hyperplasia, anemia, and increased liver weight in males)	NPR
Chronic	50 M/50 F, F344/DuCrj (SPF) rat, 6 hr/d, 5 d/wk for 104 wk	0, 80.2, 200.5, 500.2 ppm HEC: M: 0, 16.2, 40.54, 101.1[e] F: 0, 10.7, 26.75, 66.71[e]	Nasal lesions (transitional epithelium hyperplasia, squamous cell hyperplasia and metaplasia, atrophy of the olfactory epithelium, inflammation of the respiratory epithelium)	ND	NDr	10.7	Umeda et al. (2010) (Other effects include: decreased body weight in males)	PR
Chronic	50 M/50 F, B6D2F$_1$/Crlj (SPF) mouse, 6 hr/d, 5 d/wk, 104 wk	0, 32.1, 80.2, 200.5 ppm HEC: M: 0, 4.73, 11.8, 29.55[e] F: 0, 4.27, 10.7, 26.67[e]	Lesions of the nasal cavity (olfactory epithelium atrophy)	4.27	NDr	10.7	Matsumoto et al. (2013) (Other effects include: decreased absolute spleen weight in males, increased kidney weight in males, and pathological changes in the kidneys of males)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,2-Dichloropropane (CASRN 78-87-5)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Reproductive/ developmental	0 M/6−9 F, F344 rat, 8 hr/d, 7 d/wk, 3 wk	0, 50.7, 99.9, 200.7 ppm 0, 7.58, 14.9, 30.00[e]	Respiratory system effects were not evaluated	ND	ND	ND	Sekiguchi et al. (2002) (Other effects include: increased number of estrous cycles lasting ≥6 d; at highest dose ovulation was also decreased)	PR; a significant limitation of this study is that the study authors did not evaluate airway/ respiratory system effects

[a]Dosimetry: The units for oral values are expressed as an ADD (mg/kg-day). All long-term exposure values (≥4 weeks) are converted from a discontinuous to a continuous exposure. Values from animal developmental studies are not adjusted to a continuous exposure. The units for inhalation exposures are expressed as HECs (mg/m^3) for ET using the equation recommended by the U.S. EPA (1994b) (see Footnote E).
[b]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study; IRIS = utilized by Integrated Risk Information System.
[c]Subchronic = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species) (U.S. EPA, 2002b).
[d]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).
[e]HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$ (animal:human) (U.S. EPA, 1994b).

ADD = adjusted daily dose; DUB = data unamenable to benchmark dose modeling software; ET = extrathoracic respiratory effects; F = female(s); FEL = frank effect level; Hb = hemoglobin; Hct = hematocrit; HEC = human equivalent concentration; M = male(s); MW = molecular weight; NA = not applicable; ND = no data; NDr = not determined; NZW = New Zealand white; S-D = Sprague-Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for 1,2-Dichloropropane (CASRN 78-87-5)						
Category	**Number of Male/Female, Strain, Species, Study Type, and Duration**	**Dosimetry[a]**	**Critical Effects**	**BMDL/ BMCL[a]**	**Reference (comments)**	**Notes[b]**
Human						
Carcinogenicity (occupational)	62 M/0 F, workers from 1 print shop in Osaka, Japan (51 printers, 11 front-room workers), 1 factory (Osaka, Japan), inhalation exposure to DCM and/or 1,2-DCP, 8 hr/shift (unspecified shifts/wk), 1−17 yr	Printers: 880−1,400; Front-room: 320−510 (range of mean ambient exposures estimated based on amount of chemical reportedly used)	Cholangiocarcinoma in 11/51 printers (22%); 0/11 front-room workers	ND	Kumagai et al. (2013)	PR
Carcinogenicity (occupational)	88 M/23 F, workers from 1 print shop in Osaka, Japan, inhalation exposure to TCE, DCM, and/or 1,2-DCP, 6−19 yr	NR	Cholangiocarcinoma in 17/111 printers (15%)	ND	Kubo et al. (2014c)	PR
Carcinogenicity (occupational)	6 M/0 F, printers from 3 print shops in 3 Japanese cities, inhalation exposure to 1,2-DCP at all 3 shops (additional solvents used included TCE in Shop 1, DCM and DCFE at Shop 2, and DCM and TCE at Shop 3), 9−11.5 hr/shift (unspecified shifts/wk), 10−16 yr	Shop 1: 370−550; Shop 2: 290−920; Shop 3: 510−1,100 (TWA shift exposures; modeled estimates based on amount of chemical reportedly used)	Cholangiocarcinoma (case-series report)	ND	Yamada et al. (2014)	PR
Carcinogenicity (occupational)	9 M/0 F, workers from 7 print shops in 7 Japanese cities, inhalation exposure to TCE, DCM, and/or 1,2-DCP, 6−19 yr	NR	Cholangiocarcinoma (case-series report)	ND	Kubo et al. (2014a)	PR

Table 3B. Summary of Potentially Relevant Cancer Data for 1,2-Dichloropropane (CASRN 78-87-5)						
Category	**Number of Male/Female, Strain, Species, Study Type, and Duration**	**Dosimetry[a]**	**Critical Effects**	**BMDL/ BMCL[a]**	**Reference (comments)**	**Notes[b]**
Animal						
1. Oral (mg/kg-d)[a]						
Carcinogenicity	50 M/50 F, F344/N rat, gavage in corn oil, 5 d/wk, 103 wk	M: 0, 62, 125; F: 0, 125, 250 HED: M: 0, 11, 21.4 F: 0, 21.4, 43.0	Significant increases in mammary gland adenocarcinoma at high dose once adjusted for intercurrent mortality; preneoplastic lesions (hyperplasia) were observed at low dose; all in females	F: 30.4	NTP (1986)	PR
Carcinogenicity	**50 M/50 F, B6C3F$_1$ mouse, gavage in corn oil, 5 d/wk, 103 wk**	**0, 125, 250** **HED: 0, 12.5, 25.1**	**Dose-related increase in combined incidence of hepatocellular adenoma or carcinoma in both males and females, increased combined incidence of thyroid follicular cell adenoma or carcinoma in female mice**	**M: 2.71**	**NTP (1986)**	**PR, PS**
Carcinogenicity (tumor promotion)	6−15 M/0 F, hamsters, gavage in corn oil, 5 d/wk, 17 or 19 wk	0, 62.5, 125 via gavage HED: 0, 9.37, 18.8	No effects observed	NA	Gi et al. (2015b)	PR
2. Inhalation (mg/m^3)[a]						
Carcinogenicity	**50 M/50 F, F344/DuCrj (SPF) rat, 6 hr/d, 5 d/wk for 104 wk**	**0, 80.2, 200.5, 500.2 ppm** **HEC$_{ET}$:** **M: 0, 16.2, 40.54, 101.1[c]** **F: 0, 10.7, 26.75, 66.71[c]**	**Increased incidence of tumors in the nasal cavity of both male and female rats**	**M: 26.7**	**Umeda et al. (2010)**	**PR, PS**

Table 3B. Summary of Potentially Relevant Cancer Data for 1,2-Dichloropropane (CASRN 78-87-5)

Category	Number of Male/Female, Strain, Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	BMDL/ BMCL[a]	Reference (comments)	Notes[b]
Carcinogenicity	50 M/50 F, B6D2F$_1$/Crlj (SPF) mouse, 6 hr/d, 5 d/wk, 104 wk	0, 32.1, 80.2, 200.5 ppm HEC$_{PU}$: M: 0, 77.2, 192, 482.5[d] F: 0, 69.2, 173, 432.0[d]	Significant increase in combined incidence of bronchiolo-alveolar adenoma or carcinoma in females that exceeded maximal control historical incidence in the high exposure group	F: 177	Matsumoto et al. (2013) (Other effects include significant trend for increased Harderian gland adenoma in males, exceeding maximal control historical incidence in the high exposure group)	PR

[a]Dosimetry: The units for oral exposures are expressed as HEDs (mg/kg-day); HEDs were calculated using species-specific DAFs based on the animal:human BW$^{1/4}$ ratio recommended by U.S. EPA (2011b): mouse:human ratio = 0.14; rat:human ratio = 0.24. All intermittent exposures were converted to from a discontinuous to a continuous exposure. The units for inhalation exposures from animal studies are expressed as HECs (mg/m^3) for PU or ET using the equations recommended by the U.S. EPA (1994b) (see Footnotes C and D).
[b]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.
[c]HEC$_{ET}$ = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × RGDR$_{ET}$ (animal:human) (U.S. EPA, 1994b).
[d]HEC$_{PU}$ = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × RGDR$_{PU}$ (animal:human); see Equations 4−28 in U.S. EPA (1994b) for calculation of RGDR$_{PU}$ and default values for variables.

BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; F = female(s); DAF = dosimetric adjustment factors; DUB = data unamenable to benchmark dose modeling software; ET = extrathoracic respiratory effects; HEC = human equivalent concentration; HED = human equivalent dose; M = male(s); NA = not applicable; ND = no data; NR = not reported; PU = pulmonary effects; TCE = trichloroethylene; TWA = time-weighted average.

HUMAN STUDIES

Human studies include three retrospective cohort studies and two case-series reports in print-shop workers in Japan evaluating the potential correlation between exposure to 1,2-DCP (and other solvents) and cholangiocarcinoma, a rare form of bile duct cancer (Kumagai et al., 2016; Kubo et al., 2014c; Kubo et al., 2014a; Kumagai et al., 2014; Yamada et al., 2014; Kumagai et al., 2013). These key studies are summarized in Table 3B and are described in detail below. Individual case reports of cholangiocarcinoma in offset Japanese print shop workers exposed to 1,2-DCP and/or dichloromethane (DCM) support findings from the key studies (Kumagai et al., 2014; Tomimaru et al., 2014). A single case report of severe acute hepatitis has also been reported in a Japanese print shop worker exposed to chlorinated organic solvents, including 1,2-DCP, DCM, and 1,1,1-trichloroethane (TCE) (Kubo et al., 2014b).

Kumagai et al. (2014); Kumagai et al. (2013)

An occupational study evaluated the potential relationship between cholangiocarcinoma and exposure to 1,2-DCP and/or DCM in a small printing company in Osaka, Japan (Kumagai et al., 2013). Study subjects included 51 men employed as offset color proof-printers and 11 men employed in the adjacent front room of the same printing company employed for at least 1 year between 1991−2006. Between 1991−1997/1998, color proof-printers used both 1,2-DCP and DCM as solvents for ink removal 150−400 times per shift. After 1997/1998, use of DCM was discontinued and only 1,2-DCP was used for this process. Workers in the adjacent front room were exposed to lower vapor levels of the solvents used by printers (due to poor ventilation). Based on work histories, all of the printers and front-room workers were exposed to 1,2-DCP for an average of 6 and 7 years, respectively, and 27 of the printers and 8 of the front-room workers were also exposed to DCM for an average of 4 and 6 years, respectively. Workers wore gloves while using 1,2-DCP and DCM, but neither proof-printers nor front-room workers wore respiratory protection. Employees worked 8-hour shifts; the number of shifts per week was not reported. A follow-up report by Kumagai et al. (2014) reviewed blood test records of workers diagnosed with cholangiocarcinoma from annual health exams conducted during employment and after retirement, including levels of liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and γ-glutamyl transferase [GGT]) and parameters of hematology (red blood cell [RBC], hemoglobin [Hb], hematocrit [Hct]), lipid metabolism (total cholesterol, triglycerides), and glucose metabolism (fasting plasma glucose).

Chemical exposures were estimated based on reported quantities of 1,2-DCP and DCM used and experimental data generated by the Japanese National Institute of Occupational Safety and Health [NIOSH (2012) as cited in Kumagai et al. (2013)]. For printers, estimated mean exposures to 1,2-DCP were 220 ppm from 1991−1992/1993, 190 ppm from 1992/1993−1997/1998, and 310 ppm from 1997/1998−2006 and estimated mean exposures to DCM were 140 ppm from 1991−1992/1993 and 360 ppm from 1992/1993−1997/1998. For front-room workers, estimated mean exposures to 1,2-DCP were 80 ppm from 1991−1992/1993, 70 ppm from 1992/1993−1997/1998, and 110 ppm from 1997/1998−2006 and mean exposures to DCM were 50 ppm from 1991−1992/1993 and 130 ppm from 1992/1993−1997/1998. Thus, the ranges of mean ambient exposure to 1,2-DCP from 1991−2006 were 190−310 ppm (880−1,400 mg/m^3) for printers and 70−110 ppm (320−510 mg/m^3) for front-room workers.

Eleven cases of cholangiocarcinoma were identified in printers (mean age: 36 years); six cases were fatal. No cases were identified in front-room workers. All clinically diagnosed patients were exposed to 1,2-DCP for 7−17 years (mean 10 years), and 10 patients were also

exposed to DCM for 1−13 years. Diagnosis of cholangiocarcinoma was 7−20 years (mean 14 years) after initial exposure. The standardized mortality ratio (SMR) from 1991−2011 for all workers was calculated to be 2,900 based on 0.00204 expected deaths (95% confidence interval [CI]: 1,100−6,400). The vital status of 11 proof-printers and 3 front-room workers could not be determined at the time of the study; however, for the purpose of the SMR calculation, it was assumed that these individuals were alive. Therefore, the mortality risk may have been underestimated. In cholangiocarcinoma cases, the majority of blood parameters were within standard ranges; however, GGT levels exceeded the standard range during 1,2-DCP exposure for 6/11 cases. Of these six cases, two were diagnosed while still employed and the other four were diagnosed 1−9 years after ceasing 1,2-DCP exposure. In the remaining five cases, which were all diagnosed 4−10 years after ceasing 1,2-DCP exposure, GGT levels were within the normal range during 1,2-DCP exposure, but were elevated thereafter. In most cases, serum AST and ALT levels increased subsequent to increased GGT levels. These findings suggest that 1,2-DCP and/or DCM may cause cholangiocarcinoma in occupationally exposed workers, and that the elevated GGT levels may be an early marker for cholangiocarcinoma development.

Kubo et al. (2014c)

Seventeen cholangiocarcinoma cases were identified between 1996−2012 in young men currently or formerly employed in the offset color proof-printing department of a printing company in Osaka, Japan between 1981−2012. Nine cases were fatal. Based on details in the report, it appears that this is the same printing company described by Kumagai et al. (2014) and Kumagai et al. (2013) above; however, slightly different solvent usage patterns were reported for cleaning ink residues. The study authors indicated that TCE was used up until 1992, DCM was used up until 1996, and 1,2-DCP was used up until 2006. No exposure estimates were reported; however, based on job history, it was determined that all 17 individuals were exposed to 1,2-DCP, 11 were exposed to DCM, and 8 were exposed to TCE. The average length of chemical exposure was 11 years, 4 months (range 6 years, 1 month−19 years, 9 months). The mean age of diagnosis was 36 years of age, compared to the mean age of onset of 65.4 years in the general Japanese population. The study authors identified a total of 111 former or current workers (88 men and 23 women) who were exposed during the same time period, indicating that 17/111, or 15%, of exposed workers developed cholangiocarcinoma. None of the patients had known risk factors for developing cholangiocarcinoma (e.g., primary sclerosing cholangitis, hepatolithiasis, pancreaticobiliary maljunction, or infection with liver flukes). These cases support that occupational exposure to high levels of chlorinated organic solvents, including 1,2-DCP, may cause cholangiocarcinoma in humans.

In addition, Sobue et al. (2015) performed a retrospective cohort study to determine the risk of bile duct cancer in the same printing workers described by Kumagai et al. (2014), Kumagai et al. (2013), and Kubo et al. (2014c) that were exposed to 1,2-DCP and DCM. The study authors calculated standardized incidence ratios (SIRs) for the cumulative years of exposure to 1,2-DCP and DCM with reference to the nationwide incidence. For workers exposed to both chemicals, the SIR was 1,319.9 (95% CI: 658.9−2,361.7). For workers only exposed to 1,2-DCP, the SIR was 1,002.8 (95% CI: 368.0−2,182.8). There was also a tendency for SIRs to increase with longer exposure to 1,2-DCP. The study authors concluded that there was an exceptionally high risk of bile duct cancer in printing workers, which may be due to exposure to 1,2-DCP. Kumagai et al. (2016) later identified a relationship between the risk of cholangiocarcinoma in printing workers and increased cumulative exposure to 1,2-DCP.

Yamada et al. (2014)

Six cholangiocarcinoma cases were diagnosed in 1998−2013 in males currently or formerly employed in one of three small printing companies (<50 employees) in Miyagi, Fukuoka, or Hokkaido, Japan. There is no overlap between the cases presented in this study and the studies conducted by Kumagai et al. (2014), Kumagai et al. (2013), and Kubo et al. (2014c). Detailed exposure assessments were done for each employee based on work history. All workers were exposed to 1,2-DCP for 10−16 years. Employees worked 10-hour shifts in Shop 1, 9-hour shifts in Shop 2, and 11.5-hour shifts in Shop 3; the number of shifts per week was not reported. Shift time-weighted average (TWA) exposure estimates based on modeling of the amount of chemical reportedly used were 80−170 ppm (370−550 mg/m^3) for printers in Shop 1, 62−200 ppm (290−920 mg/m^3) for printers in Shop 2, and 110−240 ppm (510−1,100 mg/m^3) for printers in Shop 3. Additional solvents used in the different shops included DCM (<1 ppm in Shop 1, 0−180 ppm in Shops 2 and 3), TCE (Shops 1 and 3; estimate not reported), and 1,1-dichloro-1-fluoroethane (DCFE) (Shop 2; estimate not reported). These cases support that occupational exposure to high levels of chlorinated organic solvents, including 1,2-DCP, may cause cholangiocarcinoma in humans.

Kubo et al. (2014a)

Nine cholangiocarcinoma cases were identified between 1988−2011 in males currently or formerly employed in one of seven printing companies in Hokkaido, Aomori, Miyagi, Saitama, Aichi, Osaka, and Fukuoka, Japan. Five cases were fatal. It is unclear if the six cases included in the report by Yamada et al. (2014) (described above) are included in this report. All patients had been exposed to "high" levels of chlorinated organic solvents at work for 3−19 years (average 13 years). Five were exposed to DCM and 1,2-DCP, two were exposed to TCE, DCM, and 1,2-DCP, and two were exposed to TCE and DCM. No exposure estimates were reported. The average age at diagnosis was 44 years. None of the patients had known risk factors for developing cholangiocarcinoma (e.g., primary sclerosing cholangitis, hepatolithiasis, pancreaticobiliary maljunction, or infection with liver flukes). These cases support that occupational exposure to high levels of chlorinated organic solvents, including 1,2-DCP, may cause cholangiocarcinoma in humans.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to 1,2-DCP have been evaluated in one short-term-duration study in mice and hamsters (Gi et al., 2015a), three subchronic-duration studies in rats or mice (Bruckner et al., 1989; Dow Chemical Co, 1988b; NTP, 1986), a chronic-duration/carcinogenic study in rats and mice (NTP, 1986), a chronic study in hamsters (Gi et al., 2015b), a two-generation reproductive/developmental study in rats (Dow Chemical Co, 1990), and a teratology study in rats and rabbits with accompanying maternal dose-range finding studies (Kirk et al., 1995; Dow Chemical Co, 1989a, 1988d). These key studies are summarized in Tables 3A and 3B and are described in detail below. Additional information regarding oral exposure is available from several acute and short-term studies and a subchronic-duration study available only as an abstract (see Table 4B).

Short-term-Duration Studies

Gi et al. (2015a) (Mouse study)

Gi et al. (2015a) performed 4-hour, 3-day, and 4-week gavage experiments in male B6C3F$_1$ mice. For the 4-hour component of the study, male mice (five/group) received a single

administration of 1,2-DCP (purity >98%) at doses of 0 or 500 mg/kg-day via gavage in corn oil. Male mice were euthanized 4 hours after gavage. At sacrifice, livers were removed and weighed and preserved for histological examination. For the 3-day experiment, mice (five/group) were gavaged once a day for 3 days with 1,2-DCP at doses of 0 or 500 mg/kg-day. Mice were monitored twice daily for mortality and morbidity. Body weight and food/water consumption were recorded daily. At sacrifice, livers were removed, weighed and preserved for histological examination and analyzed for glutathione (GSH) concentration. Lung, kidney, spleen, and bile duct were also removed from these animals and preserved for histological examination. For the 4-week experiment, groups of male mice (five/group) were administered 1,2-DCP via gavage in corn oil at doses of 0, 125, or 250 mg/kg-day for 4 weeks (5 days/week). Before each gavage treatment, body weight was recorded. Food and water consumption were recorded daily. At termination, blood was collected from the vena cava for hematology and serum chemistry, and livers were removed, weighed and preserved for histological examination. Lung, kidney, spleen, and bile duct were also removed from these animals and preserved for histological examination. Livers from the 4-week component were analyzed for the following parameters: immunohistochemical staining of CYP2E1, GST-T1, and Ki-67, messenger ribonucleic acid (mRNA) and protein expression of CYP450 enzymes and GST-T1, GSH concentration, and oxidative damage.

In the 4-hour experiment, the incidence of fatty change in the liver was significantly increased at 500 mg/kg-day. Also, the concentration of GSH in the liver significantly decreased at 500 mg/kg-day. In the 3-day component of the study, the incidence of fatty change as well centrilobular necrosis in the liver was significantly increased at 500 mg/kg-day. In the 4-week experiment, absolute liver weight was statistically and biologically significantly increased at ≥125 mg/kg-day. Relative liver weight was statistically significantly increased at ≥125 mg/kg-day and biologically significantly increased at 250 mg/kg-day. The following serum biochemistry parameters were significantly increased at 250 mg/kg-day: total cholesterol, total glycerin, and albumin. The incidence of fatty change in the liver was significantly increased at ≥125 mg/kg-day. The following significant mRNA changes were observed: increased CYP1A1 at 250 mg/kg-day, increased CYP2A4 at ≥125 mg/kg-day, decreased CYP2C9 at ≥125 mg/kg-day, decreased CYP3CA11 at ≥125 mg/kg-day, increased CYP4A14 at ≥125 mg/kg-day, and decreased GST-T1 at ≥125 mg/kg-day. A lowest-observed-adverse-effect level (LOAEL) of 125 mg/kg-day is identified for significantly increased incidence of fatty change in the liver and for statistically and biologically significantly increased absolute liver weight; both observed in the 4-week experiment. Because 125 mg/kg-day is the lowest dose tested, identification of a no-observed-adverse-effect level (NOAEL) is precluded. For the 4-week component of the study, gavage doses of 125 and 250 mg/kg day were converted to adjusted daily doses (ADDs) of 89.3 or 179 mg/kg-day by multiplying the administered gavage dose by (5/7) days/week.

Gi et al. (2015a) *(Hamster study)*

Gi et al. (2015a) performed 4-hour, 3-day, and 4-week gavage experiments in male Syrian hamsters as described above for male B6C3F$_1$ mice. The only exception is that in the 3-day experiment, the dose of 500 mg/kg-day was lowered to 250 mg/kg-day due to mortality (one hamster) and morbidity observed after the first gavage treatment. In the 4-hour experiment, absolute and relative liver weight was statistically and biologically significantly decreased at 500 mg/kg-day. The incidence of fatty change in the liver was significantly increased at 500 mg/kg-day. The concentration of GSH in the liver significantly decreased at 500 mg/kg-day.

In the 3-day component of the study, final body weight was significantly decreased at 250 mg/kg-day. The incidence of fatty change as well as centrilobular necrosis in the liver was significantly increased at 250 mg/kg-day. For the 4-week experiment, final body weight was biologically (but not statistically) significantly reduced at 250 mg/kg-day. Mortality was observed at ≥125 mg/kg-day with one hamster dead in Week 1 and three hamsters dead (one each at Weeks 1, 2 and 3) at 250 mg/kg-day. Relative liver weight was statistically and biologically significantly increased at 250 mg/kg-day. The incidence of fatty change in the liver was significantly increased at ≥125 mg/kg-day. A frank effect level (FEL) of 125 mg/kg-day is identified for mortality observed in the 4-week experiment. Because 125 mg/kg-day is the lowest dose tested, identification of a LOAEL or NOAEL is precluded. For the 4-week component of the study, gavage doses of 125 and 250 mg/kg day were converted to ADDs of 89.3 or 179 mg/kg-day by multiplying the administered gavage dose by (5/7) days/week.

Subchronic-Duration Studies

Bruckner et al. (1989)

Adult male Sprague-Dawley (S-D) rats (15−16/group) were administered 1,2-DCP (purity 99%) at doses of 0, 100, 250, 500, or 750 mg/kg-day via gavage in corn oil, 5 days/week for 13 weeks. The frequency of evaluations for animal health and clinical signs of toxicity was not reported; however, the study authors indicate that all moribund animals were removed during the study and sacrificed. Body weight (BW) was measured weekly. Blood samples were collected for serum chemistry (sorbitol dehydrogenase [SDH], ALT, ornithine carbamoyl transferase [OCT], blood urea nitrogen [BUN], total bilirubin) from six to eight rats/group prior to initial dosing as well as at 2, 4, 6, 8, 10, and 12 weeks and again after a 1-week post-treatment recovery period; all animals served as blood donors 3 times during the course of the study at approximately 4-week intervals. Twenty-four-hour urine samples were collected once per month for urinalysis (total volume, protein, glucose, alkaline phosphatase [ALP], acid phosphatase, *N*-acetyl-β-D-glucosaminidase [NAG]) from animals not participating as blood donors. At the conclusion of the study, six to eight rats were sacrificed. All remaining animals were allowed a recovery period of 1 week after the last exposure prior to sacrifice. At scheduled sacrifices, blood was collected for hematology (Hct, Hb), the liver, kidney, and spleen were removed and weighed, and the liver, kidneys, lungs, brain, adrenals, spleen, stomach, testis, and epididymis were removed and preserved for histological examination. Tissues from animals sacrificed moribund were also preserved for histological examination. Portions of the liver were processed for evaluation of cytochrome P450 (CYP450) content and glucose-6-phosphatase (G-6-Pase) activity, and portions of the liver and kidney were utilized for measurement of nonprotein sulfhydryl levels.

High mortality occurred in the 750-mg/kg-day group, with approximately 55% mortality within the first 10 days; the surviving animals in this exposure group were sacrificed moribund at 10 days. In the 500-mg/kg-day group, approximately 60% mortality was observed over the 13-week exposure period; all surviving animals were sacrificed at 13 weeks (no 1-week recovery group at this dose level). Survival was ≥90% in all other groups. Clinical signs of toxicity observed in the two highest dose groups included pronounced central nervous system (CNS) depression coupled with a reduction in food and water intake. Significant, dose-dependent reductions in body weight were reported throughout the study in all dose groups; however, based on graphically presented data, it appears that body weights in the 100- and 250-mg/kg-day groups remained within 10% of control weights. Using GrabIt! Software, terminal body weights were reduced by ~4, 9, and 22% in the 100-, 250-, and 500-mg/kg-day groups, respectively. At

moribund sacrifice on Day 10, body weights in the 750-mg/kg-day group were decreased by ~45%.

Hematological evaluation at 13 weeks showed a significant 15−16% decrease in Hct and 34−38% decrease in Hb in the 250- and 500-mg/kg-day groups. After the 1-week recovery period, Hct levels were comparable to control levels in the 250-mg/kg-day group (not assessed in 500-mg/kg-day group), but Hb levels were still reduced by 20% (see Table B-1). Significant, dose-related increases in serum bilirubin levels were observed in the 250- and 500-mg/kg-day groups at the majority of evaluated time-points (see Table B-1). At 12 weeks, significant bilirubin increases of ~6−10-fold were observed in the 100-, 250-, and 500-mg/kg-day groups, compared with controls (see Table B-1). Serum OCT levels were generally higher in exposed animals, with significant increases of ~10-fold at 12 weeks in the 250- and 500-mg/kg-day groups, compared with controls (see Table B-1). No significant, biologically-relevant changes were observed in other serum markers of liver function (SDH, ALT) or kidney function (BUN). The study authors indicated that kidney toxicity was not suggested by urinary enzyme levels or urinary protein or glucose content; however, no data were presented for urinalysis parameters in the study publication. Liver and kidney nonprotein sulfhydryl levels were statistically elevated by 37−50% in the 250- and 500-mg/kg-day rats, compared with controls, at 13 weeks (see Table B-1). After the 1-week recovery period, nonprotein sulfhydryl levels were comparable to control levels in the 250-mg/kg-day group (not assessed in 500-mg/kg-day group) (see Table B-1). These findings may be attributable to a transient "rebound" or "overshoot" in compensatory GSH synthesis. No changes were observed in liver microsomal CYP450 levels of G-6-Pase activity in treated rats, compared with controls.

Significant changes in relative organ weights at 13 weeks included a 27−39% increase in liver weight at ≥250 mg/kg-day, a 100−205% increase in spleen weight at ≥250 mg/kg-day, and a 14% increase in kidney weight at 500 mg/kg-day (see Table B-1). After the 1-week recovery period, relative liver and spleen weights were partially recovered in the 250-mg/kg-day group (not assessed in 500-mg/kg-day group); however, they were still significantly elevated by 20 and 40%, respectively, compared with 13-week control values (see Table B-1). Absolute organ weights were not reported. No organ-weight effects were observed in the 100-mg/kg-day group.

Microscopic changes in the spleen, including hemosiderosis and hyperplasia of erythropoietic components, were observed at 13 weeks in most exposed animals in a dose-related manner (incidence not reported). Other histopathological changes observed at 13 weeks were limited to the 500-mg/kg-day group, including renal tubular cell hemosiderosis and hepatic Kupffer cell hemosiderosis (incidence data not reported); morphological changes in the liver (periportal vacuolization and active fibroplasia; incidence not reported); testicular degeneration, reduced sperm production, and increased spermatid giant cells (3/9 rats); excessive number of degenerate spermatogonia and reduction in the number of sperm in epididymides (4/9 rats); and increased fat storage in the adrenal cortex (5/9 rats). In high-dose rats sacrificed moribund on Day 10, histopathological changes included splenic hemosiderosis (10/10 rats), mild hepatitis (9/10 rats), vacuolization of the adrenal medulla and lipidosis of the adrenal cortex (4/10 rats), reduced spermatozoa in the epididymis (majority; incidence not reported), and testicular degeneration (2/9 rats). The only histopathological effects reported following the 1-week recovery were excessive amounts of iron in the spleen of the 250-mg/kg-day group. The study authors also reported a modest degree of hepatic fibrosis in the 500-mg/kg-day group after recovery; however, elsewhere in the report, the study authors stated that all surviving rats from

the 500-mg/kg-day group were sacrificed at 13 weeks, and none were utilized for the recovery period.

A LOAEL of 100 mg/kg-day was identified for evidence of hemolytic anemia, including significantly increased serum bilirubin levels and hemosiderosis and hyperplasia of erythropoietic elements of the spleen. Decreased Hct and Hb were also observed at higher doses. A NOAEL was not identified. A FEL of 500 mg/kg-day was identified for increased mortality. Gavage doses of 100, 250, 500, and 750 mg/kg-day were converted to ADDs of 71.4, 179, 357, or 536 mg/kg-day by multiplying the administered gavage dose by (5/7) days/week.

Dow Chemical Co (1988b)

In an unpublished neurotoxicity study, groups of F344 rats (15/sex/group) were administered 1,2-DCP (purity 99.9%) via gavage in corn oil at doses of 0, 20, 65, or 200 mg/kg-day for 13 weeks (5 days/week). Rats were observed twice daily for signs of clinical toxicity or morbidity. Body weights and detailed clinical exams were recorded weekly. Neurological function was evaluated monthly by a functional observational battery (FOB), hindlimb grip strength test, and motor activity assessment. At 13 weeks, body temperature was recorded. At the end of dosing, four rats/sex/group were sacrificed for gross necropsy. The brain was removed, and length, width, and weight were recorded. Nervous system tissues (brain, spinal cord, Gasserian ganglia, dorsal and ventral spinal nerve roots, dorsal root ganglia, sciatic nerve, tibial nerve, sural nerve) as well as the liver, kidney, and spleen from the control and high-dose rats were fixed for histopathological examination. The remaining rats were observed for a 9-week recovery period prior to sacrifice. Daily observations, weekly body-weight measurements and detailed clinical examinations, and periodic body temperature readings were collected during the recovery period. At the end of the recovery period, five rats/sex/group were sacrificed for gross necropsy; the remaining animals were sacrificed and discarded.

No mortalities were observed. Transient clinical signs of toxicity were observed immediately following gavage administration on Days 1−2 in all dose groups and on Day 3 in the high-dose group, including tearing and blinking and decreased spontaneous locomotion. No other clinical findings were reported during daily or weekly exams. Body weights were decreased in mid- and high-dose males throughout the treatment period, with significant 3 and 10% decreases, respectively, at 13 weeks (see Table B-2). At the end of the 9-week recovery period, body weights in high-dose males were still significantly reduced by 8%; male body weight in the mid-dose group was no longer significantly decreased compared with control (see Table B-2). Minor weight reductions were also observed in females; however, findings were not significant (see Table B-2). No consistent, significant differences were observed between the exposed and control rats during the FOB, hindlimb grip strength, or motor activity assessments. At 13 weeks, body temperature was slightly, but significantly, decreased by 0.3 and 0.6°C in high-dose male and females, respectively. While these changes persisted during the recovery period, this finding is not considered biologically relevant because body temperatures were still within the normal circadian variation. Brain weight, length, or width and all findings during gross or microscopic examination were similar between treated and control rats.

In male rats, a NOAEL of 65 mg/kg-day and a LOAEL of 200 mg/kg-day were identified for significant body-weight reductions >10%. Neurotoxicity was not observed in either sex. Gavage doses of 20, 65, or 200 mg/kg-day were converted to ADDs of 14, 46, or 143 mg/kg-day by multiplying the administered gavage dose by (5/7) days/week.

NTP (1986) (Rat study)

F344/N rats (10/sex/group) were administered 1,2-DCP (purity 99.4%) at doses of 0, 60, 125, 250, 500, or 1,000 mg/kg-day via gavage in corn oil 5 days/week for 13 weeks. All animals were observed twice daily for mortality and clinical signs of toxicity. Detailed clinical examinations, including palpation for tissue masses or swelling, were conducted weekly. Body weights were also recorded weekly. Animals determined to be moribund were sacrificed and necropsied. At the conclusion of the 13-week study, necropsies were performed on all of the remaining animals. A complete set of 26 tissues were microscopically examined in the control and two highest dose groups only.

All male and female rats receiving 1,000 mg/kg-day and 5/10 males receiving 500 mg/kg-day died before the conclusion of the study; no deaths were observed in other dose groups (see Table B-3). Terminal body weights were significantly decreased by 16% in males and 8% in females in the 500 mg/kg-day group, compared with controls (see Table B-3); mean body weights were not reported for the high-dose group due to 100% mortality. Body weights in lower dose groups were comparable to controls (see Table B-3). Histopathological lesions in the liver of high-dose rats attributed to exposure included centrilobular congestion in 5/10 males and 2/10 females, and hepatic fatty changes and centrilobular necrosis in 2/10 females. Histological findings for other groups were not reported.

In males, a NOAEL of 250 mg/kg-day and a LOAEL (FEL) of 500 mg/kg-day were identified based on increased mortality (50%). Significant decreases in body weight (>10%) were also observed in male rats at the FEL. Gavage doses of 60, 125, 250, 500, or 1,000 mg/kg-day were converted to ADDs of 43, 89.3, 179, 357, or 714 mg/kg-day by multiplying the administered gavage dose by (5/7) days/week.

NTP (1986) (Mouse study)

B6C3F$_1$ mice (10/sex/group) were administered 1,2-DCP (purity 99.4%) at doses of 0, 30, 60, 125, 250, or 500 mg/kg-day via gavage in corn oil 5 days/week for 13 weeks. Endpoints evaluated were identical to those described above for the 13-week National Toxicology Program (NTP) study in rats. The only mortalities included one male in the 60-mg/kg-day group and one female in the 500-mg/kg-day group. Body weights were comparable between treated and control mice; terminal body weights were all within 10% of control values. No histopathologic effects attributable to exposure were reported.

A free-standing NOAEL of 500 mg/kg-day (the highest dose tested) was identified in male and female mice for lack of effects on survival, body weight, or histology. Gavage doses of 30, 60, 125, 250, or 500 mg/kg-day were converted to ADDs of 0, 21, 43, 89.3, 179, or 357 mg/kg-day by multiplying the administered gavage dose by (5/7) days/week.

Chronic-Duration/Carcinogenicity Studies

NTP (1986) (Rat study)

Male F344/N rats (50/group) were administered 1,2-DCP (purity 94%) at doses of 0, 62, or 125 mg/kg-day via gavage in corn oil 5 days/week for 103 weeks. Groups of female F344/N rats (50/group) were similarly administered 1,2-DCP at doses of 0, 125, or 250 mg/kg-day. All animals were observed twice daily for mortality and morbidity. Clinical signs of toxicity were recorded daily. Body weights were recorded every week for the first 13 weeks and then monthly thereafter. Hematology, clinical chemistry, and urinalysis evaluation were not performed. Gross

necropsies were performed on all animals found dead or sacrificed moribund, as well as those sacrificed at the end of the study (unless precluded by autolysis or cannibalization). Examinations for grossly visible lesions were performed on major tissues and organs. A complete set of 27 tissues, as well as all gross lesions, were microscopically examined in all animals.

High-dose females had significantly reduced survival rates (32%) compared with controls (74%); survival in the low-dose group (86%) was comparable to controls (see Table B-4). No significant differences in survival were reported among males. Terminal body weights were decreased in all exposed animals; however, the changes were only biologically significant (≥10%) in the high-dose males (−10%) and females (−21%) (see Table B-4). The incidences of hemosiderosis and hematopoiesis of the spleen and clear cell foci and necrosis of the liver were significantly increased in high-dose females, compared with controls (see Table B-5). In low-dose females, but not high-dose females, a significant increase in mammary gland hyperplasia was observed, compared with control (see Table B-5). While mammary gland hyperplasia was not significantly elevated in high-dose females, mammary gland adenocarcinoma incidence was marginally increased (5/50) compared with controls (1/50); this increase was statistically significant once incidences were adjusted for intercurrent mortality (26.7 vs. 2.7%, respectively) (see Table B-5). The lack of significant increase in mammary gland hyperplasia in high-dose females may be due to the progression from hyperplasia to neoplasia and/or high mortality. Other neoplastic findings in females included a significant dose-response trend in the incidence of endometrial stromal polyps of the uterus (without significant findings in either group using pair-wise comparison) following adjustment for intercurrent mortality (see Table B-5). There were no non-neoplastic or neoplastic lesions attributable to exposure observed in any of the tissues examined in male rats.

In male rats, a NOAEL of 62 mg/kg-day and a LOAEL of 125 mg/kg-day were identified based on a 10% decrease in body weight. There was equivocal evidence of carcinogenicity in female rats exposed to doses up to 250 mg/kg-day via gavage for 5 days/week for up to 103 weeks based on a marginal, but significant, increase in mammary gland adenocarcinoma after adjustment for intercurrent mortality. There was no evidence of carcinogenicity in male rats exposed to doses up to 125 mg/kg-day via gavage for 5 days/week for up to 103 weeks. Gavage doses of 62, 125, or 250 were converted to ADDs of 0, 45, 89.3, or 179 mg/kg-day by multiplying the administered gavage dose by (5/7) days/week and to human equivalent doses (HEDs) of 0, 11, 21.4, and 43.0 mg/kg-day using the rat-to-human dosimetric adjustment factor (DAF) of 0.24 based on the animal:human $BW^{1/4}$ ratio recommended by U.S. EPA (2011b).

NTP (1986) (Mouse study)

$B6C3F_1$ mice (50/sex/group) were administered 1,2-DCP (purity 94%) at doses of 0, 125, or 250 mg/kg via gavage in corn oil 5 days/week for 103 weeks. Endpoints evaluated were identical to those described above for the 103-week NTP study in rats.

The survival of high-dose female mice (52%) was reduced compared with controls (70%); however, these findings are confounded by evidence of infection (characterized by suppurative inflammation of the reproductive tract) in 60% of all females that died. Survival of treated male mice was similar to controls. No clinical signs of toxicity or body-weight effects were observed in either sex. Significantly increased non-neoplastic lesions were only observed in the livers of high-dose males, including a 30% incidence of hepatocytomegaly and a 20%

incidence of hepatic necrosis (including focal, not otherwise specified [NOS], and centrilobular combined), compared with control incidences of 6 and 4%, respectively (see Table B-6).

Neoplastic lesions attributable to exposure were observed in the liver in male and female mice and in the thyroid of female mice (see Table B-6). A significant positive trend was observed for hepatic adenoma in both male and female mice, with significantly increased incidences in the high-dose group in males (both before and after adjustment for intercurrent mortality) and females (after adjustment for intercurrent mortality only), compared with controls. Similarly, a significant positive trend was observed for the combined incidence of hepatic adenoma or carcinoma in both male and female mice, with significantly increased incidences in the high-dose males and low- and high-dose females, compared with control, both before and after adjustment for intercurrent mortality. Incidences of hepatic carcinomas alone were not significantly elevated with exposure. In the thyroid, incidences of follicular cell adenomas (alone) or carcinomas (alone) were not significantly increased in males or females; however, a significant positive trend was observed for the combined incidence of thyroid follicular cell adenoma or carcinoma in female mice, with significantly increased incidence in the high-dose group, compared with control, after adjustment for intercurrent mortality.

A NOAEL of 125 mg/kg-day and a LOAEL of 250 mg/kg-day were identified for hepatocytomegaly and hepatic necrosis in male mice. A NOAEL/LOAEL determination was not made for female mice due to high mortality associated with an infection in the colony. There was evidence of carcinogenicity in male and female mice exposed to doses up to 250 mg/kg-day via gavage for 5 days/week for up to 103 weeks based on increased incidence of liver tumors. Gavage doses of 0, 125, or 250 mg/kg-day were converted to ADDs of 0, 89.3, or 179 mg/kg-day by multiplying the administered gavage dose by (5/7) days/week and to HEDs of 0, 12.5, or 25.1 mg/kg-day using the mouse-to-human DAF of 0.14 based on the animal:human $BW^{1/4}$ ratio recommended by U.S. EPA (2011b).

Gi et al. (2015b)

Gi et al. (2015b) investigated the modifying effects of 1,2-DCP on the known hamster carcinogen *N*-nitrosobis(2-oxopropyl)amine-induced cholangiocarcinomas in male hamsters. The study authors also determined the effect of 1,2-DCP on pancreatic, lung, and renal cancer. Gi et al. (2015b) also investigated the effect of 1,2-DCP on the expression of CYP2E1 and GST-T1 in hepatic and pancreatic preneoplastic and neoplastic lesions. At 6 weeks of age, male hamsters were divided into five groups. During Week 1, hamsters in Groups 1−3 (24/group) received four subcutaneous injections of *N*-nitrosobis(2-oxopropyl)amine (10 mg/kg) on Days 1, 3, 5, and 7. Hamsters in the remaining groups (4 and 5) received 0.9% saline injections as a vehicle. One week after hamsters received the last dose of *N*-nitrosobis(2-oxopropyl)amine, they were administered 1,2-DCP at doses of 0, 62.5, or 125 mg/kg via gavage in corn oil 5 days/week for 15 (17 weeks total treatment, 9 hamsters per dose group) or 17 (19 weeks total treatment, 15 hamsters per dose group) weeks. Hamsters receiving saline injections were then treated via gavage with 125 mg/kg of 1,2-DCP (9 hamsters per dose group) or corn oil vehicle (6 hamsters per dose group) for 17 weeks. At the end of 17 weeks, 9 hamsters from Groups 1−3 were euthanized and examined. The liver and pancreas were removed and preserved for histological examination; liver weight was also determined. All remaining hamsters were euthanized at the end of 19 weeks. The liver, pancreas, lung, kidney, spleen, and bile duct were removed from these animals and preserved for histological examination. Liver and pancreas samples from control and 125 mg/kg 1,2-DCP groups in the 19-week component of the study that were

identified to have preneoplastic or neoplastic lesions, were tested via immunohistochemistry for expression of CYP2E1, GST-T1, and Ki-67. From the 17-week component of the study, pancreas samples identified to contain neoplastic lesions were also examined for expression of CYP2E1, GST-T1, and Ki-67.

In the 19-week component of the study, one hamster from Group 2 (62.5 mg/kg 1,2-DCP + *N*-nitrosobis(2-oxopropyl)amine) died of unknown causes at Week 12; no other deaths were observed. Body weight was statistically and/or biologically significantly decreased in hamsters from Group 3 (125 mg/kg 1,2-DCP + *N*-nitrosobis[2-oxopropyl]amine) by 13 and 8.8% at the end of 17 and 19 weeks, respectively. No significant effects were observed on absolute or relative liver weight. The study authors reported no significant histopathological findings in the liver, pancreas, lung, or kidneys. There were also no significant effects on the expression of CYP2E1, GST-T1, and Ki-67. A LOAEL of 125 mg/kg-day is identified for statistically and biologically (≥10%) significantly decreased body weight with a corresponding NOAEL of 62.5 mg/kg-day. Gavage doses of 62.5 or 125 mg/kg-day were converted to ADDs of 0, 44.6, or 89.3 mg/kg-day by multiplying the administered gavage dose by (5/7) days/week and to HEDs of 9.37 and 18.8 mg/kg-day using a hamster-to-human DAF of 0.21 based on the animal:human $BW^{1/4}$ ratio recommended by U.S. EPA (2011b).

Reproductive/Developmental Studies

Dow Chemical Co (1990); Dow Chemical Co (1989b)

In an unpublished two-generation study, groups of S-D rats (30/sex/generation) were administered 1,2-DCP (purity 99.9%) via drinking water at concentrations of 0, 0.024, 0.10, or 0.24%. F0 female rats were exposed via drinking water from 10 weeks prior to mating, through mating (for up to 3 weeks), gestation, and lactation (~18 weeks). F0 males were similarly exposed, with the exception of 2 weeks during the post mating period when they received tap water (~16 weeks). F1 rats were exposed via dams during gestation and lactation and via drinking water for 12 weeks prior to mating to produce the F2 generation, through mating, gestation, and lactation (~21 weeks). Based on 1,2-DCP intakes calculated by the study authors for premating and postmating periods (gestational/lactational) using measured body weight and water intake, the TWA dose levels were determined to be 0, 24.8, 82.7, or 152 mg/kg-day for F0 males, 0, 38.8, 127, or 254 mg/kg-day for F0 females, 0, 28.3, 109, or 213 mg/kg-day for F1 males, and 0, 42.7, 148, or 293 mg/kg-day for F1 females (see footnotes for Tables B-7 to B-11).

F0 and F1 parental rats were examined daily for mortality and clinical signs of toxicity. All spontaneous deaths and moribund animals were submitted for pathologic examination. Body weights and water and food consumption were recorded weekly throughout the study except during breeding periods. All animals were given ophthalmological examinations prior to study initiation and at necropsy. For each litter, the following parameters were recorded: litter size on the day of parturition (Day 0); number of live and dead pups on Postnatal Days (PNDs) 0, 1, 4, 7, 14, and 21 (note: litters were culled to four per sex on PND 4); and the weight and sex of each pup and lactating female on PNDs 1, 4, 7, 14, and 21. Pups were also evaluated for any visible external physical abnormalities or changes in behavior during lactation. All F0 and F1 parental rats were sacrificed after weaning on PND 21 and subjected to a full necropsy. Blood was collected from 10 rats/sex/group/generation for hematology (Hct, Hb, and erythrocyte, total leukocyte, and platelet counts). Liver and kidney weights were recorded for all rats. The

following tissues were processed for histological examination in the control and 0.24% groups: bone/bone marrow, cervix, coagulating glands, epididymides, gross lesions, kidneys, ovaries, oviducts, pituitary, prostate, seminal vesicles, testes, uterus, and vagina. Tissues processed for histological examination in the 0.024 and 0.10% groups included all gross lesions and the liver. Ten pups/sex/group were randomly selected from the F1 and F2 litters for complete gross necropsy on PND 21. Also at this time, blood was collected for hematology and liver and kidney weights were recorded. Histologic examinations were not conducted in F1 or F2 pups.

Additionally, F0 male rats from all groups were bred with unexposed, virgin female rats (two successive matings) after mating to F0 females (dominant lethal study). F0 males were exposed to tap water during this 2-week breeding period. Bred female rats (confirmed by copulatory plug) were sacrificed about 14 days from the middle of the breeding period, and the numbers of corpora lutea, implantations, and resorptions were counted to determine preimplantation loss and resorption rates. Uteri of females that appeared nonpregnant were removed and stained for identification of early resorptions.

F0 generation: Two males and two females from the low-dose group and one high-dose F0 female died during the study. The deaths were not considered treatment-related. Since the high-dose female died on Day 6 of the study, it was replaced with another female. No clinical signs of toxicity were observed. Body weights were significantly decreased by 9−11% in high-dose F0 males throughout the study (see Table B-7). In high-dose F0 females, body weights at the end of the gestation and lactation periods were significantly reduced by 10−14% (see Table B-7). Body weights were within 10% of controls throughout the experiment in F0 males and females from the low- and mid-dose groups. In both male and female F0 rats, water intake was reduced by 38−47% in the high-dose group and 13−30% in the mid-dose group, suggesting a decrease in palatability (see Table B-7). Feed intake was reduced ~10% in high-dose females during lactation only; food intakes in all other groups were comparable to controls.

There were no changes in the reproductive indices of treated F0 male or female rats, compared to control, either in the main study or the dominant lethal study. There were no significant differences in mean litter size, the number of live or dead pups on PND 0, or the sex ratio in F1 litters. However, pup survival after birth was significantly reduced by 2−10% at the high dose, compared with controls; survival in the low- and mid-dose groups was comparable to controls (see Table B-8). Neonatal body weights for F1 animals from the high-dose group were significantly depressed by 8−16% throughout lactation (see Table B-8). These neonatal effects may be related to decreased water consumption and reduced body weights in dams from the high-dose group. External observations in F1 pups from treated and control groups were comparable.

At the end of the lactation period, statistically significant hematological changes in high-dose F0 rats included a 16% decrease in platelet count in males, 7−9% decreases in erythrocyte count, Hb, and Hct in females, and a 2.3-fold increase in the percent of reticulocytes in females (see Table B-9). Polychromasia was seen in a few females (1−2) at the two lower doses and in 5/10 females at the higher-dose group. These findings are suggestive of anemia in females. In F1 weanlings, Hb levels were marginally, but significantly, elevated by 7% in male pups from the high-dose group; no other hematological changes were reported in F1 weanlings.

The only significant, biologically relevant (>10%) organ-weight change in F0 animals was increased absolute and relative liver weight in females from all exposure groups, which did not, however, increase with increasing dose. Absolute liver weights were increased by 19, 14, and 12% and relative liver weights were increased by 12, 10, and 13% in the low-, mid-, and high-dose groups, respectively. No significant, biologically relevant organ-weight changes were observed in F1 weanlings. The livers in both male and female F0 rats showed an increase in incidence of "very slight-to-slight" granularity of the hepatocellular cytoplasm in the high-dose group (see Table B-10). No changes attributable to exposure were found in any other F0 organs examined, including reproductive organs. No histology was performed on F1 weanlings.

For the F0 males, NOAEL and LOAEL values of 82.7 and 152 mg/kg-day, respectively, were identified based on decreased body weight. Maternal NOAEL and LOAEL values of 127 and 254 mg/kg-day, respectively, were identified for anemia and decreased body weights in F0 females. The toxicological significance of increased "very slight-to-slight" granularity of the hepatocellular cytoplasm is unclear, as this may represent an adaptive response to 1,2-DCP exposure. F1 offspring NOAEL and LOAEL values were 127 and 254 mg/kg-day, respectively, based on decreased neonatal body weights and survival (secondary to maternal body-weight effects).

F1 generation: One female from the low-dose group died during the study due to a thrombus in the heart; this death was not considered treatment-related. At weaning, high-dose F1 males and females selected to produce the F2 generation weighed significantly less than controls (decreased 11−14%; see Table B-11). Body weights during pre- and postmating exposure (including gestation/lactation) were also significantly decreased by 9−14% in F1 parental animals; however, body-weight depression did not increase with continued exposure, suggesting that observed depressions are reflecting low neonatal body weights (see Table B-11). As with the F0 generation, water intake was significantly reduced throughout the exposure period by 28−49% in the high-dose animals, with inconsistent decreases in the low-dose males and mid-dose males and females ranging from ~4−34% (see Table B-11), suggesting a decrease in water palatability. Food consumption was slightly decreased in high-dose F1 males by an average of ~8% throughout the exposure period. In F1 females, food consumption was decreased in a dose-related manner by11−23% during the last week of gestation only. No other changes in food consumption were observed.

There were no changes in the reproductive indices of treated F1 male or female rats, compared with control. There were no significant differences in mean litter size, sex ratio, number of live or dead pups on PND 0, neonatal survival, or pup weight or growth in F2 litters. External observations in F2 pups from treated and control groups were comparable.

At the end of the lactational period, reticulocyte count was dose-dependently increased by 22−67% in F1 adult males; no other hematological changes or changes in RBC morphology were observed in F1 parental animals or F2 weanlings. Significant changes in organ weight included a 6−9% increase in relative (but not absolute) kidney weight in F1 males and females and F2 female weanlings and a 15% decrease in absolute (but not relative) liver weight in males; these findings are considered secondary to body-weight effects and therefore not biologically relevant. Similar to the F0 adults, the only histopathological observation was increased incidence of "very slight-to-slight" cytoplasmic granularity of the hepatocytes in high-dose animals (see Table B-10).

For the F1 males, NOAEL and LOAEL values of 109 and 213 mg/kg-day, respectively, were identified for decreased body weight. Maternal NOAEL and LOAEL values based on reduced body weight were 148 and 293 mg/kg-day, respectively. A NOAEL of 293 mg/kg-day was identified for lack of effects in F2 offspring. The toxicological significance of increased "very slight-to-slight" granularity of the hepatocellular cytoplasm is unclear, as this may represent an adaptive response to 1,2-DCP exposure.

Dow Chemical Co (1989c)

Dow Chemical Co (1989c) is an unpublished dose-range-finding study in rats that was performed to select the correct dose for a more comprehensive developmental toxicity study [see "Kirk et al. (1995)"below]. Groups of mated female S-D rats (10/group) were administered 1,2-DCP (purity 99.9%) at doses of 0, 50, 125, 250, or 500 mg/kg-day via gavage in corn oil gavage from Gestation Days (GDs) 6−15. All dams were observed daily for mortality and clinical signs of toxicity. A more detailed observational battery was performed by a blinded observer for approximately 60 minutes after dosing on GDs 6, 7, and 15, including the following endpoints: pupil size, respiration, movement (including muscle tone, extensor thrust reflex, behavior, tremors, convulsions, etc.), skin and haircoat (including grooming condition, piloerection, etc.), salivation, lacrimation, and urine and fecal staining. Body weights of dams were recorded on GD 0 and daily from GDs 6−16 (dosing period). Food and water consumption was measured every 3−4 days beginning on GD 0. Dams were sacrificed on GD 16, and blood was collected for hematology (Hct, Hb concentration, erythrocyte count, total leukocyte count, platelet count). All dams, including those that died prior to the conclusion of the study, underwent a full necropsy. Eyes were examined in situ by a glass slide technique. Kidney, liver, and spleen weights were recorded. Dams were examined for the number of corpora lutea, implantations, resorptions, and fetuses.

One animal in the 250-mg/kg-day group died immediately after treatment on GD 7; however, after necropsy, it was determined to be due to a gavage error. No other mortalities occurred. Clinical signs of toxicity (lethargy, salivation, and/or perineal staining) were observed on GDs 6−8 in 5/10 and 10/10 dams from the 250- and 500-mg/kg-day groups, respectively, compared with 0/10 controls. Findings from the detailed observational battery showed a significant increase in the signs of CNS depression on GD 6 in all dose groups within an hour of administration of 1,2-DCP, including decreased respiration, movement, muscle tone, and extensor thrust reflex and increased salivation and lacrimation. Perineal urine staining was also observed on GD 6 in some animals receiving doses ≥125 mg/kg-day. These effects were observed with less frequency on GD 7, and only at ≥250 mg/kg-day. The only significant observations on GD 15 were increased incidence of salivation and perineal urine staining at 500 mg/kg-day.

Numbers of confirmed pregnancies were 4, 9, 8, 6, and 10 in the 0, 50, 125, 250, and 500 mg/kg-day, respectively. In pregnant dams, maternal body-weight gain and food consumption were significantly decreased compared with controls during the first 3 days of 1,2-DCP administration (GDs 6−9) at ≥125 mg/kg-day (see Table B-12). However, food consumption and body weights in the 125- and 250-mg/kg-day groups were comparable to control from GD 9−16, and terminal body weights were not significantly altered. In contrast, body-weight gain during the entire dosing period (GDs 6−16) and gestation (GDs 0−6), as well as terminal body weight, were significantly decreased in dams from the 500-mg/kg-day group, despite food consumption comparable to control from GDs 9−16 (see Table B-12). Water intake

was also decreased from GDs 6−9 at ≥125 mg/kg-day, but not in a significant, dose-related manner. Spleen, liver, and kidney weights and hematologic parameters were comparable between exposed and control animals. At necropsy, no gross pathologic treatment-related effects were reported in animals at any dose. No changes were observed between treated and control dams in any of the pregnancy outcomes evaluated.

A maternal NOAEL of 250 mg/kg-day and LOAEL of 500 mg/kg-day were identified based on clinical signs of toxicity that persisted throughout the exposure period and decreased maternal body weight. Based on these findings, the doses selected for the teratology study were 0, 10, 30, and 125 mg/kg-day (see below).

Kirk et al. (1995) (Rat study)

Groups of mated female S-D rats (30/group) were administered 1,2-DCP (purity 99.9%) at doses of 0, 10, 30, or 125 mg/kg-day via gavage in corn oil from GDs 6−15. Animals were observed daily for mortality and clinical signs of toxicity, and an observational battery was performed on GDs 6 and 7 as described above (Dow Chemical Co, 1989c). Body weights were recorded on GD 0, daily during dosing (GDs 6−15), and on GDs 16 and 21. Food and water consumption were measured every 2−4 days beginning on GD 0. On GD 21, dams were sacrificed and weights of liver, kidney, spleen, and gravid uterus were recorded. For each dam, the number of corpora lutea and the number and position of implantations, resorptions, and live or dead fetuses were recorded. Uteri of nonpregnant females were examined for early resorptions. The sex and body weight of each fetus and any external anomalies were recorded. At least half of rat litters were randomly selected for dissection and examination for visceral or skeletal alterations.

No mortalities were observed. In the high-dose group, clinical signs of toxicity were observed on GD 6, with individual signs (decreased movement, muscle tone, and extensor thrust reflex and increased salivation and lacrimation) occurring in 6−23/30 high-dose animals, compared with 0−1/30 controls. These signs were less frequent (1−3/30) on GD 7. No significant clinical signs were observed in rats exposed to 10 or 30 mg/kg-day. High-dose dams also experienced significantly decreased body weight on GDs 9, 12, and 16 (4−5% lower than controls). Body-weight gain was significantly reduced on GDs 6−9 (−122%), GDs 16−21 (−28%), and GDs 0−21 (−10%) (see Table B-13). During the first three exposure days (GDs 6−9), food consumption was also significantly decreased by 25% in this group; consumption from GDs 9−21 was comparable to control. Water consumption was significantly increased by ~25% from GDs 9−15. There were no significant differences in organ weight between treated animals and controls.

The number of confirmed pregnancies was 25, 29, 28, and 30 in 0-, 10-, 30-, and 125-mg/kg-day groups, respectively. One dam dosed with 10 mg/kg-day delivered early (GD 20); the cause of the premature delivery could not be ascertained upon gross examination. This dam was excluded from the analysis of pregnancy outcomes and fetal malformations/variations. Pregnancy outcomes were not significantly different between exposed and control groups. In fetuses, there was a significant increase in the incidence of delayed ossification of the skull at 125 mg/kg-day (16/30 litters), compared with controls (8/25 litters) (see Table B-14). A nonsignificant increase in the incidence of delayed ossification of the thoracic centra was also observed at 125 mg/kg-day (10/30 litters), compared with controls

(4/25 litters) (see Table B-14). Delayed ossification of cervical centra was observed in all dose groups, including controls, with similar frequency (see Table B-14).

Maternal and fetal NOAEL and LOAEL values of 30 and 125 mg/kg-day, respectively were identified based on the maternal toxicity (clinical signs [CNS depression, salivation, and lacrimation], decreased body-weight gain) and delayed skull ossification in fetuses.

Dow Chemical Co (1988d)

Dow Chemical Co (1988d) is an unpublished dose-range-finding study in rabbits that was performed to select the correct dose for a more comprehensive developmental toxicity study (Kirk et al., 1995). Groups of artificially inseminated New Zealand white (NZW) rabbits (seven/group) were administered 1,2-DCP (purity 99.9%) at doses of 0, 25, 100, or 250 mg/kg-day via gavage in corn oil from GDs 7−19. Animals were observed daily for mortality and signs of clinical toxicity. Body weights were recorded on GD 0, daily throughout the exposure-period (GDs 7−19), and on the day of sacrifice (GD 20). Blood samples were collected on GD 19 for hematology (reticulocyte count, Hct, Hb, erythrocyte count, total leukocyte count, erythrocyte indices mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC], and erythrocyte morphology). Detailed necropsies were performed on all rabbits. Maternal liver, kidney, and spleen weights were recorded. Numbers of corpora lutea and numbers and position of implantations and resorptions were also documented. Uteri of females appearing nonpregnant were examined for early resorptions. Histologic examinations were not performed.

Two rabbits in the high-dose group died during the study (on GDs 15 and 18). The cause of death was not determined for either animal; however, the study authors noted that there was no apparent target organ toxicity. Two additional high-dose animals exhibited weight loss and complete litter loss. However, overall, body weight and body-weight gains were not significantly different between exposed and control groups. A higher resorption rate was observed in the high-dose group, compared with controls, but the increase was not statistically significant and values were within historical control incidence data (see Table B-15).

Significant hematological findings included 22−24% decreases in erythrocyte count, Hb, and Hct in high-dose does and a 2−3.7-fold increase in the percentage of reticulocytes in mid- and high-dose does (see Table B-16). Erythrocyte morphology showed a significant increase in the incidence of slight-to-moderate polychromasia at ≥100 mg/kg-day and a significant increase in slight-to-moderate anisocytosis at 250 mg/kg-day. These changes are indicative of regenerative anemia. At necropsy, absolute or relative organ weights and gross pathology did not differ between exposed and control groups.

A maternal NOAEL of 25 mg/kg-day and a LOAEL of 100 mg/kg-day were identified based on maternal anemia. A FEL of 250 mg/kg-day was identified based on complete litter loss and/or maternal death. Based on these findings, the doses selected for the teratology study were 0, 15, 50, and 150 mg/kg-day (see below).

Kirk et al. (1995) (Rabbit study)

Groups of artificially inseminated NZW rabbits (18/group) were administered 1,2-DCP (purity 99.9%) at doses of 0, 15, 50, or 150 mg/kg-day via gavage in corn oil from GDs 7−19. Animals were observed daily for signs of clinical toxicity. Body weights were recorded on

GD 0, daily during dosing (GDs 7−19), and on GDs 20 and 28. Food and water consumption were measured every 2−4 days beginning on GD 0. On GD 19, blood samples were collected for hematology (Hct, Hb concentration, erythrocyte count, total leukocyte count, platelet count). On GD 28, does were sacrificed. Endpoints evaluated were identical to those described above for the developmental study in rats (Kirk et al., 1995).

Two rabbits in the 150-mg/kg-day group died during the study (on GDs 17 and 22). One animal died due to an intubation error and the other animal's cause of death was not identified after pathologic examination. At the high dose, 17/18 does showed intermittent anorexia, resulting in decreased food consumption (data were not presented by the study authors). Significantly decreased weight gains were observed in high-dose rabbits during dosing (GDs 7−20), but no significant differences were observed in absolute body weight compared to controls (see Table B-17). Significantly altered hematological findings in the high-dose does included decreased erythrocytes counts, Hb concentration, and Hct and increased platelet, leukocyte, and reticulocyte counts, compared with controls (see Table B-18). Microscopic examination of erythrocytes revealed slight-to-moderate anisocytosis, poikilocytosis, and/or polychromasia in high-dose pregnant rabbits. These findings are suggestive of regenerative anemia in high-dose does. No hematological changes were observed at 15 or 50 mg/kg-day. Absolute and relative organ weights (liver, kidney, spleen, and gravid uterus) were not altered by treatment.

Numbers of litters evaluated were 18, 16, 17, and 15 in the 0-, 15-, 50-, and 150-mg/kg-day groups, respectively. Pregnancy outcomes were not significantly different between exposed and control groups. In fetuses, a significant increase in the litter incidence of delayed ossification of the skull was observed at 150 mg/kg-day (6/15 litters, 6/140 fetuses), compared with controls (0/18 litters, 0/149 fetuses). At 50 mg/kg-day, a nonsignificant increase in the litter incidence of delayed ossification of the skull was observed (2/17 litters, 2/142 fetuses). No other adverse findings were observed in exposed fetuses.

A maternal and fetal NOAEL of 50 mg/kg-day and a LOAEL of 150 mg/kg-day were identified based on maternal toxicity (anemia, anorexia) and delayed skull ossification in fetuses.

Inhalation Exposures

The effects of inhalation exposure of animals to 1,2-DCP have been evaluated in five subchronic-duration studies in three species (Matsumoto et al., 2013; Umeda et al., 2010; Dow Chemical Co, 1988a; SRI, 1975), two chronic-duration studies in two species (Matsumoto et al., 2013; Umeda et al., 2010), and a reproductive study in female rats (Sekiguchi et al., 2002). These key studies are summarized in Tables 3A and 3B and are described in detail below. Additional information regarding inhalation exposure is available from several acute, short-term, and limited subchronic- and chronic-duration studies (inadequate reporting and/or study designs) (see Table 4B).

Subchronic-Duration Studies

Umeda et al. (2010)

Groups of F344/DuCrj (SPF) rats (10/sex/group) were exposed to 1,2-DCP vapor (purity >99.5%) at target concentrations of 0, 125, 250, 500, 1,000, or 2,000 ppm, 6 hours/day, 5 days/week for 13 weeks. Mean analytical concentrations (± standard deviation [SD]) were measured at 0, 125.3 ± 0.7, 250.8 ± 1.0, 500.5 ± 2.6, 1,000.4 ± 3.4, and 2,001.3 ± 5.9 ppm.

Animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week. All rats, including those found dead or moribund, received complete necropsy. Blood was collected at terminal necropsy after overnight fasting for hematology and clinical chemistry (parameters measured were not reported by the study authors). Organs (unspecified) were removed, weighed, and examined for macroscopic lesions at necropsy. A complete set of tissues and the entire respiratory tract (including nasal cavity, pharynx, and larynx) were examined for histopathology in all animals.

A single female from the 2,000-ppm group died during the twelth week of exposure (cause of death was not reported); no other mortalities or clinical signs of toxicity were observed. Body weights were significantly reduced by 5−27% in all exposed male groups and by 5−18% in female groups at ≥500 ppm; body-weight reductions only exceeded 10% in male and female groups exposed to 1,000 ppm (see Tables B-19 and B-20). Food consumption was reduced in both male and female rats exposed to 2,000 ppm (no further information was reported). Minor, but statistically significant, changes in erythrocyte parameters included 4−19% decreases in erythrocyte count in males and females at ≥500 ppm, 3−10% decreases in Hb in males at ≥500 ppm and females at ≥1,000 ppm, and 4−5% decreases in Hct in males and females at ≥1,000 ppm (see Tables B-19 and B-20). Additionally, the percentage of reticulocytes was significantly increased approximately two- to sixfold in males at ≥1,000 ppm and females at ≥500 ppm (see Tables B-19 and B-20). Taken together, reductions in erythrocyte parameters with concomitant increases in reticulocytes are suggestive of hemolytic anemia. The number of platelets was also significantly increased by 14−23% in males at ≥1,000 ppm and females at 2,000 ppm. Significant clinical chemistry alterations included significant 25−56% increases in total serum bilirubin levels in males at 2,000 ppm and females at ≥1,000 ppm and significant ~two- to threefold increases in GGT activity in males at 2,000 ppm and females at ≥1,000 ppm (see Tables B-19 and B-20).

At necropsy, significant organ-weight changes included increased absolute and relative liver weights in female rats exposed to ≥500 ppm and increased relative spleen weight in both male and female rats exposed to 2,000 ppm, compared with controls (quantitative data not reported by study authors). Histopathological lesions attributable to exposure were observed in the nasal cavity, spleen, bone marrow, liver, and adrenal glands (see Tables B-21 and B-22). In the nasal cavity, hyperplasia of the respiratory epithelium and atrophy of the olfactory epithelium were observed in all exposed male rats and almost all exposed female rats. Lesion severity generally increased with increasing concentration in males (nasal hyperplasia and atrophy) and females (nasal atrophy). Hyperplasia of the respiratory epithelium was characterized by an increased number of ciliated columnar epithelial cells and accompanied by goblet cell hyperplasia. The hyperplasia was located diffusely in the dorsal or septum region of Level 1 (anterior nasal cavity). Atrophy of the olfactory epithelium was characterized by decreases in epithelial thickness and the number of olfactory sensory cells and often accompanied by necrosis of the olfactory sensory cells and respiratory metaplasia of the olfactory epithelium. Atrophy was located in the dorsal region of Levels 2 and 3. Inflammation of the respiratory epithelium in the nasal cavity was also significantly increased in male rats and marginally increased in female rats at ≥1,000 ppm. In the spleen, there was a significant increase in hemosiderin deposits and increased extramedullary hematopoiesis in males and females at ≥1,000 ppm; hemosiderin deposits were also significantly increased in females at 500 ppm. Bone marrow hematopoiesis was also significantly increased in both sexes at ≥1,000 ppm. In the liver, a significant increase in the incidence of centrilobular hepatocyte swelling was observed in both male and female rats

exposed at 2,000 ppm. Fatty change in the adrenal gland was significantly increased in the female rats, but not male rats, exposed to 2,000 ppm.

A LOAEL of 125 ppm was identified for nasal lesions in male and female rats; no NOAEL was identified. Analytical exposure concentrations of 125.3, 250.8, 500.5, 1,000.4, and 2,001.3 ppm were converted to human equivalent concentrations (HECs) of 0, 13.63, 27.28, 54.42, 108.79, or 217.62 mg/m^3 and 0, 10.03, 20.09, 40.08, 80.112, or 160.26 mg/m^3 for male and female rats, respectively, for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

Dow Chemical Co (1988a) (Rat study)

In an unpublished study, groups of F344 rats (10/sex/group) were exposed to 1,2-DCP (purity >99.94%) at target concentrations of 0, 15, 50, or 150 ppm 1,2-DCP, 6 hours/day, 5 days/week for 13 weeks. Mean analytical concentrations (±SD) were determined to be 15 ± 1, 50 ± 3, or 151 ± 3 ppm. The fur, eyes, mucous membranes, and respiration of all animals were evaluated after each exposure. Rats were examined daily for mortality and clinical signs of toxicity. Body weights were recorded weekly. At ~11 weeks, blood was collected for hematology (packed cell volume, erythrocyte counts, Hb, total and differential leukocyte counts, MCV, MCH, MCHC, and platelet counts) and determination of RBC and plasma cholinesterase activity levels, and urine was collected for urinalysis (specific gravity, pH, glucose, ketones, bilirubin, urobilinogen, occult blood, and protein). Eyes were examined under fluorescent illumination, and rats were weighed prior to sacrifice on the day following the last exposure to 1,2-DCP. Rats were fasted for 24 hours after final exposure prior to sacrifice. At sacrifice, blood was collected for clinical chemistry (total bilirubin, ALT, AST, ALP, BUN, and glucose) and organ weights (brain, heart, liver, kidneys, thymus, and testes) were recorded. A complete set of 47 tissues, including the respiratory tract (nasal tissues, larynx, trachea, lungs, and organs normally present on sections with these organs), was collected for histopathologic examination in the control and high-exposure groups. The respiratory tract was also examined in low- and mid-exposure groups.

No mortalities attributed to treatment or clinical signs of toxicity were observed; one low-exposure male died from hemorrhagic cystitis (considered unassociated to exposure). Body weights of male rats were significantly reduced by 7−11% throughout the entire exposure period in the 150-ppm group, with a significant 10% decrease at study termination (see Table B-23). Females in the 150-ppm group also showed significant body-weight reductions throughout the study; however, body weights remained within 10% of control and were not significantly depressed at study termination (see Table B-23). No body-weight effects were observed in the low- or mid-exposure groups. There were no biologically-relevant, concentration-related changes in hematology, clinical chemistry, urinalysis, or organ weights. At necropsy, a decrease in adipose tissue of the abdominal cavity was observed in males at 150 ppm, consistent with body-weight changes. No other gross observations were considered related to the inhalation of 1,2-DCP.

The only histopathological effects attributable to exposure were observed in the upper respiratory tract of exposed rats. Lesions of the respiratory epithelium were observed in males and females from all exposure groups. The incidence and severity of hyperplasia of the respiratory epithelium increased in a concentration-related fashion, with statistically significant

increases in incidences at ≥50 ppm (see Table B-23). Hyperplasia occurred mainly in the anterior region of the nasal cavity. Degeneration of the olfactory mucosa was also significantly increased in males and females at ≥50 ppm, with increased severity at 150 ppm (see Table B-23). In the larynx, the incidence of submucosal inflammation was significantly increased in male rats at 150 ppm only (see Table B-23). All other histopathologic effects were considered spontaneous in nature and, therefore, not related to exposure.

A LOAEL of 50 ppm was identified for increased incidence of nasal lesions in male and female rats with a corresponding NOAEL of 15 ppm. Analytical exposure concentrations of 15, 50, and 151 ppm were converted to HECs of 0, 1.6, 5.4, and 16.5 mg/m^3 for male rats and 0, 1.2, 4.0, and 12.1 for female rats for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

Matsumoto et al. (2013)

Groups of B6D2F$_1$/Crlj (SPF) mice (10/sex/group) were exposed to 1,2-DCP at concentrations of 0, 50, 100, 200, 300, or 400 ppm, 6 hours/day, 5 days/week for 13 weeks. Mean (±SD) analytical concentrations were reported as 0, 50.0 ± 0.3, 100.1 ± 0.8, 200.0 ± 1.2, 300.2 ± 1.4, and 399.9 ± 2.6 ppm, respectively. Animals were observed daily for clinical signs of toxicity. Body weight and food consumption were measured weekly. At terminal sacrifice, blood was collected for hematology (RBC and white blood count [WBC], Hb, Hct, MCV, and platelet count) and blood chemistry (bilirubin, phospholipids, AST, ALT, ALP, and lactate dehydrogenase [LDH]). All mice that died or were sacrificed were subject to gross necropsy. Major organs (not specified) were removed, weighed, and examined for gross lesions. A complete set of tissues, including nasal cavity, pharynx, and larynx, was examined microscopically for histopathological lesions.

Mortality was significantly increased in males exposed to 400 ppm (see Table B-24), with 6/10 males dying. Additionally, 2/10 males exposed to 200 ppm and 1/10 females exposed to 400 ppm died. All male deaths occurred during the first 2 weeks of exposure; no other mortalities were observed. Body weight was significantly decreased by 9−18% in males exposed to ≥200 ppm (see Table B-24). No body-weight effects were observed in females. Food consumption was decreased during the first week of exposure in males exposed to ≥200 ppm and females exposed to ≥300 ppm (data not provided by the study authors). Mild hemolytic anemia, characterized by slight but significant decreases (<20%) in erythrocyte parameters (RBC count, Hb, and Hct) and increased MCV, was observed in males exposed to ≥50 ppm and females exposed to ≥300 ppm (see Table B-25). Significant increases (7−19%) in platelets were observed in males exposed to ≥300 ppm and females exposed to 400 ppm (see Table B-25). Several significant changes were observed in blood chemistry parameters, compared with control, including increased phospholipid levels in males and females exposed to ≥300 ppm, increased ALP in males exposed to ≥300 ppm, and increased total bilirubin, AST, ALT, and LDH in males and females exposed to 400 ppm; however, biologically relevant changes (≥twofold) were only observed for AST, ALT, ALP (males only), and LDH in the 400-ppm group (see Table B-26).

Significant organ-weight changes included a 14−66% increase in absolute and relative liver weights in males and females exposed to ≥300 ppm and a 21−38% increase in relative spleen weight in males and females exposed to 400 ppm (see Table B-24). These weight

changes were accompanied by increased incidence of histopathological lesions in the liver and spleen, including swelling of centrolobular hepatocytes in males and females exposed to ≥300 ppm; fatty changes, vacuolic changes, mineralization, and necrosis in the liver of males and females exposed to 400 ppm; and atrophy, increased extramedullary hematopoiesis, hemosiderin deposits, and megakaryocytes in the spleen of males and females exposed to 400 ppm (see Table B-27). Lesions attributable to exposure were also observed in the olfactory epithelium of the nasal cavity in males and females exposed to ≥300 ppm, including respiratory metaplasia, atrophy, necrosis, and desquamation (see Table B-28). In mice exposed to 400 ppm, increased incidence of bone marrow congestion, forestomach hyperplasia, and "ground glass" appearance in the heart were also observed, compared with control (see Table B-27).

A NOAEL of 200 ppm and a LOAEL of 300 ppm were identified based on increased incidence of nasal lesions in male and females. The following systemic effects were also observed at 300 ppm: >10% decreases in body weight in males, >10% decreases in erythrocyte parameters in males and females, and liver lesions in males and females. For the nasal lesions, analytical concentrations of 50.0, 100.1, 200.0, 300.2, and 399.9 ppm were converted to HECs of 6.21, 12.43, 24.83, 37.27, and 49.66 mg/m^3 for male mice and 5.14, 10.29, 20.55, 30.86, and 41.11 for female mice for extrathoracic (nasal) respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation (U.S. EPA, 1994b): HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

Dow Chemical Co (1988a) (Mouse study)

In an unpublished study, groups of B6C3F$_1$ mice (10/sex/group) were exposed to 1,2-DCP (purity >99.94%) at target concentrations of 0, 15, 50, or 150 ppm 1,2-DCP 6 hours/day, 5 days/week for 13 weeks. Mean analytical concentrations (±SD) were determined to be 15 ± 1, 50 ± 3, or 151 ± 3 ppm. The fur, eyes, mucous membranes, and respiration of all animals were evaluated after each exposure. Mice were examined daily for mortality and clinical signs of toxicity. Body weights were recorded weekly. Eyes were examined under fluorescent illumination and mice were weighed prior to sacrifice on the day following the last exposure to 1,2-DCP. At sacrifice, blood was collected for hematology (packed cell volume, erythrocyte counts, Hb, total and differential leukocyte counts, and platelet counts), and organ weights (brain, heart, liver, kidneys, thymus, and testes) were recorded. A complete set of 48 tissues, including the respiratory tract (nasal tissues, larynx, trachea, lungs, and organs normally present on sections with these organs) was collected for histopathologic examination in the control and high-exposure groups. The respiratory tract, liver, gallbladder, kidney, and thymus were also examined in the low- and mid-exposure groups.

No mortalities due to treatment or clinical signs of toxicity were reported. Body weights of both male and female mice were comparable to control values throughout the 13-week exposure period. RBC counts, Hb, and packed cell volume were statistically significantly decreased for male mice exposed to 15 and 150 ppm; however, changes are not considered biologically relevant as they were minor (<10%) when compared with control values and were not observed in female mice. Organ weights and histology did not differ significantly between the treated and control mice.

Based on a lack of effects, a NOAEL of 150 ppm was identified for male and female mice. Analytical exposure concentrations of 15, 50, and 151 ppm were converted to HECs of 2.1, 7.3, and 22.2 mg/m^3 for male mice and 1.6, 5.6, and 17.1 for female mice for extrathoracic

respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation (U.S. EPA, 1994b): HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

Dow Chemical Co (1988a) (Rabbit study)

In an unpublished study, groups of NZW rabbits (7/sex/group) were exposed to 1,2-DCP (purity >99.94%) at target concentrations of 0, 150, 500, or 1,000 ppm 1,2-DCP 6 hours/day, 5 days/week for 13 weeks. Mean analytical concentrations (±SD) were determined to be 151 ± 3, 502 ± 7, or 1,003 ± 8 ppm. During each exposure period, the fur, eyes, mucous membranes, and respiration of all animals were evaluated. Rabbits were examined daily for mortality and clinical signs of toxicity. Body weights were recorded weekly. At ~11 weeks, blood was collected for hematology (packed cell volume, erythrocyte counts, Hb, total and differential leukocyte counts, and platelet counts). Eyes were examined under fluorescent illumination, and rabbits were weighed prior to sacrifice on the day following the last exposure to 1,2-DCP. At sacrifice, blood was collected again for hematology (see parameters above plus reticulocyte count) and clinical chemistry (total bilirubin, glutamic pyruvic transaminase [SGPT], glutamic oxaloacetic transaminase [SGOT], ALP, BUN, and glucose) and testes weights were recorded (no other organs were weighed). A complete set of 49 tissues, including the respiratory tract (nasal tissues, larynx, trachea, lungs, and organs normally present on sections with these organs), was collected for histopathologic examination in the control and high-exposure groups. The respiratory tract, liver, gallbladder, bone, bone marrow, and spleen were also examined in low- and mid-exposure groups.

No mortalities due to treatment or clinical signs of toxicity were observed. Body weights were comparable between exposed and control rabbits. At 11 weeks, statistically significant hematological findings included 10−25% reductions in erythrocyte count, Hb, and packed cell volume at ≥500 ppm in both males and females; erythrocyte count was also significantly decreased by 10% in males at 150 ppm (see Table B-29). Similar results were reported at terminal sacrifice, with additional findings of a significant two- to fourfold increase in percent reticulocytes at ≥500 ppm in both males and females and a nonsignificant fourfold increase in nucleated erythrocytes at 1,000 ppm in males only (see Table B-29). None of the clinical chemistry parameters were affected by exposure. Absolute and relative liver weights were statistically significantly increased by 21−30% in male rabbits at ≥500 ppm, compared with controls; no other significant organ-weight changes were observed.

Histopathological lesions attributed to exposure were observed only in the bone marrow and nasal cavity (see Table B-30). Slight-to-moderate bone marrow hyperplasia was significantly elevated in males at ≥500 ppm and females at 1,000 ppm. Additionally, nonsignificant increases were observed in the incidence of increased hemosiderin-laden macrophages in the bone marrow at 1,000 ppm in both sexes. A marginally significant increase in the incidence of olfactory epithelium degeneration of the nasal cavity was observed in male rabbits exposed to 1,000 ppm, compared with controls (p = 0.07), suggesting a potential treatment-related effect; observed lesions were very slight-to-slight in severity (see Table B-30). The incidence of nasal lesions in exposed female rabbits was not increased relative to controls (see Table B-30). All other microscopic changes reported in the rabbits were considered spontaneous and not related to 1,2-DCP exposure.

Based on the lack of respiratory system effects, a NOAEL of 1,003 ppm was identified. Other effects observed that may not be related to the respiratory system include: bone marrow hyperplasia and anemia in both sexes and increased liver weight in males. Analytical exposure concentrations of 151, 502, and 1,003 ppm were converted to HECs of 71, 236, and 471.8 mg/m^3 for male rabbits and 66.4, 221, and 441.2 mg/m^3 for female rabbits for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation (U.S. EPA, 1994b): HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

Chronic-Duration/Carcinogenicity Studies

Umeda et al. (2010)

Groups of F344/DuCrj (SPF) rats (50/sex/group) were exposed to 1,2-DCP vapor (purity >99.5%) at target concentrations of 0, 80, 200, or 500 ppm, 6 hours/day, 5 days/week for 104 weeks. Mean analytical concentrations (±SD) were measured at 0, 80.2 ± 0.5, 200.5 ± 1.3, and 500.2 ± 2.4 ppm. The animals were observed daily for clinical signs and mortality. Body weight and food consumption were measured once a week for the first 14 weeks and once every 4 weeks thereafter. All rats, including those found dead or moribund, received complete necropsy. Blood was collected after overnight fasting for hematology and clinical chemistry (parameters measured were not reported by the study authors). Organs (unspecified) were removed, weighed, and examined for macroscopic lesions. A complete set of tissues and the entire respiratory tract (including nasal cavity, pharynx, and larynx) were examined for histopathology in all animals.

There were no mortalities due to treatment or clinical signs of toxicity. Food consumption was similar between groups. Growth was slightly suppressed in male rats in a concentration-related manner throughout the study, and terminal body weights were statistically significantly decreased by 11% in males and 8% in females exposed to 500 ppm. The only hematological change was a 4% decrease in erythrocyte count in female rats at 500 ppm (data not provided by the study authors). Females in the 500-ppm group also had a statistically significant increase in GGT (quantitative data not provided by the study authors).

Significant increases in non-neoplastic and neoplastic nasal lesions were observed in exposed males and females, compared with controls (see Tables B-31 and B-32). Atrophy of the olfactory epithelium was observed in 96−100% of all exposed rats, compared with 0% of controls, and severity of the lesion increased with increasing concentration. All exposure groups also showed a significant increase in squamous cell metaplasia of the respiratory epithelium, compared with controls. Metaplasia incidences in the 0-, 80-, 200-, and 500-ppm groups were 10, 62, 82, and 98% in males, respectively, and 6, 30, 74, and 92% in females, respectively; severity increased with concentration in females, but not in males. Incidence of respiratory epithelium inflammation was also significantly increased in all exposure groups, compared with controls. Incidences in the 0-, 80-, 200-, and 500-ppm groups were 40, 70, 94, and 94% in males, respectively, and 20, 60, 78, and 80% in females, respectively; severity of the lesion did not increase with increasing concentration. Non-neoplastic lesions were located in the dorsal region of Levels 2 and 3. A significant increase was observed in hyperplasia of the transitional epithelium in both sexes at ≥80 ppm and squamous cell hyperplasia in males at ≥200 ppm and in females at 500 ppm. The study authors characterized these as preneoplastic lesions. Hyperplasia of the transitional epithelium was characterized by an increased number of nonciliated cuboidal epithelial cells in a focal area, and squamous cell hyperplasia was characterized by a thickening

of five or more epithelial layers. These lesions were accompanied by hyperplasia of the submucosal gland. A significant increase in the number of nasal papillomas was observed in both male and female rats at 500 ppm; tumors were located in the dorsal region at Levels 1 and 2 (anterior region). A rare nasal tumor (esthesioneuroepithelioma) was observed in two males at 80 ppm and one male at 200 ppm; since historical control data show no cases of esthesioneuroepithelioma, these tumors may be attributable to 1,2-DCP exposure. All other histopathologic effects were considered spontaneous in nature and, therefore, not related to 1,2-DCP exposure.

A LOAEL of 80 ppm was identified for nasal lesions in male and female rats; no NOAEL was identified. 1,2-DCP was carcinogenic in both male and female rats under the conditions of this study, leading to significantly increased nasal tumors in exposed rats relative to controls. Analytical exposure concentrations of 80.2, 200.5, and 500.2 ppm were converted to HECs of 16.2, 40.54, and 101.1 mg/m^3 for male rats and 10.7, 26.75, and 66.71 mg/m^3 for female rats for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation (U.S. EPA, 1994b): HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

Matsumoto et al. (2013)

Groups of B6D2F$_1$/Crlj (SPF) mice (50/sex/group) were exposed to 1,2-DCP at concentrations of 0, 32, 80, or 200 ppm, 6 hours/day, 5 days/week for 104 weeks. Mean (±SD) analytical concentrations were reported as 0, 32.1 ± 0.2, 80.2 ± 0.4, or 200.5 ± 1.2 ppm, respectively. Animals were observed daily for clinical signs of toxicity. Body weight and food consumption were measured weekly. At terminal sacrifice, blood was collected for hematology (RBC and WBC count, Hb, Hct, MCV, and platelet count) and blood chemistry (bilirubin, phospholipids, AST, ALT, ALP, and LDH). All mice that died or were sacrificed were subject to gross necropsy. Major organs (not specified) were removed, weighed, and examined for gross lesions. A complete set of tissues, including nasal cavity, pharynx, and larynx, was examined microscopically for non-neoplastic and neoplastic lesions.

No changes were observed for survival, clinical signs of toxicity, body weight, or food consumption in exposed mice, compared with controls. At terminal sacrifice, MCH concentration was decreased in males exposed to ≥80 ppm and females exposed to 200 ppm (data not provided by the study authors); no other hematological or biochemical differences were observed between exposed and control groups. In males, the absolute kidney weight was significantly increased by 13−57% in all exposure groups, and the relative kidney weight was significantly increased by 48% in the 200-ppm group (see Table B-33). The absolute spleen weight was significantly decreased by 21% in males exposed to 200 ppm, compared with controls (see Table B-33); however, the study authors attributed this finding to an extremely high spleen weight in one of the control males. No significant changes were observed in relative spleen weight in males (see Table B-33). All other organ weights were comparable between treated and control mice.

Significant increases in non-neoplastic lesions were observed in the kidney and nasal cavity of exposed mice, compared with controls (see Table B-34). In the kidney, basophilic changes and cortical mineralization were significantly increased relative to controls in male mice from all treated groups. Renal lesion incidence did not, however, increase with increasing exposure concentration. No renal lesions were seen in female mice. In the olfactory epithelium

of the nasal cavity, the incidence of atrophy was significantly increased in males exposed to ≥80 ppm. In females, atrophy was significantly elevated only at 80 ppm; however, the incidence of respiratory metaplasia of the olfactory epithelium was significantly increased in females exposed to 200 ppm. Respiratory metaplasia of the submucosal gland was also significantly elevated in males and females exposed to 200 ppm.

Significant increases in neoplastic lesions were observed in the lung, Harderian gland, and spleen of exposed mice, compared with controls (see Table B-35). In the lung, the combined incidence of bronchiolo-alveolar adenoma or carcinoma was significantly increased in males exposed to 32 and 200 ppm and females exposed to 200 ppm. A significant, concentration-related trend was only observed in females. The combined lung tumor incidence in 200-ppm female mice reportedly exceeded the maximum historical control incidence for this laboratory, although supporting data were not shown. There was a significant trend for increased Harderian gland adenomas in male mice, but not females. Incidence was not significantly greater than controls at any exposure level, but reportedly exceeded historical control values at 200 ppm. In the spleen, the combined incidence of hemangioma or hemangiosarcoma, as well as the incidence of hemangiosarcoma alone, was significantly increased in males exposed to 200 ppm. However, significant trends were not observed and incidences were reportedly within the maximum observed in historical control data. Splenic tumors were not increased in females. Significant increases in neoplastic lesions were not observed in other tissues, including the nasal cavity.

A NOAEL of 32 ppm and a LOAEL of 80 ppm were identified in male and female mice for nasal lesions, including increased incidence of atrophy of the olfactory epithelium in both sexes at 80 ppm and increased respiratory metaplasia of the olfactory epithelium and/or submucosal gland in both sexes at 200 ppm. Other effects occurring at 32 ppm not necessarily related to the respiratory system include: increased absolute kidney weight and pathological changes in males. There was some evidence of carcinogenicity in both male and female mice under the conditions of this study, the strongest being significant increases in the incidence of combined bronchiolo-alveolar adenoma or carcinoma in females and Harderian gland adenoma in males.

For this study, the analytical concentrations of 32.1, 80.2, and 200.5 ppm were converted to HECs for pulmonary and extrathoracic effects. HECs of 69.2, 173, and 432.0 mg/m^3 for female mice and 0, 77.2, 192, 482.5 mg/m^3 for male mice were calculated for pulmonary effects by treating 1,2-DCP as a Category 1 gas and using the following equation (U.S. EPA, 1994b): HEC_{PU} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{PU}$; see Equations 4−28 in U.S. EPA (1994b) for calculation of $RGDR_{PU}$ and default values for variables. HECs of 4.73, 11.8, and 29.55 mg/m^3 for male mice and 4.27, 10.7, 26.67 for female mice were calculated for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation (U.S. EPA, 1994b): HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

Reproductive/Developmental Studies

Sekiguchi et al. (2002)

Groups of female F344 rats (six to nine/group) were exposed to 1,2-DCP (purity not reported) at target concentrations of 0, 50, 100, or 200 ppm, 8 hours/day, 7 days/week for

approximately 3 weeks. Analytical concentrations were measured at 0, 50.7 ± 1.1, 99.9 ± 2.7, and 200.7 ± 4.4 ppm. Prior to exposure, three consecutive estrous cycles were monitored using a vaginal smear test. Only rats exhibiting regular cycles were used in the experiment. Daily body-weight measurements and vaginal smears were collected. Rats were sacrificed after 21−24 days during an estrous stage. At sacrifice, the reproductive organs were removed and the weights of the ovaries and uterus were measured. The number of ovulated ova and the mass of the cumulus cells collected from the oviduct were recorded.

No significant changes were observed in body or reproductive organ weights between exposed and control groups. Estrous cycle parameters show that 1,2-DCP exposure is associated with increased estrous cycle length and decreased ovulation (see Table B-36). The number of total cycles lasting ≥6 days (all rats combined/group) was significantly more at ≥100 ppm, compared with controls. Nonsignificant, concentration-related trends toward decreased number of estrous cycles/rat and increased number of rats with cycles lasting ≥6 days were observed. Additionally, the number of ovulated ova was significantly decreased by 35% in rats exposed to 200 ppm compared with controls.

Because the study authors did not evaluate respiratory system effects, a NOAEL and LOAEL cannot be determined. Reproductive effects were observed at 100 ppm. The analytical concentrations of 50.7, 99.9, and 200.7 ppm were converted to HECs of 0, 7.58, 14.9, 30.00 for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Genotoxicity Studies

The genotoxicity of 1,2-DCP has been evaluated in numerous in vitro studies and a limited number of in vivo studies. Available studies are summarized below (see Table 4A for more details). In general, the data indicate that 1,2-DCP is not a potent mutagen, but may cause deoxyribonucleic acid (DNA) damage and clastogenic effects.

Available evidence from in vitro studies indicates that 1,2-DCP is not a strong mutagen. Some early assays (pre-1985) report that 1,2-DCP was mutagenic to *Salmonella typhimurium* strains TA100 and TA1535 at high 1,2-DCP concentrations (≥750 µg/plate) (Haworth et al., 1983; Carere and Morpurgo, 1981; Principe et al., 1981; De Lorenzo et al., 1977), although Stolzenberg and Hine (1980) reported that 1,2-DCP was not mutagenic to TA100 at similar concentrations. Based on more stringent evaluation criteria implemented after 1985, these findings are not considered evidence of mutagenicity (e.g., responses seen at doses >500 µg/plate are disregarded) (Prival and Dunkel, 1989). Subsequent assays found only marginal increases (<twofold) in the number of revertants observed at high concentrations in *S. typhimurium* strains TA100 and TA1535 (≥1,000 µg/plate), and were therefore considered negative (NTP, 1986; SRI, 1975). 1,2-DCP was not mutagenic in the *S. typhimurium* strains TA98, TA1537, TA1538, or TA1978 or the *Streptomyces coelicolor* strain A3 (Prival and Dunkel, 1989; NTP, 1986; Carere and Morpurgo, 1981; Principe et al., 1981; De Lorenzo et al., 1977; SRI, 1975). In mammalian cells (L5178Y mouse lymphoma cells), 1,2-DCP increased the mutation frequency at the TK locus with metabolic activation; it was not mutagenic without metabolic activation (Myhr and Caspary, 1991).

1,2-DCP was not mutagenic in in vivo studies. The numbers of *pig*-a-gene mutations in RBCs collected from male B6C3F$_1$ mice or *gpt* mutations in liver samples collected from male *gpt* Delta C57BL/6J mice were not significantly increased in mice exposed to 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 4−6 weeks (Suzuki et al., 2014). 1,2-DCP also did not cause dominant lethal mutations in S-D rats (Dow Chemical Co, 1989b) or sex-linked recessive mutations in fruit flies (*Drosophila melanogaster*) (Kramers et al., 1991; Woodruff et al., 1985).

There is some evidence that 1,2-DCP is clastogenic. Although 1,2-DCP did not cause mitotic recombination in *Saccharomyces cerevisiae* strain D3 with or without metabolic activation (SRI, 1975), mitotic recombination was observed in the *D. melanogaster* wing spot test (Chroust et al., 2006). Chromosomal aberrations (CAs) and sister chromatid exchanges (SCEs) were observed in Chinese hamster ovary (CHO) cells both with and without metabolic activation (Galloway et al., 1987; Von Der Hude et al., 1987; NTP, 1986). In vivo, micronuclei (MN) were not induced in reticulocytes or normochromatic erythrocytes from mice exposed to 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 6 weeks (Suzuki et al., 2014).

In vitro, 1,2-DCP did not induce SOS repair in *Escherichia coli* strain PQ37 or unscheduled DNA synthesis in human lymphocytes with or without metabolic activation (von der Hude et al., 1988; Perocco et al., 1983). However, DNA damage was observed using the Comet assay in liver cells obtained from male B6C3F$_1$ mice exposed to 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 6 weeks (Suzuki et al., 2014). Additionally, immunohistochemical analysis of surgically resected specimens of human cholangiocarcinoma cases in print shop workers associated with 1,2-DCP and/or DCM exposure showed increased DNA double-strand breaks in precursor lesions (biliary intraepithelial neoplasia [BiIIN] and/or intraductal papillary neoplasm of the bile duct [IPNB]), compared with cholangiocarcinoma cases associated with other causes (e.g., hepatolithiasis) (Sato et al., 2014).

Supporting Human Studies

Several case studies have shown that accidental or intentional exposure to very high levels of 1,2-DCP via the oral, inhalation, or dermal routes can lead to CNS depression, liver toxicity, kidney damage, hemolytic anemia, and intravascular coagulation syndrome [Fiaccadori et al. (2003); Lucantoni et al. (1992); Imberti et al. (1987); Chiappino and Secchi (1968); Secchi and Alessio (1968) as cited in Imberti et al. (1990); Di Nucci et al. (1988); Thorel et al. (1986); Perbellini et al. (1985); Zedda et al. (1900); Pozzi et al. (1985)]. Contact dermatitis has also been reported in case studies with occupational exposure to 1,2-DCP (Baruffini et al., 1989; Grzywa and Rudzki, 1981).

Supporting Animal Toxicity Studies

A number of inadequately reported animal toxicity studies, studies available only from secondary sources, short-term studies, and studies via other routes (e.g., dermal, injection, etc.) were identified. Together, these studies identify the liver and kidney as the main targets of 1,2-DCP toxicity; limited evidence also suggests that the spleen may also be a target. Key findings are summarized below (see Table 4B for additional details).

Supporting Studies for Noncarcinogenic Effects in Animals

Several acute and short-term duration oral and inhalation studies indicate that the liver is a target of 1,2-DCP toxicity in animals. Histopathological liver damage (e.g., centrilobular

swelling and necrosis; fatty degeneration) was observed in rats exposed via gavage to ≥500 mg/kg-day for 1−10 days (Bruckner et al., 1989), rats and rabbits exposed to ≥300 mg/kg-day via gavage for 13−14 days (Dow Chemical Co, 1989a, 1988c), rats and guinea pigs exposed to 10,200 mg/m^3 for 1−5 daily 7-hour exposures (Highman and Heppel, 1946), and mice exposed to 1,800 mg/m^3 for 7 hours/day for up to 12 exposures (Heppel et al., 1948). Another short-term inhalation study reported unspecified morphological changes in the centrilobular region of the liver and increased hepatocyte proliferation were observed in rats continuously exposed to 500 mg/m^3 for 1−2 weeks (Belyaeva et al., 1977). Subchronic/chronic-duration inhalation studies considered inadequate due to limited reporting and/or study design also indicate that the liver is a target organ of 1,2-DCP toxicity; however, these studies are difficult to interpret due to limitations (Matsumoto et al., 1982; Sidorenko et al., 1979; Belyaeva et al., 1977; Heppel et al., 1948; Mellon Institute of Industrial Research, 1947a, b; Heppel and Neal, 1946). Liver damage and altered biochemistry have also been reported in acute, short-term, and subchronic-duration parental exposure studies (Trevisan et al., 1991; Trevisan et al., 1989; Matsumoto et al., 1982).

Several acute and short-term duration oral and inhalation studies indicate that the kidney is a target of 1,2-DCP toxicity in animals. Impaired kidney function (based on biochemical findings) was reported in rats after a single gavage administration of 930 mg/kg (Imberti et al., 1990). In short-term gavage studies, gross kidney changes (red renal medullae and pale kidneys) were reported in rats exposed to 2,000 mg/kg-day, mice exposed to ≥500 mg/kg-day, and rabbits exposed to ≥250 mg/kg-day via gavage for 13−14 days (Dow Chemical Co, 1988c; NTP, 1986) and tubular cell hemosiderosis was observed in rats exposed to ≥500 mg/kg-day for 10 days (Bruckner et al., 1989). However, no histopathological changes were observed in rats exposed up to 500 mg/kg-day via gavage for 14 days (Dow Chemical Co, 1989a). In inhalation studies, fatty degeneration of the kidney was reported in rats and guinea pigs exposed to 10,200 mg/m^3 for 7 hours/day for up to 5 days (Highman and Heppel, 1946) and in mice exposed to 1,800 mg/m^3 for 7 hours/day for up to 12 exposures (Heppel et al., 1948). Subchronic/chronic duration inhalation studies considered inadequate due to limited reporting and/or study design also indicate that the kidney is a target organ of 1,2-DCP toxicity; however, these studies are difficult to interpret due to limitations (Heppel et al., 1948; Heppel and Neal, 1946). Kidney damage and altered biochemistry have also been reported following acute or subchronic-duration parental exposure (Trevisan et al., 1988).

One oral and two inhalation studies suggest that the spleen may be a target of 1,2-DCP exposure. Hemosiderin accumulation and hyperplasia of the hematopoietic elements was observed in the spleen of rats exposed to ≥500 mg/kg-day via gavage for 5 or 10 days (Bruckner et al., 1989). Hemosiderin accumulation was also observed in rats and guinea pigs following 1−5 daily 7-hour exposures to 2,200 ppm (10,200 mg/m^3) (Highman and Heppel, 1946). A chronic-duration inhalation study in dogs considered inadequate due to limited reporting also indicates increased hemosiderin accumulation in the spleen following 1,2-DCP exposure; however, data reporting is inadequate for independent review (Heppel et al., 1948).

Acute-duration lethality studies with 1,2-DCP report oral median lethal dose (LD_{50}) values of 487−1,900 mg/kg and 960 mg/kg in rats and mice, respectively (Kennedy and Graepel, 1991; Matsumoto et al., 1982; Shell Oil Co, 1982; Bio Dynamics, 1981), a 10-hour inhalation median lethal concentration (LC_{50}) of 480 ppm (1,850 mg/m^3) in mice (Dow Chemical Co, 1968), and a 24-hour dermal LC_{50} > 2,340 mg/kg (Shell Oil Co, 1982). A 4-hour approximate

lethal concentration (ALC) (lowest dose causing mortality) was reported as 2,000 ppm (9,200 mg/m^3) in rats (Kennedy and Graepel, 1991). Numerous clinical signs of toxicity were observed in these acute-duration lethality studies (see Table 4B for details).

Supporting Studies for Carcinogenic Effects in Animals

Carcinogenicity of 1,2-DCP was evaluated in mice in a short-term-duration tumor assay consisting of 37 exposures to 400 ppm (1,800 mg/m^3) followed by a 7-month observation period (Heppel et al., 1948). While hepatomas were observed in surviving exposed mice, high mortality (77/88) and a lack of control data preclude drawing any conclusions from this study.

Absorption, Distribution, Metabolism, and Elimination (ADME) Studies

1,2-DCP is readily absorbed following oral, inhalation, or dermal exposure and distributed throughout the body via the blood, with preferential distribution to body fat (Take et al., 2014; Timchalk et al., 1991; Fiserova-Bergerova et al., 1990). The blood:air partition coefficients for human and rats are 8.75 ± 0.50 and 18.7 ± 0.5 , respectively (Gargas et al., 1989). The EPA calculated a human skin permeability constant of 0.01 cm/hour and a permeability coefficient of 0.206 cm/hour (U.S. EPA, 1992). Following absorption in rats, 1,2-DCP is rapidly metabolized and eliminated from the body, generally in <24 hours (Take et al., 2014; Timchalk et al., 1991; Di Nucci et al., 1990; Trevisan et al., 1989; Di Nucci et al., 1988). The primary routes of elimination after oral or inhalation exposure include urinary excretion and respiratory expiration, and the contribution of respiratory expiration increases with increasing dose/concentration (Timchalk et al., 1991). Following a single oral dose of radiolabeled 1,2-DCP, 90% of the administered radioactivity was shown to be eliminated in urine [Hutson et al. (1971) as cited in ACGIH (2014a)]. Elimination patterns were similar with single and repeat oral exposures, indicating that 1,2-DCP is not likely to accumulate in the body with repeated oral exposures (Timchalk et al., 1991). However, Take et al. (2014) indicated that 1,2-DCP will concentrate in body fat if the metabolic capacity is exceeded following high acute inhalation exposure.

The major urinary metabolites of 1,2-DCP in rats include three mercapturic acids: (*N*-acetyl-*S*-[2-hyroxypropyl]-*L*-cysteine, *N*-acetyl-*S*-([-ocopropyl]-*L*-cysteine, and *N*-acetyl-*S*-[1-carboxyethyl]-*L*-cysteine) (Timchalk et al., 1991; Bartels and Timchalk, 1990; Jones and Gibson, 1980). Minor metabolites included *N*-acetyl-*S*-(2,3-dihydroxypropl)cysteine, *β*-chlorolactaldehyde, and *β*-chlorolactate (Jones and Gibson, 1980). It is proposed that metabolites result from oxidation of the C-1 position of the parent compound followed by GSH conjugation (Bartels and Timchalk, 1990). In vitro data support this proposal, indicating that 1,2-DCP is conjugated to GSH following oxidation by human CYP2E1 (Guengerich et al., 1991).

Mode-of-Action/Mechanism Studies

There are very few studies regarding the mechanism(s) of 1,2-DCP toxicity. Proposed mechanisms of toxicity include GSH depletion and DNA damage subsequent to the generation of GSH-conjugated reactive metabolites (Sato et al., 2014; Imberti et al., 1990).

Imberti et al. (1990) proposed that acute 1,2-DCP toxicity may be mediated by GSH depletion. Acute oral exposure to high levels of 1,2-DCP (2 mL/kg) resulted in GSH depletion in the liver and kidney of Wistar rats that was statistically associated with altered clinical chemistry parameters and hemolysis. Pretreatment with a GSH-depleting agent

(buthionine-sulfoximine) increased the mortality of the acute 1,2-DCP dose, while pretreatment with a GSH precursor (*N*-acetylcysteine) prevented GSH depletion and reduced the extent of injury to target tissues.

Sato et al. (2014) proposed that cholangiocarcinoma observed in printers exposed to 1,2-DCP and/or DCM may be caused by DNA damage in biliary epithelial cells caused by GSH-conjugated reactive metabolites. In this study, immunohistochemical analysis of surgically resected specimens of cholangiocarcinoma cases associated with 1,2-DCP and/or DCM exposure showed increased DNA double-strand breaks in precursor lesions (BiIIN and/or IPNB) compared with cholangiocarcinoma cases associated with other causes (e.g., hepatolithiasis). In printing company cases, p53 expression was observed in non-neoplastic biliary epithelial cells and BiIIN cellGSHs, and KRAS and GNAS mutations were detected in foci of BiIIN in 1/3 cases. Sato et al. (2014) also confirmed constitutional expression of GST T1-1 in the normal hepatobiliary tract, which is known to catalyze DCM into its reactive intermediates implicated for genotoxic actions of DCM. Additionally, 1,2-DCP has been shown to damage liver DNA in male B6C3F_1 mice exposed to 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 6 weeks (Suzuki et al., 2014), supporting DNA damage as a possible mode of action (MOA) for liver damage.

Zhang et al. (2015) investigated the effect of 1,2-DCP exposure on the hepatic distribution of GSTT1, GSTM1, and GSTPi and on the expression of Ki67 (a marker proliferation). C57BL/6J mice, Balb/cA mice, F344 rats, Syrian hamsters, and guinea pigs for 7 or 14 days (mice and hamsters only). The study authors reported that 1,2-DCP exposure had no effect on any of the tested parameters.

Table 4A. Summary of 1,2-Dichloropropane Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results without Activation[a]	Results with Activation[a]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538	0, 10 µL/plate (~12 mg/plate)[b]	+ TA100, TA1535 − TA98, TA1537, TA1538	+ TA100, TA1535 − TA98, TA1537, TA1538	Spot test. A two- to fourfold increase was observed in the number of revertants in strains TA100 and TA1535.	Carere and Morpurgo (1981); Principe et al. (1981)
Mutation	*S. typhimurium* strains TA100, TA1535	1−10 µL/plate (~1−12 mg/plate)[b]	+ TA100, TA1535	+ TA100, TA1535	Plate incorporation assay.	Carere and Morpurgo (1981); Principe et al. (1981)
Mutation	*S. typhimurium* strains TA100, TA1535, TA1978	0, 10, 20, 50 mg/plate	+ TA1535, TA100 − TA1978	+ TA1535, TA100 − TA1978	Plate incorporation assay. A 21-fold increase was observed in the number of revertants in strains TA100 and TA1535.	De Lorenzo et al. (1977)
Mutation	*S. typhimurium* strain TA100	0, 1, 10, 100 µmol/plate (~113, 1,130, 11,300 µg/plate)[c]	−	−	Plate incorporation assay. Cytotoxicity was observed at 100 µmol/plate.	Stolzenberg and Hine (1980)

Table 4A. Summary of 1,2-Dichloropropane Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results without Activation[a]	Results with Activation[a]	Comments	References
Mutation	*S. typhimurium* strains TA98, TA100, TA1535, TA1537	Study 1 (Case Western Reserve University): 0, 10, 33, 100, 333, 750, 1,000, 1,500, 1,667, 3,333, 6,667, 10,000 µg/plate Study 2 (EG&G Mason Research Institute): 0, 100, 333, 750, 1,000, 1,500 µg/plate	–	–	Preincubation assay. In Study 1, marginal induction of revertants (<twofold) was only observed at ≥1,667 µg/plate in TA100 without metabolic activation. Toxicity was observed at 10,000 µg/plate. In Study 2, marginal induction of revertants (<twofold) was only observed at ≥750 µg/plate in TA100 with or without metabolic activation. Studies reported as positive by Haworth et al. (1983), but considered negative by stricter evaluation criteria used by Prival and Dunkel (1989), including disregard for responses <twofold and any response seen at doses >500 µg/plate.	Prival and Dunkel (1989); Haworth et al. (1983)
Mutation	*S. typhimurium* strains TA98, TA100, TA1535, TA1537	0, 33, 100, 333, 1,000, 2,000 µg/plate	–	–	Plate incorporation assay. Marginal induction of revertants (<twofold) was only observed at ≥1,000 µg/plate without metabolic activation in TA100.	NTP (1986)
Mutation	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538	0, 1, 10, 50, 100, 500, 1,000, 2,000, 3,000, 4,000, 5,000 µg/plate	–	–	Plate incorporation assay. Marginal induction of revertants (<twofold) was only observed at 5,000 µg/plate in TA100 and TA1535. Reduced number of revertants compared with control was observed with metabolic activation, indicating cytotoxicity.	SRI (1975)

Table 4A. Summary of 1,2-Dichloropropane Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results without Activation[a]	Results with Activation[a]	Comments	References
Mutation	*Streptomyces coelicolor* A3	2−100 µL/plate (~2−116 mg/plate)[b]	−	ND	Spot test and plate incorporation assay.	Carere and Morpurgo (1981); Principe et al. (1981)
SOS repair induction	*Escherichia Coli* PQ37	3−5 concentrations at half-log intervals (actual concentrations not reported)	−	−	Three methods used to determine the SOS induction: (1) centrifugation method; (2) subtraction method; and (3) X-gal method.	von der Hude et al. (1988)
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mitotic recombination	*Saccharomyces cerevisiae* D3	0, 0.01, 0.05, 0.1, 0.5%	−	−	Cytotoxicity was observed at 0.5%. 1,2-DCP did not cause an increase in mitotic recombinants at doses that did not cause toxicity.	SRI (1975)
Mitotic recombination (wing spot assay)	*Drosophila melanogaster mwh* and *flr*^{3} mutants were exposed to 1,2-DCP via inhalation for 48 hr.	0, 8.8 µg/L	+	ND	1,2-DCP caused an increase in the total number of wing spots observed at 48 hr. Tested dose was the LC_{50}.	Chroust et al. (2006)
Sex-linked recessive lethal mutations	*D. melanogaster* wild-type males were exposed to 1,2-DCP for 24 or 96 hr or 2 wk via inhalation; treated males were mated to new groups of three unexposed virgin females of the *Basc* strain at 2−3 d intervals for up to 5 mating cycles.	24 hr: 1,600, 4,800 mg/m^3 96 hr: 680, 1,360 mg/m^3 2 wk: 680 mg/m^3	−	ND	1,2-DCP exposure did not increase the number of sex-linked recessive lethal mutations.	Kramers et al. (1991)

Table 4A. Summary of 1,2-Dichloropropane Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results without Activation[a]	Results with Activation[a]	Comments	References
Sex-linked recessive lethal mutations	*D. melanogaster* males (*Basc* strain) were exposed to 1,2-DCP for 4 hr via inhalation or via a single injection; exposed males were mated to new groups of unexposed females (*Basc* strain) at 2−3-d intervals for 3 mating cycles; mating occurred immediately after inhalation exposure or 24−48 hr after injection.	Inhalation 0, 7,200 ppm Injection 0, 4,200 ppm	−	ND	1,2-DCP exposure did not increase the number of sex-linked recessive lethal mutations.	Woodruff et al. (1985)
Genotoxicity studies in mammalian cells—in vitro						
Unscheduled DNA synthesis	Human lymphocytes	10^{-4}, 10^{-3}, 10^{-2} M	−	−	No cytotoxicity was observed.	Perocco et al. (1983)
Mutation	L5178Y mouse lymphoma cells	Without activation (3 trials): 0−1,000 nL/mL With activation (2 trials): 0−100 nL/mL	−	+	1,2-DCP did not cause an increase in mutation frequency at the TK locus at doses up to 750 nL/mL (highest soluble dose) without activation. With activation, 1,2-DCP caused 1.6−10-fold increase in mutation frequency at ≥10 nL/mL. Doses ≥80 nL/mL were lethal.	Myhr and Caspary (1991)
CAs	CHO cells	Without activation: 0, 1,180, 1,370, 1,580 µg/mL With activation: 0, 460, 660, 950 µg/mL	+	+	1,2-DCP induced a >twofold increase in aberrations/100 cells at ≥1,370 µg/mL without activation and at ≥660 µg/mL with activation.	Galloway et al. (1987); NTP (1986)
SCE	CHO cells	0, 112.7, 376.0, 1,127.0 µg/mL	+	+	1,2-DCP induced a >twofold increase in SCE/cell at ≥376.0 µg/mL with and without activation.	Galloway et al. (1987); NTP (1986)

Table 4A. Summary of 1,2-Dichloropropane Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results without Activation[a]	Results with Activation[a]	Comments	References
SCE	CHO cells	0, 1.0, 3.3, 10.0 mM	+	+	1,2-DCP significantly induced SCEs at ≥3.3 mM by 1.6−2.7-fold without metabolic activation (28 hr) and 1.5−1.8-fold with metabolic activation (3 hr).	Von Der Hude et al. (1987)
Cell transformation	HL-60 cells	0, 200 nM	−	ND	At 20 hr, cells had 67.7% viability. Surviving cells were not transformed into macrophages.	Utsumi et al. (1992)
Genotoxicity studies in mammals—in vivo						
Dominant lethal mutagenicity	Male S-D rats (30/group) were administered 1,2-DCP via drinking water for 14 wk; exposed males were then mated to unexposed females; females were sacrificed 14 d after the middle of their breeding period and uteri were examined.	0, 28, 91, 162 mg/kg-d	−	−	1,2-DCP did not significantly alter male fertility index, preimplantation loss, or resorption rate.	Dow Chemical Co (1989b)
Mutation	Male B6C3F$_1$ mice (8−10/group) were exposed to 1,2-DCP via inhalation for 6 hr/d, 5 d/wk for 6 wk; blood was collected at 3 and 6 wk and evaluated for the *Pig*-a-gene mutation assay in RBCs.	0, 150, 300, 600 ppm (TWA: 0, 120, 250, 500 mg/m^3)	−	−	NA	Suzuki et al. (2014)
Mutation	Male *gpt* Delta C57BL/6J mice (five/group) were exposed to 1,2-DCP via inhalation for 6 hr/d, 5 d/wk for 4 wk; at 4 wk, animals were sacrificed and liver samples were assessed for *gpt* mutations.	0, 300 ppm (TWA: 0, 250 mg/m^3)	−	−	A nonsignificant 32% increase in *gpt* mutations was observed.	Suzuki et al. (2014)

Table 4A. Summary of 1,2-Dichloropropane Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results without Activation[a]	Results with Activation[a]	Comments	References
MN	Male B6C3F$_1$ mice (8−10/group) were exposed to 1,2-DCP via inhalation for 6 hr/d, 5 d/wk for 6 wk; blood was collected at 6 wk for the MN assays in reticulocytes and normochromatic erythrocytes.	0, 150, 300, 600 ppm (TWA: 0, 120, 250, 500 mg/m^3)	−	−	NA	Suzuki et al. (2014)
DNA damage	DNA damage was assessed in cells obtained from precursor lesions (BiIIN and IPNB) from human cholangiocarcinoma cases in print shop workers associated with 1,2-DCP and/or DCM exposure (n = 8), human cholangiocarcinoma cases associated with hepatolithiasis (n = 16), and conventional IPNB cases (n = 19). DNA damage was determined using γ-H2AX immunohistochemical staining.	NR	+	+	DNA double-strand breaks were observed in IPNB invasive foci in 7/8 cholangiocarcinoma cases associated with 1,2-DCP and/or DCM exposure, compared with 7/16 cases associated with hepatolithiasis and 6/19 cases of conventional IPNB. DNA double-strand breaks were observed in BiIIN preneoplastic lesions in 6/8 cholangiocarcinoma cases associated with 1,2-DCP and/or DCM exposure, compared with 3/16 cases associated with hepatolithiasis.	Sato et al. (2014)
DNA damage	Male B6C3F$_1$ mice (8−10/group) were exposed to 1,2-DCP via inhalation for 6 hr/d, 5 d/wk for 6 wk; at 6 wk, animals were sacrificed and DNA damage in the liver was assessed using the comet assay.	0, 150, 300, 600 ppm (TWA: 0, 120, 250, 500 mg/m^3)	+	+	1,2-DCP increased the percent tail intensity in a concentration-dependent manner, with significant increases at ≥300 ppm.	Suzuki et al. (2014)

[a]+ = positive; ± = equivocal or weakly positive; − = negative; ND = no data; NR = not reported.
[b]Dose was converted from µL/plate to mg/plate based on the density of 1,2-DCP (1.159 g/mL) for comparison purposes.
[c]Dose was converted from µmol/plate to µg/plate based on the density of 1,2-DCP (1.159 g/mL) for comparison purposes.

BiIIN = biliary intraepithelial neoplasia; CA = chromosomal aberration; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; flr^3 = flare; HL-60 = human leukemia; IPNB = intraductal papillary neoplasm of the bile duct; LC_{50} = median lethal concentration; MN = micronuclei; mwh = multiple wing hairs; NA = not applicable; RBC = red blood cell; SCE = sister chromatid exchange; S-D = Sprague-Dawley; TWA = time-weighted average.

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting evidence—noncancer effects in animals following oral exposure				
Acute[a] (oral)	The LD_{50} was determined in groups of rats. No further details were provided.	ND	LD_{50} = 1,900 mg/kg	Kennedy and Graepel (1991)
Acute (oral)	Groups of male Wistar rats (5−12/group/time-point) were given 1,2-DCP dissolved in corn oil (40% v/v) at a volume of 2 mL/kg via gavage. Based on the density of 1,2-DCP (1.159 g/mL), the administered dose was ~2 g/kg. Rats were sacrificed 24, 48, and 96 hr later. Serum ALP, ALT, AST, GGT, 5'-nucleotidase, urea, creatinine, and glucose were measured. Blood was evaluated for hemolysis. GSH and GSSG levels were measured in the liver, kidney, and blood.	Serum ALT, AST, 5'-nucleotidase, urea, and creatinine and hemolysis were significantly increased in exposed rats at 24 hr postexposure, and serum ALP and GGT were significantly increased in exposed rats at 48 hr postexposure. GSH was decreased in the liver, kidney, and blood 24 hr postexposure; no change was observed in GSSG levels. Several indices of liver and kidney damage were correlated with GSH depletion in the liver and kidney, respectively. All values returned to control levels by 96 hr. Treatment with the GSH precursor, *N*-acetylcysteine, 2 and 16 hr after 1,2-DCP exposure reduced GSH depletion and led to a more rapid restoration of control levels of GSH by 48 hr.	Based on biochemical indicators, the administered dose of ~2 g/kg is a LOAEL for impaired liver and kidney function. Data indicate that these effects are caused by GSH depletion.	Imberti et al. (1990)
Acute (oral)	Groups of male S-D rats were given a single dose of 1,2-DCP at doses of 0, 100, 250, 500, or 1,000 mg/kg via gavage (6−8/group). Endpoints evaluated included clinical signs, body weight, serum chemistry, urinalysis, liver and kidney weight, histology (liver, kidney, lungs, brain, adrenals, spleen, stomach, testis, and epididymis).	Transient CNS depression and dose-related body-weight depression were observed in exposed animals (data not reported). Serum SDH was significantly elevated by sevenfold at 1,000 mg/kg. Hepatic nonprotein sulfhydryl levels were significantly decreased by 62% at 1,000 mg/kg. In contrast, a significant 42−65% increase in nonprotein sulfhydryl levels was observed in the kidney at ≥250 mg/kg. Slight to moderate cytoplasmic condensation was observed in centrilobular hepatocytes at ≥500 mg/kg.	NOAEL: 250 mg/kg LOAEL: 500 mg/kg (liver and spleen effects)	Bruckner et al. (1989)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute (oral)	Groups of Wistar rats (5/group), were given single dose of 1,2-DCP at doses of 0 or 55 mg/kg via gavage in propylene glycol. Rats were sacrificed 4, 8, 24, 72, and 144 hr after treatment. Endpoints evaluated included liver weight and liver biochemistry (GSH, thiobarbituric acid reactants, and total protein levels).	No changes were observed in liver weight at any time-point. Total protein and GSH levels were significantly reduced by 23−29 and 45−96%, respectively, at all time-points evaluated. Based on levels of thiobarbituric acid reactants, lipid peroxidation was significantly increased by 72% at 72 hr and 51% at 144 hr after treatment, compared with control. Levels at 4−24 hr postexposure did not differ relative to controls.	Data are consistent with mechanistic studies reporting lipid peroxidation and/or GSH depletion following exposure to 1,2-DCP.	Di Nucci et al. (1988)
Acute (oral)	Groups of ddY male mice (number unspecified) were administered 1,2-DCP in olive oil to determine LD_{50} (dose and route unspecified). Toxicity was monitored for 24 hr prior to sacrifice and gross necropsy. Additional groups of mice (number unspecified) were administered 1,2-DCP at 5 and 10% of the LD_{50}. After 24 hr, blood was collected for analysis of liver function (AST, ALT, and cholinesterase).	The LD_{50} was determined to be 960 mg/kg. At necropsy, peeling of the mucous membrane and bleeding were noted in the stomach and intestines. No gross pathological changes were noted for brain, cerebellum, lung, liver, or kidney. AST, ALT, and cholinesterase were increased following a single administration of 10% of the LD_{50} (quantitative data not reported). It is unclear if control animals were evaluated.	Oral LD_{50} = 960 mg/kg Available data are inadequate to make a NOAEL/LOAEL determination based on liver function.	Matsumoto et al. (1982) [abstract only]
Acute (oral)	Groups of Wistar rats (six/sex/group) were given single doses of 1,2-DCP at doses of 145, 230, 366, 582, 926, or 1,472 mg/kg via gavage (undiluted). Rats were observed for mortality and clinical signs of toxicity for 14 d.	100% mortality at 1,472 mg/kg, ≥8/12 died at ≥582 mg/kg; clinical signs included cyanosis, gait abnormalities, lethargy, increased salivation and/or lacrimation, and discolored urine.	Oral LD_{50} (95% CI) = 487 (387−613) mg/kg	Shell Oil Co (1982)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute (oral)	Groups of rats (five/sex/group) were administered 1,2-DCP at doses of 1,000, 1,470, 2,150, 3,160, 4,680, 6,810, or 10,000 mg/kg via gavage (no vehicle). Rats were observed for 14 d prior to sacrifice. Endpoints evaluated included mortality, clinical signs, body weight, and gross necropsy.	Mortality was 2/10, 3/10, 8/10, 10/10, 10/10, 10/10, 10/10 in the 1,000-, 1,470-, 2,150-, 3,160-, 4,680-, 6,810-, or 10,000-mg/kg groups, respectively. Time-to-death was dose-related, with the majority of deaths occurring within 24 hr. Clinical signs of toxicity on the day of dosing included ataxia, hypopnea, hypoactivity, prostration, hypothermia, wet rales, and oral, nasal, or ocular discharge. Clinical signs persisted for up to 6 d. Most surviving animals showed weight losses at 7 d, which recovered by 14 d. No adverse changes were observed at necropsy in animals sacrificed at 14 d; animals that died showed a variety of changes in the lungs and gastrointestinal tract (unspecified).	Male: LD_{50} (95% CI) = 1,100 (800−1,700) mg/kg Female: LD_{50} (95% CI) = 1,800 (1,200−2,400) mg/kg Combined: LD_{50} (95% CI) = 1,600 (1,300−1,900) mg/kg	Bio Dynamics (1981)
Short-term[b] (oral)	Groups of male S-D rats (six to eight/group/time-point) were given 1,2-DCP at doses of 0, 100, 250, 500, or 1,000 mg/kg-d via gavage in corn oil for up to 10 d (six to eight/group/time-point). Endpoints evaluated included clinical signs, body weight, serum chemistry, urinalysis, histology (liver, kidney, lungs, brain, adrenals, spleen, stomach, testis, epididymis).	Transient CNS depression and dose-related body-weight depression were observed in exposed animals (data not reported). Various biochemical changes were observed in exposed animals, including elevated bilirubin levels at ≥250 mg/kg-d and elevated serum BUN at 1,000 mg/kg-d at both time-points, elevated SDH at 1,000 mg/kg-d at 5 d, and increased serum ALT at 1,000 mg/kg-d at 5 d. Hepatic nonprotein sulfhydryl levels were significantly decreased at ≥250 mg/kg-d after 5 d and at 1,000 mg/kg-d after 10 d. In contrast, significantly increased nonprotein sulfhydryl levels were observed in the kidney at ≥250 mg/kg-d at both time-points. Histopathological findings attributed to exposure in rats treated at ≥500 mg/kg-d (incidence data not reported) included slight-to-moderate toxic hepatitis, tubular cell hemosiderosis, and splenic hemosiderosis and hyperplasia of the hematopoietic elements of the red pulp.	NOAEL: 250 mg/kg LOAEL: 500 mg/kg (liver, kidney, and spleen effects)	Bruckner et al. (1989)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term (oral)	Groups of F344/N rats (five/sex/group) were administered 1,2-DCP at doses of 0, 125, 250, 500, 1,000, or 2,000 mg/kg-d via gavage in corn oil, 5 d/wk for 14 d. Endpoints evaluated included clinical signs, body weight, and gross necropsy.	100% mortality was observed at 2,000 mg/kg-d. Body weights were significantly reduced by 14% in males at 500 and 1,000 mg/kg-d and nonsignificantly reduced by 15% in females at 1,000 mg/kg-d (Student *t*-test performed for this review). The only finding at gross necropsy attributed to exposure was red renal medullae reported in 4/5 males and 5/5 females at 2,000 mg/kg-d.	NOAEL: 250 mg/kg-d LOAEL: 500 mg/kg-d (↓ body weight in males)	NTP (1986)
Short-term (oral)	Groups of $B6C3F_1$ mice (five/sex/group) were administered 1,2-DCP at doses of 0, 125, 250, 500, 1,000, or 2,000 mg/kg-d via gavage in corn oil, 5 d/wk for 14 d. Endpoints evaluated included clinical signs, body weight, and gross necropsy.	Increased mortality was observed in males at ≥500 mg/kg-d (60−100%) and females at ≥1,000 mg/kg-d (80−100%). Body-weight effects were not observed in surviving mice. The only finding at gross necropsy attributed to exposure was red renal medullae in 60−100% of mice at ≥500 mg/kg-d.	NOAEL: 250 mg/kg-d FEL: 500 mg/kg-d (↑ mortality in males)	NTP (1986)
Short-term (oral)	Groups of NZW rabbits (two females/group) were administered 1,2-DCP at doses of 0, 250, 500, or 1,000 mg/kg-d via gavage in corn oil for 13 d. Endpoints evaluated included clinical signs, body weight, gross necropsy, and histology of liver, kidney, and all gross lesions.	Increased mortality was observed (2/2 high dose; 2/2 mid dose; 1/2 low dose, 0/2 controls). Clinical signs of toxicity (lethargy, ataxia, anorexia) and hepatic necrosis were increased at ≥500 mg/kg-d, compared with control. "Some" exposed rabbits had pale kidneys associated with dilation of the collecting ducts/renal tubules.	An apparent FEL of 250 mg/kg-d is identified for increased mortality; however, interpretation of data is limited based on small animal groups.	Dow Chemical Co (1988c)
Short-term (oral)	Groups of F344 rats (10/sex/group) were administered 1,2-DCP at doses of 0, 300, or 500 mg/kg-d via gavage for 14 d. Endpoints evaluated included clinical signs, body weight, FOB, motor activity, hematology, organ weights (liver, kidney, and spleen), gross necropsy, and histology of liver and kidney.	Significant findings attributed to treatment included transient clinical signs at ≥300 mg/kg-d (increased lacrimation and blinking, decreased respiration, lethargy); decreased terminal body weight (11−18% in males at ≥300 mg/kg-d; 6% in females at 500 mg/kg-d group); increased liver and kidney weights at ≥300 mg/kg-d; and mild histopathological changes in the liver of exposed males and females, including prominent nucleoli of hepatocytes in the centrilobular region of the hepatic lobule (80−100% incidence at ≥300 mg/kg-d) and degeneration and necrosis of individual hepatocytes (~50% incidence at ≥300 mg/kg-d).	NOAEL: not identified LOAEL: 300 mg/kg-d (clinical signs of toxicity, increased liver weight, hepatic lesions, ↓ body weight in males).	Dow Chemical Co (1989a)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term (oral)	Groups of ddY mice (number and sex not specified) were administered 1,2-DCP at doses of 400−600 mg/kg-d via gavage in olive oil for 30 d. It is unclear if a control group was used. Endpoints evaluated included body weight, clinical chemistry (liver function), and histology (brain, cerebellum, lung, stomach, intestine, liver, kidney).	No body-weight effects were noted. Fatty degeneration of the liver was observed in treated mice (dose not reported). No changes in liver function were detected with clinical chemistry.	Available data are inadequate to make a NOAEL/LOAEL determination.	Matsumoto et al. (1983) [abstract only]
Supporting evidence—noncancer effects in animals following inhalation exposure				
Acute (inhalation)	The ALC, or the concentration at which mortality was first observed following a 4-hr exposure, was determined in rats. No further details were provided.	Effects due to exposure of 1,2-DCP were not reported.	ALC (4-hr) = 2,000 ppm (9,200 mg/m^3)	Kennedy and Graepel (1991)
Acute (inhalation)	Groups of Wistar rats (10 males/group) were given a single 4-hr inhalation exposure to 1,2-DCP at concentrations of 0, 15, 50, 100, 250, 450, 1,000, 1,300, or 4,900 mg/m^3; rats were sacrificed immediately or 20 hr after exposure ceased. Endpoints evaluated included blood serum chemistry (ALP, ALT, AST) and liver biochemistry (GSH, thiobarbituric acid, and total protein).	No adverse changes were observed in serum biochemistry, total liver protein content, or lipid peroxidation (as determined by thiobarbituric acid levels). Liver GSH concentration was significantly reduced at concentrations ≥100 mg/m^3 immediately after exposure, although findings were not concentration-dependent (decreased 24, 62, 43, 33, and 28% at 100, 250, 450, 1,000, 1,300, and 4,900 mg/m^3, respectively). After 20 hr, GSH concentration was significantly increased by 23−26% at concentrations ≥1,300 mg/m^3.	Data are consistent with mechanistic studies reporting GSH depletion following exposure to 1,2-DCP.	Di Nucci et al. (1990)
Acute (inhalation)	Groups of mice (10−30/group, sex and species not specified) were exposed to 300, 380, 390, 700, 715, and 1,625 ppm for 10 hr. Mortality was assessed during exposure and postexposure (undefined period).	Mortality during exposure was 0/30, 1/10, 2/20, 5/10, 11/30, and 9/10 in the 300-, 380-, 390-, 700-, 715-, and 1,625-ppm groups, respectively. Total mortality (during exposure + postexposure observation period) was 2/10, 11/20, 7/10, 30/30, and 10/10.	LC_{50} (10-hr) = 480 ppm (1,850 mg/m^3)	Dow Chemical Co (1968)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute (inhalation)	S-D rats and "stock" guinea pigs (33/species, sex unspecified) were given a single 7-hr exposure to 2,200 ppm. The control group contained three unexposed animals/species. Animals were sacrificed at intervals (two to five/time-point) up to 14 d for rats and 21 d for guinea pigs and subjected to gross necropsy. Tissues (unspecified) were fixed for histologic examination.	Rats: Transient hepatic effects were observed 1−4 d after exposure (fine droplet fatty degeneration, centrilobular necrosis, marked glycogen depletion, and hemosiderin in Kupffer cells). Depletion of the lipoid material of the adrenal cortex was also observed immediately and 1 d after exposure. Guinea pigs: Transient hepatic effects were observed 1−4 d after exposure (centrilobular swelling, altered glycogen content). Necrosis of the adrenal glands was observed in all exposed guinea pigs at all time-points.	2,200 ppm (10,200 mg/m^3) is a free-standing LOAEL in both species (liver and adrenal lesions)	Highman and Heppel (1946)
Acute/short-term (inhalation)	Groups of rats, guinea pigs, and rabbits (2−13/group) were exposed to 0 or 1,600 ppm (7,400 mg/m^3) for 7 hr for 1 or 5 d.	**Single exposure:** Mortality: 3/12 rats, 0/6 guinea pigs, 0/2 rabbits; Rats showed incoordination towards the end of the 7 hr exposure. No clinical signs of toxicity were observed in guinea pigs or rabbits. **5-d exposure:** Mortality: 0/13 rats, 0/10 guinea pigs, 1/2 rabbits; Rats and guinea pigs showed weight loss during exposure period, which recovered after exposure ceased.	A NOAEL/LOAEL determination could not be made due to lack of control.	Heppel and Neal (1946)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute/short-term (inhalation)	Groups of S-D rats and "stock" guinea pigs (three to six/group/species; sex unspecified) were exposed to 2,200 ppm for 7 hr/d for 1−5 d; and additional 3 animals/species were given a single 4-hr exposure to 2,200 ppm. The control group contained 6 unexposed rats. Rats were sacrificed immediately after exposure and subjected to gross necropsy. Tissues (unspecified) were fixed for histologic examination.	Rats: Fatty degeneration and hepatic centrilobular necrosis were observed, with increased lesion severity with repeated exposure. Fatty degeneration in the kidney was increased with 1−3 d of exposure, but was minimal after 4−5 d of exposure. Depletion of the lipoid material of the adrenal cortex was observed within 1−3 d of exposure. Hemosiderin was observed in the spleen after 4−5 d of exposure. Guinea pigs: Fatty degeneration of the liver was observed with 1−3 d of exposure, but was minimal after 4−5 d of exposure. Fatty degeneration was also observed in the kidney. In the adrenal gland, cortical necrosis and congested medulla were observed in all exposed animals, increasing with severity with repeated exposure. Cortical hyperplasia was also observed following 3−4 d of exposure.	Rat: 2,200 ppm (10,200 mg/m^3) is a free-standing LOAEL (liver, kidney, spleen, and adrenal lesions) Guinea pig: 2,200 ppm (10,200 mg/m^3) is a free-standing LOAEL (liver, kidney, and adrenal lesions)	Highman and Heppel (1946)
Short-term (inhalation)	Groups of rats, mice, guinea pigs and rabbits (4−20/species/group) were exposed to 2,200 ppm (10,000 mg/m^3) for 7 hr/d for up to 8 d.	Mortality: 8/20 rats, 10/11 mice, 11/15 guinea pigs, 2/4 rabbits; Clinical signs of toxicity observed in rats, mice, and guinea pigs included gross incoordination, prostration, shallow and labored respiration, crusting around nose, and rough coat. Guinea pigs also had severe conjunctival swelling. Rabbits did not show clinical signs of toxicity.	The single exposure concentration of 2,200 ppm (10,000 mg/m^3) was an FEL for all species tested.	Heppel and Neal (1946)
Short-term (inhalation)	18 C57 mice (sex unspecified) were exposed to 400 ppm for up to 12 exposures (7 hr/exposure, exposure schedule not reported); five unexposed controls were used for comparison in "histologic" examinations.	Two mice died during the first exposure, and an additional eight mice died within 48 hr of the first exposure. Slight fatty degeneration of the liver was observed in five of eight mice that died within the first 2 d. Slight fatty degeneration of the kidney was observed in one of two mice sacrificed after the second exposure. No further information was provided.	The only exposure level (400 ppm; 1,800 mg/m^3) is an apparent FEL for mortality.	Heppel et al. (1948)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute/short-term/ subchronic[c] (inhalation)	Groups of rats (noninbred albino, sex unspecified) were continuously exposed to 1,2-DCP at concentrations of 0 or 2.2 mg/L for 20 hr or 3 d (four to seven/group); 0 or 1.1 mg/L for 1 wk (2 exposed, 13 control); 0, 0.1, or 0.5 mg/L for 2 wk (three to four/group); or 0, 0.00045, 0.0017, or 0.009 mg/L for 3 mo (four to six/group). At the end of exposure, rats were sacrificed and the liver was examined for morphological changes and percentages of hepatocytes of different ploidy were determined.	Morphological changes (unspecified) were observed in the livers of rats exposed for 1 or 2 wk, with most severe damage in the centrolobular region. Lesions were also observed in rats exposed to lower concentrations for 3 mo (incidence data not provided). Histopathological findings from the 1- and 3-d studies were not reported. No liver lesions were observed in any control rats. Increased intermediate ploidy of hepatocytes (indicative of proliferation) was observed following exposure to 2.2 mg/L for 1 or 3 d, 1.1 mg/L for 1 wk, or ≥0.1 mg/L for 2 wk. In the 3-mo study, the percentages of hepatocytes of different ploidy were comparable to control.	An acute/short-term LOAEL of 0.5 mg/L (500 mg/m^3) was identified for liver damage. A subchronic NOAEL/LOAEL determination could not be made due to inadequate data reporting.	Belyaeva et al. (1977)
Short-term/ subchronic (inhalation)	Male white rat (strain and number not specified), were exposed to 9, 100, 500, 1,000, or 2,000 mg/m^3 via inhalation for up to 7 d with high concentrations (1,000 and 2,000 mg/m^3) or up to 86 d with lower concentrations. It is unclear if exposure was continuous or for limited periods during the day. Endpoints evaluated included body weight, serum catalase activity, blood cholinesterase activity, and hematology at various points during exposure. At the end of the experiment, liver and lungs were removed for histology and electron microscopy (lungs only), and the content of RNA and activity of oxidizing enzymes in the organs were evaluated.	Increased catalase and cholinesterase activity were reliable markers of exposure to 1,2-DCP, with the latency to statistically significant changes decreasing with increasing concentrations. Enzyme activity changes were phasic response with high concentrations: enzyme activity increased and dropped within first 2−3 d of exposure. Histopathological effects in the lungs were observed at all exposure levels, including increased macrophages, edema, and accumulation of osmiophilic corpuscles in alveolar cells. Histopathological effects in the liver included degranulation of cloudy cells with occasional degeneration. Oxidizing enzymes in the lungs (SDH, NAD, NADPH-diaphorase, DDG, T-6-phDG [the last two enzymes were not defined in the paper and these acronyms are not currently in common usage]) were increased at low concentrations and suppressed at 2,000 mg/m^3; SDH and T-6-phDG were suppressed in the liver at 9 mg/m^3 (effects, or lack thereof, unclear at higher concentrations).	Inadequate methods reporting and lack of a control group preclude a NOAEL/LOAEL determination.	Sidorenko et al. (1979)

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Subchronic (inhalation)	Rats, mice, guinea pigs, and rabbits were exposed to 1,2-DCP at concentrations of 0 or 1,500 ppm 7 hr/d, 5 d/wk for up to 2 mo. Animal numbers ranged from 4−22/group per species. Endpoints examined included clinical signs, body weight, hematology, clinical chemistry, and gross necropsy. Sections of the liver and spleen were examined for hemosiderin and sections of the heart, liver, and kidney were stained for fat.	Rats: Mortality was 40% (8/18) in the exposed group, compared with 7% (1/14) in the control group. Transient clinical signs of toxicity (unsteadiness) were observed during the exposure periods. Growth was "adversely affected." Slight centrolobular fatty degeneration of the liver and increased hemosiderin in the spleen were observed in exposed animals. Mice: All exposed mice (22/22) died during the first exposure period. Liver and kidney damage, including fatty degeneration and centrolobular congestion, were observed in several of the mice that died. Guinea pigs: Mortality was 28% (5/18) in the exposed group, compared with 4% (1/25) in the control group. Transient clinical signs of toxicity (drowsiness) were observed during the exposure periods. Growth was "adversely affected." Necrosis in the adrenal gland and liver and fatty degeneration of the liver and kidney were observed in exposed animals. Rabbits: Mortality was 25% (1/4) in the exposed group, compared with 0% (0/4) in the control group. No histopathological changes attributable to exposure were reported.	The only exposure level (1,500 ppm) is an apparent FEL for all species; however, reporting of study design and results are inadequate for independent review.	Highman and Heppel (1946)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Chronic[d] (inhalation)	Rats, mice, guinea pigs, rabbits, and dogs (adults and puppies) were exposed to 1,2-DCP at concentrations of 0 or 1,000 ppm 7 hr/d, 5 d/wk for up to 4−6 mo. Animal numbers ranged from 2−45/group per species. Endpoints examined included clinical signs, body weight, hematology, and clinical chemistry. Gross necropsy was performed, but was only reported for rabbits and dogs.	Rats: Mortality was 55% (25/45) in exposed rats, compared with 3% (1/37). Transient clinical signs of toxicity (unsteadiness) were observed in all animals during initial exposure periods. Body-weight gain in the exposed rats was decreased by 73−80% during the first 2 mo of exposure, compared with unexposed controls; body-weight data were not reported for Mo 3 and 4. Average daily food intake was also decreased by 41% in exposed rats. Mice: All exposed mice (26/26) died during the first exposure period. Guinea pigs: Mortality was 25% (3/12) in exposed rats, compared with 7% (1/14). Transient clinical signs of toxicity (drowsiness) were observed in all animals during initial exposure periods. No body-weight effects were noted. Rabbits: There were no mortalities in exposed (0/4) or control (0/4) animals. No adverse effects were observed. Dogs: Mortality was 60% (3/5) for exposed adult dogs and 50% (1/2) for exposed puppies, compared with 0% (0/3) for adult controls. Clinical signs of toxicity included lethargy, vomiting, and severe anorexia. All dogs that died showed moderate to marked fatty degeneration of the liver and convoluted tubules of the kidney. Two also showed marked fatty degeneration and lipoid depletion of the adrenal cortex. These lesions were not observed in surviving dogs or controls.	The only exposure level (1,000 ppm) is an apparent FEL for rats, mice, guinea pigs, and dogs. The same exposure level (1,000 ppm) was an apparent NOAEL for rabbits. However, reporting of study design and results are inadequate for independent review.	Heppel and Neal (1946)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Chronic (inhalation)	Rats, "young" guinea pigs, "mature" guinea pigs, and dogs were exposed to 0 or 400 ppm 7 hr/d, 5 d/wk for a total of 128−140 exposures (~6 mo). Animal numbers ranged from 5−26/sex/group per species. Animals were observed for mortality and clinical signs, and body weight was monitored throughout the study (details not provided). The majority of surviving animals were sacrificed immediately after the exposure period for pathological examination (no further details were provided). Recovery groups (10−21 rats/group, 5−7 guinea pigs/group) were maintained for 6−8 mo postexposure prior to sacrifice.	Rats: Mortality was 6% (3/49) in exposed rats, compared with 0% (0/30) in the controls. Terminal body weights were decreased by 11−15% in exposed rats. The only pathological finding attributed to exposure was hemosiderin deposition in the liver, predominantly in the Kupffer cells, in 24/49 exposed rats. Guinea pigs: Survival and body weights were similar between exposed and control groups. Histopathological lesions attributed to exposure included minimal fatty changes in the heart, liver, and kidney, and slight-to-moderate hemosiderosis of the spleen and adrenal gland (incidence data were not reported; it is unclear if these changes were observed in young or mature animals). After 134 exposures, 2/12 guinea pigs had extensive renal fibrosis, amyloidosis, and only a small amount of normal renal parenchyma. Tubular atrophy and fatty degeneration were apparent in areas; dilated tubules contained eosinophilic hyaline and Hb casts. "Several" additional exposed and control animals experienced similar, but less marked, kidney effects. Dogs: No changes in mortality, clinical signs, or body weight were observed between exposed and control dogs. Hemosiderosis was observed in the spleen of 5/5 exposed dogs and liver of 1/5 exposed dogs. Scattered granulomatous lesions in the kidney were also observed in 2/5 dogs, and 1/5 dogs showed a large calcified area in the adventitia of the aorta. Lesion incidences were not reported for control dogs.	The single concentration tested (400 ppm) is an apparent LOAEL for rats and dogs, based on decreased body weight and liver lesions in rats and spleen lesions in dogs. The same concentration is an apparent NOAEL for guinea pigs, based on a lack of adverse pathological changes. However, data reporting is inadequate for independent review.	Heppel et al. (1948)

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Chronic (inhalation)	Groups of S-D rats (12/sex/group) and mongrel dogs (one male/group) were exposed to 1,2-DCP at concentration of 0 or 200 ppm 7 hr/d every other day for 6 mo (75 total exposure d). Due to an infection of the rat colony, replacement rats (1−4/sex/group) were added (receiving a maximum of 45 exposures). Endpoints examined included body weight and length, hematology, clinical chemistry (dogs only), liver and kidney weight and length, and histological examination of the adrenal gland, kidney, liver, lung, spleen, testis, and nervous tissue (dogs only).	Rats: A lung infection in the colony led to a high number of deaths prior to the thirtieth exposure. The total mortality rate was 55 and 57% in the exposed and control group, respectively. Body weights in the exposed group were generally within 10% of controls. No adverse hematological changes were observed. No adverse changes were observed for liver or kidney weight. Major pathology of the kidney, liver, or lung was observed in ~50% of the animals, with similar incidence in exposed and control groups. Dogs: Both dogs survived until terminal sacrifice. The male dog exposed to 1,2-DCP had no functional testes and showed a trend toward obesity, confounding assessment of any potential body-weight effects of 1,2-DCP exposure. Liver and kidney function tests and hematology values were generally within normal limits. Cloudy swelling of the liver and lung congestion were observed in the dog exposed to 1,2-DCP; other examined tissues were pathologically normal. No major pathology was observed in any of the examined tissues in the control dog.	A NOAEL/LOAEL determination for the rat study is precluded based on high mortality (>50%) in both exposed and control groups due to an endemic infection in the colony. A NOAEL/LOAEL determination cannot be made for dogs based on inadequate animal numbers.	Mellon Institute of Industrial Research (1947a, 1947b)
Supporting evidence—noncancer effects in animals following other exposure routes (dermal, injection, etc.)				
Acute (dermal)	Wistar rats (six/sex/group) were given a single dermal application of 1,2-DCP at 2,340 mg/kg (undiluted) under occluded conditions for 24 hr. Rats were observed for mortality and clinical signs of toxicity for 14 d.	No deaths were observed. Clinical signs of toxicity included reddened and inflamed skin, increased salivation, and discolored urine.	Dermal 24-hr LC_{50} >2,340 mg/kg.	Shell Oil Co (1982)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term (i.p.)	Groups of Wistar rats (five males/group) were given i.p. injections of 1,2-DCP in corn oil at doses of 0, 50, 100, 250, or 500 mg/kg-d for 5 d. 24 hr after exposure, rats were sacrificed and kidneys were removed and weighed. Renal proximal tubule of kidney measured for ACE.	Kidney weights did not differ between exposed and control rats. ACE activity was significantly increased by 23% at 250 mg/kg-d and significantly decreased by 16% at 500 mg/kg-d. Enlargement and fraying of microvilli of brush border of the proximal tubule was observed at ≥250 mg/kg-d. Epithelial coagulative necrosis of the brush border was observed at higher doses. In the glomerulus, mesangial proliferative glomerulonephritis was observed at all doses with increased severity with increasing dose.	NOAEL: Not identified LOAEL: 50 mg/kg-d (kidney lesions)	Trevisan et al. (1988)
Short-term (i.p.)	Groups of Wistar rats (five males/group) were given i.p. injections of 1,2-DCP in corn oil at doses of 0, 10, 25, 50, 100, 250, or 500 mg/kg-d for 5 d. 24 hr after exposure, rats were sacrificed and evaluated for liver biochemistry and histology.	Liver GST activity was significantly increased at 500 mg/kg-d. No significant changes were observed in GSH content or CYP450 activity. Liver hyperplasia was observed in 5/5 rats at ≥10 mg/kg-d and slight steatosis was observed in 3/5 rats at 100 mg/kg-d and 5/5 rats at ≥250 mg/kg-d. Incidence of liver necrosis was not dose related.	NOAEL: Not determined LOAEL: 10 mg/kg-d (liver lesions)	Trevisan et al. (1989)
Short-term (injection)	ddY male mice (number unspecified) were given daily injections of 1,2-DCP for 11 d; type of injection and administered dose(s) were not reported. After exposure, liver histology was examined.	The study authors reported slight swelling of cells and increase in lipid droplets in the liver of exposed mice. It is unclear if control animals were examined.	Inadequate data reporting and lack of control data preclude a NOAEL/LOAEL determination.	Matsumoto et al. (1982) [abstract only]

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Subchronic (i.p.)	Groups of Wistar rats (10 males/group) were given i.p. injections of 1,2-DCP in corn oil at doses of 0, 50, 100, 250, or 500 mg/kg-d, 5 d/wk for 4 wk. Half the rats were sacrificed 24 hr after the last exposure; the remaining rats were sacrificed 4 wk later. Endpoints evaluated included serum biochemistry (AST, ALT), Phase I (AOH, ADEM, and CYP450) and Phase II (GSH, GST) enzymes in liver and kidney, and ACE in the proximal renal tubule brush border.	Main group: No adverse changes were observed in serum chemistry values. Significant changes in liver included an 18−78% increase in GSH and GST at ≥50 mg/kg-d, a 41−62% decrease in ADEM at ≥100 mg/kg-d, and a 26% decrease in CYP450 at 500 mg/kg-d. Significant changes in kidney biochemistry included a 16−35% decrease in ACE at ≥100 mg/kg-d, a 14−30% increase in GSH at ≥250 mg/kg-d, a 53% increase in GST at 500 mg/kg-d, and a 30% decrease in CYP450 at 500 mg/kg-d. Recovery group: The only significant finding after the recovery period was a marginal 21% increase in GSH in the liver at 500 mg/kg-d. All other endpoints were comparable to controls.	The toxicological significance of altered enzymes in the absence of altered serum biochemistry (and lack of histological examination) is unclear.	Trevisan et al. (1991)
Subchronic (i.p.)	Groups of Wistar rats (five males/group) were given i.p. injections of 1,2-DCP in corn oil at doses of 0, 10, 25, 50, 100, 250, or 500 mg/kg-d, 5 d/wk for 4 wk. 24 hr after exposure, rats were sacrificed and evaluated for liver biochemistry and histology.	Significant, dose-dependent increases were observed in GSH content and GST activity at ≥50 mg/kg-d; CYP450 activity was significantly decreased at 250 and 500 mg/kg-d. Liver hyperplasia was observed in all exposed rats, slight steatosis was also observed at ≥250 mg/kg-d.	NOAEL: Not identified LOAEL: 10 mg/kg-d (liver lesions)	Trevisan et al. (1989)
Subchronic (i.p.)	Groups of Wistar rats (five males/group) were given i.p. injections of 1,2-DCP in corn oil at doses of 0, 50, 100, 250, or 500 mg/kg-d 5 d/wk for 4 wk. 24 hr after exposure, rats were sacrificed and kidneys were removed and weighed. One kidney was examined microscopically while the other one was evaluated for ACE levels in the renal proximal tubule brush border.	Kidney weights did not differ between exposed and control rats. ACE levels were significantly decreased by 17−41% at ≥100 mg/kg-d, compared to controls. Dose-dependent enlargement and fraying of microvilli of brush border of the proximal tubule was observed. Epithelial coagulative necrosis of the brush border was observed at higher doses. In the glomerulus, mesangial proliferative glomerulonephritis was observed at all doses with increased severity with increasing dose.	NOAEL: Not identified LOAEL: 50 mg/kg-d (kidney lesions)	Trevisan et al. (1988)

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting evidence—cancer in animals following inhalation exposure				
Short-term tumor assay	C3H mice (80, sex unspecified) were exposed to 400 ppm (1,800 mg/m^3) for a total of 37 exposures (4−7 hr/exposure; exposure schedule not specified); mice were observed for 7 mo after exposure prior to sacrifice for hepatic histology.	The majority of mice died during the exposure period; only three mice survived the exposure and observation periods. All three mice showed multiple hepatomas. Nine rats that died between 14 and 28 exposures showed non-neoplastic liver lesions. It is unclear if a control group was used.	High mortality (and lack of control data) precludes conclusions regarding the hepatic carcinogenicity of 1,2-DCP.	Heppel et al. (1948)

[a]Acute = exposure for ≤24 hours (U.S. EPA, 2002b).
[b]Short-term = repeated exposure for >24 hours ≤30 days (U.S. EPA, 2002b).
[c]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).
[d]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).

ACE = angiotensin converting enzyme; ADEM = aminopyrine-*N*-demethylase; AOH = aniline hydroxylase; ALC = approximate lethal concentration; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CI = confidence interval; CNS = central nervous system; FEL = frank effect level; FOB = functional observational battery; GGT = γ-glutamyl transferase; GSH = reduced glutathione; GSSG = oxidized glutathione; GST = glutathione-*S*-transferase; Hb = hemoglobin; i.p. = intraperitoneal; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; NAD = nicotinamide adenine dinucleotide; NADPH = nicotinamide adenine dinucleotide phosphate; ND = no data; NOAEL = no-observed-adverse-effect level; NZW = New Zealand white; RNA = ribonucleic acid; S-D = Sprague-Dawley; SDH = sorbitol dehydrogenase.

DERIVATION OF PROVISIONAL VALUES

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

Table 5. Summary of Noncancer Reference Values for 1,2-Dichloropropane (CASRN 78-87-5)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/M and F pups	Delayed skeletal ossification of skull bones	4×10^{-2}	$BMDL_{05}$ (HED)	1.3	30	Kirk et al. (1995)
Chronic p-RfD (mg/kg-d)	Rat/M and F pups	Delayed skeletal ossification of skull bones	4×10^{-2}	$BMDL_{05}$ (HED)	1.3	30	Kirk et al. (1995)
Subchronic p-RfC (mg/m^3)	Rat/F	Hyperplasia of respiratory mucosa of the nasal cavity	4×10^{-3}	$BMCL_{10}$ (HEC)	0.12	30	Dow Chemical Co (1988a)
Chronic RfC (mg/m^3)	Inhalation RfC value of 4×10^{-3} is available on IRIS.						

BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; F = female(s); HEC = human equivalent concentration; HED = human equivalent dose; M = male(s); POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 6. Summary of Cancer Values for 1,2-Dichloropropane (CASRN 78-87-5)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	Mouse/M	Hepatocellular adenoma or carcinoma	3.7×10^{-2}	NTP (1986)
p-IUR $(mg/m^3)^{-1}$	Rat/M	Total nasal cavity tumors (papillomas or esthesioneuroepithelioma)	3.7×10^{-3}	Umeda et al. (2010)

M = male(s); p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of a Subchronic Provisional Referece Dose

The database of potentially relevant studies for derivation of a subchronic oral reference value for 1,2-DCP includes a short-term-duration study in both mice and hamsters (Gi et al., 2015a), three subchronic-duration studies in rats (Bruckner et al., 1989; Dow Chemical Co, 1988b; NTP, 1986), a subchronic-duration study in mice (NTP, 1986), a two-generation reproductive study in rats (Dow Chemical Co, 1990, 1989b), and developmental studies in rats and rabbits along with associated dose-range-finding studies (Kirk et al., 1995;

Dow Chemical Co, 1989c, 1988d). The developmental study in rats (Kirk et al., 1995) was selected as the principal study, and delayed fetal ossification was identified as the critical effect.

Justification of the Critical Effect

All potential 1,2-DCP-induced effects observed in the studies listed above were evaluated to determine the most sensitive response. The most sensitive effects, with LOAELs ranging from 71.4−150 mg/kg-day (and corresponding NOAELs of 25−50 mg/kg-day), included reduced body weight, clinical signs of toxicity (CNS depression), hematological changes and histopathological changes in the spleen consistent with anemia, and delayed fetal ossification in the studies by Bruckner et al. (1989), Dow Chemical Co (1988b), and Kirk et al. (1995) (see Table 7). All endpoints in Table 7 with adequate data were modeled with Benchmark Dose Software (BMDS, Version 2.5), and the estimated benchmark dose lower confidence limits (BMDLs) are also summarized in Table 7 (see Appendix C for benchmark dose [BMD] modeling methodology and detailed results). Among all of the candidate endpoints for potential critical effect, the increased litter incidence of delayed fetal ossification in rats following gestational exposure to 1,2-DCP, reported by Kirk et al. (1995), resulted in the lowest candidate point of departure (POD) ($BMDL_{05}$ = 5.6 mg/kg-day). The next lowest candidate POD was increased litter incidence of delayed fetal ossification in rabbits ($BMDL_{05}$ = 10. mg/kg-day), also reported by Kirk et al. (1995).

The delays in skeletal ossification were considered by the study authors to be related to decreased maternal body weight. However, in the rat component of the Kirk et al. (1995) study, only body-weight gain, not actual body weight, was significantly decreased. Furthermore, the EPA *Guidelines for Developmental Toxicity Risk Assessment* note that even when developmental effects are associated with maternal toxicity, they are still toxic manifestations and are "generally considered a reasonable basis for Agency regulation and/or toxicity assessment" (U.S. EPA, 1991). Delays in skeletal ossification of skull bones were also seen in rabbits (Kirk et al., 1995), with rats being the more sensitive species. The developmental period is recognized as a susceptible life-stage where exposure during certain time windows is more relevant to the induction of developmental effects than a subchronic-duration or lifetime exposure (U.S. EPA, 1991). Therefore, the developmental effects in rats are considered appropriate for deriving the subchronic p-RfD.

Justification of the Principal Study

The oral developmental toxicity study by Kirk et al. (1995) with a NOAEL of 30 mg/kg-day and a LOAEL of 125 mg/kg-day for delayed skeletal ossification of skull in fetus is selected as the principal study for derivation of a subchronic p-RfD. The critical effect is increased incidence of delayed ossification of the bones of the skull in fetuses. This study is a peer-reviewed published study with an adequate number of dose groups and dose spacing, sufficient group sizes, comprehensive endpoint assessment, and quantitation of results to describe dose-response relationships for the critical effects in rats associated with gestational oral exposure to 1,2-DCP. Among the available candidate endpoints (see Table 7), delayed ossifications in rats reported by Kirk et al. (1995) represents the lowest candidate POD for deriving a subchronic p-RfD ($BMDL_{05}$ of 5.6 mg/kg-day).

Table 7. Candidate Points of Departure for the Derivation of the Subchronic p-RfD[a]

Endpoint	Male				Female				Reference	Comments
	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	BMDL[b] (mg/kg-d)	POD	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	BMDL[b] (mg/kg-d)	POD		
Hemosiderosis and hyperplasia of the spleen; increased bilirubin in S-D rats	NDr	71.4	DU	LOAEL	NDr	NDr	NDr	NDr	Bruckner et al. (1989)	Data reporting inadequate for BMD analysis; spleen incidence data not reported, exact animal number not provided for bilirubin data.
Reduced body weight in F344 rats	46	143	DU	NOAEL	143	NDr	NDr	NDr	Dow Chemical Co (1988b)	NA
Transient CNS depression (maternal) in S-D rat	NDr	NDr	NDr	NDr	30	125	DU	NOAEL	Kirk et al. (1995)	Data reporting inadequate for BMD analysis (no summary incidence data).
Increased litter incidence of delayed ossification (fetal) in S-D rat	**NDr**	**NDr**	**NDr**	**NDr**	**30**	**125**	**5.6**	**$BMDL_{05}$**	**Kirk et al. (1995)**	**Most-sensitive endpoint.**
Increased reticulocytes (maternal) in NZW rabbit	NDr	NDr	NDr	NDr	50	150	30	$BMDL_{1SD}$	Kirk et al. (1995)	Elevated reticulocytes showed the clearest dose-response effect of observed hematological effects at 150 mg/kg-d, so it was the only hematological effect modeled from this study.

Table 7. Candidate Points of Departure for the Derivation of the Subchronic p-RfD[a]

Endpoint	Male				Female				Reference	Comments
	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	BMDL[b] (mg/kg-d)	POD	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	BMDL[b] (mg/kg-d)	POD		
Increased litter incidence of delayed ossification (fetal) in NZW rabbit	NDr	NDr	NDr	NDr	50	150	10	$BMDL_{05}$	Kirk et al. (1995)	Second-most sensitive endpoint.

[a]The units for oral values are expressed as ADDs (mg/kg-day). All long-term exposure values (≥4 weeks) are converted from a discontinuous to a continuous exposure. Values from animal developmental studies are not adjusted to a continuous exposure.
[b]All modeling was conducted using U.S. EPA BMDS (Version 2.5). BMD analysis details are available in Appendix C.

ADD = adjusted daily dose; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; BMDS = Benchamark Dose Software; CNS = central nervous system; DU = data unsuitable; LOAEL = lowest-observed-adverse-effect level; NA = not applicable; NDr = not determined; NOAEL = no-observed-adverse-effect level; NZW = New Zealand white; POD = point of departure; p-RfD = provisional reference dose; S-D = Sprague-Dawley; SD = standard deviation.

Approach for Deriving the Subchronic p-RfD

The $BMDL_{05}$ of 5.6 mg/kg-day is the selected POD for derivation of the subchronic p-RfD. In *Recommended Use of Body Weight 3/4 as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite but not for portal-of-entry effects or developmental endpoints.

A validated human PBPK model for 1,2-DCP is not available for use in extrapolating doses from animals to humans. In addition, the selected POD of 5.6 mg/kg-day is based on increased incidence of delayed ossification, which is associated with the parent compound or a stable metabolite. Furthermore, this fetal skeletal variation is not a portal-of-entry effect. Therefore, scaling by $BW^{3/4}$ is relevant for deriving HEDs for this effect.

Following U.S. EPA (2011b) guidance, the POD for the developmental study in rats is converted to a HED through the application of a DAF derived as follows:

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

where:

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

Using a reference BW_a of 0.25 kg for rats and a reference BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.24. Applying this DAF to the $BMDL_{05}$ identified in the developmental rat study yields a $BMDL_{05}$ (HED) as follows:

$$\begin{aligned} \text{POD (HED)} &= BMDL_{05}\text{ (mg/kg-day)} \times \text{DAF} \\ &= BMDL_{05}\text{ (mg/kg-day)} \times 0.24 = 5.6\text{ mg/kg-day} \times 0.24 \\ &= 1.3\text{ mg/kg-day} \end{aligned}$$

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \text{POD (HED)} \div UF_C \\ &= 1.3\text{ mg/kg-day} \div 30 \\ &= \mathbf{4 \times 10^{-2}\text{ mg/kg-day}} \end{aligned}$$

Table 8 summarizes the uncertainty factors for the subchronic p-RfD for 1,2-DCP.

Table 8. Uncertainty Factors for the Subchronic p-RfD for 1,2-Dichloropropane

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 when cross-species dosimetric adjustment (HED calculation) is performed.
UF_H	10	A UF_H of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1,2-DCP in humans.
UF_D	1	A UF_D of 1 is applied because the database is relatively complete, with a short-term-duration study in mice and hamsters, three subchronic-duration studies in rats and mice (Bruckner et al., 1989; Dow Chemical Co, 1988b; NTP, 1986), chronic-duration/carcinogenic studies in rats and mice (NTP, 1986), a two-generation reproductive toxicity study in rats (Dow Chemical Co, 1990), and developmental toxicity studies in rats and rabbits (Kirk et al., 1995), all via the oral route.
UF_L	1	A UF_L of 1 is applied because POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because developmental toxicity resulting from a narrow period of exposure was used as the critical effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	30	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor.

The confidence of the subchronic p-RfD for 1,2-DCP is high as explained in Table 9.

Table 9. Confidence Descriptors for the Subchronic p-RfD for 1,2-Dichloropropane

Confidence Categories	Designation	Discussion
Confidence in principal study	H	Confidence in the principal study is high. This study is a peer-reviewed published study with an adequate number of dose groups and dose spacing, sufficient group sizes, comprehensive endpoint assessment, and quantitation of results to describe dose-response relationships for the critical effects in rats associated with gestational oral exposure to 1,2-DCP. Although other effects were observed in studies at varying administered doses, the delayed skeletal ossification in rats represents the most sensitive effect, and this effect was also seen in a 2nd species (rabbit). The selection of delayed skeletal ossification as the critical effect is confirmed through BMD analysis, increasing confidence in the study.
Confidence in database	H	Confidence in the database is high as it includes a short-term-duration study in mice and hamsters, three subchronic-duration studies in rats and mice, chronic-duration/carcinogenic studies in rats, mice, and hamsters, a two-generation reproductive toxicity study in rats, and developmental toxicity studies in rats and rabbits (Kirk et al., 1995; Dow Chemical Co, 1990; Bruckner et al., 1989; Dow Chemical Co, 1988b; NTP, 1986). The majority of these study results were reported in peer-reviewed journals, increasing confidence in the database.
Confidence in subchronic p-RfD[a]	H	The overall confidence in the subchronic p-RfD is high.

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

BMD = benchmark dose; H = high; p-RfD = provisional reference dose.

Derivation of a Chronic Provisional Reference Dose

The database of potentially relevant studies for derivation of a chronic oral reference value for 1,2-DCP includes NTP-sponsored chronic studies in rats and mice (NTP, 1986) and hamsters (Gi et al., 2015b) in addition to the subchronic-duration (Bruckner et al., 1989; Dow Chemical Co, 1988b; NTP, 1986), two-generation reproductive (Dow Chemical Co, 1990, 1989b) and developmental studies (Kirk et al., 1995; Dow Chemical Co, 1989c, 1988d). The developmental study in rats (Kirk et al., 1995) was selected as the principal study, and delayed fetal ossification was identified as the critical effect.

Table 10 shows candidate endpoints for derivation of the chronic p-RfD from the chronic (NTP, 1986) and developmental (Kirk et al., 1995) studies. All endpoints listed in Table 10 with adequate data were modeled with BMDS (Version 2.5); the BMDLs are summarized in Table 10 (see Appendix C for BMD modeling methodology and detailed results).

While chronic toxicity testing of 1,2-DCP has been conducted, the effects in fetal rats appears to be more sensitive when comparing potential POD values. It should be noted however that the only chronic effect that could be modeled (e.g., liver effects in mice) were modeled at a benchmark response (BMR) level of 10% whereas developmental effects (e.g., delayed ossification) were modeled at a BMR 5%. The selected critical endpoint is delayed ossification of skull bones in rat fetuses in the study by Kirk et al. (1995), which is the same study and critical effect used to derive the subchronic p-RfD. A full description concerning the selection of this endpoint as the critical effect and calculation of the POD (HED) is provided in the section on

the derivation of the subchronic p-RfD. Consistent with current EPA practice, the developmental period is recognized as a susceptible life-stage where exposure during certain time windows are more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991). Therefore, an uncertainty factor (UF) for extrapolation from less-than-chronic exposure durations is not applied. As a result, the chronic p-RfD is 4×10^{-2} mg/kg-day, the same value as the subchronic p-RfD.

Table 10. Candidate Points of Departure for the Derivation of the Chronic p-RfD[a]

Endpoints	Male				Female				Reference	Comments
	NOAEL	LOAEL	BMDL[b]	POD	NOAEL	LOAEL	BMDL[b]	POD		
Reduced mean body weight in F344 rats, chronic-duration gavage study	45	89.3	DU	NOAEL	89.3	179	DU	NOAEL	NTP (1986)	BMD modeling not possible because SDs not reported
Hyperplasia of mammary gland in female F344 rats, chronic-duration gavage study	NDr	NDr	NDr	NDr	NDr	89.3	DU	LOAEL	NTP (1986)	Data unsuitable for BMD analysis (nonmonotonic dose-response). Lack of increase at high-dose consistent with progression to neoplasms and high mortality observed in high-dose group
Hepatocytomegaly and necrosis in male $B6C3F_1$ mice, chronic-duration gavage study	89.3	179	58.5 (hepato-cytomegaly)	$BMDL_{10}$	NDr	NDr	NDr	NDr	NTP (1986)	BMD modeling provided appropriate fit for hepatocytomegaly; BMD not attempted for necrosis (lower incidence)
Increased litter incidence of delayed ossification (fetal) in S-D rat	**NDr**	**NDr**	**NDr**	**NDr**	**30**	**125**	**5.6**	**$BMDL_{05}$**	**Kirk et al. (1995)**	**Most sensitive endpoint for derivation of the chronic p-RfD**
Increased litter incidence of delayed ossification (fetal) in NZW rabbit	NDr	NDr	NDr	NDr	50	150	10.	$BMDL_{05}$	Kirk et al. (1995)	Second-most sensitive endpoint

[a]The units for oral values are expressed as an ADD (mg/kg-day). All long-term exposure values (≥4 weeks) are converted from a discontinuous to a continuous exposure. Values from animal developmental studies are not adjusted to a continuous exposure.
[b]All modeling was conducted using U.S. EPA BMDS (Version 2.5). BMD analysis details are available in Appendix C.

BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; BMDS = Benchmark Dose Software; DU = data unsuitable; LOAEL = lowest-adverse-effect level; NDr = not determined; NOAEL = no-observed-adverse-effect level; NZW = New Zealand white; p-RfD = provisional reference dose; S-D = Sprague-Dawley; SD = standard deviation.

The chronic p-RfD for 1,2-DCP, based on the $BMDL_{05}$ of 5.6 mg/kg-day ($BMDL_{05}$ [HED] of 1.3 mg/kg-day) for delayed ossification in rat offspring (Kirk et al., 1995), is derived as follows:

Chronic p-RfD = POD (HED) ÷ UF_C
= 1.3 mg/kg-day ÷ 30
= **4×10^{-2} mg/kg-day**

Table 11 summarizes the uncertainty factors for the chronic p-RfD for 1,2-DCP.

Table 11. Uncertainty Factors for the Chronic p-RfD for 1,2-Dichloropropane

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 when cross-species dosimetric adjustment (HED calculation) is performed.
UF_H	10	A UF_H of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1,2-DCP in humans.
UF_D	1	A UF_D of 1 is applied because the database is relatively complete, with chronic-duration/carcinogenic studies in rats and mice (NTP, 1986), three subchronic-duration studies in rats and mice (Bruckner et al., 1989; Dow Chemical Co, 1988b; NTP, 1986), a short-term study in mice and hamsters, a two-generation reproductive toxicity study in rats (Dow Chemical Co, 1990), and developmental toxicity studies in rats and rabbits (Kirk et al., 1995), all via the oral route.
UF_L	1	A UF_L of 1 is applied because POD is a BMDL.
UF_S	1	A UF_S of 1 is applied to account for subchronic-to-chronic extrapolation because developmental toxicity resulting from a narrow period of exposure was used as the critical effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	30	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor.

The confidence of the chronic p-RfD for 1,2-DCP is high as explained in Table 12.

Table 12. Confidence Descriptors for Chronic p-RfD for 1,2-Dichloropropane

Confidence Categories	Designation	Discussion
Confidence in principal study	H	Confidence in the principal study is high. This study is a peer-reviewed published study with an adequate number of dose groups and dose spacing, sufficient group sizes, comprehensive endpoint assessment, and quantitation of results to describe dose-response relationships for the critical effects in rats associated with gestational oral exposure to 1,2-DCP. Although other effects were observed in studies at varying administered doses, the delayed skeletal ossification in rats represents the most sensitive effect, and this effect was also seen in a second species (rabbit). The selection of delayed skeletal ossification as the critical effect is confirmed through BMD analysis, increasing confidence in the study.
Confidence in database	H	Confidence in the database is high as it includes chronic-duration/carcinogenic studies in rats and mice, three subchronic-duration studies in rats, mice, and hamsters, a short-term study in mice and hamsters, a two-generation reproductive toxicity study in rats, and developmental toxicity studies in rats and rabbits (Kirk et al., 1995; Dow Chemical Co, 1990; Bruckner et al., 1989; Dow Chemical Co, 1988b; NTP, 1986). The majority of these study results were reported in peer-reviewed journals, increasing confidence in the database.
Confidence in chronic p-RfD[a]	H	The overall confidence in the chronic p-RfD is high.

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

BMD = benchmark dose; H = high; p-RfD = provisional reference dose.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of a Subchronic Provisional Reference Concentration

The database of potentially relevant studies for derivation of a subchronic inhalation reference value for 1,2-DCP includes two studies in F344 rats (Umeda et al., 2010; Dow Chemical Co, 1988a), a study in B6C3F$_1$ mice (Dow Chemical Co, 1988a), a study in B6D2F$_1$/Crlj (SPF) mice (Matsumoto et al., 2013), and a study in NZW rabbits (Dow Chemical Co, 1988a). The subchronic-duration study in F344 rats (Dow Chemical Co, 1988a) was selected as the principal study, and nasal lesions were identified as the critical effect.

Justification of the Critical Effect

All potential 1,2-DCP-induced effects following subchronic exposure were evaluated to determine the most sensitive response. The most sensitive effect in rats and mice was nasal lesions, with increases in lesion incidence in rats at HECs ≥4.0 mg/m^3 (Umeda et al., 2010; Dow Chemical Co, 1988a) and in mice at HECs ≥30.86 mg/m^3 (Matsumoto et al., 2013). In rabbits, nasal lesions were observed (not statistically significant) at an HEC of 471.8 mg/m^3, which was slightly higher than the HEC of 414 mg/m^3 associated with systemic effects in rabbits for bone marrow hyperplasia and anemia (Dow Chemical Co, 1988a).

Nasal effects in rats and mice were considered candidate critical effects and selected for BMD modeling (see Table 13; additional BMD details in Appendix C). Among the candidate endpoints for potential critical effect, the increased incidence of nasal lesions in female rats following inhalation exposure to 1,2-DCP for 13 weeks (Dow Chemical Co, 1988a) resulted in

the lowest candidate POD (benchmark concentration lower confidence limit $[BMCL]_{10}$ [HEC] = 0.12 mg/m^3). The next lowest candidate POD was nasal lesions in male rats from the same study ($BMCL_{10}$ [HEC] = 0.26 mg/m^3).

Table 13. Candidate Point of Departures for the Derivation of the Subchronic p-RfC

Endpoints	Male				Female				Reference	Comments
	NOAEL (HEC)	**LOAEL (HEC)**	**BMCL (HEC)[a]**	**POD**	**NOAEL (HEC)**	**LOAEL (HEC)**	**BMCL (HEC)[a]**	**POD**		
Nasal cavity lesions in F344rats[b]	**1.6**	**5.4**	**0.26**	**$BMCL_{10}$ (HEC)**	**1.2**	**4.0**	**0.12**	**$BMCL_{10}$ (HEC)**	**Dow Chemical Co (1988a)**	**BMCL for females is most sensitive POD**
Nasal cavity lesions in F344/DuCrj (SPF) rats[b]	NDr	13.63	DU	LOAEL (HEC)	NDr	10.03	DU	LOAEL (HEC)	Umeda et al. (2010)	Data not amenable to BMD modeling (incidence goes from 0/10 in controls to 10/10 in all exposure groups)
Nasal cavity lesions in $B6D2F_1$/Crlj (SPF) mice[b]	24.83	37.27	11.6	$BMCL_{10}$ (HEC)	20.55	30.86	17.1	$BMCL_{10}$ (HEC)	Matsumoto et al. (2013)	

[a]All modeling was conducted using U.S. EPA BMDS (Version 2.5). BMD analysis details are available in Appendix C.
[b]HEC values (mg/m^3) are based on extrathoracic respiratory effects.

BMCL = benchmark concentration lower confidence limit; BMD = benchmark dose; BMDS = Benchmark Dose Software; DU = data unsuitable; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration.

Justification of the Principal Study

The subchronic-duration inhalation study by Dow Chemical Co (1988a) with a LOAEL (HEC) of 4.0 mg/m^3, and a $BMCL_{10}$ (HEC) of 0.12 mg/m^3 for nasal lesions in female F344 rats is selected as the principal study for derivation of a subchronic p-RfC. The critical effect is increased incidence of hyperplasia of the nasal mucosa in female rats. While this study is unpublished, it has an adequate number of exposure groups and exposure spacing, sufficient group sizes, comprehensive endpoint assessment, and quantitation of results to describe concentration-response relationships for the critical effects in rats associated with subchronic inhalation exposure to 1,2-DCP. This study and critical effect were used in the derivation of the IRIS chronic RfC (U.S. EPA, 2002a); therefore, the study is considered suitable for derivation of a subchronic p-RfC. The following dosimetric adjustments are made for inhalation with a LOAEL for respiratory effects in the ET region.

Exposure concentration adjustment for continuous exposure:

$CONC_{ADJ}$ = Exposure CONC × (MW ÷ 24.45) × (hours exposed ÷ 24) × (days exposed ÷ 7 days per week)[1]
= 15 ppm × (112.99 ÷ 24.45) × (6 hours ÷ 24 hours) × (5 days ÷ 7 days)
= 12 mg/m^3

HEC conversion for respiratory effects:

$$CONC\ (HEC) = CONC_{ADJ} \times RGDR_{ET}$$

where:

$$RGDR_{ET} = \frac{(V_E \div SA_{ET})_{rat}}{(V_E \div SA_{ET})_{human}}$$

where:

$V_{E[rat]}$ = Rat minute volume (rat = 0.101 L/min and 0.137 L/min, based on a default body weight of 0.124 kg for F344 female rat and 0.180 kg for F344 male rat, respectively) (U.S. EPA, 1994b)
$V_{E[human]}$ = 13.8 L/min
$SA_{[rat]}$ = Rat default surface area of the ET region (15 cm^2)
$SA_{[human]}$ = Human default surface area of the ET region (200 cm^2)

Female rat $RGDR_{ET}$ = (0.101 L/min ÷ 15 cm^2) ÷ (13.8 L/min ÷ 200 cm^2)
= 0.097

Male rat $RGDR_{ET}$ = (0.137 L/min ÷ 15 cm^2) ÷ (13.8 L/min ÷ 200 cm^2)
= 0.132

$CONC_{RESP}$ (HEC) = $CONC_{ADJ} \times RGDR_{ET}$
= 0.097 for females, 0.132 for males
= 1.2 mg/m^3 for female rats or 1.6 mg/m^3 for male rats

[1]CONC = concentration from the Dow Chemical Co (1988a) study.

Approach for Deriving the Subchronic p-RfC

The $BMCL_{10}$ (HEC) for increased incidence of nasal lesions in female rats exposed to 1,2-DCP by inhalation for 13 weeks is selected as the POD for derivation of the subchronic p-RfC.

$$\textbf{Subchronic p-RfC} = BMCL_{10}\text{ (HEC)} \div UF$$
$$= 0.12\text{ mg/m}^3 \div 30$$
$$= \mathbf{4 \times 10^{-3}\text{ mg/m}^3}$$

Table 14 summarizes the uncertainty factors for the subchronic p-RfC for 1,2-DCP.

Table 14. Uncertainty Factors for Subchronic p-RfC for 1,2-Dichloropropane

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 when cross-species dosimetric adjustment (HEC calculation) is performed.
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1,2-DCP in humans.
UF_D	1	A UF_D of 1 has been applied because there are subchronic inhalation studies available in three species, and the critical effect (nasal lesions) has been observed in all three species, with increased sensitivity in rats and mice compared with rabbits (Matsumoto et al., 2013; Umeda et al., 2010; Dow Chemical Co, 1988a). Systemic effects were also observed in several of the inhalation studies, however the effects occurred at concentrations equal to or greater than those that induced nasal lesions. Further, while there are no acceptable two-generation reproductive toxicity or developmental toxicity studies following inhalation exposure, oral reproductive and developmental studies indicate that reproductive or developmental effects will not occur at doses that do not cause systemic effects (Kirk et al., 1995; Dow Chemical Co, 1990, 1989c, 1988d). The oral p-RfDs are based on a developmental effect (delayed ossification) that co-occurred with maternal toxicity (clinical signs, decreased body weight).
UF_L	1	A UF_L of 1 is applied because POD is a BMCL.
UF_S	1	A UF_S of 1 has been applied because a subchronic-duration study was selected as the principal study.
UF_C	30	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF = uncertainty factor.

The confidence of the subchronic p-RfC for 1,2-DCP is high as explained in Table 15.

Table 15. Confidence Descriptors for the Subchronic p-RfC for 1,2-Dichloropropane

Confidence Categories	Designation	Discussion
Confidence in principal study	H	The confidence in the principal study is high. Dow Chemical Co (1988a) conducted a series of subchronic experiments in rats, mice, and rabbits. The studies utilized an adequate number of exposure groups and exposure spacing, sufficient group sizes, comprehensive endpoint assessment, and quantitation of results to describe concentration-response relationships for the critical effects of subchronic inhalation exposure to 1,2-DCP. Additionally, the study conducted in rats (Dow Chemical Co, 1988a) was used to derive the IRIS chronic RfC (U.S. EPA, 2002a).
Confidence in database	H	The confidence in the database is high. Multiple subchronic-duration inhalation studies are available in three species (Matsumoto et al., 2013; Umeda et al., 2010; Dow Chemical Co, 1988a) and a reproductive study is available in female rats (Sekiguchi et al., 2002); however, while there are no male reproductive or developmental studies following inhalation exposure, there are oral reproductive and developmental studies to indicate that reproductive or developmental effects will not occur at doses that do not cause systemic effects (Kirk et al., 1995; Dow Chemical Co, 1990, 1989c, 1988d).
Confidence in subchronic p-RfC[a]	H	The overall confidence in the subchronic p-RfC is high.

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

H = high; IRIS = Integrated Risk Information System; p-RfC = provisional reference concentration.

Derivation of a Chronic Provisional Reference Concentratoin

A chronic p-RfC value was not derived because an inhalation RfC value is available on EPA's IRIS database.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

The cancer weight-of-evidence (WOE) descriptor for 1,2-DCP is *"Likely to be Carcinogenic to Humans"* (see details below and in Table 16).

Table 16. Cancer WOE Descriptor for 1,2-Dichloropropane			
Possible WOE Descriptor	**Designation**	**Route of Entry (oral, inhalation, or both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	There are insufficient data to support this descriptor.
"Likely to Be Carcinogenic to Humans"	**Selected**	**Both oral and inhalation route of exposure**	**Recent human epidemiological studies and case-series reports in Japanese workers indicate a potential correlation between occupational exposure to 1,2-DCP (and other solvents) and cholangiocarcinoma. There is equivocal evidence of mammary gland tumors in female rats and evidence of liver tumors in male and female mice in two-year oral bioassays (NTP, 1986). There is evidence of nasal tumors in male and female rats, Harderian gland tumors in male mice, and lung tumors in female mice in two-year inhalation bioassays (Matsumoto et al., 2013; Umeda et al., 2010).**
"Suggestive Evidence of Carcinogenic Potential"	NS	NS	Evidence of the carcinogenic potential of 1,2-DCP supports a stronger descriptor.
"Inadequate Information to Assess Carcinogenic Potential"	NS	NS	Adequate information is available to assess the carcinogenic potential of 1,2-DCP.
"Not Likely to Be Carcinogenic to Humans"	NS	NA	Evidence of the carcinogenic potential of 1,2-DCP is available in humans and animals.

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

Following U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, the database for exposure to 1,2-DCP provides evidence that it is *"Likely to be Carcinogenic to Humans."* Recent epidemiological studies and case-series reports indicate that occupational exposure to 1,2-DCP (and other solvents) in the Japanese printing industry may be associated with the development of cholangiocarcinoma, a rare form of bile duct cancer (Kubo et al., 2014c; Kubo et al., 2014a; Yamada et al., 2014; Kumagai et al., 2013). In animals, various tumors types have been observed in both rats and mice following long-term exposure to 1,2-DCP, including:

1) A marginal increase in mammary gland tumors in female F344 rats administered 1,2-DCP by gavage for 103 weeks (NTP, 1986);
2) Significant increases in liver tumors in B6C3F$_1$ mice of both sexes administered 1,2-DCP by gavage for 103 weeks (NTP, 1986);
3) Significant increases in nasal tumors in F344 rats of both sexes exposed to 1,2-DCP via inhalation for 104 weeks (Umeda et al., 2010); and
4) A significant increase in combined incidence of bronchiolo-alveolar adenoma or carcinoma in female SPF mice and a significant trend for increased Harderian gland adenoma in male SPF mice exposed to 1,2-DCP via inhalation for 104 weeks (Matsumoto et al., 2013).

While evidence for cancer following exposure to 1,2-DCP is available from both human and animal studies, a stronger cancer hazard descriptor (*"Carcinogenic to Humans"*) is not appropriate due to limitations of the available human evidence including: (1) evidence is from a small number of studies limited to case-series reports with small numbers of subjects from a few Japanese factories; (2) affected workers were often exposed to several solvents, limiting the ability to identify a causal relationship for 1,2-DCP alone; (3) exposure assessments were not available in all studies; and (4) statistical analyses adjusted for confounding variables were not conducted.

MODE-OF-ACTION DISCUSSION

The *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005) 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 suggests that 1,2-DCP is not a potent mutagen, but may cause DNA damage and clastogenic effects (see "Genotoxicity Studies" section for more details). While Sato et al. (2014) propose that cholangiocarcinoma observed in printers exposed to 1,2-DCP may be caused by DNA damage in biliary epithelial cells caused by reactive intermediates formed via GST T1-1 catalyzation, data regarding the metabolism of 1,2-DCP are insufficient to determine if this mechanism is relevant (see "Mode-of-Action/Mechanism Studies" section above for more details). Thus, a detailed MOA discussion for 1,2-DCP is precluded, and a linear approach is applied as recommended by U.S. EPA (2005).

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of a Provisonal Oral Slope Factor

An NTP 2-year bioassay in rats and mice is available for the development of a provisional oral slope factor (p-OSF) (NTP, 1986). This study was conducted in accordance with Good Laboratory Practice (GLP) principles, the results are peer-reviewed, and the study meets the standards of study design and performance with respect to the number of animals used, the examination of potential toxicity endpoints, and the presentation of information.

In the rat study, equivocal evidence of carcinogenicity was observed in female rats based on a marginal increase in mammary gland adenocarcinomas; no evidence of carcinogenicity was observed in male rats. In the mouse study, there was some evidence of carcinogenicity in male and female mice based on increases in combined adenoma or carcinoma of the liver at all treatment doses. BMD modeling was performed for each of these tumor types (see Table 17; additional BMD details in Appendix D). Prior to modeling, all doses were converted to HEDs using $BW^{3/4}$ scaling, as described in the "Derivation of a Subchronic p-RfD" section. Among all of the candidate endpoints, the increased incidence of combined hepatocellular adenomas or carcinomas in male mice resulted in the lowest POD ($BMDL_{10}$ (HED) = 2.71 mg/kg-day).

Table 17. Benchmark Dose Modeling Results for Possible Tumor Endpoints for Derivation of the p-OSF[a]

Study Citation	Tumor Endpoint	Model Type	Goodness-of-Fit *p*-Value	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)	Potential p-OSF $(mg/kg\text{-}d)^{-1}$
NTP (1986)	**Hepatocellular adenoma or carcinoma in male mice**	**Multistage-Cancer -1st order**	**0.878**	**4.25**	**2.71**	**3.7×10^{-2}**
NTP (1986)	Hepatocellular adenoma or carcinoma in female mice	Multistage-Cancer-1st order	0.417	14.5	8.51	1.2×10^{-2}
NTP (1986)	Mammary gland tumor in female rats	Multistage-Cancer-2nd order	0.985	47.7	30.4	3.3×10^{-3}

[a]All modeling was conducted using U.S. EPA BMDS (Version 2.5). BMD analysis details are available in Appendix D.

BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; BMDS = Benchmark Dose Software; HED = human equivalent dose; p-OSF = provisional oral slope factor.

The p-OSF is derived as follows:

$$\textbf{p-OSF} = BMR \div BMDL_{10}\ (HED)$$
$$= 0.1 \div 2.71\ mg/kg\text{-}day$$
$$= \mathbf{3.7 \times 10^{-2}\ (mg/kg\text{-}day)^{-1}}$$

Derivation of a Provisional Inhalation Unit Risk

One chronic inhalation study in rats and one chronic inhalation study in mice were available for the development of a provisional inhalation unit risk (p-IUR) (Matsumoto et al., 2013; Umeda et al., 2010). Both studies were well conducted, and data are able to support a quantitative cancer dose-response assessment. The studies are peer-reviewed, published, and were performed according to GLP principles.

The rat study reported significant increases in the incidences of total nasal cavity tumors including papillomas in both male and female rats and esthesioneuroepitheliomas in male rats exposed to 1,2-DCP via inhalation for 104 weeks (Umeda et al., 2010). The mouse study reported a significant increase in the combined incidence of bronchiolo-alveolar adenoma or carcinoma in females and a significant trend for increased incidence of Harderian gland adenoma in males exposed to 1,2-DCP via inhalation for 104 weeks (Matsumoto et al., 2013). All tumor types described above were selected for BMD modeling (see Table 18; additional BMD details in Appendix D). Among the candidate endpoints, the increased incidence of nasal tumors in male rats resulted in the lowest POD ($BMCL_{10}$ (HEC) = 26.7 mg/m^3).

Table 18. Benchmark Dose Modeling Results for Possible Tumor Endpoints for Derivation of the p-IUR

Study Citation	Tumor Endpoint	Model Type	Goodness-of-Fit *p*-Value	BMC_{10} (HEC) (mg/m^3)	$BMCL_{10}$ (HEC) (mg/m^3)	Potential p-IUR $(mg/m^3)^{-1}$
Umeda et al. (2010)	**Nasal tumors in male rats**	**Multistage-Cancer -3rd order**	**0.944**	**45.1**	**26.7**	**3.7×10^{-3}**
Umeda et al. (2010)	Nasal tumors in female rats	Multistage-Cancer-3rd order	0.877	55.4	46.2	2.2×10^{-3}
Matsumoto et al. (2013)	Harderian gland adenoma in male mice	Multistage-Cancer-1st order	0.994	476	251	4.0×10^{-4}
Matsumoto et al. (2013)	Bronchiolo-alveolar adenoma or carcinoma in female mice	Multistage-Cancer-1st order	0.904	342	177	5.6×10^{-4}

[a]All modeling was conducted using U.S. EPA BMDS (Version 2.5). BMD analysis details are available in Appendix D.

BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; BMD = benchmark dose; BMDS = Benchmark Dose Software; HEC = human equivalent concentration; p-IUR = provisional inhalation unit risk.

The following is the HEC conversion from bioassay inhalation concentrations by Umeda et al. (2010) based on respiratory effects in the ET region (e.g., nasal tumors).

Exposure concentration unit conversation (ppm to mg/m^3) and adjustment for continuous exposure:

$$\begin{aligned} CONC_{ADJ} &= \text{Exposure CONC} \times (MW \div 24.45) \times \\ &\quad (\text{hours exposed} \div 24) \times (\text{days exposed} \div 7 \text{ days per week})^2 \\ &= 80.2 \text{ ppm} \times (112.99 \div 24.45) \times (6 \text{ hours} \div 24 \text{ hours}) \times \\ &\quad (5 \text{ days} \div 7 \text{ days}) \\ &= 66.2 \text{ mg/m}^3 \end{aligned}$$

HEC conversion for respiratory effects:

$$CONC\ (HEC) = CONC_{ADJ} \times RGDR_{ET}$$

where:

$$RGDR_{ET} = \frac{(V_E \div SA_{ET})_{rat}}{(V_E \div SA_{ET})_{human}}$$

[2]CONC = concentration from the Umeda et al. (2010) study.

where:

$V_{E[rat]}$ = Rat minute volume (rat = 0.167 L/min and 0.254 L/min, based on a default body weight of 0.229 kg for F344 female rat and 0.380 kg for F344 male rat, respectively) [see U.S. EPA (1994a)]
$V_{E[human]}$ = 13.8 L/min
$SA_{[rat]}$ = Rat default surface area of the ET region (15 cm^2)
$SA_{[human]}$ = Human default surface area of the ET region (200 cm^2)

Female rat $RGDR_{ET}$ = (0.101 L/min ÷ 15 cm^2) ÷ (13.8 L/min ÷ 200 cm^2)
= 0.161

Male rat $RGDR_{ET}$ = (0.137 L/min ÷ 15 cm^2) ÷ (13.8 L/min ÷ 200 cm^2)
= 0.245

$CONC_{RESP}$ (HEC) = $CONC_{ADJ} \times RGDR_{ET}$
= 66.2 mg/m^3 × 0.161 for females,
66.2 mg/m^3 × 0.245 for males
= 10.7 mg/m^3 for female or 16.2 mg/m^3 for male rats

The p-IUR is derived as follows:

p-IUR = $BMR \div BMCL_{10}$ (HEC)
= 0.1 ÷ 26.7 mg/m^3
= **3.7×10^{-3} $(mg/m^3)^{-1}$**

APPENDIX A. SCREENING PROVISIONAL VALUES

No provisional screening values are derived.

APPENDIX B. DATA TABLES

Table B-1. Selected Hematology, Clinical Chemistry, and Organ Weight Findings in Male S-D Rats Administered 1,2-Dichloropropane via Gavage for 13 Weeks[a]

Endpoint[c]	Dose Group, mg/kg-d (ADD, mg/kg-d)[b]			
	0	100 (71.4)	250 (179)	500 (357)
Hematology				
Hct (%):				
13 wk	46.9 ± 0.5	46.4 ± 0.6 (−1%)	39.8 ± 1.1* (−15%)	39.3 ± 2.2* (−16%)
14 wk (1-wk recovery)	46.9 ± 0.5	47.4 ± 0.8 (+1%)	46.6 ± 1.1 (−1%)	NDr[d]
Hb (g/dL):				
13 wk	15.8 ± 0.1	15.2 ± 0.4 (−4%)	10.4 ± 0.4* (−34%)	9.8 ± 0.5* (−38%)
14 wk (1-wk recovery)	15.8 ± 0.1	15.0 ± 0.2 (−5%)	12.6 ± 1.0* (−20%)	NDr[d]
Clinical chemistry				
OCT (nmol CO_2 released/mL serum/24 hr):				
2 wk	49 ± 17	76 ± 8 (+55%)	92 ± 6 (+88%)	66 ± 9 (+35%)
4 wk	22 ± 6	54 ± 5 (+145%)	69 ± 12* (+214%)	64 ± 7* (+191%)
6 wk	45 ± 2	52 ± 9 (+16%)	28 ± 6* (−38%)	64 ± 6 (+42%)
8 wk	38 ± 4	46 ± 8 (+21%)	52 ± 4 (+37%)	81 ± 9* (+113%)
10 wk	69 ± 11	68 ± 7 (−1%)	85 ± 7 (+23%)	114 ± 21 (+65%)
12 wk	15 ± 8	33 ± 9 (+120%)	141 ± 16* (+840%)	148 ± 30* (+887%)
Bilirubin (mg/dL):				
2 wk	0.06 ± 0.02	0.06 ± 0.01 (0%)	0.25 ± 0.03* (+317%)	0.32 ± 0.08* (+433%)
4 wk	0.09 ± 0.02	0.22 ± 0.10 (+144%)	0.21 ± 0.01* (+133%)	0.30 ± 0.05* (+233%)
6 wk	0.08 ± 0.00	0.14 ± 0.03 (+75%)	0.26 ± 0.06* (+225%)	1.36 ± 0.06* (+1,600%)
8 wk	0.09 ± 0.01	0.15 ± 0.03 (+67%)	0.24 ± 0.03* (+167%)	0.75 ± 0.18* (+733%)
10 wk	0.39 ± 0.02	0.56 ± 0.04* (+44%)	0.62 ± 0.12 (+59%)	1.15 ± 0.19* (+195%)
12 wk	0.03 ± 0.00	0.27 ± 0.04* (+800%)	0.20 ± 0.02* (+567%)	0.32 ± 0.04* (+967%)
Nonprotein sulfhydryls (µmol/g tissue)				
Liver:				
13 wk	7.2 ± 0.3	6.9 ± 0.3 (−4%)	9.9 ± 0.4* (+38%)	10.3 ± 0.5* (+43%)
14 wk (1-wk recovery)	7.2 ± 0.3	8.0 ± 0.3 (+11%)	8.2 ± 0.4 (+14%)	NDr[d]
Kidney:				
13 wk	2.2 ± 0.2	2.6 ± 0.1 (+18%)	3.3 ± 0.2* (+50%)	3.1 ± 0.4* (+41%)
14 wk (1-wk recovery)	2.2 ± 0.2	2.9 ± 0.1 (+32%)	2.6 ± 0.1 (+18%)	NDr[d]

Table B-1. Selected Hematology, Clinical Chemistry, and Organ Weight Findings in Male S-D Rats Administered 1,2-Dichloropropane via Gavage for 13 Weeks[a]

Endpoint[c]	Dose Group, mg/kg-d (ADD, mg/kg-d)[b]			
	0	100 (71.4)	250 (179)	500 (357)
Relative organ weights[e] (g/100 g body weight)				
Liver:				
13 wk	3.04 ± 0.08[b]	3.29 ± 0.15 (+8%)	3.86 ± 0.08* (+27%)	4.23 ± 0.24* (+39%)
14 wk (1-wk recovery)	NDr	3.25 ± 0.06 (+7%)	3.64 ± 0.09* (+20%)	NDr[d]
Kidney:				
13 wk	0.63 ± 0.03	0.62 ± 0.02 (−2%)	0.65 ± 0.03 (+3%)	0.72 ± 0.03* (+14%)
14 wk (1-wk recovery)	NDr	0.62 ± 0.02 (−2%)	0.65 ± 0.01 (+3%)	NDr[d]
Spleen:				
13 wk	0.20 ± 0.01	0.21 ± 0.01 (+5%)	0.40 ± 0.04* (+100%)	0.61 ± 0.06* (+205%)
14 wk (1-wk recovery)	NDr	0.19 ± 0.00 (−5%)	0.28 ± 0.01* (+40%)	NDr[d]

[a]Bruckner et al. (1989).
[b]ADD = dose × (5 days/7 days).
[c]Values are expressed as mean ± SEM (percent change compared with control) for 6−8 rats/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]NDr = not determined; all surviving rats in the high-dose group were sacrificed at 13 weeks.
[e]Absolute organ weights were not reported by the study authors. Body weights were reported graphically.
*Significantly different from controls at $p \leq 0.05$, as reported by the study authors (ANOVA or Kruskal-Wallis method).

ADD = adjusted daily dose; Hb = hemoglobin; Hct = hematocrit; NDr = not determined; S-D = Sprague-Dawley; SEM = standard error of the mean.

Table B-2. Body Weight in Rats Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 13 Weeks[a]

Parameters[c]	Dose Group, mg/kg-d (ADD, mg/kg-d)[b]			
	0	20 (14)	65 (46)	200 (143)
Males				
Initial weight (g) (D 1)	188.7 ± 6.6	188.2 ± 6.2 (0)	187.9 ± 7.0 (0)	189.1 ± 5.3 (0%)
Weight at end of exposure (g) (D 91)	341.7 ± 11.2	334.9 ± 13.7 (−2%)	331.0 ± 25.7* (−3%)	308.0 ± 14.8* (−10%)
Weight at end of recovery period (g) (D 152)	377.0 ± 11.0	367.4 ± 16.5 (−3%)	363.2 ± 16.1 (−4%)	345.4 ± 22.7* (−8%)
Females				
Initial weight (g) (D 1)	138.0 ± 5.5	139.7 ± 4.3 (+1%)	139.9 ± 4.6 (+1%)	142.6 ± 8.4 (+3%)
Weight at end of exposure (g) (D 91)	195.8 ± 10.2	201.0 ± 11.4 (+3%)	199.2 ± 10.3 (+2%)	189.3 ± 10.1 (−3%)
Weight at end of recovery period (g) (D 152)	213.5 ± 7.9	218.9 ± 13.4 (+3%)	213.5 ± 12.4 (0)	205.7 ± 12.2 (−4%)

[a]Dow Chemical Co (1988b).
[b]ADD = dose × (5 days/7 days).
[c]Values expressed as mean ± SD (percent change compared with control) for 11−15 rats; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
*Statistically significantly different from the controls at $p < 0.05$, as reported by the study authors (by Dunnett's or Wilcoxon's test).

ADD = adjusted daily dose; SD = standard deviation.

Table B-3. Survival and Terminal Body Weights of F334/N Rats Administered 1,2-Dichloropropane via Gavage for 13 Weeks[a]

Parameter	Dose Group, mg/kg-d (ADD, mg/kg-d)[b]					
Males	**0 (0)**	**60 (43)**	**125 (89.3)**	**250 (179)**	**500 (357)**	**1,000 (714)**
Survival	10/10	10/10	10/10	10/10	5/10[d]	0/10[d]
Terminal body weight (g)[c]	300.1 ± 7.8	334.3 ± 7.7[d] (+11%)	308.2 ± 8.3 (+3%)	297.7 ± 4.0 (−1%)	252.4 ± 14.7[d] (−16%)	NA[e]
Females	**0 (0)**	**60 (43)**	**125 (89.3)**	**250 (179)**	**500 (357)**	**1,000 (714)**
Survival	10/10	10/10	10/10	10/10	10/10	0/10[d]
Terminal body weight (g)[c]	188.2 ± 2.9	191.5 ± 3.7 (+2)	191.2 ± 3.7 (+2)	183.7 ± 4.5 (−2)	173.3 ± 3.0[d] (−8)	NA[e]

[a]NTP (1986).
[b]ADD = dose × (5 days/7 days).
[c]Values are expressed as mean ± SEM (percent change compared with control) for rats surviving to 13 weeks; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test, Student *t*-test; 2-tailed).
[e]NA = not applicable; no body-weight data were presented by the study authors due to 100% mortality in the high-dose animals.

ADD = adjusted daily dose; NA = not applicable; SEM = standard error of the mean.

Table B-4. Survival and Terminal Body Weights for F334/N Rats Administered 1,2-Dichloropropane via Gavage for 103 Weeks[a]

Parameter	Dose Group, mg/kg-d (ADD, mg/kg-d)[b]		
Males	**0 (0)**	**62 (45)**	**125 (89.3)**
Survival[c]	39/50 (78%)	42/50 (84%)	41/50 (82%)
Terminal body weight (g)[d]	459	444 (−3%)	413 (−10%)
Females	**0 (0)**	**125 (89.3)**	**250 (179)**
Survival[c]	37/50 (74%)	43/50 (86%)	16/50* (32%)
Terminal body weight (g)[d]	321	308 (−4%)	252 (−21%)

[a]NTP (1986).
[b]ADD = dose × (5 days/7 days).
[c]Values expressed as number of animals alive at 103 weeks/number of animals at start of study (% survival).
[d]Values are expressed as mean (percent change compared with control) for rats surviving to 103 weeks; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
*Statistically significantly different from controls at $p < 0.001$, as reported by the study authors (Cox's method).

ADD = adjusted daily dose.

Table B-5. Non-neoplastic and Neoplastic Lesions in Female F334/N Rats Administered 1,2-Dichloropropane via Gavage for 103 Weeks[a]

	Dose Group, mg/kg-d (ADD, mg/kg-d) [HED, mg/kg-d][b]		
	0 (0)	**125 (89.3) [21.4]**	**250 (179) [42.9]**
Non-neoplastic lesions[c]			
Mammary gland hyperplasia	10/50 (20%)	20/50[d] (40%)	1/50 (2%)
Spleen:			
Hemosiderosis	0/50 (0%)	0/50 (0%)	20/47[d] (43%)
Hematopoiesis	1/50 (2%)	1/50 (2%)	7/47[d] (15%)
Liver:			
Clear cell foci	3/50 (6%)	5/50 (10%)	11/50[d] (22%)
Necrosis (combined):	2/50 (4%)	1/50 (2%)	12/50[d] (24%)
Focal necrosis	1/50 (2%)	0/50 (0%)	3/50 (6%)
Centrilobular necrosis	1/50 (2%)	1/50 (2%)	9/50[d] (18%)
Neoplastic lesions			
Mammary gland adenocarcinoma:			
Overall rates[c]	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted rates[e]	2.7%	4.7%	26.7%*
Uterine endometrial stromal polyp:			
Overall rates[c]	10/50 (20%)	17/49 (35%)	11/50 (22%)
Adjusted rates[e]	25.1%†	37.5%	45.6%

[a]NTP (1986).
[b]ADD = dose × (5 days/7 days); HEDs were calculated using species-specific DAFs based on the animal:human $BW^{1/4}$ ratio recommended by U.S. EPA (2011b); rat:human ratio = 0.24.
[c]Values reported as number of animals with lesion/number of animals evaluated (% incidence).
[d]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test).
[e]Adjusted for intercurrent mortality.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Fisher's exact test, life table test, or incidental tumor test).
†Statistically significant dose-related trend ($p < 0.05$), as reported by the study authors (Cochran-Armitage trend test, life table test, or incidental tumor test).

ADD = adjusted daily dose; BW = body weight; DAF = dosimetric adjustment factor; HED = human equivalent dose.

Table B-6. Non-neoplastic and Neoplastic Lesions in Male and Female B6C3F$_1$ Mice Administered 1,2-Dichloropropane via Gavage for 103 Weeks[a]

	Dose Group, mg/kg-d (ADD, mg/kg-d) [HED, mg/kg-d][b]		
	0 (0)	**125 (89.3) [12.5]**	**250 (179) [25.1]**
Non-neoplastic lesions in males[c]			
Liver:			
Hepatocytomegaly	3/50 (6%)	5/49 (10%)	15/50[d] (30%)
Necrosis (focal, NOS and centrilobular, combined)	2/50 (4%)	5/49 (10%)	10/50[d] (20%)
Neoplastic lesions in males			
Liver tumors:			
Adenoma			
Overall rates[c]	7/50† (14%)	10/50 (20%)	17/50* (34%)
Adjusted rates[e]	20%†	28.8%	45.5%*
Carcinoma			
Overall rates[c]	11/50 (22%)	17/50 (34%)	16/50 (32%)
Adjusted rates[e]	28.1%	41.9%	37.3%
Carcinoma or adenoma (combined)			
Overall rates[c]	18/50† (36%)	26/50 (52%)	33/50* (66%)
Adjusted rates[e]	46.7%†	62.9%	74.7%*
Neoplastic lesions in females			
Liver tumors:			
Adenoma			
Overall rates[c]	1/50 (2%)	5/50 (10%)	5/50 (10%)
Adjusted rates[e]	2.9%†	17.2%	19.25%*
Carcinoma			
Overall rates[c]	1/50 (2%)	3/50 (6%)	4/50 (8%)
Adjusted rates[e]	2.9%	9.7%	12.6%
Ademona or carcinoma (combined)			
Overall rates[c]	2/50† (4%)	8/50* (16%)	9/50* (18%)
Adjusted rates[e]	5.7%†	26.4%*	30.8%*
Thyroid follicular cell tumors:			
Ademona or carcinoma (combined)			
Overall rates[c]	1/48† (2%)	0/45 (0%)	5/46 (11%)
Adjusted rates[e]	2.9%†	0%	20.8%*

[a]NTP (1986).
[b]ADD = dose × (5 days/7 days); HEDs were calculated using species-specific DAFs based on the animal:human $BW^{1/4}$ ratio recommended by U.S. EPA (2011b); mouse:human ratio = 0.14.
[c]Values reported as number of animals with lesion/number of animals evaluated (% incidence).
[d]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test).
[e]Adjusted for intercurrent mortality.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Fisher's exact test, life table test, or incidental tumor test).
†Statistically significant dose-related trend ($p < 0.05$), as reported by the study authors (Cochran-Armitage trend test, life table test, or incidental tumor test).

ADD = adjusted daily dose; BW = body weight; DAF = dosimetric adjustment factor; HED = human equivalent dose.

Table B-7. Body Weights and Water Intake for F0 Male and Female S-D Rats Administered 1,2-Dichloropropane in Drinking Water for 16–18 Weeks[a]

F0 Males[c]	Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[b]			
	0	**0.024 (24.8)**	**0.10 (82.7)**	**0.24 (152)**
Body weights (g)				
Wk 1	263.1 ± 27.7	261.4 ± 21.9 (−1%)	253.2 ± 25.7 (−4%)	237.8 ± 31.9* (−10%)
End of premating (Wk 10)	524.8 ± 39.9	522.2 ± 40.3 (0)	501.5 ± 46.3 (−4%)	465.7 ± 38.3* (−11%)
End of postmating (Wk 18)	575.8 ± 47.9	577.8 ± 45.5 (0)	559.6 ± 55.0 (−3%)	525.0 ± 45.0* (−9%)
Water intake (g/day)				
Wk 1	36.4 ± 5.6	35.5 ± 5.1 (−2%)	28.7 ± 3.7[e] (−21%)	20.4 ± 3.2[e] (−44%)
End of premating (Wk 10)	41.5 ± 4.8	40.4 ± 7.9 (−3%)	36.1 ± 6.7[e] (−13%)	23.6 ± 4.3[e] (−43%)
End of postmating (Wk 18)	40.7 ± 10.2	40.9 ± 7.5 (0)	30.9 ± 5.0[e] (−24%)	23.5 ± 4.1[e] (−42%)
F0 Females[c]	**Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[d]**			
	0	**0.024 (38.8)**	**0.10 (127)**	**0.24 (254)**
Body weights (g)				
Wk 1	149.8 ± 8.0	151.7 ± 11.9 (+1%)	150.3 ± 9.3 (0)	146.8 ± 8.7 (−2%)
End of premating (Wk 10)	279.1 ± 25.9	293.1 ± 24.0 (+5%)	285.1 ± 31.1 (+2%)	268.3 ± 21.0 (−4%)
End of gestation (Wk 15)	428.9 ± 38.4	441.5 ± 36.4 (+3%)	416.9 ± 31.9 (−3%)	383.9 ± 30.6* (−10%)
End of lactation (Wk 18)	337.7 ± 25.1	334.7 ± 19.0 (−1%)	317.8 ± 22.6* (−6%)	290.6 ± 18.9* (−14%)
Water intake (g/day)				
Wk 1	28.4 ± 6.4	27.4 ± 6.3 (−4%)	21.5 ± 2.1[e] (−24%)	15.4 ± 2.2[e] (−46%)
End of premating (Wk 10)	34.7 ± 11.6	33.9 ± 7.0 (−2%)	27.9 ± 6.7[e] (−20%)	19.1 ± 3.4[e] (−45%)
End of gestation (Wk 15)	57.2 ± 8.2	62.9 ± 14.7 (+10%)	45.1 ± 12.9[e] (−21%)	30.4 ± 5.4[e] (−47%)
End of lactation (Wk 18)	129.0 ± 29.5	112.8 ± 16.5[e] (−13%)	90.9 ± 15.8[e] (−30%)	79.7 ± 19.2[e] (−38%)

[a]Dow Chemical Co (1990).
[b]1,2-DCP intakes for F0 males in the 0.024, 0.1, and 0.24% exposure groups were calculated by the study authors using body weight and water consumption data for the premating time period (28.0, 91.1, and 162 mg/kg-day, respectively) and postmating time period (18.1, 65.2, and 131 mg/kg-day, respectively). A TWA dose was calculated for the entire study duration for this review using the following formula: ([premating dose × premating duration] + [postmating dose × postmating duration]) ÷ total duration. Pre- and postmating durations for the F0 generation were 71 and 34 days, respectively.
[c]Values expressed as mean ± SD (percent change compared with control) for 14−29 rats/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]1,2-DCP intakes for F0 females in the 0.024, 0.1, and 0.24% exposure groups were calculated by the study authors using body weight and water consumption data for the premating time period (33.2, 108, and 189 mg/kg-day, respectively), gestation time period (38.4, 121, and 217 mg/kg-day, respectively), and lactation time period (58.3, 197, and 507 mg/kg-day, respectively). A TWA dose was calculated for the entire study duration for this review using the following formula: ([premating dose × premating duration] + [gestation dose × gestation duration] + [lactation dose × lactation duration]) ÷ total duration. Premating, gestation, and lactation durations for the F0 generation were 71, 21, and 21 days, respectively.
[e]Statistically significantly different from the controls at $p < 0.05$, as calculated for this review (Student's *t*-test).
*Statistically significantly different from control at $p \leq 0.05$, as reported by the study authors (Dunnett's test).

S-D = Sprague-Dawley; TWA = time-weighted average; SD = standard deviation.

Table B-8. Neonatal Survival and Body Weights of F1 Pups of S-D Rats Administered 1,2-Dichloropropane in Drinking Water for 18 Weeks[a]

	Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[b]			
	0	**0.024 (38.8)**	**0.10 (127)**	**0.24 (254)**
Survival index				
PND 0[c]	98.7 (441/447)	98.3 (410/417)	99.5 (374/376)	99.0 (378/382)
PND 1[d]	99.1 (437/441)	98.8 (405/410)	97.9 (366/374)	96.8 (366/378)*
PND 4[d]	98.2 (433/441)	94.5 (388/410)	94.7 (354/374)	88.4 (334/378)*
PND 7[e]	100 (231/231)	99.5 (219/220)	99.0 (196/198)	95.6 (196/205)*
PND 14[e]	100 (231/231)	99.5 (219/220)	99.0 (196/198)	92.2 (189/205)*
PND 21[e]	99.6 (230/231)	99.5 (219/220)	99.0 (196/198)	91.7 (188/205)*
Body weights (g)[f]				
PND 1	6.4 ± 0.6	6.8 ± 0.6* (+6%)	6.4 ± 0.9 (0)	5.9 ± 0.6* (−8%)
PND 4:				
Before culling	8.7 ± 1.1	9.4 ± 1.4 (+8%)	8.8 ± 1.9 (+1%)	7.7 ± 1.3* (−11%)
After culling	8.7 ± 1.1	9.4 ± 1.4 (+8%)	8.8 ± 1.8 (+1%)	7.7 ± 1.3* (−11%)
PND 7:				
Male	15.1 ± 1.9	15.7 ± 2.2 (+4%)	14.9 ± 2.6 (−1%)	13.2 ± 2.5* (−13%)
Female	14.5 ± 1.6	15.2 ± 2.0 (+5%)	14.1 ± 2.1 (−3%)	12.4 ± 2.2* (−14%)
PND 14:				
Male	32.0 ± 2.8	32.9 ± 3.4 (+3%)	31.2 ± 3.5 (−2%)	27.9 ± 3.5* (−13%)
Female	31.4 ± 2.6	32.1 ± 3.3 (+2%)	29.5 ± 2.4 (−6%)	26.3 ± 3.3 (−16%)
PND 21:				
Male	51.7 ± 5.1	53.9 ± 5.6 (+4%)	50.7 ± 5.6 (−2%)	44.3 ± 5.2* (−14%)
Female	49.9 ± 4.1	51.9 ± 5.1 (+4%)	48.2 ± 3.9 (−3%)	42.6 ± 4.1* (−15%)

[a]Dow Chemical Co (1990).
[b]1,2-DCP intake for nursing offspring is based on TWA maternal doses. See Footnote D in Table B-6 for TWA dose calculations for F0 females.
[c]Value expressed as % (number of live pups at birth/total number of pups at birth).
[d]Value expressed as % (number of live pups/number of live pups at birth).
[e]Values expressed % (number of live pups/number of pups after culling).
[f]Values expressed as mean ± SD (percent change compared with control) for 334−443 pups/group (prior to culling) and 94−116 per sex per group after culling; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
*Statistically significantly different from control at $p \leq 0.05$, as reported by the study authors (Dunnett's test).

S-D = Sprague-Dawley; TWA = time-weighted average; SD = standard deviation.

Table B-9. Hematological Parameters for F0 Male and Female S-D Rats Administered 1,2-Dichloropropane in Drinking Water for 18 Weeks[a]

F0 Males	Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[b]			
	0	**0.024 (24.8)**	**0.10 (82.7)**	**0.24 (152)**
Hematology[c]				
RBC (× 10^6/mm^3)	7.41 ± 0.32	7.07 ± 0.22* (−5%)	7.25 ± 0.20 (−2%)	7.11 ± 0.37 (−4%)
Hb (g/dL)	16.4 ± 1.2	15.9 ± 9.5 (−3%)	16.0 ± 0.4 (−2%)	16.3 ± 0.9 (−1%)
Hct (%)	43.9 ± 2.3	42.7 ± 1.3 (−3%)	43.4 ± 1.1 (−1%)	44.1 ± 2.3 (0%)
Platelet (× 10^3/mm^3)	1,170 ± 156	1,064 ± 114 (−9%)	1,132 ± 104 (−3%)	984 ± 144* (−16%)
Reticulocytes (%)	1.5 ± 0.8	1.0 ± 0.3 (−33%)	1.2 ± 0.3 (−20%)	0.9 ± 0.3 (−40%)
F0 Females	**Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[d]**			
	0	**0.024 (38.8)**	**0.10 (127)**	**0.24 (254)**
Hematology[c]				
RBC (× 10^6/mm^3)	7.21 ± 0.45	6.77 ± 0.36 (−6%)	6.98 ± 0.48 (−3%)	6.56 ± 0.33* (−9%)
Hb (g/dL)	17.8 ± 1.1	16.6 ± 0.6* (−7%)	17.1 ± 1.4 (−4%)	16.2 ± 0.5* (−9%)
Hct (%)	46.4 ± 2.5	44.3 ± 2.1 (−5%)	45.3 ± 3.3 (−2%)	43.0 ± 1.5* (−7%)
Platelet (× 10^3/mm^3)	1,080 ± 120	960 ± 172 (−11%)	1,124 ± 93 (+4%)	1,033 ± 124 (−4%)
Reticulocytes (%)	0.3 ± 0.1	0.5 ± 0.2 (+67%)	0.4 ± 0.2 (+33%)	0.7 ± 0.3* (+133%)

[a]Dow Chemical Co (1990).
[b]See Footnote B in Table B-7 for TWA dose calculations for F0 males.
[c]Values expressed as mean ± SD (percent change compared with control) for 10/sex/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]See Footnote D in Table B-7 for TWA dose calculations for F0 females.
*Statistically significantly different from control at $p \leq 0.05$, as reported by the study authors (Dunnett's test).

Hb = hemoglobin; Hct = hematocrit; RBC = red blood cell; S-D = Sprague-Dawley; TWA = time-weighted average; SD = standard deviation.

Table B-10. Select Histopathological Observations of the Liver of F0 and F1 S-D Rats Administered 1,2-Dichloropropane in Drinking Water for 18−21 Weeks[a]

F0 Males	Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[b]			
	0	**0.024 (24.8)**	**0.10 (82.7)**	**0.24 (152)**
Increased cytoplasmic granularity[c]:				
Panlobular, slight	0/30 (0%)	0/30 (0%)	0/30 (0%)	3/30 (10%)
Central lobular and midzonal, very slight	2/30 (7%)	3/30 (10%)	2/30 (7%)	2/30 (7%)
Central lobular and midzonal, slight	0/30 (0%)	2/30 (7%)	4/30 (13%)	7/30[d] (23%)
F0 Females	**Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[e]**			
	0	**0.024 (38.8)**	**0.10 (127)**	**0.24 (254)**
Increased cytoplasmic granularity[c]:				
Panlobular, slight	0/30 (0%)	0/30 (0%)	1/30 (3%)	2/30 (7%)
Central lobular and midzonal, very slight	0/30 (0%)	4/30 (13%)	2/30 (7%)	6/30[d] (20%)
Central lobular and midzonal, slight	0/30 (0%)	4/30 (13%)	1/30 (3%)	9/30[d] (30%)
F1 Males	**Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[f]**			
	0	**0.024 (28.3)**	**0.10 (109)**	**0.24 (213)**
Increased cytoplasmic granularity[c]:				
Central lobular and midzonal, very slight	1/30 (3%)	3/30 (10%)	2/30 (7%)	2/30 (7%)
Central lobular and midzonal, slight	0/30 (0%)	1/30 (3%)	2/30 (7%)	3/30 (10%)
F1 Females	**Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[g]**			
	0	**0.024 (42.7)**	**0.10 (148)**	**0.24 (293)**
Increased cytoplasmic granularity[c]:				
Central lobular and midzonal, very slight	2/30 (7%)	2/30 (7%)	2/30 (7%)	5/30 (17%)
Central lobular and midzonal, slight	0/30 (0%)	1/30 (3%)	0/30 (0%)	5/30[h] (17%)

[a]Dow Chemical Co (1990).
[b]See Footnote B in Table B-7 for TWA dose calculations for F0 males.
[c]Values expressed as number of animals with lesion/number of animals examined (% incidence).
[d]Statistically significantly different from the controls at $p < 0.05$, as calculated for this review (2-tailed, Fisher's exact test).
[e]See Footnote D in Table B-7 for TWA dose calculations for F0 females.
[f]1,2-DCP intakes for F1 males in the 0.024, 0.1, and 0.24% exposure groups were calculated by the study authors using body weight and water consumption data for the premating time period (32.7, 128, and 250 mg/kg-day, respectively) and postmating time period (19.4, 69.5, and 137 mg/kg-day, respectively). A TWA dose was calculated for the entire study duration for this review using the following formula: ([premating dose × premating duration] + [postmating dose × postmating duration]) ÷ total duration. Premating and postmating durations for the F1 generation were 88 and 43 days, respectively.
[g]1,2-DCP intakes for F1 females in the 0.024, 0.1, and 0.24% exposure groups were calculated by the study authors using body weight and water consumption data for the premating time period (40.6, 140.0, and 269 mg/kg-day, respectively), gestation time period (37.9, 126, and 239 mg/kg-day, respectively), and lactation time period (26.4, 200.0, and 450.0 mg/kg-day, respectively). A TWA dose was calculated for the entire study duration for this review using the following formula: ([premating dose × premating duration] + [gestation dose × gestation duration] + [lactation dose × lactation duration]) ÷ total duration. Premating, gestation, and durations for the F1 generation were 88, 21, and 21 days, respectively.
[h]Near-significant different from the controls at $p = 0.0522$, as calculated for this review (2-tailed, Fisher's exact test).

S-D = Sprague-Dawley; TWA = time-weighted average.

Table B-11. Body Weights and Water Intake for F1 Male and Female S-D Rats Administered 1,2-Dichloropropane in Drinking Water for 21 Weeks[a]

F1 Males	Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[b]			
	0	**0.024 (28.3)**	**0.10 (109)**	**0.24 (213)**
Body weights (g)[c]				
PND 21 (weaning)	118.6 ± 23.1	126.8 ± 17.6 (+7%)	121.0 ± 21.0 (+2%)	105.2 ± 15.9* (−11%)
End of premating (Wk 11)	582.1 ± 47.7	585.8 ± 53.2 (+1%)	578.1 ± 55.5 (−1%)	503.2 ± 36.6* (−14%)
End of postmating (Wk 21)	666.8 ± 64.0	662.5 ± 61.5 (−1%)	656.8 ± 68.2 (−1%)	572.2 ± 43.6* (−14%)
Water intake (g/day)[c]				
Wk 1	30.0 ± 5.3	28.9 ± 7.0 (−4%)	27.3 ± 3.8[d] (−9%)	19.3 ± 3.2[d] (−36%)
End of premating (Wk 11)	66.8 ± 21.8	54.0 ± 14.0[d] (−19%)	47.6 ± 17.0[d] (−29%)	33.9 ± 6.7[d] (−49%)
End of postmating (Wk 21)	54.4 ± 12.0	41.6 ± 9.9[d] (−24%)	39.8 ± 7.8[d] (−27%)	29.6 ± 7.7[d] (−46%)
F1 Females	**Exposure Group, % in Drinking Water (TWA doses, mg/kg-d)[e]**			
	0	**0.024 (42.7)**	**0.10 (148)**	**0.24 (293)**
Body weights (g)[c]				
PND 21 (weaning)	112.1 ± 23.4	119.2 ± 11.3 (+6%)	114.8 ± 17.5 (+2%)	96.4 ± 13.8* (−14%)
End of premating (Wk 11)	323.8 ± 37.7	328.6 ± 25.4 (+1%)	313.6 ± 32.5 (−3%)	293.6 ± 32.0* (−9%)
End of gestation (Wk 18)	465.7 ± 48.4	461.2 ± 40.5 (−1%)	434.6 ± 58.1 (−7%)	402.8 ± 44.0* (−14%)
End of lactation (Wk 21)	347.8 ± 26.0	343.1 ± 20.5 (−1%)	337.6 ± 31.0 (−3%)	306.3 ± 27.8* (−12%)
Water intake (g/day)[c]				
Wk 1	32.6 ± 8.5	27.3 ± 3.1[d] (−16%)	25.2 ± 4.8[d] (−23%)	17.8 ± 3.0[d] (−45%)
End of premating (Wk 11)	39.6 ± 7.5	36.2 ± 6.3 (−9%)	39.6 ± 16.1 (0%)	26.0 ± 6.4[d] (−34%)
End of gestation (Wk 18)	67.8 ± 21.5	69.6 ± 30.1 (+3%)	44.9 ± 11.1[d] (−34%)	30.7 ± 8.2[d] (−55%)
End of lactation (Wk 21)	119.8 ± 28.6	124.6 ± 23.4 (+4%)	104.1 ± 13.7[d] (−13%)	85.8 ± 18.7[d] (−28%)

[a]Dow Chemical Co (1990).
[b]See Footnote F in Table B-10 for TWA dose calculations for F1 males.
[c]Values expressed as mean ± SD (percent change compared with control) for 21−30 rats/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Statistically significantly different from the controls at $p < 0.05$, as calculated for this review (Student's *t*-test).
[e]See Footnote G in Table B-10 for TWA dose calculations for F1 females.
*Statistically significantly different from control at $p \leq 0.05$, as reported by the study authors (Dunnett's test).

PND = postnatal day; S-D = Sprague-Dawley; TWA = time-weighted average; SD = standard deviation.

Table B-12. Body Weight and Food Consumption Data for Pregnant S-D Rats Administered 1,2-Dichloropropane via Gavage on GDs 6–15[a]

Parameter[b]	Dose Group (mg/kg-d)				
	0	**50**	**125**	**250**	**500**
Number of pregnant animals[c]	4/10	9/10	8/10	6/9[d]	10/10
Body-weight gain (g):					
GDs 6−9	9.6 ± 2.7	6.9 ± 15.4 (−28%)	−19.3 ± 15.7* (−301%)	−25.9 ± 7.8* (−370%)	−35.2 ± 11.2* (−467%)
GDs 6−16	56.1 ± 14.6	39.8 ± 21.4 (−29%)	37.4 ± 10.5 (−33%)	49.9 ± 11.5 (−11%)	−7.0 ± 34.1* (−112%)
GDs 0−16	99.4 ± 13.4	82.5 ± 17.9 (−17%)	88.1 ± 16.1 (−11%)	102.4 ± 16.8 (+3%)	41.8 ± 33.3* (−58%)
Terminal body weight (g)	339.9 ± 12.2	336.0 ± 11.7 (−1%)	341.8 ± 25.4 (+1%)	355.1 ± 24.5 (+4%)	297.1 ± 31.7* (−13%)
Food consumption (g/d):					
GDs 6−9	22.0 ± 1.6	19.8 ± 2.8 (−10%)	15.2 ± 5.6[e] (−31%)	12.6 ± 3.3[e] (−43%)	11.5 ± 5.7[e] (−48%)
GDs 9−12	23.5 ± 1.3	21.2 ± 2.4 (−10%)	21.3 ± 1.7[e] (−9%)	22.9 ± 5.1 (−3%)	18.4 ± 7.4 (−22%)
GDs 12−16	24.5 ± 1.9	24.6 ± 5.2 (0%)	24.2 ± 2.3 (−1%)	23.6 ± 1.2 (−4%)	28.9 ± 11.2 (+18%)

[a]Dow Chemical Co (1989c).
[b]Values are expressed as mean ± SD (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[c]Body weight and food consumption data were only reported for the females with confirmed pregnancies.
[d]One dam died on GD 7 due to gavage error.
[e]Statistically significantly different from the controls at $p < 0.05$, as calculated for this review (2-tailed Student's *t*-test).
*Statistically significantly different from the controls at $p < 0.05$, as reported by the study authors.

GD = gestation day; S-D = Sprague-Dawley; SD = standard deviation.

Table B-13. Maternal Body Weights and Body-Weight Gain in Pregnant S-D Rats Administered 1,2-Dichloropropane via Gavage on GDs 6–15[a]

Parameter[b]	Dose Group (mg/kg-d)			
	0	10	30	125
Body weight (g)				
GD 0	261.5 ± 14.8	268.1 ± 16.9 (+3%)	267.2 ± 15.8 (+2%)	268.2 ± 17.2 (+3%)
GD 6	302.3 ± 17.6	306.0 ± 17.6 (+1%)	304.6 ± 16.7 (+1%)	303.8 ± 17.9 (0%)
GD 9	314.1 ± 19.8	318.4 ± 17.1 (+1%)	315.2 ± 17.0 (0%)	301.2 ± 18.0* (−4%)
GD 12	332.4 ± 22.4	335.3 ± 17.9 (+1%)	332.0 ± 18.7 (0%)	316.5 ± 19.2* (−5%)
GD 16	365.1 ± 24.5	368.1 ± 19.5 (+1%)	364.5 ± 22.0 (0%)	348.8 ± 19.3* (−4%)
GD 21	450.7 ± 36.0	457.8 ± 27.6 (+2%)	456.1 ± 30.7 (+1%)	438.7 ± 26.7[c] (−3%)
Body-weight gain (g)				
GDs 0−6	40.8 ± 8.4	37.9 ± 7.2 (−7%)	37.2 ± 8.0 (−9%)	35.6 ± 10.7 (−13%)
GDs 6−9	11.8 ± 5.1	12.4 ± 5.7 (+5%)	10.5 ± 4.5 (−11%)	−2.6 ± 9.9* (−122%)
GDs 9−12	18.8 ± 6.5	16.9 ± 5.1 (−10%)	16.9 ± 6.1 (−10%)	15.3 ± 8.3 (−19%)
GDs 12−16	32.2 ± 7.5	32.7 ± 7.0 (+2%)	32.5 ± 6.0 (+1%)	32.4 ± 8.3 (+1%)
GDs 6−16	85.6 ± 14.6	88.3 ± 14.0 (+3%)	91.6 ± 14.4 (+7%)	89.8 ± 14.8 (+5%)
GDs 16−21	62.9 ± 12.1	62.1 ± 9.7 (−1%)	59.9 ± 9.8 (−5%)	45.0 ± 8.6[c]* (−28%)
GDs 0−21	189.2 ± 30.0	188.8 ± 23.7 (0%)	188.7 ± 23.5 (0%)	170.5 ± 23.7[c]* (−10%)

[a]Kirk et al. (1995); Dow Chemical Co (1989d).
[b]Values are expressed as mean ± SD (percent change compared with control) of 25−30 dams/dose; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[c]Data from dam that delivered early were excluded from analysis.
*Statistically significantly different from control at $p \leq 0.05$, as reported by the study authors (Dunnett's or Wilcoxon's test).

GD = gestation day; S-D = Sprague-Dawley; SD = standard deviation.

Table B-14. Skeletal Variations in Fetuses from S-D Dams Administered 1,2-Dichlropropane via Gavage on GDs 6–15[a]

Parameter	Dose Group (mg/kg-d)			
	0	10	30	125
Delayed ossification, skull:				
Fetal incidence[b]	9/378 (2%)	8/435 (2%)	19/440 (4%)	37/449* (8%)
Litter incidence[c]	8/25 (32%)	8/28 (29%)	10/28 (36%)	16/30* (53%)
Delayed ossification, cervical centra:				
Fetal incidence[b]	50/378 (13%)	68/435 (16%)	48/440 (11%)	51/449 (11%)
Litter incidence[c]	21/25 (84%)	22/28 (79%)	18/28 (64%)	22/30 (73%)
Delayed ossification, thoracic centra:				
Fetal incidence[b]	8/378 (2%)	14/435 (3%)	13/440 (3%)	21/449 (5%)
Litter incidence[c]	4/25 (16%)	9/28 (32%)	6/28 (21%)	10/30 (33%)

[a]Kirk et al. (1995); Dow Chemical Co (1989d).
[b]Number of fetuses affected/number of fetuses examined (% incidence).
[c]Number of litters affected/number of fetuses examined (% incidence).
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (censored Wilcoxon's test).

GD = gestation day; S-D = Sprague-Dawley.

Table B-15. Reproductive Parameters of Pregnant NZW Rabbits Dosed via Gavage with 1,2-Dichloropropane on GDs 7–19[a]

Parameter	Dose Group (mg/kg-d)			
	0	25	100	250
Number pregnant (%)	4/7 (57%)	3/7 (43%)	5/7 (71%)	7/7 (100%)
Mortality (%)	0/7 (0%)	0/7 (0%)	0/7 (0%)	2/7 (29%)
Number of live litters (%)	4/4 (100%)	3/3 (100%)	5/5 (100%)	3/5 (60%)
Number of litters totally resorbed (%)	0/4 (0%)	0/3 (0%)	0/5 (0%)	2/5[b] (40%)
Resorptions/litter[c,d]	0.5 ± 0.6	1.0 ± 0.0 (+2-fold)	1.6 ± 2.6 (+3.2-fold)	2.0 ± 2.0 (+4-fold)
% Litters with resorptions	50	100	40	80

[a]Dow Chemical Co (1988d).
[b]Both dams exhibited weight loss.
[c]Values expressed as mean ± SD (fold-change compared with control) for all dams (included dams with complete litter resorption); fold-change control = treatment mean ÷ control mean.
[d]Historical control values for this laboratory are 0.75 (range 0−2.2) resorptions/litter (data from 29 studies; average of 7 control does/study).

Note: None of the findings were statistically significant (as reported by the study authors).

GD = gestation day; NZW = New Zealand white; SD = standard deviation.

Table B-16. Selected Hematology in Pregnant NZW Rabbits Dosed via Gavage with 1,2-Dichloropropane on GDs 7–19[a]

Parameter	Dose Group (mg/kg-d)			
	0	25	100	250
RBC ($\times 10^6$/mm^3)[b]	5.67 ± 0.43	6.01 ± 0.25 (+6%)	4.75 ± 0.81 (−16%)	4.35 ± 0.44* (−23%)
Hb (g/dL)[b]	12.7 ± 1.1	12.9 ± 0.3 (+2%)	10.8 ± 1.7 (−15%)	9.7 ± 1.3* (−24%)
Hct (%)[b]	42.6 ± 3.1	44.1 ± 1.7 (+4%)	36.1 ± 5.8 (−15%)	33.4 ± 4.2* (−22%)
Reticulocyte (%)[b]	2.1 ± 1.2	2.5 ± 0.4 (+19%)	4.5 ± 1.0* (+114%)	7.8 ± 1.5* (+271%)
Erythrocyte morphology[c]:				
Polychromasia	0/7 (0%)	1/7 (14%)	4/7[d] (57%)	3/5[d] (60%)
Anisocytosis	0/7 (0%)	0/7 (0%)	2/7 (29%)	4/5[d] (80%)

[a]Dow Chemical Co (1988d).
[b]Values expressed as mean ± SD (percent change compared with control) for 3−5 rats/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[c]Values expressed as number of animals with altered morphology/number of animals evaluated (% incidence).
[d]Statistically significantly different from control at $p \leq 0.05$, as calculated for this review (Fisher's exact test).
*Statistically significantly different from control at $p \leq 0.05$, as reported by the study authors (Dunnett's test).

GD = gestation day; Hb = hemoglobin; Hct = hematocrit; NZW = New Zealand white; RBC = red blood cell; SD = standard deviation.

Table B-17. Maternal Body Weights and Body-Weight Gain in Pregnant NZW Rabbits Administered 1,2-Dichloropropane via Gavage on GDs 7–19[a]

Parameter[b]	Dose Group (mg/kg-d)			
	0	15	50	150
Body weight (g)				
GD 0	3,764.5 ± 181.4	3,826.2 ± 187.2 (+2%)	3,849.1 ± 283.5 (+2%)	3,860.9 ± 233.6 (+3%)
GD 7	3,924.7 ± 199.6	3,962.4 ± 167.1 (+1%)	4,007.4 ± 266.6 (+2%)	4,004.2 ± 231.4 (+2%)
GD 10	3,930.7 ± 201.9	4,014.0 ± 166.4 (+2%)	4,043.7 ± 304.5 (+3%)	3,987.0 ± 243.4 (+1%)
GD 13	3,960.6 ± 214.3	4,043.8 ± 184.0 (+2%)	4,084.3 ± 335.0 (+3%)	4,009.1 ± 254.5 (+1%)
GD 16	3,985.5 ± 249.0	4,098.6 ± 196.6 (+3%)	4,125.0 ± 346.6 (+4%)	3,947.1 ± 290.3 (−1%)
GD 20	3,973.3 ± 243.3	4,079.6 ± 229.3 (+3%)	4,120.9 ± 350.0 (+4%)	3,834.7 ± 324.5 (−3%)
GD 28	4,104.9 ± 298.2	4,173.8 ± 215.2 (+2%)	4,144.6 ± 250.4 (+1%)	4,065.1 ± 334.6 (−1%)
Body-weight gain (g)				
GDs 0−7	160.2 ± 64.5	136.2 ± 93.7 (−15%)	158.3 ± 84.3 (−1%)	143.3 ± 59.9 (−11%)
GDs 7−10	6.0 ± 51.7	51.6 ± 54.0 (+760%)	36.3 ± 60.0 (+505%)	−17.2 ± 56.7 (−387%)
GDs 10−13	29.9 ± 61.7	29.9 ± 68.1 (0%)	40.6 ± 79.6 (+36%)	22.1 ± 70.0 (−26%)
GDs 13−16	24.9 ± 70.3	54.7 ± 67.4 (+120%)	40.8 ± 104.8 (+64%)	−53.3 ± 100.5* (−314%)
GDs 16−20	−12.2 ± 107.8	−18.9 ± 105.6 (−55%)	−4.2 ± 113.9 (+66%)	−112.4 ± 130.6*[c] (−821%)
GDs 7−20	48.6 ± 151.5	117.2 ± 146.0 (+141%)	113.5 ± 197.3 (+134%)	−165.1 ± 234.4*[c] (−440%)
GDs 20−28	131.7 ± 139.4	94.2 ± 182.6 (−28%)	23.8 ± 244.9 (−84%)	191.2 ± 151.2[c,d] (+45%)
GDs 0−28	340.4 ± 218.8	347.6 ± 153.2 (+2%)	295.5 ± 192.2 (−13%)	194.7 ± 211.0[c,d] (−43%)

[a]Kirk et al. (1995).
[b]Values are expressed as mean ± SD (percent change compared with control) of 15−18 dams/dose; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[c]Data from a dam that died on GD 17 was excluded from analysis.
[d]Data from a dam that died on GD 22 was excluded from analysis.
*Statistically significantly different from control at $p \leq 0.05$, as reported by the study authors (Dunnett's test).

GD = gestation day; NZW = New Zealand white; SD = standard deviation.

Table B-18. Hematology in Pregnant NZW Rabbits Administered 1,2-Dichloropropane via Gavage on GDs 7–19[a]

Parameter[b]	Dose Group (mg/kg-d)			
	0	15	50	150
RBC ($\times 10^6$/mm^3)	5.69 ± 0.45	5.40 ± 0.39 (−5%)	5.46 ± 0.39 (−4%)	4.54 ± 0.57* (−20%)
Hb (g/dL)	12.5 ± 0.8	12.2 ± 0.9 (−2%)	12.3 ± 0.8 (−2%)	10.2 ± 1.4* (−18%)
Hct (%)	42.9 ± 3.2	41.2 ± 2.3 (−4%)	41.9 ± 2.9 (−2%)	34.9 ± 4.3* (−19%)
Platelets ($\times 10^3$/mm^3)	427 ± 94	396 ± 93 (−7%)	468 ± 120 (+10%)	512 ± 103* (+20%)
WBC ($\times 10^3$/mm^3)	6.8 ± 1.5	7.2 ± 1.7 (+6%)	6.9 ± 1.6 (+1%)	8.6 ± 2.7* (+26%)
Reticulocyte (%)	3.2 ± 0.6	3.6 ± 0.7 (+13%)	3.8 ± 0.9 (+19%)	6.7 ± 1.7* (+109%)

[a]Kirk et al. (1995).
[b]Values are expressed as mean ± SD (percent change compared with control) of 15−18 does/dose; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
*Statistically significantly different from control at $p \leq 0.05$, as reported by the study authors (Dunnett's or Wilcoxon's test).

GD = gestation day; Hb = hemoglobin; Hct = hematocrit; NZW = New Zealand white; RBC = red blood cell; SD = standard deviation; WBC = white blood cell.

Table B-19. Terminal Body Weights and Selected Hematology and Clinical Chemistry Findings from Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks[a]

Parameters[c]	Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]					
	0 (0)	**125.3 (13.63)**	**250.8 (27.28)**	**500.5 (54.42)**	**1,000.4 (108.79)**	**2,001.3 (217.62)**
Terminal body weight (g)	307 ± 16	286 ± 10[d] (−7%)	292 ± 14[d] (−5%)	281 ± 12[d] (−8%)	257 ± 19[d] (−16%)	223 ± 21[d] (−27%)
Hematology:						
RBC ($10^6/\mu L$)	9.31 ± 0.21	9.36 ± 0.19 (+1%)	9.33 ± 0.16 (0%)	8.95 ± 0.17** (−4%)	8.00 ± 0.22** (−14%)	7.58 ± 0.36** (−19%)
Hb (g/dL)	15.9 ± 0.4	16.0 ± 0.4 (+1%)	15.8 ± 0.4 (−1%)	15.4 ± 0.3* (−3%)	14.7 ± 0.2** (−8%)	14.6 ± 0.5** (−8%)
Hct (%)	45.6 ± 1.2	46.1 ± 1.1 (+1%)	46.0 ± 0.7 (+1%)	45.2 ± 0.8 (−1%)	43.4 ± 0.8** (−5%)	43.7 ± 1.2** (−4%)
Reticulocyte (%)	1.9 ± 0.1	1.8 ± 0.2 (−5%)	1.9 ± 0.2 (0%)	2.3 ± 0.2 (+21%)	5.5 ± 0.6** (+189%)	10.5 ± 3.0** (+453%)
Platelet ($10^6/\mu L$)	780 ± 57	804 ± 39 (+3%)	809 ± 53 (+4%)	816 ± 67 (+5%)	925 ± 59** (+19%)	959 ± 64** (+23%)
Clinical chemistry						
Total bilirubin (mg/dL)	0.13 ± 0.02	0.13± 0.01 (0%)	0.13± 0.01 (0%)	0.13 ± 0.01 (0%)	0.14 ± 0.01 (+8%)	0.18 ± 0.02** (+38%)
GGT (IU/L)	2 ± 1	4 ± 5 (+100%)	3 ± 1 (+50%)	2 ± 1 (0%)	2 ± 1 (0%)	6 ± 10* (+200%)

[a]Umeda et al. (2010).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are expressed as mean ± SD (percent change compared with control) for 9−10 rats/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (2-tailed Student's *t*-test).
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Dunnett's test).
**Statistically significantly different from controls at $p < 0.01$, as reported by the study authors (Dunnett's test).

ET = extrathoracic respiratory effects; GGT = γ-glutamyl transferase; Hb = hemoglobin; Hct = hematocrit; HEC = human equivalent concentration; MW = molecular weight; RBC = red blood cell; SD = standard deviation.

Table B-20. Terminal Body Weights and Selected Hematology and Clinical Chemistry Findings from Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks[a]

Parameters[c]	Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]					
	0 (0)	**125.3 (10.03)**	**250.8 (20.09)**	**500.5 (40.08)**	**1,000.4 (80.112)**	**2,001.3 (160.26)**
Terminal body weight (g)	173 ± 9	167 ± 7 (−3%)	166 ± 9 (−4%)	164 ± 4[d] (−5%)	157 ± 3[d] (−9%)	142 ± 12[d] (−18%)
Hematology						
RBC (10^6/µL)	8.60 ± 0.21	8.59 ± 0.20 (0%)	8.44 ± 0.24 (−2%)	8.13 ± 0.27** (−5%)	7.77 ± 0.24** (−10%)	7.18 ± 0.39** (−17%)
Hb (g/dL)	15.9 ± 0.5	15.8 ± 0.4 (−1%)	15.7 ± 0.4 (−1%)	15.4 ± 0.6 (−3%)	15.1 ± 0.4** (−5%)	14.3 ± 0.8** (−10%)
Hct	44.3 ± 0.9	44.4 ± 1.0 (0%)	44.2 ± 1.0 (0%)	43.7 ± 1.2 (−1%)	43.7 ± 1.1 (−1%)	42.5 ± 1.4** (−4%)
Reticulocyte (%)	1.9 ± 0.2	1.9 ± 0.3 (0%)	2.5 ± 0.3 (+32%)	3.5 ± 0.4* (+84%)	6.4 ± 2.7** (+237%)	11.5 ± 4.5** (+505%)
Platelet (10^6/µL)	817 ± 64	783 ± 56 (−4%)	825 ± 58 (+1%)	863 ± 78 (+6)	874 ± 54 (+7%)	932 ± 114** (+14%)
Clinical chemistry						
Total bilirubin (mg/dL)	0.16 ± 0.02	0.16± 0.03 (0%)	0.15± 0.03 (−6%)	0.16 ± 0.02 (0%)	0.20 ± 0.03* (+25%)	0.25 ± 0.06** (+56%)
GGT (IU/L)[e]	3 ± 1	2 ± 1 (−33%)	3 ± 1 (0%)	3 ± 1 (0%)	5 ± 2** (+67%)	10 ± 2** (+233%)

[a]Umeda et al. (2010).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are expressed as mean ± SD (percent change compared with control) for 9−10 rats/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (2-tailed Student's *t*-test).
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Dunnett's test).
**Statistically significantly different from controls at $p < 0.01$, as reported by the study authors (Dunnett's test).

ET = extrathoracic respiratory effects; GGT = γ-glutamyl transferase; Hb = hemoglobin; Hct = hematocrit; HEC = human equivalent concentration; MW = molecular weight; RBC = red blood cell; SD = standard deviation.

Table B-21. Selected Histopathological Lesions in Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks[a]

Parameters[c]	Exposure Group (ppm) (HEC_{ET}, mg/m^3)[b]					
	0 (0)	**125.3 (13.63)**	**250.8 (27.28)**	**500.5 (54.42)**	**1,000.4 (108.79)**	**2,001.3 (217.62)**
Spleen:						
Hemosiderin deposits	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	10/10* (100%)	10/10* (100%)
Increased extramedullary hematopoiesis	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	10/10* (100%)	10/10* (100%)
Bone marrow:						
Increased hematopoiesis	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	10/10* (100%)	10/10* (100%)
Liver:						
Centrilobular swelling	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	9/10* (90%)
Severity[d]						[1.0]
Adrenal gland:						
Fatty change	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)
Nasal cavity:						
Respiratory epithelium						
Hyperplasia	0/10 (0%)	10/10* (100%)	10/10* (100%)	10/10* (100%)	10/10* (100%)	10/10* (100%)
Severity[d]		[1.0]	[1.3]	[1.3]	[2.0]	[2.0]
Inflammation	0/10 (0%)	0/10 (0%)	2/10 (20%)	4/10 (40%)	8/10* (80%)	8/10* (80%)
Olfactory epithelium						
Atrophy	0/10 (0%)	10/10* (100%)	10/10* (100%)	10/10* (100%)	10/10* (100%)	10/10* (100%)
Severity[d]		[1.0]	[1.2]	[1.5]	[2.2]	[2.7]

[a]Umeda et al. (2010).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
*Statistically significantly different from controls at $p < 0.01$, as reported by the study authors (Dunnett's test).
[c]Values are presented as number of animals with lesion/number of animals evaluated (% incidence).
[d]Severity was graded as follows: 1 = slight, 2 = moderate, 3 = marked, 4 = severe.

ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight; SD = standard deviation.

Table B-22. Selected Histopathological Lesions in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks[a]

Parameters[c]	Exposure Group (ppm) (HEC_{ET}, mg/m^3)[b]					
	0 (0)	**125.3 (10.03)**	**250.8 (20.09)**	**500.5 (40.08)**	**1,000.4 (80.112)**	**2,001.3 (160.26)**
Spleen:						
Hemosiderin deposits	0/10 (0%)	0/10 (0%)	4/10 (40%)	10/10* (100%)	10/10* (100%)	9/9* (100%)
Increased extramedullary hematopoiesis	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	8/10* (80%)	9/9* (100%)
Bone marrow:						
Increased hematopoiesis	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	10/10* (100%)	9/9* (100%)
Liver:						
Centrilobular swelling	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	6/9 (67%)
Severity[d]					[NR]	[1.8]
Adrenal gland:						
Fatty change	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)	9/9* (100%)
Nasal cavity:						
Respiratory epithelium						
Hyperplasia	0/10 (0%)	7/10* (70%)	10/10* (100%)	9/10* (90%)	10/10*	9/9* (100%)
Severity[d]		[1.0]	[1.0]	[1.0]	(100%) [1.2]	[1.1]
Inflammation	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	3/10 (30%)	4/9 (44%)
Olfactory epithelium						
Atrophy	0/10 (0%)	10/10*	10/10* (100%)	10/10*	10/10*	9/9* (100%)
Severity[d]		(100%) [1.0]	[1.0]	(100%) [1.1]	(100%) [1.0]	[2.1]

[a]Umeda et al. (2010).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are presented as number of animals with lesion/number of animals evaluated (% incidence).
[d]Severity was graded as follows: 1 = slight, 2 = moderate, 3 = marked, 4 = severe.
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (Dunnett's test).

ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight; NR = not reported.

Table B-23. Terminal Body Weights and Upper Respiratory Lesion Incidence for F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks[a]

Parameter[c]	Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]			
	0 (0)	**15 (1.6)**	**50 (5.4)**	**151 (16.5)**
Males				
Terminal body weight (g)[d]	295.3 ± 23.1	289.3 ± 15.0 (−2%)	272.7 ± 27.0 (−8%)	264.6 ± 24.6* (−10%)
Nasal respiratory epithelium:				
Hyperplasia (combined)	0/10 (0%)	2/9 (22%)	5/10 (50%)[e]	9/10 (90%)[e]
Very slight	0/10 (0%)	2/9 (22%)	4/10[f] (40%)	5/10 (50%)[e]
Slight	0/10 (0%)	0/9 (0%)	1/10 (10%)	4/10[f] (40%)
Nasal olfactory mucosa:				
Degeneration of olfactory mucosa (combined)	0/10 (0%)	0/9 (0%)	10/10 (100%)[e]	10/10 (100%)[e]
Very slight	0/10 (0%)	0/9 (0%)	10/10 (100%)[e]	2/10 (20%)
Slight	0/10 (0%)	0/9 (0%)	0/10 (0%)	8/10 (80%)[e]
Larynx (submucosa):				
Inflammation, subacute, slight	0/10 (0%)	0/9 (0%)	0/10 (0/%)	4/10[f] (40%)
Females				
	0 (0)	**15 (1.2)**	**50 (4.0)**	**151 (12.1)**
Terminal body weight (g)[d]	177.0 ± 13.0	172.8 ± 9.1 (−2%)	169.6 ± 5.2 (−4%)	164.3 ± 5.0* (−7%)
Nasal respiratory epithelium:				
Hyperplasia (combined)	0/10 (0%)	3/10 (30%)	7/10 (70%)[e]	9/10 (90%)[e]
Very slight	0/10 (0%)	3/10 (30%)	5/10 (50%)[e]	4/10[f] (40%)
Slight	0/10 (0%)	0/10 (0%)	2/10 (20%)	5/10 (50%)[e]
Nasal olfactory mucosa:				
Degeneration of olfactory mucosa (combined)	0/10 (0%)	0/10 (0%)	10/10 (100%)[e]	10/10 (100%)[e]
Very slight	0/10 (0%)	0/10 (0%)	9/10 (90%)[e]	3/10 (30%)
Slight	0/10 (0%)	0/10 (0%)	1/10 (10%)	7/10 (70%)[e]
Larynx (submucosa):				
Inflammation, subacute, slight	0/10 (0%)	0/10 (0%)	0/10 (0/%)	0/10 (0%)

[a]Dow Chemical Co (1988a).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are expressed as number of rats with lesion/number of rats evaluated (% incidence).
[d]Values are expressed as mean ± SD (percent change from control) for 9−10 animals/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[e]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (2-tailed Fisher's exact test).
[f]Marginally significantly different from controls ($0.05 < p < 0.1$), as calculated for this review (2-tailed Fisher's exact test).
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (Dunnett's test).

ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight; SD = standard deviation.

Table B-24. Survival and Body and Selected Organ Weights in B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks[a]

Parameter	Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]					
	0 (0)	**50.0 (6.21)**	**100.1 (12.43)**	**200.0 (24.83)**	**300.2 (37.27)**	**399.9 (49.66)**
Males						
Survival	10/10	10/10	10/10	10/10	8/10	4/10[d]
Terminal body weight (g)[c]	29.3 ± 1.7	29.5±3.1 (+1%)	28.1 ± 2.1 (−4%)	26.6 ± 1.4* (−9%)	25.6 ± 1.0** (−13%)	24.1 ± 0.8** (−18%)
Liver weight[c]:						
Absolute (g)	1.17 ± 0.05	1.21 ± 0.10 (+3%)	1.19 ± 0.06 (+2%)	1.15 ± 0.09 (−2%)	1.33 ± 0.13** (+14%)	1.52 ± 0.08** (+30%)
Relative (% BW)	3.99 ± 0.23	4.11 ± 0.27 (+3%)	4.25 ± 0.28 (+7%)	4.33 ± 0.21 (+9%)	5.19 ± 0.41** (+30%)	6.29 ± 0.38** (+58%)
Spleen weight[c]:						
Absolute (g)	0.05 ± 0.01	0.05 ± 0.01 (0%)	0.04 ± 0.01 (−20%)	0.04 ± 0.01 (−20%)	0.04 ± 0.00 (−20%)	0.05 ± 0.01 (0%)
Relative (% BW)	0.16 ± 0.04	0.16 ± 0.02 (0%)	0.15 ± 0.02 (−6%)	0.15 ± 0.02 (−6%)	0.17 ± 0.02 (+6%)	0.22 ± 0.03** (+38%)
Females						
	0 (0)	**50.0 (5.14)**	**100.1 (10.29)**	**200.0 (20.55)**	**300.2 (30.86)**	**399.9 (41.11)**
Survival	10/10	10/10	10/10	10/10	10/10	9/10
Terminal BW (g)[c]	21.7 ± 1.1	22.1 ± 1.4 (+2%)	21.3 ± 0.9 (−2%)	21.7 ± 1.9 (0%)	22.0 ± 0.7 (+1%)	21.1 ± 0.5 (−3%)
Liver weight[c]:						
Absolute (g)	0.95 ± 0.08	1.01 ± 0.08 (+6%)	0.98 ± 0.05 (+3%)	1.03 ± 0.08 (+8%)	1.21 ± 0.10** (+27%)	1.53 ± 0.15** (+61%)
Relative (% BW)	4.38 ± 0.25	4.58 ± 0.26 (+5%)	4.62 ± 0.23 (+5%)	4.76 ± 0.20 (+9%)	5.48 ± 0.34** (+25%)	7.29 ± 0.78** (+66%)
Spleen weight[c]:						
Absolute (g)	0.05 ± 0.01	0.06 ± 0.02 (+20%)	0.05 ± 0.01 (0%)	0.05 ± 0.01 (0%)	0.05 ± 0.01 (0%)	0.06 ± 0.01 (+20%)
Relative (% BW)	0.24 ± 0.03	0.25 ± 0.06 (+4%)	0.24 ± 0.03 (0%)	0.22 ± 0.02 (−8%)	0.24 ± 0.02 (0%)	0.29 ± 0.03* (+21%)

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are expressed as mean ± SD (percent change compared with control) for surviving animals; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Statistically significantly different from controls at $p < 0.01$, as calculated for this study (2-tailed Fischer's exact test).
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Dunnett's test).
**Statistically significantly different from controls at $p < 0.01$, as reported by the study authors (Dunnett's test).

BW = body weight; ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight; SD = standard deviation.

Table B-25. Hematological Findings in B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks[a]

Parameter[c]	Exposure Group, ppm (HEC$_{ET}$, mg/m^3)[b]					
	0 (0)	**50.0 (6.21)**	**100.1 (12.43)**	**200.0 (24.83)**	**300.2 (37.27)**	**399.9 (49.66)**
Males						
RBC (10^6/µL)	10.94 ± 0.29	10.36 ± 0.38** (−5%)	10.28 ± 0.43** (−6%)	10.26 ± 0.39** (−6%)	9.69 ± 0.47 (−11%)	8.81 ± 0.16** (−19%)
Hb (g/dL)	15.7 ± 0.3	15.1 ± 0.6* (−4%)	15.0 ± 0.6* (−4%)	14.9 ± 0.6* (−5%)	14.3 ± 0.6** (−9%)	13.4 ± 0.3** (−15%)
Hct (%)	50.4 ± 0.9	48.6 ± 1.2* (−4%)	48.6 ± 2.0* (−4%)	48.7 ± 1.4* (−3%)	48.1 ± 1.5* (−5%)	45.5 ± 0.6** (−10%)
MCV	46.0 ± 0.8	46.9 ± 0.7* (+2%)	47.3 ± 0.5** (+3%)	47.5 ± 0.7** (+3%)	49.7 ± 1.1** (+8%)	51.7 ± 0.5** (+12%)
Platelet (10^3/µL)	1,490 ± 78	1,437 ± 54 (−4%)	1,430 ± 52 (−4%)	1,461 ± 70 (−2%)	1,590 ± 77* (+7%)	1,772 ± 99** (+19%)
WBC (10^3/µL)	2.52 ± 1.74	1.72 ± 1.06 (−32%)	1.49 ± 0.93 (−41%)	1.95 ± 1.23 (−23%)	2.24 ± 1.23 (−11%)	1.68 ± 1.20 (−33%)
Females						
	0 (0)	**50.0 (5.14)**	**100.1 (10.29)**	**200.0 (20.55)**	**300.2 (30.86)**	**399.9 (41.11)**
RBC (10^6/µL)	10.63 ± 0.64	10.49 ± 0.37 (−1%)	10.52 ± 0.30 (−1%)	10.28 ± 0.41 (−3%)	9.21 ± 0.46** (−13%)	8.79 ± 0.44** (−17%)
Hb (g/dL)	15.6 ± 1.2	15.5 ± 0.6 (−1%)	15.5 ± 0.4 (−1%)	15.2 ± 0.7 (−3%)	14.1 ± 0.7** (−10%)	13.7 ± 0.8** (−12%)
Hct (%)	49.2 ± 3.1	49.0 ± 1.2 (0%)	48.8 ± 1.1 (−1%)	48.9 ± 1.8 (−1%)	46.7 ± 2.0* (−5%)	45.2 ± 2.2** (−8%)
MCV	46.3 ± 0.6	46.7 ± 0.7 (+1%)	46.5 ± 0.6 (0%)	47.6 ± 0.7** (+3%)	50.7 ± 0.7** (+10%)	51.5 ± 0.9** (+11%)
Platelet (10^3/µL)	1,395 ± 98	1,388 ± 172 (−1%)	1,300 ± 62 (−7%)	1,256 ± 361 (−10%)	1,458 ± 51 (+5%)	1,657 ± 149** (+19%)
WBC (10^3/µL)	1.76 ± 1.13	1.52 ± 0.77 (−14%)	1.55 ± 1.07 (−12%)	1.66 ± 1.55 (−6%)	1.60 ± 1.12 (−9%)	2.54 ± 1.56 (+44%)

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are expressed as mean ± SD (percent change compared with control) for 4−10 mice/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Dunnett's test).
**Statistically significantly different from controls at $p < 0.01$, as reported by the study authors (Dunnett's test).

ET = extrathoracic respiratory effects; Hb = hemoglobin; Hct = hematocrit; HEC = human equivalent concentration; MCV = mean corpuscular volume; MW = molecular weight; RBC = red blood cell; WBC = white blood cell; SD = standard deviation.

Table B-26. Serum Biochemistry Findings in B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks[a]

Parameter[c]	Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]					
	0	**50.0 (6.21)**	**100.1 (12.43)**	**200.0 (24.83)**	**300.2 (37.27)**	**399.9 (49.66)**
Males						
T-bilirubin (mg/dL)	0.15 ± 0.01	0.15 ± 0.01 (0%)	0.15 ± 0.01 (0%)	0.16 ± 0.01 (+7%)	0.16 ± 0.03 (+7%)	0.18 ± 0.02* (+20%)
Phospholipid (mg/dL)	179 ± 23	163 ± 13 (−9%)	155 ± 18* (−13%)	162 ± 25 (−9%)	206 ± 8* (+15%)	213 ± 17* (+19%)
AST (U/L)	40 ± 4	43 ± 6 (+8%)	41 ± 7 (+3%)	39 ± 6 (−3%)	52 ± 12 (+30%)	139 ± 24** (+248%)
ALT (U/L)	17 ± 2	16 ± 3 (−6%)	17 ± 3 (0%)	18 ± 3 (+6%)	21 ± 5 (+24%)	95 ± 37** (+459%)
ALP (U/L)	141 ± 10	142 ± 15 (+1%)	134 ± 10 (−5%)	144 ± 12 (+2%)	174 ± 8** (+23%)	325 ± 45** (+130%)
LDH (U/L)	183 ± 35	180 ± 27 (−2%)	218 ± 118 (+19%)	171 ± 30 (−7%)	212 ± 50 (+16%)	397 ± 64* (+117%)
Females						
	0	**50.0 (5.14)**	**100.1 (10.29)**	**200.0 (20.55)**	**300.2 (30.86)**	**399.9 (41.11)**
T-bilirubin (mg/dL)	0.14 ± 0.01	0.14 ± 0.03 (0%)	0.14 ± 0.02 (0%)	0.14 ± 0 (0%)	0.15 ± 0.02 (+7%)	0.18 ± 0.03** (+29%)
Phospholipid (mg/dL)	160 ± 20	156 ± 17 (−3%)	147 ± 19 (−8%)	158 ± 15 (−1%)	185 ± 16* (+16%)	227 ± 19** (+42%)
AST (U/L)	53 ± 10	60 ± 31 (+13%)	54 ± 13 (+2%)	45 ± 9 (−15%)	75 ± 45 (+42%)	206 ± 173* (+289%)
ALT (U/L)	21 ± 4	21 ± 8 (0%)	20 ± 3 (−5%)	18 ± 3 (−14%)	27 ± 25 (+29%)	95 ± 180 (+352%)
ALP (U/L)	237 ± 56	217 ± 27 (−8%)	209 ± 20 (−12%)	201 ± 28 (−15%)	195 ± 29 (−18%)	197 ± 16 (−17%)
LDH (U/L)	201 ± 21	233 ± 93 (+16%)	207 ± 54 (+3%)	226 ± 96 (+12%)	276 ± 119 (+37%)	568 ± 364** (+183%)

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are expressed as mean ± SD (percent change compared with control) for 4−10 mice/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Dunnett's test).
**Statistically significantly different from controls at $p < 0.01$, as reported by the study authors (Dunnett's test).

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ET = extrathoracic respiratory effects; HEC = human equivalent concentration; LDH = lactate dehydrogenase; MW = molecular weight; SD = standard deviation.

Table B-27. Selected Extrarespiratory Non-neoplastic Lesions in B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks[a]

Parameter[c]	Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]					
	0 (0)	**50.0 (6.21)**	**100.1 (12.43)**	**200.0 (24.83)**	**300.2 (37.27)**	**399.9 (49.66)**
Males						
Stomach:						
Hyperplasia: forestomach	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (0%)	2/10 (20%)	4/10* (40%)
Liver, central:						
Swelling	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	8/10** (80%)	4/10* (40%)
Fatty change	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	5/10* (50%)
Vacuolic change	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	7/10** (70%)
Mineralization	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	4/10 (40%)
Necrosis	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	3/10 (30%)
Bone marrow:						
Congestion	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	6/10** (60%)
Increased erythropoiesis	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	3/10 (30%)	2/10 (20%)
Spleen:						
Atrophy	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	5/10* (50%)
Increased extramedullary hematopoiesis	0/10 (0%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	3/10 (30%)	4/10* (40%)
Hemosiderin deposits	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	4/10* (40%)
Increased megakaryocyte	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	3/10 (30%)	4/10* (40%)
Heart:						
Ground glass appearance	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	3/10 (30%)	9/10** (90%)
Females						
	0 (0)	**50.0 (5.14)**	**100.1 (10.29)**	**200.0 (20.55)**	**300.2 (30.86)**	**399.9 (41.11)**
Stomach:						
Hyperplasia: forestomach	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (0%)	10/10** (100%)	10/10** (100%)
Liver, central:						
Swelling	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	7/10** (70%)	9/10** (90%)
Fatty change	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Vacuolic change	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)
Mineralization	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	9/10** (90%)
Necrosis	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Bone marrow:						
Congestion	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Increased erythropoiesis	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	4/10* (40%)	4/10* (40%)
Spleen:						
Atrophy	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)
Increased extramedullary hematopoiesis	0/10 (0%)	1/10 (10%)	0/10 (0%)	0/10 (0%)	5/10* (50%)	10/10** (100%)
Hemosiderin deposits	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	10/10** (100%)
Increased megakaryocyte	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	3/10 (30%)	9/10** (90%)

Table B-27. Selected Extrarespiratory Non-neoplastic Lesions in B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks[a]

Parameter[c]	Exposure Group, ppm (HEC$_{ET}$, mg/m^3)[b]					
	0 (0)	**50.0 (6.21)**	**100.1 (12.43)**	**200.0 (24.83)**	**300.2 (37.27)**	**399.9 (49.66)**
Females						
Heart:						
Ground glass appearance	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	3/10 (30%)	9/10** (90%)

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are presented as number of animals with lesion/number of animals evaluated (% incidence).
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Fischer's exact test).
**Statistically significantly different from controls at $p < 0.01$, as reported by the study authors (Fischer's exact test).

ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight.

Table B-28. Nasal Lesions in B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks[a]

Parameter[c]	Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]					
	0 (0)	**50.0 (6.21)**	**100.1 (12.43)**	**200.0 (24.83)**	**300.2 (37.27)**	**399.9 (49.66)**
Males						
Olfactory epithelium:						
Respiratory metaplasia	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	3/10 (30%)	3/10 (30%)
Atrophy	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	7/10** (70%)	4/10* (40%)
Necrosis	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	4/10* (40%)	1/10 (10%)
Desquamation	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	6/10** (60%)
Females						
	0 (0)	**50.0 (5.14)**	**100.1 (10.29)**	**200.0 (20.55)**	**300.2 (30.86)**	**399.9 (41.11)**
Olfactory epithelium:						
Respiratory metaplasia	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	4/10* (40%)	3/10 (30%)
Atrophy	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	7/10** (70%)	9/10** (90%)
Necrosis	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	4/10* (40%)	2/10 (20%)
Desquamation	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are presented as number of animals with lesion/number of animals evaluated (% incidence).
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Fischer's exact test).
**Statistically significantly different from controls at $p < 0.01$, as reported by the study authors (Fischer's exact test).

ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight.

Table B-29. Hematological Findings for NZW Rabbits Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 11 or 13 Weeks[a]

Parameter[c]	Exposure Group, ppm (HEC_{ET}, mg/m³)[b]			
	0 (0)	**151 (71.0)**	**502 (236)**	**1,003 (471.8)**
Males				
Wk 11				
Erythrocyte count (× 10^6/mm³)	6.25 ± 0.46	5.62 ± 0.22* (−10%)	4.94 ± 0.12* (−21%)	4.67 ± 0.41* (−25%)
Hb (g/dL)	13.2 ± 0.7	12.8 ± 0.5 (−3%)	11.5 ± 0.5* (−13%)	11.3 ± 0.9* (−14%)
Packed cell volume (%)	46.7 ± 2.5	44.0 ± 2.1 (−6%)	39.8 ± 1.4* (−15%)	38.8 ± 3.2* (−17%)
Wk 13				
Erythrocyte count (× 10^6/mm³)	6.37 ± 0.28	5.61 ± 0.17* (−12%)	4.82 ± 0.23* (−24%)	4.51 ± 0.36* (−29%)
Hb (g/dL)	13.3 ± 0.3	12.5 ± 0.5* (−6%)	11.2 ± 0.4* (−16%)	11.0 ± 0.9* (−17%)
Packed cell volume (%)	48.5 ± 1.1	45.4 ± 1.9* (−6%)	40.2 ± 1.8* (−17%)	39.0 ± 3.3* (−20%)
Reticulocytes (%)	1.2 ± 0.4	1.6 ± 0.4 (+33%)	3.4 ± 1.0* (+183%)	5.2 ± 1.1* (+333%)
Nucleated erythrocytes (per 100 WBC)	1 ± 1	1 ± 1 (0%)	2 ± 2 (+100%)	4 ± 6 (+300%)
Females				
	0 (0)	**151 (66.4)**	**502 (221)**	**1,003 (441.2)**
Wk 11				
Erythrocyte count (× 10^6/mm³)	5.70 ± 0.52	5.70 ± 0.51 (0%)	4.86 ± 0.43* (−15%)	4.44 ± 0.32* (−22%)
Hb (g/dL)	12.3 ± 0.6	12.5 ± 0.8 (+2%)	11.1 ± 0.7* (−10%)	10.4 ± 0.5* (−15%)
Packed cell volume (%)	44.4 ± 2.6	44.6 ± 3.2 (+0.5%)	39.4 ± 2.4* (−11%)	36.8 ± 1.8* (−17%)

Table B-29. Hematological Findings for NZW Rabbits Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 11 or 13 Weeks[a]

Parameter[c]	Exposure Group, ppm (HEC_{ET}, mg/m³)[b]			
	0 (0)	151 (71.0)	502 (236)	1,003 (471.8)
Females				
Wk 13				
Erythrocyte count (× 10^6/mm³)	5.9 ± 0.60	5.73 ± 0.42 (−3%)	4.85 ± 0.48* (−18%)	4.47 ± 0.32* (−24%)
Hb (g/dL)	12.7 ± 0.5	12.3 ± 0.8 (−3.1%)	11.1 ± 0.8* (−13%)	10.2 ± 0.5* (−20%)
Packed cell volume (%)	45.6 ± 2.6	44.2 ± 2.7 (−3.0%)	39.2 ± 3.0* (−14%)	36.7 ± 2.1* (−20%)
Reticulocytes	1.3 ± 0.3	1.3 ± 0.2 (0%)	2.85 ± 0.4* (+119%)	3.95 ± 1.0* (+204%)
Nucleated erythrocytes	1 ± 1	0 ± 0 (−100%)	0 ± 0 (−100%)	1 ± 2 (0%)

[a]Dow Chemical Co (1988a).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are expressed as mean ± SD (percent change compared with control) for seven rabbits/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100; rats were fasted for 24 hours prior to sacrifice.
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (Dunnett's or Wilcoxon's test).

ET = extrathoracic respiratory effects; Hb = hemoglobin; HEC = human equivalent concentration; MW = molecular weight; NZW = New Zealand white; SD = standard deviation; WBC = white blood cell.

Table B-30. Selected Histopathology in NZW Rabbits Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks[a]

Parameter[c]	Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]			
	0 (0)	**151 (71.0)**	**502 (236)**	**1,003 (471.8)**
Bone marrow lesions				
Males:				
Hyperplasia	0/7 (0%)	2/7 (29%)	6/7[d] (86%)	7/7[d] (100%)
Slight	0/7 (0%)	1/7 (14%)	3/7 (43%)	3/7 (43%)
Moderate	0/7 (0%)	1/7 (14%)	3/7 (43%)	4/7[d] (57%)
Increased hematogenous pigment (macrophages)	1/7 (14%)	1/7 (14%)	2/7 (29%)	6/7[d] (86%)
	0 (0)	**151 (66.4)**	**502 (221)**	**1,003 (441.2)**
Females:				
Hyperplasia	2/7 (29%)	0/7 (0%)	5/7 (71%)	7/7[d] (100%)
Slight	2/7 (29%)	0/7 (0%)	5/7 (71%)	2/7 (29%)
Moderate	0/7 (0%)	0/7 (0%)	0/7 (0%)	3/7 (43%)
Increased hematogenous pigment (macrophages)	2/7 (29%)	0/7 (0%)	0/7 (0%)	5/7 (71%)
Parameter[c]	**Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]**			
	0 (0)	**151 (71.0)**	**502 (236)**	**1,003 (471.8)**
Nasal lesions				
Males:				
Degeneration of olfactory epithelium	2/7 (29%)	3/7 (43%)	2/7 (29%)	5/7 (71%)
Very slight	2/7 (29%)	3/7 (43%)	2/7 (29%)	1/7 (14%)
Slight	0/7 (0%)	0/7 (0%)	0/7 (0%)	4/7[e] (57%)
	0 (0)	**151 (66.4)**	**502 (221)**	**1,003 (441.2)**
Females:				
Degeneration of olfactory epithelium	2/7 (29%)	2/7 (29%)	2/7 (29%)	2/7 (29%)
Very slight	2/7 (29%)	1/7 (14%)	0/7 (0%)	1/7 (14%)
Slight	0/7 (0%)	1/7 (14%)	2/7 (29%)	1/7 (14%)

[a]Dow Chemical Co (1988a).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are expressed as number of animals with lesions/number of animals examined (% incidence).
[d]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (2-tailed Fisher's exact test).
[e]Marginally significantly different from controls ($0.05 < p < 0.1$), as calculated for this review (2-tailed Fisher's exact test).
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (Dunnett's test).

ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight; NZW = New Zealand white.

Table B-31. Selected Histopathological Lesions in Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for up to 104 Weeks[a]

Parameter[c]	Exposure Group (ppm) (HEC_{ET}, mg/m^3)[b]			
	0 (0)	80.2 (16.2)	200.5 (40.54)	500.2 (101.1)
Males				
Non-neoplastic lesions: Respiratory epithelium:				
Squamous cell metaplasia	5/50 (10%)	31/50** (62%)	41/50** (82%)	49/50** (98%)
Severity[d]	[1.0]	[1.0]	[1.0]	[1.2]
Inflammation	20/50 (40%)	35/50** (70%)	47/50** (94%)	47/50** (94%)
Severity	[1.0]	[1.0]	[1.0]	[1.2]
Non-neoplastic lesions: Olfactory epithelium:				
Atrophy	0/50 (0%)	48/50** (96%)	50/50** (100%)	49/50** (98%)
Severity		[1.1]	[1.9]	[2.0]
Preneoplastic lesions (combined):	0/50 (0%)	31/50** (62%)	39/50** (78%)	50/50** (100%)
Transitional epithelium hyperplasia	0 (0%)	31/50** (62%)	39/50** (78%)	48/50** (96%)
Severity		[1.1]	[1.1]	[1.8]
Squamous hyperplasia	0 (0%)	2/50 (4%)	6/50* (12%)	27/50** (54%)
Severity		[1.0]	[1.0]	[1.1]
Neoplastic nasal lesions (combined):	0/50 (0%)†	2/50 (4%)	4/50 (8%)	15/50** (30%)
Papilloma	0/50 (0%)†	0/50 (0%)	3/50 (6%)	15/50** (30%)
Esthesioneuroepithelioma	0/50 (0%)	2/50 (4%)	1/50 (2%)	0/50 (0%)

[a]Umeda et al. (2010).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are presented as number of animals with lesion/number of animals evaluated (% incidence).
[d]Severity was graded as follows: 1 = slight, 2 = moderate, 3 = marked, 4 = severe.
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (Fisher's exact test or χ^2 test).
**Statistically significantly different from controls at $p \leq 0.01$, as reported by the study authors (Fisher's exact test or χ^2 test).
†Statistically significantly dose-related trend at $p \leq 0.01$, as reported by the study authors (Peto test).

ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight.

Table B-32. Selected Histopathological Lesions in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for up to 104 Weeks[a]

Parameter[c]	Exposure Group (ppm) (HEC_{ET}, mg/m^3)[b]			
	0 (0)	**80.2 (10.7)**	**200.5 (26.75)**	**500.2 (66.71)**
Non-neoplastic lesions: Respiratory epithelium:				
Squamous cell metaplasia	3/50 (6%)	15/50** (30%)	37/50** (74%)	46/50** (92%)
Severity[d]	[1.0]	[1.0]	[1.2]	[1.5]
Inflammation	10/50 (20%)	30/50** (60%)	39/50** (78%)	40/50** (80%)
Severity	[1.0]	[1.0]	[1.0]	[1.1]
Non-neoplastic lesions: Olfactory epithelium:				
Atrophy	0/50 (0%)	50/50** (100%)	50/50** (100%)	50/50** (100%)
Severity		[1.0]	[1.9]	[2.0]
Preneoplastic lesions (combined):	2/50 (10%)	21/50** (42%)	39/50** (78%)	48/50** (96%)
Transitional epithelium hyperplasia	2/50 (10%)	21/50** (42%)	39/50** (78%)	48/50** (96%)
Severity	[1.0]	[1.2]	[1.1]	[1.5]
Squamous hyperplasia	0/50 (0%)	0/50 (0%)	3/50 (6%)	20/50** (40%)
Severity			[1.0]	[1.3]
Neoplastic nasal lesions (combined):	0/50 (0%)†	0/50 (0%)	0/50 (0%)	9/50** (18%)
Papilloma	0/50 (0%)†	0/50 (0%)	0/50 (0%)	9/50** (18%)
Esthesioneuroepithelioma	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)

[a]Umeda et al. (2010).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are presented as number of animals with lesion/number of animals evaluated (% incidence).
[d]Severity was graded as follows: 1 = slight, 2 = moderate, 3 = marked, 4 = severe.
*Statistically significantly different from controls at $p \leq 0.05$, as reported by the study authors (Fisher's exact test or χ^2 test).
**Statistically significantly different from controls at $p \leq 0.01$, as reported by the study authors (Fisher's exact test or χ^2 test).
†Statistically significantly dose-related trend at $p \leq 0.01$, as reported by the study authors (Peto test).

ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight.

Table B-33. Body and Selected Organ Weights in Male B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 2 Years[a]

Parameter[c]	Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]			
	0 (0)	**32.1 (4.73)**	**80.2 (11.8)**	**200.5 (29.55)**
Terminal body weight (g)	41.9 ± 7.5	46.8 ± 7.4 (+12%)	45.5 ± 8.0 (+9%)	44.0 ± 8.1 (+5%)
Spleen weight:				
Absolute (g)	0.19 ± 0.56	0.16 ± 0.35 (−16%)	0.12 ± 0.11 (−37%)	0.15 ± 0.11* (−21%)
Relative (g/g BW)	0.50 ± 1.46	0.42 ± 1.09 (−16%)	0.28 ± 0.29 (−44%)	0.34 ± 0.26 (−32%)
Kidney weight:				
Absolute (g)	0.63 ± 0.05	0.71 ± 0.05** (+13%)	0.76 ± 0.21** (+21%)	0.99 ± 1.69** (+57%)
Relative (g/g BW)	1.55 ± 0.27	1.54 ± 0.25 (−1%)	1.73 ± 0.56 (+12%)	2.29 ± 3.83* (+48%)

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are expressed as mean ± SD (percent change compared with control) for 26−41 mice; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Dunnett's test).
**Statistically significantly different from controls at $p < 0.01$, as reported by the study authors (Dunnett's test).

BW = body weight; ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight; SD = standard deviation.

Table B-34. Selected Non-neoplastic Lesions in B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 2 Years[a]

Parameter[c]	Exposure Group, ppm (HEC$_{ET}$, mg/m^3)[b]			
	0 (0)	**32.1 (4.73)**	**80.2 (11.8)**	**200.5 (29.55)**
Nasal cavity, males				
Olfactory epithelium:				
Atrophy	1/50 (2%)	1/50 (2%)	19/50** (38%)	20/50** (40%)
Respiratory metaplasia	19/50 (38%)	27/50 (54%)	23/50 (46%)	21/50 (42%)
Submucosal gland:				
Respiratory metaplasia	9/50 (18%)	13/50 (26%)	12/50 (24%)	18/50* (36%)
Nasal cavity, females	**0 (0)**	**32.1 (4.27)**	**80.2 (10.7)**	**200.5 (26.67)**
Olfactory epithelium:				
Atrophy	8/50 (16%)	8/50 (16%)	19/50* (38%)	16/50 (32%)
Respiratory metaplasia	32/50 (64%)	14/50 (28%)	34/50 (68%)	44/50* (88%)
Submucosal gland:				
Respiratory metaplasia	16/50 (32%)	11/50 (22%)	13/50 (26%)	43/50** (86%)
Kidney, males	**0 (0)**	**32.1 (4.73)**	**80.2 (11.8)**	**200.5 (29.55)**
Basophilic change	11/50 (22%)	30/50** (60%)	28/50** (56%)	33/50** (66%)
Cortical mineralization	7/50 (14%)	23/50** (46%)	30/50** (60%)	18/50** (36%)
Kidney, females	**0 (0)**	**32.1 (4.27)**	**80.2 (10.7)**	**200.5 (26.67)**
Basophilic change	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Cortical mineralization	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Values are expressed as number of animals with lesion/number of animals evaluated (% incidence).
*Statistically significantly increased from controls at $p < 0.05$, as reported by the study authors (Fischer's exact test).
**Statistically significantly increased from controls at $p < 0.01$, as reported by the study authors (Fischer's exact test).

ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight.

Table B-35. Selected Neoplastic Lesions in B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 2 Years[a]

Parameter[c]	Exposure Group, ppm (HEC$_{PU}$, mg/m^3)[b]			
	0 (0)	**32.1 (77.2)**	**80.2 (192)**	**200.5 (482.5)**
Males				
Lung:				
Bronchiolo-alveolar adenoma and/or carcinoma	9/50 (18%)	18/50* (36%)	14/50 (28%)	18/50* (36%)
Bronchiolo-alveolar adenoma	5/50 (10%)	14/50* (28%)	9/50 (18%)	12/50 (24%)
Bronchiolo-alveolar carcinoma	4/50 (8%)	6/50 (12%)	6/50 (12%)	8/50 (16%)
Females				
	0 (0)	**32.1 (69.2)**	**80.2 (173)**	**200.5 (432.0)**
Lung:				
Bronchiolo-alveolar adenoma and/or carcinoma	2/50 (4%)†	4/50 (8%)	5/50 (10%)	8/50* (16%)
Bronchiolo-alveolar adenoma	1/50 (2%)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Bronchiolo-alveolar carcinoma	1/50 (2%)†	1/50 (2%)	1/50 (2%)	4/50 (8%)
Males				
	0 (0)	**32.1 (77.2)**	**80.2 (192)**	**200.5 (482.5)**
Harderian gland:				
Adenoma	1/50 (2%)†	2/50 (4%)	3/50 (6%)	6/50 (12%)
Spleen:				
Hemangioma and/or hemangiosarcoma	0/50 (0%)	4/50 (8%)	3/50 (6%)	6/50* (12%)
Hemangioma	0/50 (0%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Hemangiosarcoma	0/50 (0%)	3/50 (6%)	3/50 (6%)	5/50* (10%)
Females				
	0 (0)	**32.1 (69.2)**	**80.2 (173)**	**200.5 (432.0)**
Harderian gland:				
Adenoma	2/50 (4%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Spleen:				
Hemangioma and/or hemangiosarcoma	2/50 (4%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Hemangioma	0/50 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Hemangiosarcoma	2/50 (4%)	0/50 (0%)	0/50 (0%)	0/50 (0%)

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for pulmonary respiratory effects using the following equation: HEC_{PU} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{PU}$. $RGDR_{PU}$ is the pulmonary regional gas dose ratio (animal:human); see Equations 4−28 in U.S. EPA (1994b) for calculation of $RGDR_{PU}$ and default values for variables.
[c]Values are expressed as number of animals with lesion/number of animals evaluated (% incidence).
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Fischer's exact test).
†Statistically significant dose-related trend at $p < 0.05$, as reported by the study authors (Peto's test).

HEC = human equivalent concentration; MW = molecular weight; PU = pulmonary effects.

Table B-36. Estrous Cycle and Ovulation Parameters in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 3 Weeks[a]

Endpoint	Exposure Group, ppm (HEC_{ET}, mg/m^3)[b]			
	0	**50.7 (7.58)**	**99.9 (14.9)**	**200.7 (30.00)**
Number of rats	8	6	6	9
Total number of cycles[c]	36	25	24	36
Number of cycles/rat[d]	4.50 ± 0.76	4.17 ± 1.17 (−7%)	4.00 ± 0.89 (−11%)	3.78 ± 0.44 (−16%)
D/cycle[d]	5.21 ± 0.43	6.04 ± 2.43 (16%)	6.05 ± 1.08 (16%)	5.94 ± 0.56 (14%)
Number of rats with cycles lasting ≥6 d[e]	3/8 (38%)	2/6 (33%)	6/6 (100%)	9/9 (100%)
Number of total cycles lasting ≥6 d[f]	3/36 (8.3%)	3/25 (12%)	13/24** (54%)	17/36** (47%)
Number of ovulated ova/rat[d]	8.83 ± 1.17	7.00 ± 2.45 (−21%)	6.33 ± 2.52 (−28%)	5.75 ± 1.91* (−35%)

[a]Sekiguchi et al. (2002).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) (U.S. EPA, 1994b).
[c]Total number of all estrous cycles observed in each group.
[d]Values are expressed as mean ± SD (percent change compared with control) for 6−9 rats/group; % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[e]Number presented as the number of animals showing at least one estrous cycle lasting ≥6 days/number of animals in each group (% incidence).
[f]Number presented as the number of estrous cycles observed lasting ≥6 days/number of estrous cycles observed in each group (% incidence).
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors (Dunnett's multiple comparison test).
**Statistically significantly different from controls at $p < 0.01$, as reported by the study authors (χ^2 test with Yate's correction for continuity).

ET = extrathoracic respiratory effects; HEC = human equivalent concentration; MW = molecular weight; SD = standard deviation.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE FOR DICHOTOMOUS DATA

The benchmark dose (BMD) modeling of dichotomous data was conducted with EPA's Benchmark Dose Software (BMDS, Version 2.5). For these data, all of the dichotomous models (i.e., Gamma, Multistage, Logistic, Log-Logistic, Probit, Log-Probit, and Weibull) available within the software were fit using a default benchmark response (BMR) of 10% extra risk with the exception of developmental/fetal effects, for which a BMR of 5% extra risk was used [as outlined in the Benchmark Dose Technical Guidance; U.S. EPA (2012c)]. Adequacy of model fit was judged base on the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among all models providing adequate fit, the lowest benchmark dose lower confidence limit/benchmark concentration lower confidence limit (BMDL/BMCL) was selected if the BMDL/BMCL estimates from different models varied >threefold; otherwise, the BMDL/BMCL from the model with the lowest Akaike's information criterion (AIC) was selected as a potential point of departure (POD) from which to derive the reference dose/reference concentration (RfD/RfC).

In addition, 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, 2012c). Because the focus of BMD analysis is on the low-dose regions of the response curve, elimination of the high-dose group is deemed reasonable.

MODELING PROCEDURE FOR CONTINUOUS DATA

The BMD modeling of continuous data was conducted with EPA's BMDS (Version 2.5). For these data, all continuous models available within the software were fit using a default BMR of 1 standard deviation (SD) relative risk unless a biologically determined BMR was available (e.g., BMR 10% relative deviation for body weight based on a biologically significant weight loss of 10%), as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012c). An adequate fit was judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was homogeneous. If a homogeneous variance model was deemed appropriate based on the statistical test provided by BMDS (i.e., Test 2), the final BMD results were estimated from a homogeneous variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model did not adequately fit the data (i.e., Test 3; p-value < 0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL/BMCL was selected if the BMDL/BMCL estimates from different models varied >threefold; otherwise, the BMDL/BMCL from the model with the lowest AIC was selected as a potential POD from which to derive the RfD/RfC.

As described above for dichotomous data, if data did not fit any models due to characteristics of the dose-response data for high doses, modeling was performed with elimination of the high-dose group.

BMD MODELING TO IDENTIFY POTENTIAL PODs FOR THE DERIVATION OF A SUBCHRONIC p-RfD

The following data sets were selected for BMD modeling:

- Litter incidence data for delayed ossification in rat fetuses following maternal administration of 1,2-dichloropropane (1,2-DCP) via gavage from Gestation Days (GDs) 6−15 (Kirk et al., 1995); ***selected as critical endpoint for subchronic p-RfD derivation.***
- Litter incidence data for delayed ossification in rabbit fetuses following maternal administration of 1,2-DCP via gavage from GDs 7−19 (Kirk et al., 1995).
- Continuous data for decreased body weight in male F344 rats administered 1,2-DCP via gavage 5 days/week for 13 weeks (Dow Chemical Co, 1988b).
- Continuous data for increased reticulocytes in pregnant New Zealand white (NZW) rabbits administered 1,2-DCP via gavage from GDs 7−19 (Kirk et al., 1995).

Increased Litter Incidence of Delayed Skull Ossification in Rat Fetuses Exposed to 1,2-DCP on GDs 6−15

The procedure outlined above was applied to the data for increased litter incidence of delayed skull ossification in fetuses from Sprague Dawley (S-D) rat dams administered 1,2-DCP via gavage from GDs 6−15 (Kirk et al., 1995) (see Table C-1). Table C-2 summarizes the BMD modeling results. All models provided adequate fit to the data. BMDLs for models providing adequate fit differed by >threefold, so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{05}$ of 5.6 mg/kg-day from this model is selected for this endpoint (see Figure C-1 and the BMD text output for details).

Table C-1. Litter Incidence of Delayed Skull Ossification in Fetuses from S-D Rat Dams Administered 1,2-Dichloropropane via Gavage on GDs 6–15[a]

	Dose (mg/kg-d)			
	0	**10**	**30**	**125**
Sample size (number of litters)	25	28	28	30
Litter incidence	8	8	10	16

[a]Kirk et al. (1995).

GD = gestation day; S-D = Sprague-Dawley.

Table C-2. BMD Modeling Results for Litter Incidence of Delayed Skull Ossification in Fetuses from S-D Rat Dams Administered 1,2-Dichloropropane via Gavage on GDs 6–15

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{05} (mg/kg-d)	$BMDL_{05}$ (mg/kg-d)
Gamma[b]	1	0.70	148.95	26.10	8.00
Logistic	2	0.92	146.98	20.54	12.81
LogLogistic[c,d]	1	0.71	148.95	25.33	5.63
LogProbit[c]	2	0.91	146.98	37.64	21.13
Multistage (1-degree)[e]	2	0.90	147.01	15.69	7.96
Multistage (2-degree)[e]	1	0.68	148.97	24.76	7.99
Multistage (3-degree)[d,e]	1	0.68	148.97	24.76	7.99
Probit	2	0.92	146.98	20.12	12.52
Weibull[b]	1	0.70	148.95	25.74	8.00

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

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 BMR: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degrees of freedom; GD = gestation day; S-D = Sprague-Dawley.

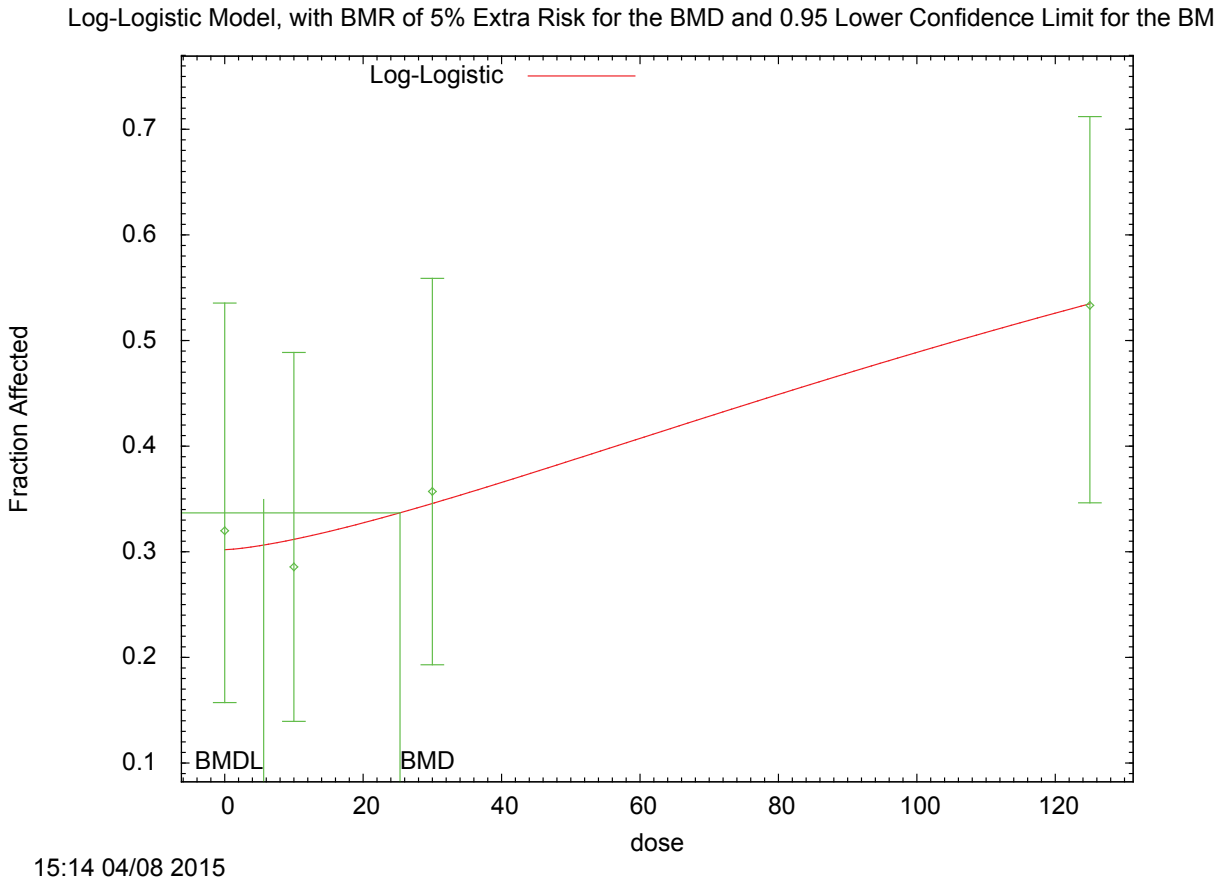

Figure C-1. LogLogistic Model for Litter Incidence of Delayed Skull Ossification in Fetuses from S-D Rat Dams Administered 1,2-Dichloropropane via Gavage on GDs 6−15 (Kirk et al., 1995)

Text Output for LogLogistic Model for Litter Incidence of Delayed Skull Ossification in Fetuses from S-D Rat Dams Administered 1,2-Dichloropropane via Gavage on GDs 6−15 (Kirk et al., 1995)

```
 ================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/BMDS250_2014/Data/12-DCP/lnl_DelaySkullOss_Lnl-BMR05-Restrict.(d)
        Gnuplot Plotting File:
C:/BMDS250_2014/Data/12-DCP/lnl_DelaySkullOss_Lnl-BMR05-Restrict.plt
                                          Wed Apr 08 15:14:30 2015
 ================================================================
 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

```
   Total number of observations = 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
   User has chosen the log transformed model

                Default Initial Parameter Values
                   background =         0.32
                    intercept =     -7.11782
                        slope =      1.29855

          Asymptotic Correlation Matrix of Parameter Estimates

            background    intercept        slope

background            1        -0.64         0.61

 intercept        -0.64            1           -1

     slope         0.61           -1            1

                              Parameter Estimates

                                                      95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background         0.301998            *                 *                   *
      intercept          -7.5024            *                 *                   *
          slope          1.41029            *                 *                   *

* - Indicates that this value is not calculated.

                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -71.4002         4
   Fitted model        -71.4723         3      0.144302      1           0.704
  Reduced model        -73.6224         1       4.44442      3          0.2173

           AIC:         148.945

                                  Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.3020         7.550     8.000          25        0.196
   10.0000     0.3118         8.729     8.000          28       -0.298
   30.0000     0.3457         9.680    10.000          28        0.127
  125.0000     0.5347        16.040    16.000          30       -0.015

 Chi^2 = 0.14      d.f. = 1        P-value = 0.7050

   Benchmark Dose Computation

Specified effect =           0.05

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        25.3282
```

```
BMDL =         5.62668
```

Increased Litter Incidence of Delayed Skull Ossification in Rabbit Fetuses Exposed to 1,2-Dichloropropane on GDs 7−19

The procedure outlined above was applied to the data for increased litter incidence of delayed skull ossification in fetuses from NZW rabbit does administered 1,2-DCP via gavage from GDs 7−19 (Kirk et al., 1995) (see Table C-3). Table C-4 summarizes the BMD modeling results. All models provided adequate fit to the data. BMDLs for models providing adequate fit differed by >threefold, so the model with the lowest BMDL was selected (LogLogistic). Thus, the $BMDL_{05}$ of 10 mg/kg-day from this model is selected for this endpoint (see Figure C-2 and the BMD text output for details).

Table C-3. Litter Incidence of Delayed Skull Ossification in Fetuses from NZW Rabbit Does Administered 1,2-Dichloropropane via Gavage on GDs 7−19[a]

	Dose (mg/kg-d)			
	0	**15**	**50**	**150**
Sample size (number of litters)	18	16	17	15
Litter Incidence	0	0	2	6

[a]Kirk et al. (1995).

GD = gestation day; NZW = New Zealand white.

Table C-4. BMD Modeling Results for Litter Incidence of Delayed Skull Ossification in Fetuses from NZW Rabbit Does Administered 1,2-Dichloropropane via Gavage on GDs 7−19

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{05} (mg/kg-d)	$BMDL_{05}$ (mg/kg-d)
Gamma[b]	2	0.84	37.04	34.58	11.75
Logistic	2	0.39	38.86	56.17	35.26
LogLogistic[c,d]	2	0.85	37.02	34.10	10.45
LogProbit[c]	3	0.98	34.81	35.57	23.83
Multistage (1-degree)[e]	3	0.82	36.08	18.00	10.55
Multistage (2-degree)[e]	2	0.77	37.28	34.26	11.43
Multistage (3-degree)[e]	2	0.77	37.28	34.26	11.43
Probit	2	0.45	38.48	50.97	31.92
Weibull[b]	2	0.82	37.11	33.76	11.64

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

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 BMR: i.e., $_{05}$ = dose associated with 5% extra risk); DF = degrees of freedom; GD = gestation day; NZW = New Zealand white.

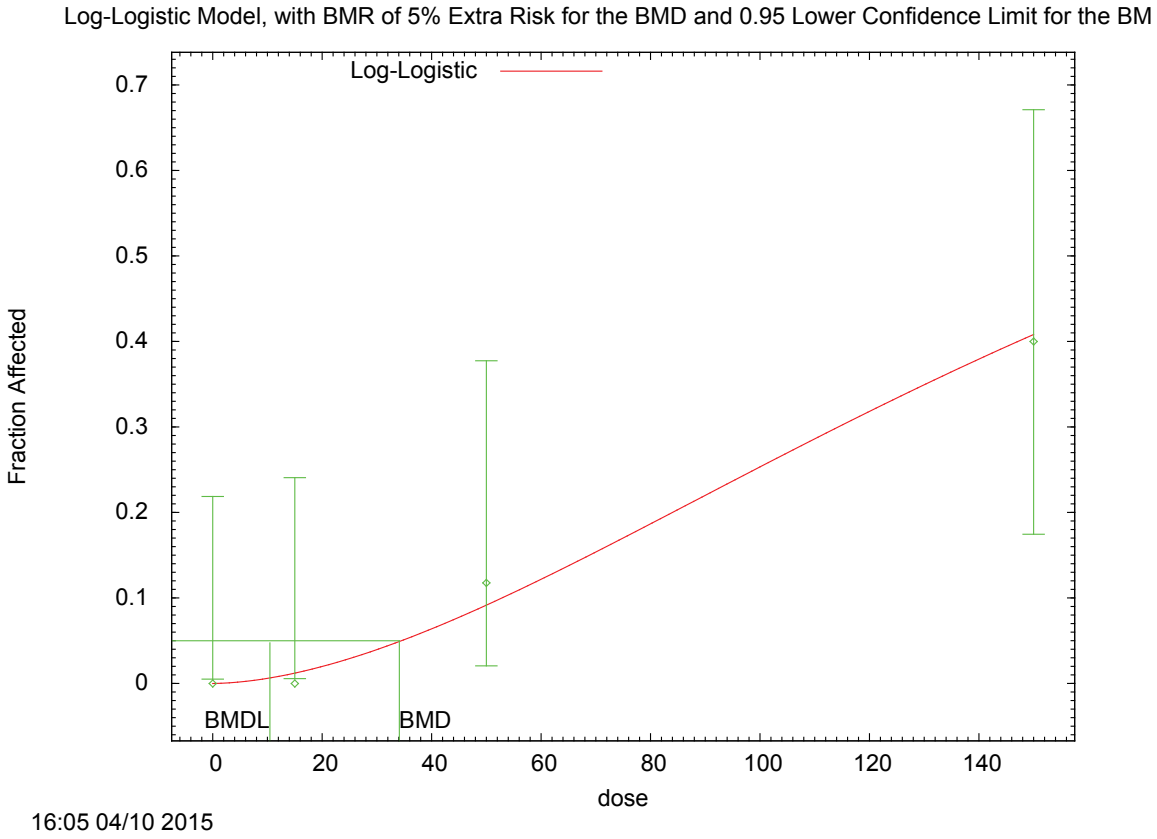

Figure C-2. LogLogistic Model for Litter Incidence of Delayed Skull Ossification in Fetuses from NZW Rabbit Does Administered 1,2-Dichloropropane via Gavage on GDs 7−19 (Kirk et al., 1995)

Text Output for LogLogistic Model for Litter Incidence of Delayed Skull Ossification in Fetuses from NZW Rabbit Does Administered 1,2-Dichloropropane via Gavage on GDs 7−19 (Kirk et al., 1995)

```
 ================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/BMDS250_2014/Data/12-DCP/Kirk1995_rabbit/lnl_skulloss_Lnl-BMR05-Restrict.(d)
        Gnuplot Plotting File:
C:/BMDS250_2014/Data/12-DCP/Kirk1995_rabbit/lnl_skulloss_Lnl-BMR05-Restrict.plt
                                          Fri Apr 10 16:05:12 2015
 ================================================================
 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 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

   User has chosen the log transformed model
                 Default Initial Parameter Values
                    background =           0
                     intercept =     -7.16982
                         slope =      1.34064

           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 )

              intercept        slope

 intercept            1        -0.99

     slope        -0.99            1

                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0            *                *                   *
      intercept         -9.13596            *                *                   *
          slope          1.75429            *                *                   *

* - Indicates that this value is not calculated.

                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -16.2528         4
   Fitted model        -16.5124         2      0.519275      2          0.7713
  Reduced model         -24.376         1       16.2465      3        0.001009

           AIC:         37.0248

                                  Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          18        0.000
   15.0000     0.0123         0.197     0.000          16       -0.446
   50.0000     0.0934         1.587     2.000          17        0.344
  150.0000     0.4144         6.216     6.000          15       -0.113

 Chi^2 = 0.33      d.f. = 2        P-value = 0.8477


   Benchmark Dose Computation
```

```
Specified effect =           0.05

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        34.1023
            BMDL =        10.4498
```

Decreased Body Weight in Male Rats Exposed to 1,2-Dichloropropane via Gavage for 13 Weeks

The procedure outlined above was applied to the data for decreased body weight in male F344 rats exposed to 1,2-DCP via gavage 5 days/week for 13 weeks (Dow Chemical Co, 1988b) (see Table C-7). Table C-8 summarizes the BMD modeling results. Neither the constant nor the nonconstant variance models provide adequate fit to the variance data using the full data set.

Table C-7. Body Weight in Male F344 Rats Exposed to 1,2-Dichloropropane via Gavage 5 Days/Week for 13 Weeks[a]

	Dose (mg/kg-d)[b]			
	0	**14**	**46**	**143**
Sample size	15	15	15	15
Mean (g)	341.7	334.9	331	308
SD (g)	11.2	13.7	25.7	14.8

[a]Dow Chemical Co (1988b).
[b]Gavage doses were converted to ADDs by multiplying the administered gavage dose by (5/7) days/week.

ADD = adjusted daily dose; SD = standard deviation.

Table C-8. BMD Modeling Results for Body Weight in F344 Rats Exposed to 1,2-Dichloropropane via Gavage 5 Days/Week for 13 Weeks

Model	Test for Significant Difference *p*-Value[a]	Variance *p*-Value[b]	Means *p*-Value[b]	AIC	BMD_{10} (mg/kg-d, ADD)	$BMDL_{10}$ (mg/kg-d, ADD)
Exponential (Model 2)[d]	<0.0001	0.001889	0.5859	406.7058	−136.516	NA
Exponential (Model 3)[d]	<0.0001	0.001889	0.5859	433.0087	−136.516	NA
Exponential (Model 4)[d]	<0.0001	0.001889	<0.0001	409.276593	NA	NA
Exponential (Model 5)[d]	<0.0001	0.001889	NA	431.008749	NA	NA
Hill[d]	<0.0001	0.001889	NA	431.008749	NA	NA
Linear[c]	<0.0001	0.001889	<0.0001	406.049023	−9,999	1,528.76
Polynomial (2-degree)[c]	<0.0001	0.001889	<0.0001	406.7058	−9,999	491.02
Polynomial (3-degree)[c]	<0.0001	0.001889	<0.0001	406.7058	−9,999	329.09
Power[d]	<0.0001	0.001889	0.8137	433.0087	150.976	117.157

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be negative.
[d]Power restricted to ≥1.

ADD = adjusted daily dose; AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure dose associated with 10% extra risk); NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested).

Increased Reticulocytes in Pregnant Rabbits Exposed to 1,2-Dichloropropane via Gavage on GDs 7−19

The procedure outlined above was applied to the data for increased reticulocytes in pregnant NZW rabbits administered 1,2-DCP via gavage on GDs 7−19 (Kirk et al., 1995) (see Table C-9). Table C-10 summarizes the BMD modeling results. Constant variance model did not fit the variance data, but nonconstant variance model did. With nonconstant variance model applied, all models except for Exponential Models 4 and 5 and the Hill Model provided adequate fit to means. BMDLs for models providing adequate fit were sufficiently close (differed by <threefold), so the model with the lowest AIC was selected (Exponential Model 2). Thus, the $BMDL_{1SD}$ of 30 mg/kg-day from this model is selected for this endpoint (see Figure C-5 and the BMD text output for details).

Table C-9. Reticulocytes in Pregnant NZW Rabbits Administered 1,2-Dichloropropane via Gavage on GDs 7−19[a]

	Dose (mg/kg-d)			
	0	**15**	**50**	**150**
Sample size	18	16	17	15
Mean (%)	3.2	3.6	3.8	6.7
SD (%)	0.6	0.7	0.9	1.7

[a]Kirk et al. (1995).

GD = gestation day; NZW = New Zealand white; SD = standard deviation.

Table C-10. BMD Modeling Results for Reticulocytes in Pregnant NZW Rabbits Administered 1,2-Dichloropropane via Gavage on GDs 7−19

Model	Test for Significant Difference *p*-Value[a]	Variance *p*-Value[b]	Means *p*-Value[b]	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Constant Variance						
Linear[c]	<0.0001	<0.0001	0.13	77.01	44.72	36.79
Nonconstant Variance						
Exponential (Model 2)[d,e]	<0.0001	0.73	0.35	55.14	37.17	29.92
Exponential (Model 3)[d]	<0.0001	0.73	0.19	56.75	47.26	30.40
Exponential (Model 4)[d]	<0.0001	0.73	0.04	59.30	28.90	22.02
Exponential (Model 5)[d]	<0.0001	0.73	NA	59.18	50.04	25.39
Hill[d]	<0.0001	0.73	NA	59.18	50.06	NA
Linear[c]	<0.0001	0.73	0.12	57.30	28.90	22.02
Polynomial (2-degree)[c]	<0.0001	0.73	0.21	56.63	47.95	26.81
Polynomial (3-degree)[c]	<0.0001	0.73	0.28	56.22	48.93	27.45
Power[d]	<0.0001	0.73	0.14	57.18	50.04	25.39

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Coefficients restricted to be positive.
[d]Power restricted to ≥1.
[e]Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure dose associated with 10% extra risk); GD = gestation day; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); NZW = New Zealand white; SD = standard deviation.

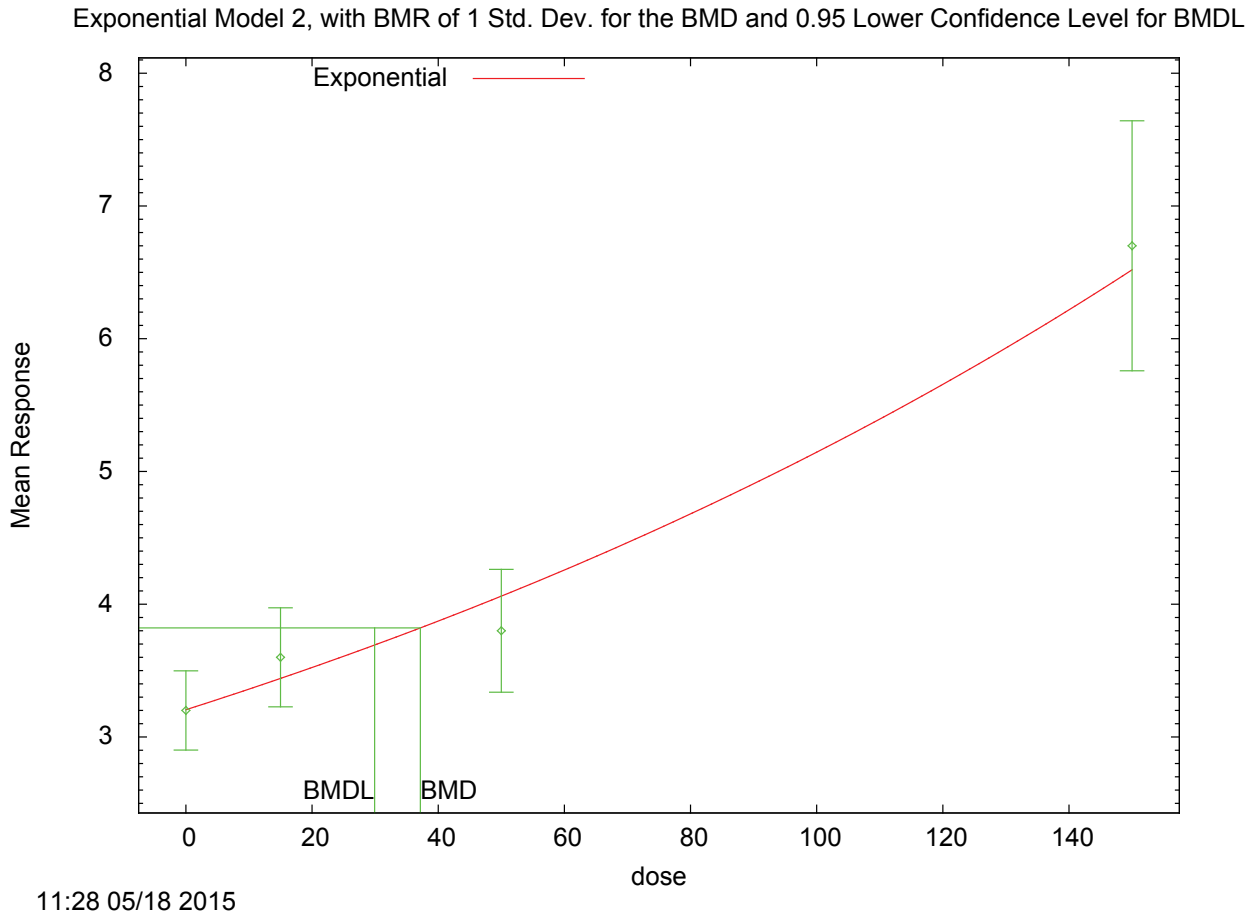

Figure C-5. Exponential 2 Model for Percent Reticulocytes in Pregnant NZW Rabbits Administered 1,2-Dichloropropane via Gavage on GDs 7−19 (Kirk et al., 1995)

Text Output for Exponential 2 Model for Percent Reticulocytes in Pregnant NZW Rabbits Administered 1,2-Dichloropropane via Gavage on GDs 7−19 (Kirk et al., 1995)

```
================================================================
        Exponential Model. (Version: 1.9;  Date: 01/29/2013)
        Input Data File:
C:/BMDS250_2014/Data/12-DCP/Kirk1995_rabbit/exp_reticulocyte_Exp-ModelVariance-BMR1Std
-Up.(d)
        Gnuplot Plotting File:
                                                Mon May 18 11:28:21 2015
 ================================================================
 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 = 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

MLE solution provided: Exact

              Initial Parameter Values

              Variable          Model 2
              --------          --------
                lnalpha           -4.11723
                    rho            2.74317
                      a            3.19097
                      b          0.00481343
                      c                   0
                      d                   1

                 Parameter Estimates

               Variable          Model 2
               --------          -------
                lnalpha          -4.28274
                    rho           2.84625
                      a           3.20531
                      b        0.00473261
                      c                 0
                      d                 1

         Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
      0     18          3.2          0.6
     15     16          3.6          0.7
     50     17          3.8          0.9
    150     15          6.7          1.7

             Estimated Values of Interest

   Dose      Est Mean      Est Std     Scaled Residual
 ------    ----------    ---------    ----------------
      0         3.205       0.6165         -0.03653
     15         3.441        0.682           0.9318
     50         4.061       0.8633           -1.247
    150         6.519        1.693           0.4144

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	-33.44203	5	76.88405
A2	-22.20314	8	60.40629
A3	-22.51772	6	57.03545
R	-67.36346	2	138.7269
2	-23.5711	4	55.14221

Additive constant for all log-likelihoods = -60.65. 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	90.32	6	<0.0001
Test 2	22.48	3	<0.0001
Test 3	0.6292	2	0.7301
Test 4	2.107	2	0.3488

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 = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 37.1709
BMDL = 29.9179

BMD MODELING TO IDENTIFY POTENTIAL PODs FOR THE DERIVATION OF A CHRONIC p-RfD

The following data sets were selected for BMD modeling:

- Litter incidence data for delayed ossification in rat fetuses following maternal administration of 1,2-DCP via gavage on GDs 6−15 (Kirk et al., 1995); ***selected as critical endpoint for chronic p-RfD derivation.***
- Litter incidence data for delayed ossification in rabbit fetuses following maternal administration of 1,2-DCP via gavage on GDs 7−19 (Kirk et al., 1995).
- Incidence data for increased hepatocytomegaly in male B6C3F$_1$ mice administered 1,2-DCP via gavage for 103 weeks (NTP, 1986).

Increased Litter Incidence of Delayed Skull Ossification in Rat Fetuses Exposed to 1,2-Dichloropropane on GDs 6−15

See BMD modeling results in the subchronic section above (Tables C-1−C-2, Figure C-1, and associated BMD output text).

Increased Litter Incidence of Delayed Skull Ossification in Rabbit Fetuses Exposed to 1,2-Dichloropropane on GDs 7−19

See BMD modeling results in the subchronic section above (Tables C-3−C-4, Figure C-2, and associated BMD output text).

Increased Incidence of Hepatocytomegaly in Male Mice Exposed to 1,2-Dichloropropane via Gavage for 103 Weeks

The procedure outlined above was applied to the data for increased incidence of hepatocytomegaly in male B6C3F$_1$ mice administered 1,2-DCP via gavage 5 days/week for 103 weeks (NTP, 1986) (see Table C-13). Table C-14 summarizes the BMD modeling results. The Logistic, Multistage 1-degree, and Probit models provided adequate fit to the data. The BMDLs for models providing adequate fit are sufficiently close (differed by <threefold), so the model with the lowest AIC was selected (Multistage 1-degree). Thus, the BMDL$_{10}$ of 58.5 mg/kg-day from this model is selected for this endpoint (see Figure C-6 and the BMD text output for details).

Table C-13. Incidence of Hepatocytomegaly in Male B6C3F$_1$ Mice Administered 1,2-Dichloropropane via Gavage for 103 Weeks[a]

	Dose (mg/kg-d)[b]		
	0	**89.3**	**179**
Sample size	50	49	50
Incidence	3	5	15

[a]NTP (1986)
[b]Gavage doses were converted to ADDs by multiplying the administered gavage dose by (5/7) days/week.

ADD = adjusted daily dose.

Table C-14. BMD Output Data for Incidence of Hepatocytomegaly in Male B6C3F$_1$ Mice Administered 1,2-Dichloropropane via Gavage for 103 Weeks

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0	NA	122.079	119.845	60.1885
Logistic	1	0.5145	120.508	102.606	82.2716
LogLogistic[c]	0	NA	122.079	120.637	59.3308
LogProbit[c]	0	NA	122.079	117.866	76.9345
Multistage (1-degree)[d,e]	1	0.654	120.285	108.35	58.46
Multistage (2-degree)[d]	1	NA	122.079	123.197	60.1885
Probit	1	0.4379	120.694	97.8117	77.136
Weibull[b]	0	NA	122.079	121.783	60.1885

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]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 BMR: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degrees of freedom; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested).

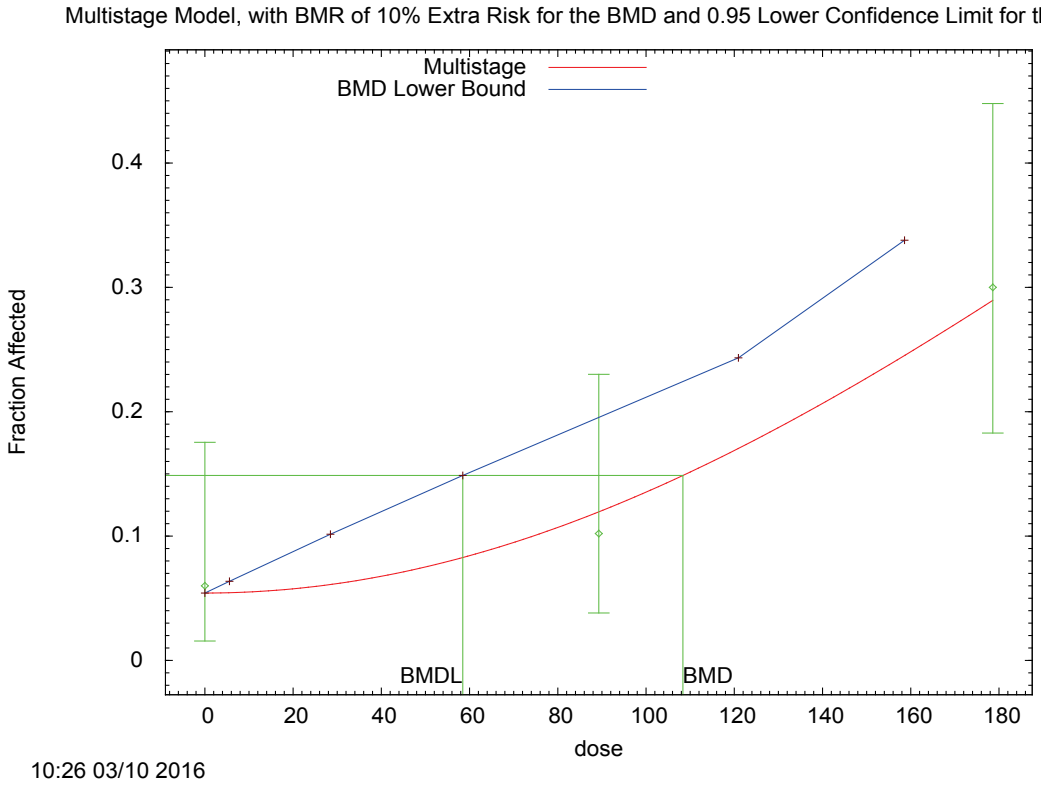

Figure C-6. Multistage (2-degree) Model for Incidence of Hepatocytomegaly in Male B6C3F$_1$ Mice Administered 1,2-Dichloropropane via Gavage for 103 Weeks (NTP, 1986)

Text Output for Multistage (2-degree) Model for Incidence of Hepatocytomegaly in Male B6C3F$_1$ Mice Administered 1,2-Dichloropropane via Gavage for 103 Weeks (NTP, 1986)

```
=================================================================
        Multistage Model. (Version: 3.3;  Date: 02/28/2013)
        Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/mst_hepatcyt_MM_ntp86_Mst2-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/mst_hepatcyt_MM_ntp86_Mst2-BMR10-Restrict.plt
                                          Tue Mar 15 13:59:05 2016
 =================================================================

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

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 3
```

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

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0.0478073
Beta(1) = 0
Beta(2) = 9.51136e-006

Asymptotic Correlation Matrix of Parameter Estimates

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

	Background	Beta(2)
Background	1	-0.66
Beta(2)	-0.66	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0541837	*	*	*
Beta(1)	0	*	*	*
Beta(2)	8.97479e-006	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-58.0393	3			
Fitted model	-58.1423	2	0.206101	1	0.6498
Reduced model	-64.1001	1	12.1217	2	0.002332

AIC: 120.285

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0542	2.709	3.000	50	0.182
89.2860	0.1195	5.855	5.000	49	-0.377
178.6000	0.2896	14.482	15.000	50	0.161

```
 Chi^2 = 0.20      d.f. = 1        P-value = 0.6540


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         108.35

            BMDL =          58.46

            BMDU =        152.691

Taken together, (58.46  , 152.691) is a 90     % two-sided confidence
interval for the BMD
```

BMC MODELING TO IDENTIFY POTENTIAL PODs FOR THE DERIVATION OF A SUBCHRONIC p-RfC

The following data sets were selected for BMD modeling:

- Incidence data for nasal cavity lesions in male and female F344/DuCrj (SPF) rats exposed to 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 13 weeks (Dow Chemical Co, 1988a); ***female POD selected as critical endpoint for subchronic p-RfC derivation.***
- Incidence data for nasal cavity lesions in male and female B6D2F$_1$/Crlj (SPF) mice exposed to 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 13 weeks (Matsumoto et al., 2013).

Increased Incidence of Nasal Cavity Lesions in Male Rats Exposed to 1,2-Dichloropropane via inhalation for 13 Weeks

The procedure outlined above was applied to the data for increased incidence of nasal respiratory epithelium hyperplasia in male F344/DuCrj (SPF) rats administered 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 13 weeks (Dow Chemical Co, 1988a) (see Table C-15). Table C-16 summarizes the BMC modeling results. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >threefold), so the model with the lowest BMCL was selected (LogLogistic). Thus, the BMCL$_{10}$ (HEC) of 0.26 mg/m^3 from this model is selected for this endpoint (see Figure C-7 and the BMC text output for details).

Table C-15. Incidence of Nasal Respiratory Epithelium Hyperplasia in Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks[a]

	HEC (mg/m^3)[b]			
	0	**1.6**	**5.4**	**16.5**
Sample size	10	9	10	10
Incidence	0	2	5	9

[a]Dow Chemical Co (1988a).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

HEC = human equivalent concentration; MW = molecular weight.

Table C-16. BMC Modeling Results for Nasal Respiratory Epithelium Hyperplasia in Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3, HEC_{ET})	$BMCL_{10}$ (mg/m^3, HEC_{ET})
Gamma[b]	3	0.9962	31.9576	0.766618	0.492999
Logistic	2	0.3154	37.286	2.30795	1.44566
LogLogistic[c,d]	2	0.8374	34.2581	0.961257	0.262207
LogProbit[c]	3	0.9016	32.4352	1.25292	0.803737
Multistage (2-degree)[e]	2	0.9712	33.9564	0.774685	0.493044
Multistage (3-degree)[e]	2	0.3129	37.2675	2.27866	1.50938
Probit	2	0.9962	31.9576	0.766618	0.492999
Weibull[b]	3	0.9962	31.9576	0.766618	0.492999

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Selected model.
[e]Betas restricted to ≥0.

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); DF = degrees of freedom; ET = extrathoracic respiratory effects; HEC = human equivalent concentration.

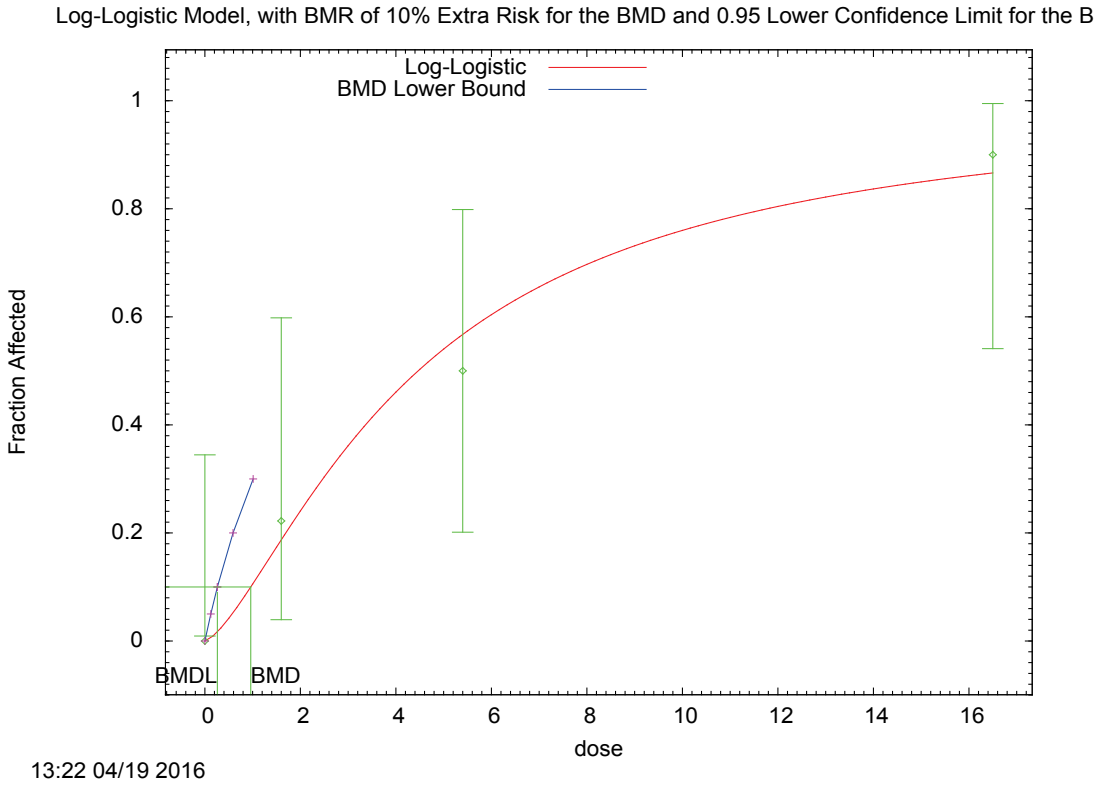

Figure C-7. LogLogistic Model for Incidence of Nasal Respiratory Epithelium Hyperplasia in Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks (Dow Chemical Co, 1988a)

Text Output for LogLogistic Model for Incidence of Nasal Respiratory Epithelium Hyperplasia in Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks (Dow Chemical Co, 1988a)

```
================================================================
         Logistic Model. (Version: 2.14; Date: 2/28/2013)
         Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/lnl_nose_MR_DCC88a_Lnl-BMR10-Restrict.(d)
         Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/lnl_nose_MR_DCC88a_Lnl-BMR10-Restrict.plt
                                          Tue Apr 19 13:27:34 2016
 ================================================================

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

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

Total number of observations = 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

User has chosen the log transformed model

Default Initial Parameter Values
background = 0
intercept = -2.11862
slope = 1.47191

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)

	intercept	slope
intercept	1	-0.89
slope	-0.89	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	*	*	*
intercept	-2.14082	*	*	*
slope	1.42761	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-14.9497	4			
Fitted model	-15.129	2	0.358749	2	0.8358
Reduced model	-26.4011	1	22.9029	3	<.0001

AIC: 34.2581

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	10	0.000
1.6000	0.1870	1.683	2.000	9	0.271
5.4000	0.5663	5.663	5.000	10	-0.423
16.5000	0.8654	8.654	9.000	10	0.320

```
 Chi^2 = 0.35      d.f. = 2        P-value = 0.8374


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.961257

            BMDL =       0.262207
```

Increased Incidence of Nasal Cavity Lesions in Female Rats Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks

The procedure outlined above was applied to the data for increased incidence of nasal respiratory epithelium hyperplasia in female F344/DuCrj (SPF) rats administered 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 13 weeks (Dow Chemical Co, 1988a) (see Table C-17). Table C-18 summarizes the BMC modeling results. All models except the Logistic and Probit models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >threefold), so the model with the lowest BMCL was selected (LogLogistic). Thus, the $BMCL_{10}$ (HEC) of 0.12 mg/m^3 from this model is selected for this endpoint (see Figure C-8 and the BMC text output for details).

Table C-17. Incidence of Nasal Respiratory Epithelium Hyperplasia in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks[a]

	HEC (mg/m^3)[b]			
	0	**1.2**	**4.0**	**12.1**
Sample size	10	10	10	10
Incidence	0	3	7	9

[a]Dow Chemical Co (1988a).

[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

HEC = human equivalent concentration; MW = molecular weight.

Table C-18. BMC Modeling Results for Nasal Respiratory Epithelium Hyperplasia in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks

Model[b]	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3, HEC_{ET})	BMC_{10} (mg/m^3, HEC_{ET})
Gamma[c]	3	0.8383	33.6682	0.424155	0.277086
Logistic	2	0.0836	41.1432	1.22889	0.773713
LogLogistic[d,e]	2	0.9934	34.9494	0.428241	0.117119
LogProbit[d]	3	0.893	33.455	0.665604	0.426139
Multistage (2-degree)[f]	3	0.8383	33.6682	0.424155	0.277086
Multistage (3-degree)[f]	3	0.8383	33.6682	0.424155	0.277086
Probit	2	0.0809	41.5273	1.29404	0.871488
Weibull[c]	3	0.8383	33.6682	0.424155	0.277086

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals for dose group above and below the BMC.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model.
[f]Betas restricted to ≥0.

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); DF = degrees of freedom; ET = extrathoracic respiratory effects; HEC = human equivalent concentration.

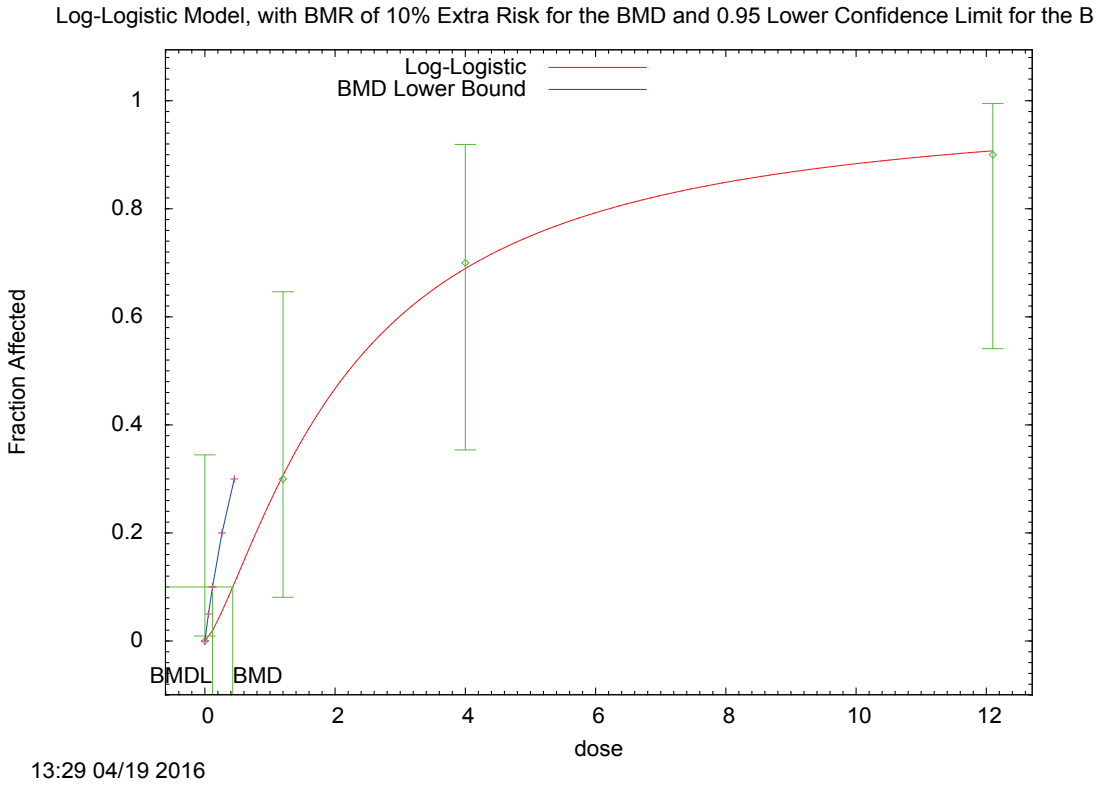

Figure C-8. LogLogistic Model for Incidence of Nasal Respiratory Epithelium Hyperplasia in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks (Dow Chemical Co, 1988a)

Text Output for LogLogistic Model for Incidence of Nasal Respiratory Epithelium Hyperplasia in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks (Dow Chemical Co, 1988a)

```
================================================================================
         Logistic Model. (Version: 2.14; Date: 2/28/2013)
         Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/lnl_nose_FR_DCC88a_Lnl-BMR10-Restrict.(d)
         Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/lnl_nose_FR_DCC88a_Lnl-BMR10-Restrict.plt
                                                Tue Apr 19 13:29:25 2016
 ================================================================================

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

   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1
```

Total number of observations = 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

User has chosen the log transformed model

Default Initial Parameter Values
background = 0
intercept = -1.05315
slope = 1.31878

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)

	intercept	slope
intercept	1	-0.79
slope	-0.79	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	*	*	*
intercept	-1.06342	*	*	*
slope	1.33692	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-15.4681	4			
Fitted model	-15.4747	2	0.013218	2	0.9934
Reduced model	-27.6759	1	24.4155	3	<.0001

AIC: 34.9494

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	10	0.000
1.2000	0.3058	3.058	3.000	10	-0.040
4.0000	0.6878	6.878	7.000	10	0.083
12.1000	0.9063	9.063	9.000	10	-0.069

```
 Chi^2 = 0.01      d.f. = 2        P-value = 0.9934


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.428241

            BMDL =       0.117119
```

Increased Incidence of Nasal Atrophy in Male Mice Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks

The procedure outlined above was applied to the data for increased incidence of nasal respiratory epithelium hyperplasia in male B6D2F$_1$/Crlj (SPF) mice administered 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 13 weeks (Matsumoto et al., 2013) (see Table C-19). Table C-20 summarizes the BMC modeling results. Only the multistage (2-degree) model fit the data. Thus, the BMCL$_{10}$ (HEC) of 11.6 mg/m^3 from this model is selected for this endpoint (see Figure C-9 and the BMC text output for details).

Table C-19. Incidence of Nasal Atrophy in Male B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks[a]

	HEC (mg/m^3)[b]					
	0	**6.21**	**12.43**	**24.83**	**37.27**	**49.66**
Sample size	10	10	10	10	10	10
Incidence	0	0	0	0	7	4

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

HEC = human equivalent concentration; MW = molecular weight.

Table C-20. BMC Modeling Results for Nasal Atrophy in Male B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks

Model[b]	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3, HEC_{ET})	BMC_{10} (mg/m^3, HEC_{ET})
Gamma[c]	4	0.0739	39.0073	24.0954	14.2339
Logistic	4	0.0254	41.5701	24.9982	17.7041
LogLogistic[d]	4	0.0803	38.9623	23.6942	14.1415
LogProbit[d]	4	0.0922	38.4711	24.3111	14.802
Multistage (2-degree)[e,f]	5	0.1141	38.4902	18.542	11.6023
Multistage (3-degree)[f]	5	0.0888	37.9183	23.9897	12.8322
Probit	4	0.0348	40.6044	24.896	17.1826
Weibull[c]	4	0.0571	39.8494	22.7104	12.7051

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals for dose group above and below the BMC.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model.
[f]Betas restricted to ≥0.

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); DF = degrees of freedom; ET = extrathoracic respiratory effects; HEC = human equivalent concentration.

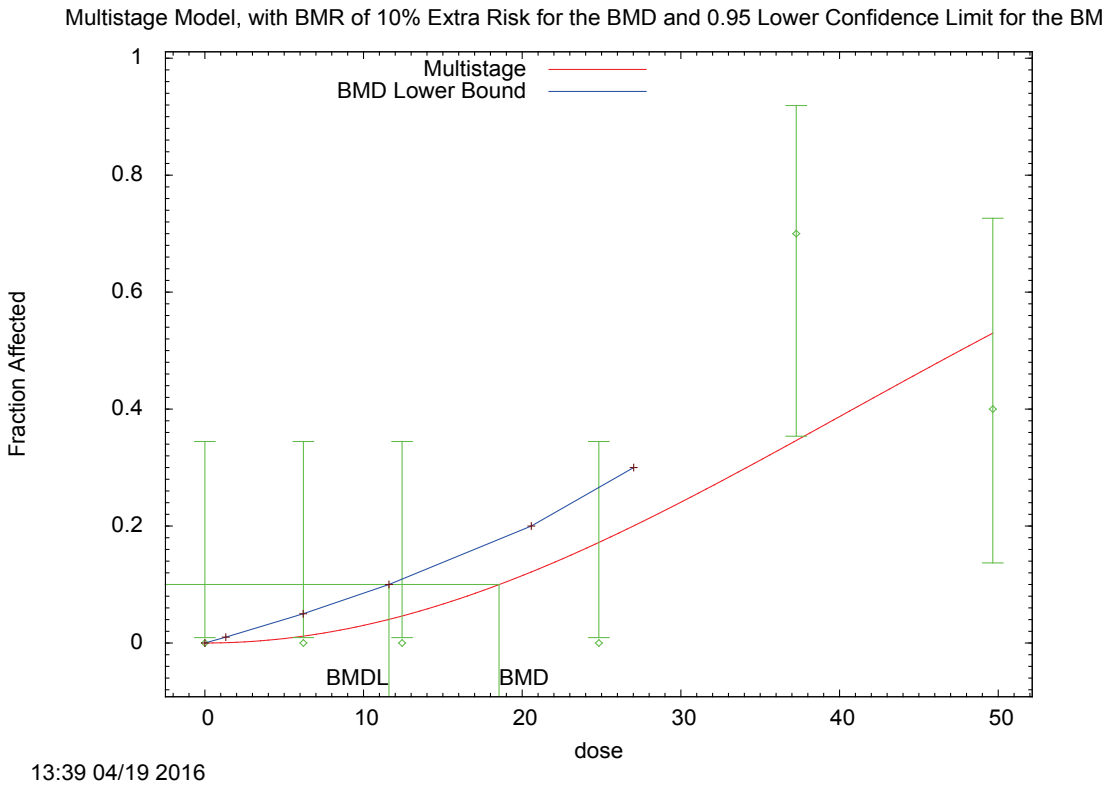

Figure C-9. Multistage (2-degree) Model for Incidence of Nasal Atrophy in Male B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks (Matsumoto et al., 2013)

Text Output for Multistage (2-degree) Model for Incidence of Nasal Atrophy in Male B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks (Matsumoto et al., 2013)

```
=================================================================
        Multistage Model. (Version: 3.3;  Date: 02/28/2013)
        Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/mst_nose_MM_Matsu_sc_Mst2-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/mst_nose_MM_Matsu_sc_Mst2-BMR10-Restrict.plt
                                          Tue Apr 19 13:39:56 2016
 =================================================================

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

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
```

```
   Independent variable = Dose

 Total number of observations = 6
 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) =    0.0180099
                        Beta(2) =            0


           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            *                *                   *
        Beta(1)                0            *                *                   *
        Beta(2)      0.000306454            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -12.8388         6
   Fitted model        -18.2451         1       10.8127      5         0.05522
  Reduced model        -28.5846         1       31.4917      5         <.0001

           AIC:         38.4902


                                Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
   0.0000     0.0000         0.000     0.000          10        0.000
   6.2100     0.0117         0.117     0.000          10       -0.345
```

```
   12.4300     0.0462          0.462     0.000          10       -0.696
   24.8300     0.1722          1.722     0.000          10       -1.442
   37.2700     0.3467          3.467     7.000          10        2.348
   49.6600     0.5303          5.303     4.000          10       -0.826

 Chi^2 = 8.88      d.f. = 5        P-value = 0.1141


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         18.542

            BMDL =        11.6023

            BMDU =        24.3641

Taken together, (11.6023, 24.3641) is a 90     % two-sided confidence
interval for the BMD
```

Increased Incidence of Nasal Atrophy in Female Mice Exposed to 1,2-Dichloropropane via Inhalation for 13 Weeks

The procedure outlined above was applied to the data for increased incidence of nasal respiratory epithelium hyperplasia in female B6D2F$_1$/Crlj (SPF) mice administered 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 13 weeks (Matsumoto et al., 2013) (see Table C-21). Table C-22 summarizes the BMC modeling results. All models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <threefold), so the model with the lowest AIC was selected (Gamma). Thus, the BMCL$_{10}$ (HEC) of 17.1 mg/m^3 from this model is selected for this endpoint (see Figure C-10 and the BMC text output for details).

Table C-21. Incidence of Nasal Atrophy in Female B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks[a]

	HEC (mg/m^3)[b]					
	0	**5.14**	**10.29**	**20.55**	**30.86**	**41.11**
Sample size	10	10	10	10	10	10
Incidence	0	0	0	0	7	9

[a]Matsumoto et al. (2013).

[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

HEC = human equivalent concentration; MW = molecular weight.

Table C-22. BMC Modeling Results for Nasal Atrophy in Female B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks

Model[b]	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3, HEC_{ET})	BMC_{10} (mg/m^3, HEC_{ET})
Gamma[c,e]	5	0.9019	23.0732	21.4307	17.0653
Logistic	4	0.6171	25.5692	22.529	16.7963
LogLogistic[d]	4	0.8421	24.3627	23.0514	17.8769
LogProbit[d]	4	0.8356	24.408	22.9217	17.9987
Multistage (2-degree)[f]	5	0.1934	32.2902	11.134	8.33021
Multistage (3-degree)[f]	5	0.5497	27.2424	15.4578	12.0465
Probit	4	0.6303	25.697	22.2822	16.3196
Weibull[c]	4	0.5734	26.541	20.8038	15.0447

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals for dose group above and below the BMC.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model.
[f]Betas restricted to ≥0.

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); DF = degrees of freedom; ET = extrathoracic respiratory effects; HEC = human equivalent concentration.

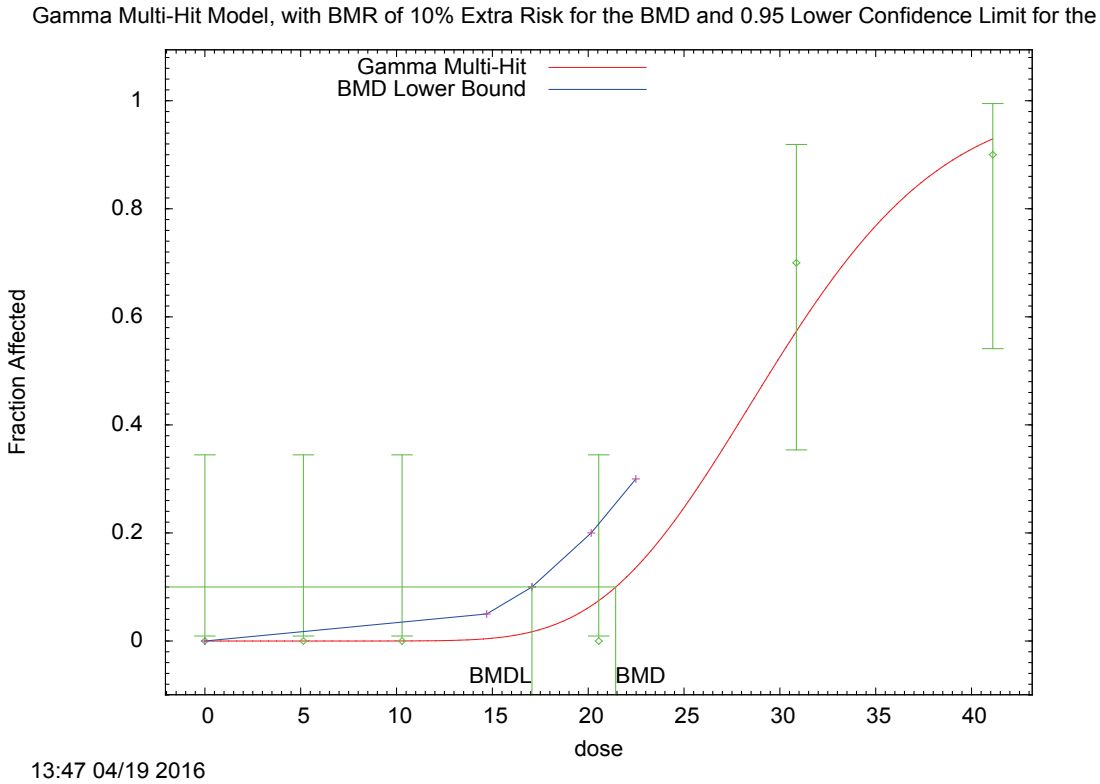

Figure C-10. Gamma Model for Incidence of Nasal Atrophy in Female B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks (Matsumoto et al., 2013)

Text Output for Gamma Model for Incidence of Nasal Atrophy in Female B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 13 Weeks (Matsumoto et al., 2013)

```
================================================================================
        Gamma Model. (Version: 2.16;  Date: 2/28/2013)
        Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/gam_nose_FM_Matsu_sc_Gam-BMR10-Restrict.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/gam_nose_FM_Matsu_sc_Gam-BMR10-Restrict.plt
                                          Tue Apr 19 13:47:28 2016
 ================================================================================

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

   The form of the probability function is:

   P[response]= background+(1-background)*CumGamma[slope*dose,power],
   where CumGamma(.) is the cummulative Gamma distribution function


   Dependent variable = Effect
   Independent variable = Dose
   Power parameter is restricted as power >=1

   Total number of observations = 6
```

```
   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 (and Specified) Parameter Values
                     Background =    0.0833333
                          Slope =     0.232975
                          Power =      7.24694


           Asymptotic Correlation Matrix of Parameter Estimates

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

                  Slope

     Slope            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
          Slope         0.598283         0.041013            0.517899
0.678667
          Power               18              NA

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        -9.35947         6
   Fitted model        -10.5366         1        2.3543      5          0.7983
  Reduced model        -34.7949         1       50.8709      5         <.0001

           AIC:         23.0732


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size          Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          10          0.000
    5.1400     0.0000         0.000     0.000          10         -0.000
   10.2900     0.0001         0.001     0.000          10         -0.028
   20.5500     0.0750         0.750     0.000          10         -0.900
   30.8600     0.5741         5.741     7.000          10          0.805
   41.1100     0.9297         9.297     9.000          10         -0.368
```

```
 Chi^2 = 1.59      d.f. = 5        P-value = 0.9019

   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        21.4307

            BMDL =       17.0653
```

APPENDIX D. BENCHMARK DOSE CALCULATIONS FOR PROVISIONAL CANCER POTENCY VALUES

MODEL-FITTING PROCEDURE FOR CANCER INCIDENCE DATA

The model-fitting procedure for dichotomous cancer incidence is as follows. The Multistage-Cancer model in the EPA's Benchmark Dose Software (BMDS, Version 2.5) 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 benchmark response (BMR). Among all of the models providing adequate fit to the data, the benchmark dose lower confidence limit/benchmark concentration level (BMDL/BMCL) for the model with the lowest Akaike's information criterion (AIC) is selected as the point of departure (POD). In accordance with U.S. EPA (2012c) guidance, benchmark dose/benchmark concentration (BMD/BMC) and BMDL/BMCL values associated with an extra risk of 10% are calculated.

BMD MODELING TO IDENTIFY POTENTIAL PODs FOR p-OSF DERIVATION

The following data sets were selected for BMD modeling:

- Incidence data for combined hepatocellular adenoma or carcinoma in male mice exposed to 1,2-dichloropropane (1,2-DCP) via gavage for 2 years (NTP, 1986); ***selected as critical endpoint for provisional oral slope factor (p-OSF) derivation***
- Incidence data for combined hepatocellular adenoma or carcinoma in female mice exposed to 1,2-DCP via gavage for 2 years (NTP, 1986);
- Incidence data for mammary gland tumor in female mice exposed to 1,2-DCP via gavage for 2 years (NTP, 1986)

Increased Combined Incidence of Hepatocellular Adenoma or Carcinoma in Male Mice Exposed to 1,2-Dichloropropane for 2 Years

The procedure outlined above was applied to the data for increased combined incidence of hepatocellular adenoma or carcinoma in male mice exposed to 1,2-DCP via gavage 5 days/week for 2 years (NTP, 1986) (see Table D-1). Table D-2 summarizes the BMD modeling results. Only the 1-degree Multistage cancer model provided adequate fit to the data. Thus, the $BMDL_{10}$ (HED) of 2.71 mg/kg-day from this model is selected for this endpoint (see Figure D-1 and the BMD text output for details).

Table D-1. Combined Incidence of Hepatocellular Adenoma or Carcinoma in Male B6C3F1 Mice Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks[a]

	HED (mg/kg-d)[b]		
	0	**12.5**	**25.1**
Sample size	50	50	50
Incidence	18	26	33

[a]NTP (1986).
[b]Gavage doses were converted to ADDs by multiplying the administered gavage dose by (5/7) days/week and converted into HEDs using $BW^{3/4}$ scaling.

ADD = adjusted daily dose; BW = body weight; HED = human equivalent dose.

Table D-2. BMD Modeling Results for Combined Incidence of Hepatocellular Adenoma or Carcinoma in Male B6C3F1 Mice Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d, HED)	$BMDL_{10}$ (mg/kg-d, HED)
Multistage cancer (1-degree)[b,c]	1	0.8829	202.702	4.25256	2.71195
Multistage cancer (2-degree)[b]	0	NA	204.68	4.85779	2.71604

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]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 BMR: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degrees of freedom; HED = human equivalent dose; NA = not applicable.

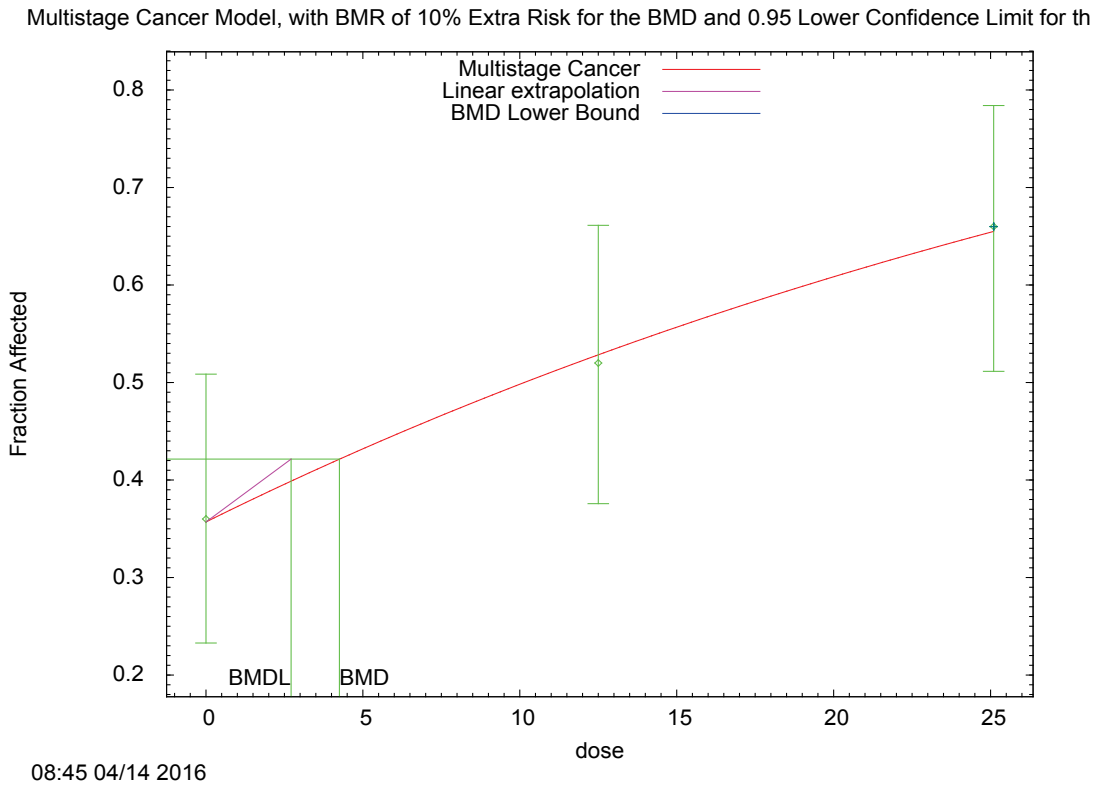

Figure D-1. Multistage (1-degree) Model for Combined Incidence of Hepatocellular Adenoma or Carcinoma in Male B6C3F$_1$ Mice Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks (NTP, 1986)

Text Output for Multistage (1-degree) Model for Combined Incidence of Hepatocellular Adenoma or Carcinoma in Male B6C3F$_1$ Mice Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks (NTP, 1986)

```
=================================================================
         Multistage Cancer Model. (Version: 1.10;  Date: 02/28/2013)
         Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_livercancer_MM_NTP86_Msc1-BMR10.(d)
         Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_livercancer_MM_NTP86_Msc1-BMR10.plt
                                                Thu Apr 14 08:45:17 2016
 =================================================================

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

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
```

Independent variable = Dose

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

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0.354122
Beta(1) = 0.025203

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.7
Beta(1)	-0.7	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.35716	*	*	*
Beta(1)	0.0247758	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-99.34	3			
Fitted model	-99.3509	2	0.0217131	1	0.8829
Reduced model	-103.919	1	9.15741	2	0.01027

AIC: 202.702

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.3572	17.858	18.000	50	0.042
12.5000	0.5284	26.418	26.000	50	-0.119
25.1000	0.6548	32.742	33.000	50	0.077

Chi^2 = 0.02 d.f. = 1 P-value = 0.8829

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        4.25256

            BMDL =        2.71195

            BMDU =        9.34791

Taken together, (2.71195, 9.34791) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0368738
```

Increased Combined Incidence of Hepatocellular Adenoma or Carcinoma in Female Mice Exposed to 1,2-Dichloropropane For 2 Years

The procedure outlined above was applied to the data for increased combined incidence of hepatocellular adenoma or carcinoma in female mice exposed to 1,2-DCP via gavage 5 days/week for 2 years (NTP, 1986) (see Table D-3). Table D-4 summarizes the BMD modeling results. Both models provided adequate fit; the 2-degree Multistage model converged to the 1-degree Multistage cancer model. Thus, the $BMDL_{10}$ (HED) of 8.51 mg/kg-day from this model is selected for this endpoint (see Figure D-2 and the BMD text output for details).

Table D-3. Combined Incidence of Hepatocellular Adenoma or Carcinoma in Female $B6C3F_1$ Mice Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks[a]

	HED (mg/kg-d)[b]		
	0	**12.5**	**25.1**
Sample size	50	50	50
Incidence	2	8	9

[a]NTP (1986).
[b]Gavage doses were converted to ADDs by multiplying the administered gavage dose by (5/7) days/week and converted into HEDs using $BW^{3/4}$ scaling.

ADD = adjusted daily dose; BW = body weight; HED = human equivalent dose.

Table D-4. BMD Results for Combined Incidence of Hepatocellular Adenoma or Carcinoma in Female B6C3F$_1$ Mice Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD$_{10}$ (mg/kg-d, HED)	BMDL$_{10}$ (mg/kg-d, HED)
Multistage cancer (1-degree)[b,c]	1	0.414	112.548	14.4772	8.51111
Multistage cancer (2-degree)[b]	1	0.414	112.548	14.4773	8.51111

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]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 BMR: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degrees of freedom.

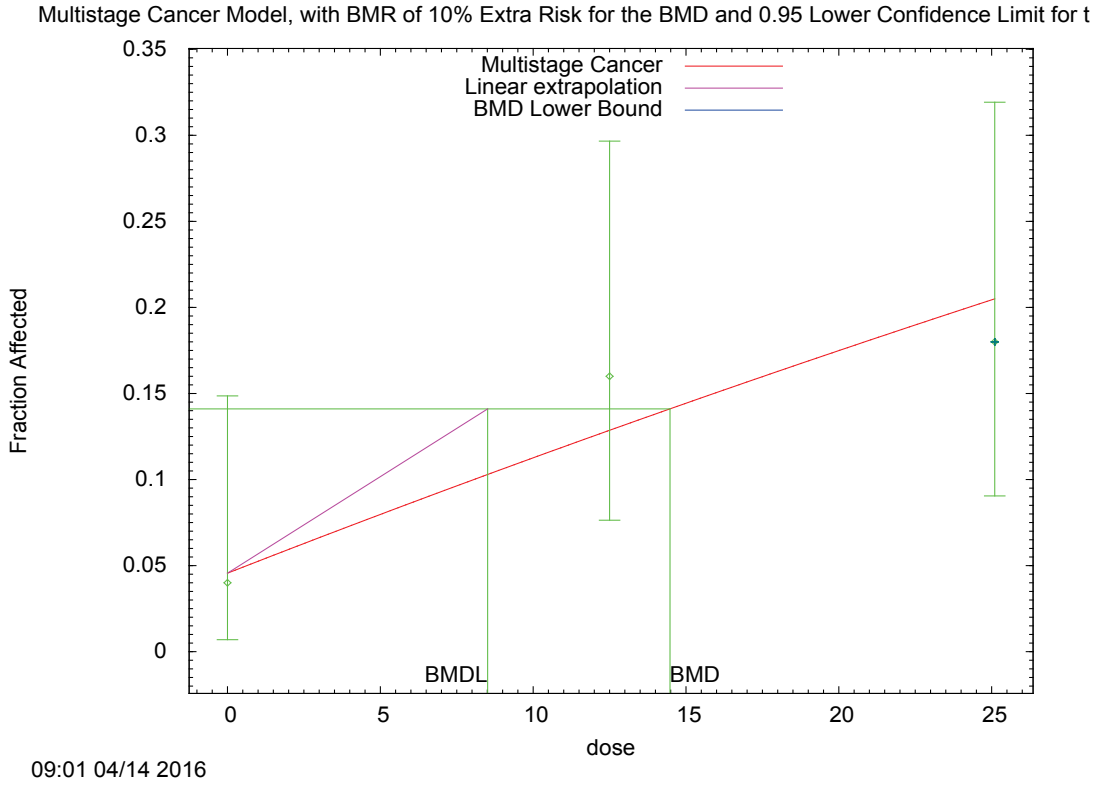

Figure D-2. Multistage (1-degree) Model for Combined Incidence of Hepatocellular Adenoma or Carcinoma in Female B6C3F$_1$ Mice Administered 1,2-Dicloropropane via Gavage 5 Days/Week for 103 Weeks (NTP, 1986)

Text Output for Multistage (1-degree) Model for Combined Incidence of Hepatocellular Adenoma or Carcinoma in Female B6C3F$_1$ Mice Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks (NTP, 1986)

```
================================================================
        Multistage Cancer Model. (Version: 1.10;  Date: 02/28/2013)
        Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_livercancer_FM_NTP86_Msc1-BMR10.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_livercancer_FM_NTP86_Msc1-BMR10.plt
                                                Thu Apr 14 09:01:29 2016
 ================================================================

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

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

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


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0575182
                        Beta(1) =   0.00627421


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.78

   Beta(1)        -0.78            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background         0.045592            *                *                 *
        Beta(1)       0.00727766           *                *                 *
```

```
* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -53.9504         3
   Fitted model        -54.2742         2      0.647608      1          0.421
  Reduced model        -57.0001         1       6.09946      2         0.04737

           AIC:         112.548


                                 Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.0456         2.280     2.000          50       -0.190
   12.5000     0.1286         6.429     8.000          50        0.664
   25.1000     0.2049        10.247     9.000          50       -0.437

 Chi^2 = 0.67      d.f. = 1        P-value = 0.4140


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        14.4772

            BMDL =        8.51111

            BMDU =        46.5151

Taken together, (8.51111, 46.5151) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0117494
```

Increased Incidence of Mammary Gland Adenocarcinomas in Female Rats Exposed to 1,2-Dichloropropane for 2 Years

The procedure outlined above was applied to the data for increased incidence of mammary gland adenocarcinomas in female rats exposed to 1,2-DCP via gavage 5 days/week for 2 years (NTP, 1986) (see Table D-5). Table D-6 summarizes the BMD modeling results. The 2-degree Multistage cancer model provided the best fit to the data. Thus, the $BMDL_{10}$ (HED) of 30.4 mg/kg-day from this model is selected for this endpoint (see Figure D-3 and the BMD text output for details).

Table D-5. Incidence of Mammary Gland Adenocarcinomas in Female F344 Rats Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks[a]

	HED (mg/kg-d)[b]		
	0	**21.4**	**43.0**
Sample size	50	50	50
Incidence	1	2	5

[a]NTP (1986).
[b]Gavage doses were converted to ADDs by multiplying the administered gavage dose by (5/7) days/week and converted into HEDs using $BW^{3/4}$ scaling.

ADD = adjusted daily dose; BW = body weight; HED = human equivalent dose.

Table D-6. BMD Modeling Results for Incidence of Mammary Gland Adenocarcinomas in Female F344 Rats Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d, HED)	$BMDL_{10}$ (mg/kg-d, HED)
Multistage cancer (1-degree)[b]	1	0.5948	0.5948	60.2832	29.4027
Multistage cancer (2-degree)[b,c]	0	0.9847	0.9847	47.7125	30.3983

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]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 BMR: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degrees of freedom; HED = human equivalent dose; NA = not applicable.

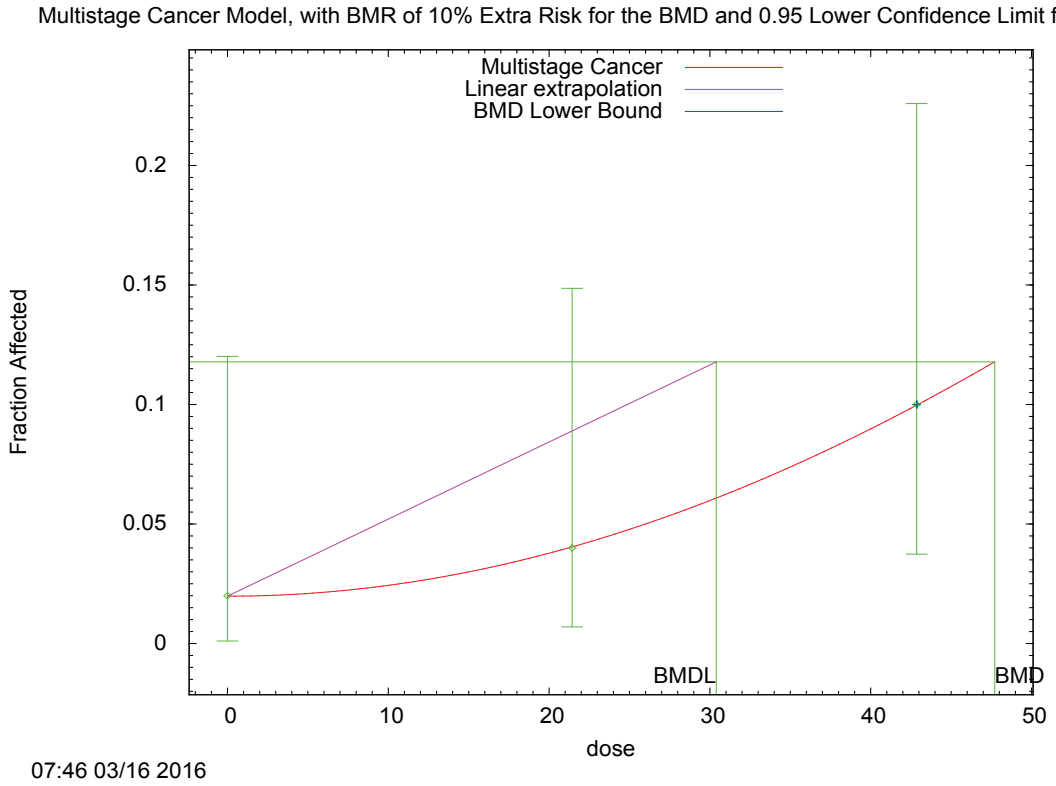

Figure D-3. Multistage (1-degree) Model for Incidence of Mammary Gland Adenocarcinomas in Female F344 Rats Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks (NTP, 1986)

Text Output for Multistage (1-degree) Model for Incidence of Mammary Gland Adenocarcinomas in Female F344 Rats Administered 1,2-Dichloropropane via Gavage 5 Days/Week for 103 Weeks (NTP, 1986)

```
=================================================================
        Multistage Cancer Model. (Version: 1.10;  Date: 02/28/2013)
        Input Data File: C:/Users/JKaiser/Desktop/BMDS240/Data/msc_mgland_ntp86_Msc2-
BMR10.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_mgland_ntp86_Msc2-BMR10.plt
                                                Wed Mar 16 08:46:10 2016
 =================================================================

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

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose
```

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


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0196977
                        Beta(1) =            0
                        Beta(2) = 4.64694e-005


           Asymptotic Correlation Matrix of Parameter Estimates

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

             Background      Beta(2)

Background            1        -0.69

   Beta(2)        -0.69            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background        0.0198356            *                *                  *
        Beta(1)                0            *                *                  *
        Beta(2)     4.62822e-005            *                *                  *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -29.5533         3
   Fitted model        -29.5535         2   0.000370021      1          0.9847
  Reduced model        -31.2323         1       3.35802      2          0.1866

           AIC:          63.107



                               Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size          Residual
  ---------------------------------------------------------------------------
    0.0000     0.0198         0.992     1.000          50          0.008
   21.4290     0.0404         2.022     2.000          50         -0.016
```

```
   42.8600     0.0997         4.986     5.000          50        0.007

 Chi^2 = 0.00      d.f. = 1        P-value = 0.9847


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        47.7125

            BMDL =        30.3983

            BMDU =        497.562

Taken together, (30.3983, 497.562) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00328965
```

BMD MODELING TO IDENTIFY POTENTIAL PODs FOR p-IUR DERIVATION

The following data sets were selected for BMD modeling:

- Incidence data for nasal tumors (papilloma or esthesioneuropeithelima) in male rats exposed to 1,2-DCP via inhalation for 2 years (Umeda et al., 2010); ***selected as critical endpoint for provisional inhalation unit risk (p-IUR) derivation.***
- Incidence data for nasal tumors (only papillomas were observed) in female rats exposed to 1,2-DCP via inhalation for 2 years (Umeda et al., 2010).
- Incidence data for Harderian gland adenoma in male mice exposed to 1,2-DCP via inhalation for 2 years (Matsumoto et al., 2013).
- Incidence data for combined bronchiolo-alveolar adenoma or carcinoma in female mice exposed to 1,2-DCP via inhalation for 2 years (Matsumoto et al., 2013).

Increased Incidence of Nasal Tumors in Male Rats Exposed to 1,2-Dichloropropane for 2 Years

The procedure outlined above was applied to the data for increased incidence of nasal tumors (papilloma or esthesioneuroepithelioma) in male rats exposed to 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 104 weeks (Umeda et al., 2010) (see Table D-7). Table D-8 summarizes the BMD modeling results. The 3-degree Multistage Cancer Model provided the best fit to the data. Thus, the $BMCL_{10}$ (HEC) of 26.7 mg/m^3 from this model is selected for this endpoint (see Figure D-4 and the BMD text output for details).

Table D-7. Incidence of Nasal Tumors (Papilloma or Estheioneuroepithelioma) in Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks[a]

	HEC (mg/m^3)[b]			
	0	**16.2**	**40.54**	**101.1**
Sample size	50	50	50	50
Incidence	0	2	4	15

[a]Umeda et al. (2010).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

HEC = human equivalent concentration; MW = molecular weight.

Table D-8. BMC Modeling Results for Incidence of Nasal Tumors (Papilloma or Estheioneuroepithelioma) in Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3, HEC_{ET})	$BMCL_{10}$ (mg/m^3, HEC_{ET})
Multistage cancer (1-degree)[b]	3	0.7941	108.841	35.1022	24.9885
Multistage cancer (2-degree)[b]	2	0.8965	109.973	42.8701	26.4536
Multistage cancer (3-degree)[b,c]	2	0.9438	109.871	45.072	26.6569

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]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); DF = degrees of freedom; ET = extrathoracic respiratory effects; HEC = human equivalent concentration.

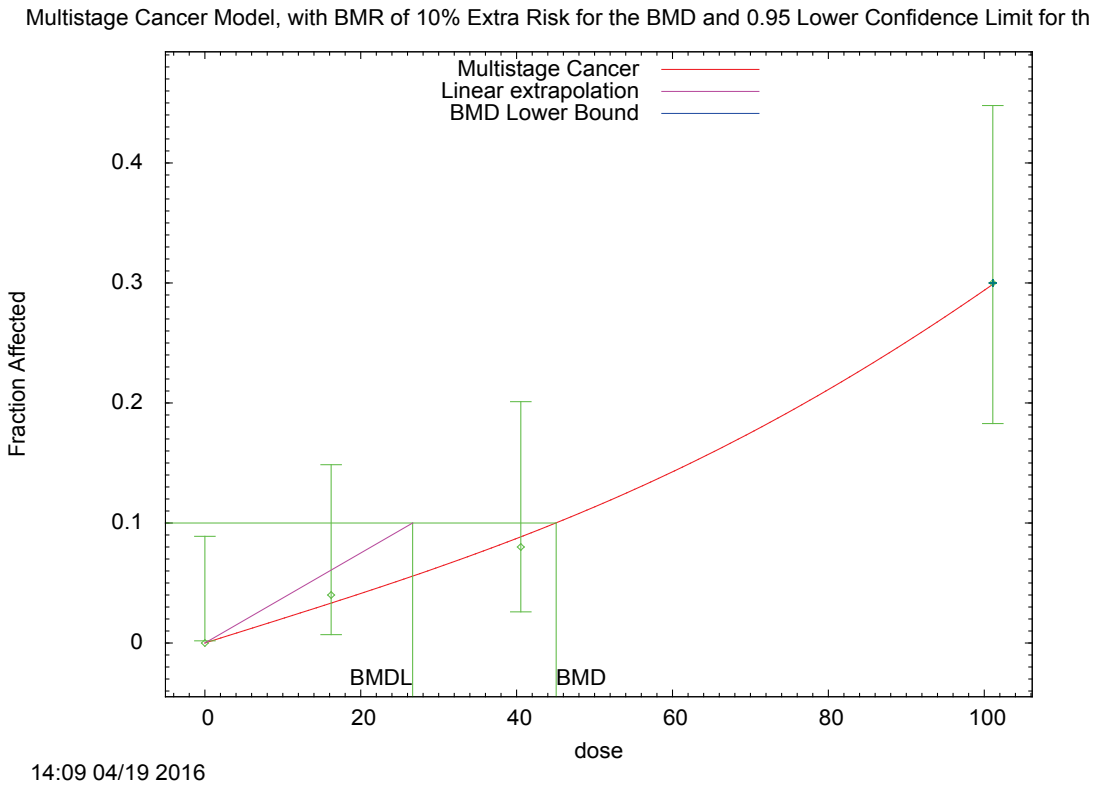

Figure D-4. Multistage (1-degree) Model for Incidence of Nasal Tumors (Papilloma or Estheioneuroepithelioma) in Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Umeda et al., 2010)

Text Output for Multistage (1-degree) Model for Incidence of Nasal Tumors (Papilloma or Estheioneuroepithelioma) in Male F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Umeda et al., 2010)

```
================================================================================
        Multistage Cancer Model. (Version: 1.10;  Date: 02/28/2013)
        Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_nosetumors_MR_Umeda10_Msc3-BMR10.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_nosetumors_MR_Umeda10_Msc3-BMR10.plt
                                                Tue Apr 19 14:09:58 2016
 ================================================================================

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

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose
```

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


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =   0.00415118
                        Beta(1) =   0.00176184
                        Beta(2) =            0
                        Beta(3) = 1.68578e-007


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)      Beta(3)

   Beta(1)            1        -0.93

   Beta(3)        -0.93            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0           *               *                   *
        Beta(1)       0.00204785           *               *                   *
        Beta(2)                0           *               *                   *
        Beta(3)     1.42636e-007           *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -52.8789         4
   Fitted model        -52.9353         2      0.112741      2          0.9452
  Reduced model        -67.1864         1       28.6151      3         <.0001

           AIC:         109.871


                                Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size          Residual
  ---------------------------------------------------------------------------
```

```
    0.0000     0.0000          0.000     0.000          50         0.000
   16.2000     0.0332          1.661     2.000          50         0.268
   40.5400     0.0884          4.419     4.000          50        -0.209
  101.1000     0.2984         14.921    15.000          50         0.024

 Chi^2 = 0.12      d.f. = 2        P-value = 0.9438


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         45.072

            BMDL =        26.6569

            BMDU =        66.4762

Taken together, (26.6569, 66.4762) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00375138
```

Increased Incidence of Nasal Tumors in Female Rats Exposed to 1,2-Dichloropropane for 2 Years

The procedure outlined above was applied to the data for increased incidence of nasal tumors (only papillomas were observed) in female rats exposed to 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 104 weeks (Umeda et al., 2010) (see Table D-9). Table D-10 summarizes the BMD modeling results. All models provided adequate fit to the data, so the model with the lowest AIC was selected (Multistage Cancer, 3-degree). Thus, the $BMCL_{10}$ (HEC) of 46.2 mg/m^3 from this model is selected for this endpoint (see Figure D-5 and the BMD text output for details).

Table D-9. Incidence of Nasal Tumors (Only Papillomas were Observed) in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks[a]

	HEC (mg/m^3)[b]			
	0	**10.7**	**26.75**	**66.71**
Sample size	50	50	50	50
Incidence	0	0	0	9

[a]Umeda et al. (2010).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects by treating 1,2-DCP as a Category 1 gas and using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$.

HEC = human equivalent concentration; MW = molecular weight.

Table D-10. BMC Modeling Results for Incidence of Nasal Tumors (only Papillomas were observed) in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3, HEC_{ET})	$BMCL_{10}$ (mg/m^3, HEC_{ET})
Multistage cancer (1-degree)[b]	3	0.135	57.8068	57.3825	34.7054
Multistage cancer (2-degree)[b]	3	0.6012	52.5047	53.3842	41.5097
Multistage cancer (3-degree)[b,c]	3	0.877	50.4516	55.3501	46.1932

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]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); DF = degrees of freedom; ET = extrathoracic respiratory effects; HEC = human equivalent concentration.

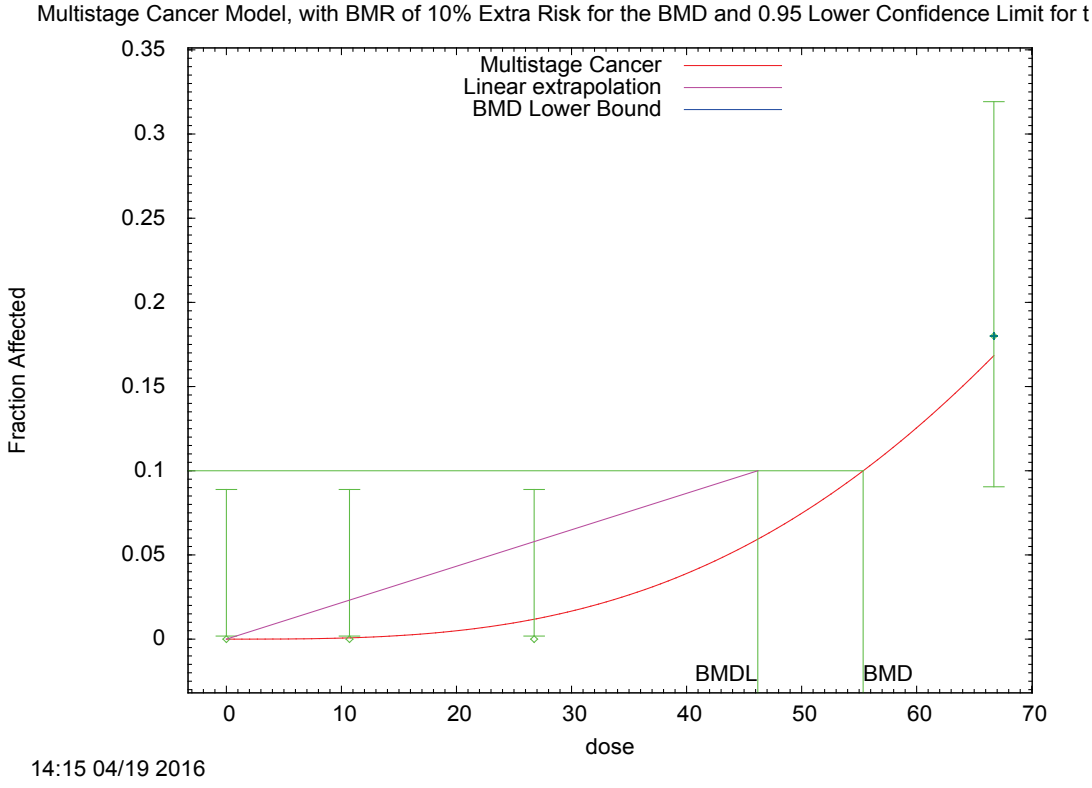

Figure D-5. Multistage (3-degree) Model for Incidence of Nasal Tumors (only Papillomas were observed) in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Umeda et al., 2010)

Text Output for Multistage (3-degree) Model for Incidence of Nasal Tumors (only Papillomas were observed) in Female F344 Rats Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Umeda et al., 2010)

```
================================================================
        Multistage Cancer Model. (Version: 1.10;  Date: 02/28/2013)
        Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_nosetumors_FR_Umeda10_Msc3-BMR10.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_nosetumors_FR_Umeda10_Msc3-BMR10.plt
                                                Tue Apr 19 14:15:18 2016
 ================================================================

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

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

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


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 6.81631e-007


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(3)

   Beta(3)            1



                                Parameter Estimates
```

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	6.21329e-007	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-23.5697	4			
Fitted model	-24.2258	1	1.31225	3	0.7262
Reduced model	-36.7042	1	26.2691	3	<.0001

AIC: 50.4516

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	50	0.000
10.7000	0.0008	0.038	0.000	50	-0.195
26.7500	0.0118	0.591	0.000	50	-0.773
66.7100	0.1684	8.422	9.000	50	0.218

Chi^2 = 0.68 d.f. = 3 P-value = 0.8770

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 55.3501

BMDL = 46.1932

BMDU = 67.6939

Taken together, (46.1932, 67.6939) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00216482

Increased Incidence of Harderian Gland Adenomas in Male Mice Exposed to 1,2-Dichloropropane for 2 Years

The procedure outlined above was applied to the data for increased incidence of Harderian gland adenomas in male mice exposed to 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 104 weeks (Matsumoto et al., 2013) (see Table D-11). Table D-12 summarizes the BMD modeling results. All models provided adequate fit to the data, and converged to the 1-degree model. Thus, the $BMCL_{10}$ (HEC) of 251 mg/m^3 from this model is selected for this endpoint (see Figure D-6 and the BMD text output for details).

Table D-11. Incidence of Harderian Gland Adenoma in Male B6D2F1/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks[a]

	HEC (mg/m^3)[b]			
	0	**77.2**	**192**	**482.5**
Sample size	50	50	50	50
Incidence	1	2	3	6

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for pulmonary respiratory effects using the following equation: HEC_{PU} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{PU}$. $RGDR_{PU}$ is the pulmonary regional gas dose ratio (animal:human); see Equations 4−28 in U.S. EPA (1994b) for calculation of $RGDR_{PU}$ and default values for variables.

HEC = human equivalent concentration; MW = molecular weight.

Table D-12. BMC Modeling Results for Incidence of Harderian Gland Adenoma in Male B6D2F1/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3, HEC_{PU})	$BMCL_{10}$ (mg/m^3, HEC_{PU})
Multistage cancer (1-degree)[b,c]	2	0.9935	90.001	475.928	251.121
Multistage cancer (2-degree)[b]	2	0.9935	90.001	475.928	251.121
Multistage cancer (3-degree)[b]	2	0.9935	90.001	475.928	251.121

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]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); DF = degrees of freedom; HEC = human equivalent concentration; PU = pulmonary effects.

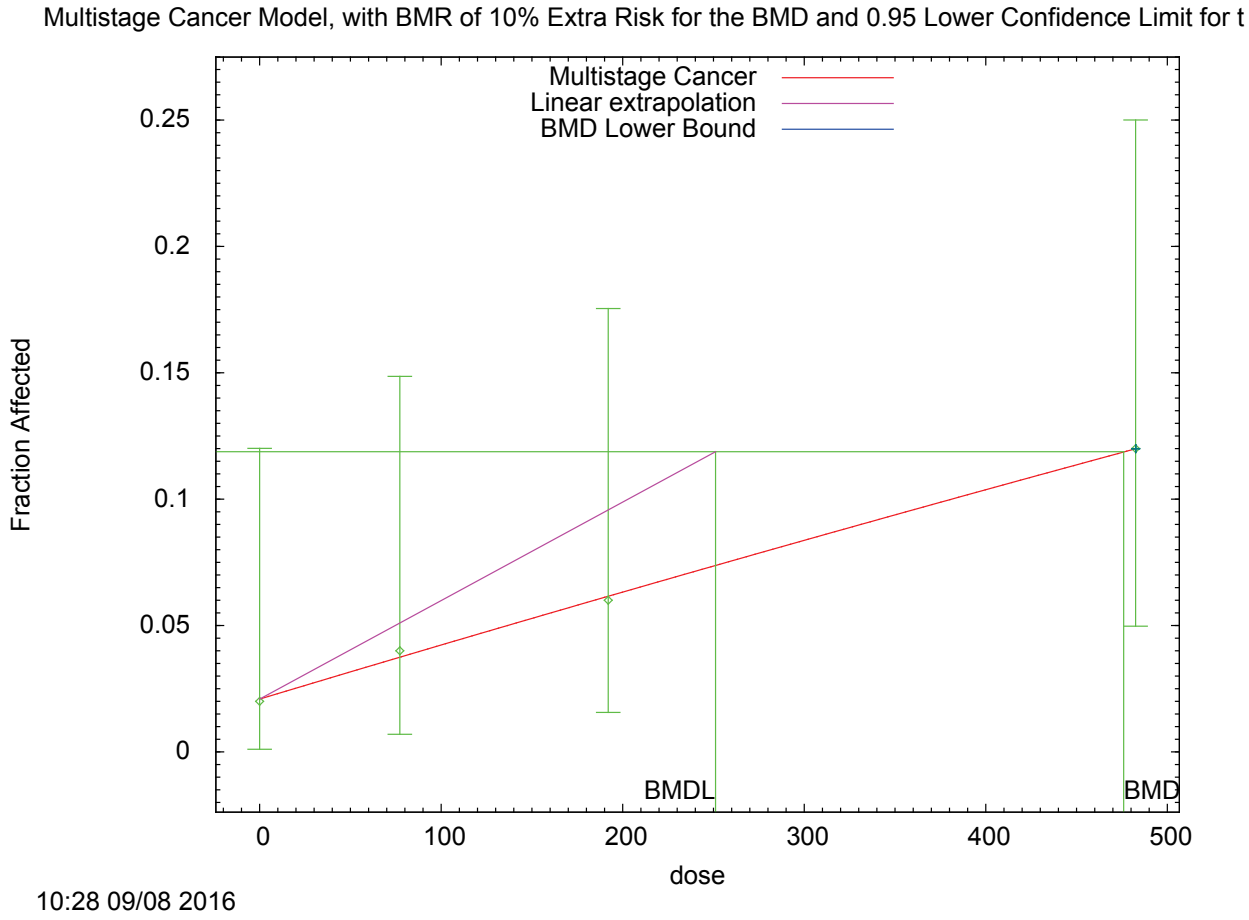

Figure D-6. Multistage (1-degree) Model for Incidence of Harderian Gland Adenoma in Male B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Matsumoto et al., 2013)

Text Output for Multistage (1-degree) Model for Incidence of Harderian Gland Adenoma in Male B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Matsumoto et al., 2013)

```
=================================================================================
        Multistage Cancer Model. (Version: 1.10;  Date: 02/28/2013)
        Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_hardgland_MM_Matsu13_Msc1-BMR10.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_hardgland_MM_Matsu13_Msc1-BMR10.plt
                                                Thu Sep 08 10:28:32 2016
 =================================================================================

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

   The form of the probability function is:

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

The parameter betas are restricted to be positive

Dependent variable = Effect
Independent variable = Dose

Total number of observations = 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 = 0.0210709
Beta(1) = 0.000220233

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.71
Beta(1)	-0.71	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0208629	*	*	*
Beta(1)	0.000221379	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-42.9938	4			
Fitted model	-43.0002	2	0.0129026	2	0.9936
Reduced model	-45.3935	1	4.79943	3	0.1871

AIC: 90.0005

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0209	1.043	1.000	50	-0.043
77.2000	0.0375	1.873	2.000	50	0.095

```
  192.0000     0.0616         3.080     3.000          50       -0.047
  482.5000     0.1201         6.003     6.000          50       -0.001

 Chi^2 = 0.01      d.f. = 2        P-value = 0.9935


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        475.928

            BMDL =        251.121

            BMDU =        2014.42

Taken together, (251.121, 2014.42) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =   0.000398215
```

Increased Combined Incidence of Bronchiolo-Alveolar Adenoma or Carcinoma in Female Mice Exposed to 1,2-DCP for 2 Years

The procedure outlined above was applied to the data for increased combined incidence of bronchiolo-alveolar adenoma or carcinoma in female mice exposed to 1,2-DCP via inhalation for 6 hours/day, 5 days/week for 104 weeks (Matsumoto et al., 2013) (see Table D-13). Table D-14 summarizes the BMD modeling results. All models provided adequate fit to the data, and converged to the 1-degree model. Thus, the $BMCL_{10}$ (HEC) of 177 mg/m^3 from this model is selected for this endpoint (see Figure D-7 and the BMD text output for details).

Table D-13. Combined Incidence of Bronchiolo-alveolar Adenoma or Carcinoma in Female B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks[a]

	HEC (mg/m^3)[b]			
	0	**69.2**	**173**	**432.0**
Sample size	50	50	50	50
Incidence	2	4	5	8

[a]Matsumoto et al. (2013).
[b]Analytical exposure concentrations were converted to HECs for pulmonary respiratory effects using the following equation: HEC_{PU} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{PU}$. $RGDR_{PU}$ is the pulmonary regional gas dose ratio (animal:human); see Equations 4–28 in U.S. EPA (1994b) for calculation of $RGDR_{PU}$ and default values for variables.

HEC = human equivalent concentration; MW = molecular weight.

Table D-14. BMC Modeling Results for Combined Incidence of Bronchiolo-Alveolar Adenoma or Carcinoma in Female B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks

Model	DF	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMC_{10} (mg/m^3, HEC_{PU})	$BMCL_{10}$ (mg/m^3, HEC_{PU})
Multistage cancer (1-degree)[b,c]	2.00	0.904	125.347	341.97	177.213
Multistage cancer (2-degree)[b]	2.00	0.904	125.347	341.97	177.213
Multistage cancer (3-degree)[b]	2.00	0.904	125.347	341.97	177.213

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]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); DF = degrees of freedom; HEC = human equivalent concentration; PU = pulmonary effects.

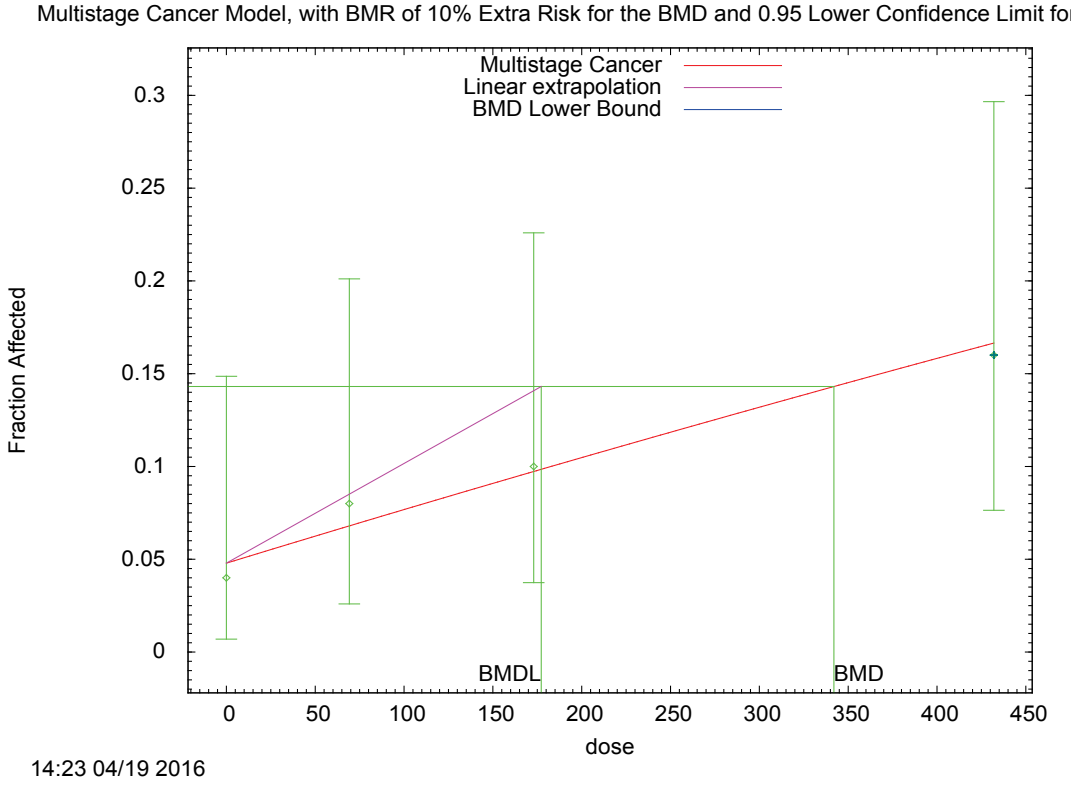

Figure D-7. Multistage (1-degree) Model for Combined Incidence of Bronchiolo-Alveolar Adenoma or Carcinoma in Female B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Matsumoto et al., 2013)

Text Output for Multistage (1-degree) Model for Combined Incidence of Bronchiolo-Alveolar Adenoma or Carcinoma in Female B6D2F$_1$/Crlj (SPF) Mice Exposed to 1,2-Dichloropropane via Inhalation for 6 Hours/Day, 5 Days/Week for 104 Weeks (Matsumoto et al., 2013)

```
=================================================================
        Multistage Cancer Model. (Version: 1.10;  Date: 02/28/2013)
        Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_broncho_FM_Matsu13_Msc1-BMR10.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/msc_broncho_FM_Matsu13_Msc1-BMR10.plt
                                                Tue Apr 19 14:23:18 2016
 =================================================================

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

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 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 =    0.0507611
                        Beta(1) =   0.00029003


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.72

   Beta(1)        -0.72            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
```

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0.0479005	*	*	*
Beta(1)	0.000308099	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-60.5733	4			
Fitted model	-60.6734	2	0.200217	2	0.9047
Reduced model	-62.7912	1	4.4357	3	0.2181

AIC: 125.347

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0479	2.395	2.000	50	-0.262
69.2000	0.0680	3.399	4.000	50	0.338
173.0000	0.0973	4.866	5.000	50	0.064
432.0000	0.1666	8.328	8.000	50	-0.124

Chi^2 = 0.20 d.f. = 2 P-value = 0.9040

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 341.97

BMDL = 177.213

BMDU = 1802.72

Taken together, (177.213, 1802.72) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000564294

APPENDIX E. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2014a). Propylene dichloride. Documentation of the threshold limit values for chemical substances, 7th edition [TLV/BEI]. Cincinatti, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). (2014b). Propylene dichloride. TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices [TLV/BEI]. In ACGIH Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs) Appendix B (pp. 51). Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). (1989). Toxicological profile for 1,2-dichloropropane [ATSDR Tox Profile]. (RISKLINE/1991090047). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=831&tid=162

ATSDR (Agency for Toxic Substances and Disease Registry). (2016). Minimal risk levels (MRLs). March 2016. Atlanta, GA: Agency for Toxic Substances and Disease Registry (ATSDR). Retrieved from http://www.atsdr.cdc.gov/mrls/index.asp

Bartels, MJ; Timchalk, C. (1990). 1,2-Dichloropropane: Investigation of the mechanism of mercapturic acid formation in the rat. Xenobiotica 20: 1035-1042.

Baruffini, A; Cirla, AM; Pisati, G; Ratti, R; Zedda, S. (1989). Allergic contact dermatitis from 1,2-dichloropropane. Contact Derm 20: 379-380. http://dx.doi.org/10.1111/j.1600-0536.1989.tb03178.x

Belyaeva, NN; Bonashevskaya, TI; Marshak, TL; Brodskii, VY. (1977). Investigation of the effect of certain chlorinated hydrocarbons on the composition of the hepatocyte population of the rat liver. Bull Exp Biol Med 83: 396-400. http://dx.doi.org/10.1007/BF00799375

Benbrahim-Tallaa, L; Lauby-Secretan, B; Loomis, D; Guyton, KZ; Grosse, Y; El Ghissassi, F; Bouvard, V; Guha, N; Mattock, H; Straif, K. (2014). Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone. Lancet Oncol 15: 924-925. http://dx.doi.org/10.1016/S1470-2045(14)70316-X

Bio Dynamics (Bio/dynamics Inc.). (1981). Acute oral toxicity study in rats. (TSCATS/017993. OTS84003A. EPA I.D. 878211460). East Millstone, NJ: Exxon Corporation.

Bruckner, JV; Mackenzie, WF; Ramanathan, R; Muralidhara, S; Kim, HJ; Dallas, CE. (1989). Oral toxicity of 1,2-dichloropropane: acute, short-term, and long-term studies in rats. Toxicol Sci 12: 713-730. http://dx.doi.org/10.1016/0272-0590(89)90003-1

Cal/EPA (California Environmental Protection Agency). (1999). Public health goal for 1,2-dichloropropane in drinking water. Sacramento, CA: Office of Environmental Health Hazard Assessment. http://oehha.ca.gov/water/phg/pdf/12dcp_f.pdf

Cal/EPA (California Environmental Protection Agency). (2004). No significant risk level (NSRL) for the proposition 65 carcinogen 1,2-dichloropropane. Sacramento, CA: Office of Environmental Health Hazard Assessment. http://oehha.ca.gov/prop65/law/pdf_zip/oehha2004a.pdf

Cal/EPA (California Environmental Protection Agency). (2014). All OEHHA acute, 8-hour and chronic reference exposure levels (chRELs) as of June 2014. Sacramento, CA: Office of Health Hazard Assessment. http://www.oehha.ca.gov/air/allrels.html

Cal/EPA (California Environmental Protection Agency). (2016a). Chemicals known to the state to cause cancer or reproductive toxicity July 15, 2016. (Proposition 65 list). Sacramento, CA: California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. http://oehha.ca.gov/proposition-65/proposition-65-list

Cal/EPA (California Environmental Protection Agency). (2016b). OEHHA toxicity criteria database [Database]. Sacramento, CA: Office of Environmental Health Hazard Assessment. Retrieved from http://www.oehha.ca.gov/tcdb/index.asp

Carere, A; Morpurgo, G. (1981). Comparison of the mutagenic activity of pesticides in vitro in various short-term assays. In Progress in environmental mutagenesis and carcinogenesis: Proceedings of the 10th annual meeting of the European Environmental Mutagen Society (EEMS), Athens, Greece, 14-19 September 1980. New York, NY: Elsevier/North-Holland Biomedical Press.

Chiappino, G; Secchi, GC. (1968). [Description of a case of acute intoxication from accidental ingestion of 1,2-dichloropropane sold as trilene]. G Ital Med Lav Ergon 59: 334-341.

Chroust, K; Pavlova, M; Prokop, Z; Mendel, J; Bozkova, K; Kubat, Z; Zaji, CV; Damborsky, J. (2006). Quantitative structure-activity relationships for toxicity and genotoxicity of halogenated aliphatic compounds: Wing spot test of Drosophila melanogaster. Chemosphere 67: 152-159. http://dx.doi.org/10.1016/j.chemosphere.2006.09.020

De Lorenzo, F; Deglinnocenti, S; Ruocco, A; Silengo, L; Cortese, R. (1977). Mutagenicity of pesticides containing 1,3-dichloropropene. Cancer Res 37: 1915-1917.

Di Nucci, A; Gregotti, C; Manzo, L; Imbriani, M; Ghittori, S; Bianco, L; Maestri, L; Capodaglio, E. (1990). 1,2-dichloropropane hepatotoxicity in rats after inhalation exposure. J Appl Toxicol 10: 391-394. http://dx.doi.org/10.1002/jat.2550100602

Di Nucci, A; Imbriani, M; Ghittori, S; Gregotti, C; Baldi, C; Locatelli, C; Manzo, L; Capodaglio, E. (1988). 1,2-Dichloropropane-induced liver toxicity: Clinical data and preliminary studies in rats. Arch Toxicol 12: 370-374.

Dow Chemical Co (Dow Chemical Company). (1968). Hepatotoxic potency of propylene dichloride vapors relative to their narcotic and lethal potencies in mice with cover letter. (OTS0206134. TSCATS/017436. EPA Doc #878210624). Washington, D.C.: U.S. Environmental Protection Agency.

Dow Chemical Co (Dow Chemical Company). (1988a). Final report on propylene dichloride 13-week inhalation toxicity study with rats, mice and rabbits with cover letter dated 032888. (FYIOTS04880399). Midland, MI.

Dow Chemical Co (Dow Chemical Company). (1988b). Neurotoxicologic examination of rats exposed to 1,2-dichloropropane (PDC) via gavage for 13 weeks. In Letter from Dow Chemical Company to US EPA regarding submission of final study reports for 1,2-dichloropropane with attachments. (OTS0527733 (STUDY ID: K-002127-013)). Midland, MI.

Dow Chemical Co (Dow Chemical Company). (1988c). Propylene dichloride: a 13-day repeated oral gavage study in New Zealand white rabbits with attached appendix and cover letter dated 011389. (OTS0516642. Doc I.D. 86890000079). Midland, MI.

Dow Chemical Co (Dow Chemical Company). (1988d). Propylene dichloride: Oral teratology probe study in New Zealand white rabbits with cover letter dated 100188. (TSCATS/401132. OTS0516583. EPA I.D. 86-890000004). Midland, MI.

Dow Chemical Co (Dow Chemical Company). (1989a). Neurotoxicologic examination of Fischer 344 rats exposed to 1,2-dichloropropane via gavage for 2 weeks with cover letter dated 022389. (TSCATS/311076. OTS0517725. EPA I.D. 86890000125).

Dow Chemical Co (Dow Chemical Company). (1989b). Propylene dichloride: dominant lethal study in Sprague-Dawley rats (final) with cover letters. (OTS0527736. EPA I.D. 408967206). https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0527736

Dow Chemical Co (Dow Chemical Company). (1989c). Propylene dichloride: Oral teratology probe study in Sprague-Dawley rats with cover letter. (OTS0527712). Midland, MI.

Dow Chemical Co (Dow Chemical Company). (1989d). Propylene dichloride: oral teratology probe study in Sprague-Dawley rats with cover letter dated 041389. Washington, D.C.: U.S. Environmental Protection Agency.

Dow Chemical Co (Dow Chemical Company). (1990). Propylene dichloride: two-generation reproduction study in sprague-dawley rats (final) with cover letter. (TSCATS/411990. OTS0527738. EPA Doc. ID 40-9067215). Midland, MI: Dow Chemical.

Fiaccadori, E; Maggiore, U; Rotelli, C; Giacosa, R; Ardissino, D; De Palma, G; Bergamaschi, E; Mutti, A. (2003). Acute renal and hepatic failure due to accidental percutaneous absorption of 1,2-dichlorpropane contained in a commercial paint fixative [Letter]. Nephrol Dial Transplant 18: 219-220. http://dx.doi.org/10.1093/ndt/18.1.219

Fiserova-Bergerova, V; Pierce, JT; Droz, PO. (1990). Dermal absorption potential of industrial chemicals: Criteria for skin notation. Am J Ind Med 17: 617-635. http://dx.doi.org/10.1002/ajim.4700170507

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.

Gi, M; Fujioka, M; Yamano, S; Shimomura, E; Ishii, N; Kakehashi, A; Takeshita, M; Wanibuchi, H. (2015a). Determination of hepatotoxicity and its underlying metabolic basis of 1,2-dichloropropane in male Syrian hamsters and B6C3F1 mice. Toxicol Sci 145: 196-208. http://dx.doi.org/10.1093/toxsci/kfv045

Gi, M; Fujioka, M; Yamano, S; Shimomura, E; Kanki, M; Kawachi, S; Tachibana, H; Tatsumi, K; Fang, H; Ishii, N; Kakehashi, A; Wanibuchi, H. (2015b). Modifying effects of 1,2-dichloropropane on N-nitrosobis(2-oxopropyl)amine-induced cholangiocarcinogenesis in male Syrian hamsters. J Toxicol Sci 40: 647-656. http://dx.doi.org/10.2131/jts.40.647

Grzywa, Z; Rudzki, E. (1981). Dermatitis from dichloropropane. Contact Derm 7: 151-152. http://dx.doi.org/10.1111/j.1600-0536.1981.tb04589.x

Guengerich, FP; Kim, DH; Iwasaki, M. (1991). Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. Chem Res Toxicol 4: 168-179. http://dx.doi.org/10.1021/tx00020a008

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

Heppel, LA; Highman, B; Peake, EG. (1948). Toxicology of 1,2-dichloropropane (propylene dichloride): IV. Effects of repeated exposures to a low concentration of the vapor. J Ind Hyg Toxicol 30: 189-191.

Heppel, LA; Neal, PA. (1946). Toxicology of 1,2-dichloropropane (propylene dichloride) studies on effects of daily inhalations. J Ind Hyg Toxicol 28: 1-8.

Highman, B; Heppel, LA. (1946). Toxicology of 1,2-dichloropropane (propylene dichloride); pathologic changes produced by a short series of daily exposures. Arch Pathol 42: 525-534.

HSDB (Hazardous Substances Data Bank). (2014). 1,2-Dichloropropane (CASRN: 78-87-5). Bethesda, MD: U.S. National Library of Medcine. http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~cGQoLf:3

IARC (International Agency for Research on Cancer). (2015). IARC Monographs on the evaluation of carcinogenic risk to humans. Geneva, Switzerland: International Agency for Research on Cancer, WHO. http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php

Imberti, R; Calabrese, SR; Emilio, G; Marchi, L; Giuffrida, L. (1987). [Acute poisoning with solvents: chlorinated aliphatic hydrocarbons]. Minerva Anestesiol 53: 399-403.

Imberti, R; Mapelli, A; Colombo, P; Richelmi, P; Berte, F; Bellomo, G. (1990). 1,2-dichloropropane (DCP) toxicity is correlated with DCP-induced glutathione (GSH) depletion and is modulated by factors affecting intracellular GSH. Arch Toxicol 64: 459-465. http://dx.doi.org/10.1007/BF01977627

IPCS (International Programme on Chemical Safety). (2016). INCHEM: Chemical safety information from intergovernmental organizations [Database]: 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/

Jones, AR; Gibson, J. (1980). 1,2-dichloropropane: metabolism and fate in the rat. Xenobiotica 10: 835-846. http://dx.doi.org/10.3109/00498258009033814

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

Kirk, HD; Berdasco, NM; Breslin, WJ; Hanley, TRJ. (1995). Developmental toxicity of 1,2-dichloropropane (PDC) in rats and rabbits following oral gavage. Fundam Appl Toxicol 28: 18-26. http://dx.doi.org/10.1006/faat.1995.1141

Kramers, PGN; Mout, HCA; Bissumbhar, B; Mulder, CR. (1991). Inhalation exposure in Drosophila mutagenesis assays: Experiments with aliphatic halogenated hydrocarbons, with emphasis on the genetic activity profile of 1,2-dichloroethane. Mutat Res 252: 17-33. http://dx.doi.org/10.1016/0165-1161(91)90248-7

Kubo, S; Kinoshita, M; Takemura, S; Tanaka, S; Shinkawa, H; Nishioka, T; Hamano, G; Ito, T; Abue, M; Aoki, M; Nakagawa, K; Unno, M; Hijioka, S; Fujiyoshi, T; Shimizu, Y; Mizuguchi, T; Shirabe, K; Nishie, A; Oda, Y; Takenaka, K; Kobarai, T; Hisano, T; Saiura, A; Numao, H; Toda, M; Kuwae, Y; Nakanuma, Y; Endo, G. (2014a). Characteristics of printing company workers newly diagnosed with occupational cholangiocarcinoma. J Hepatobiliary Pancreat Sci 21: 809-817. http://dx.doi.org/10.1002/jhbp.137

Kubo, S; Matsuzaki, K; Seki, T; Ohsawa, M; Kumagai, S; Endo, G. (2014b). Severe acute hepatitis in a printing company worker: a case study. J Occup Health 57: 87-90. http://dx.doi.org/10.1539/joh.14-0122-CS

Kubo, S; Nakanuma, Y; Takemura, S; Sakata, C; Urata, Y; Nozawa, A; Nishioka, T; Kinoshita, M; Hamano, G; Terajima, H; Tachiyama, G; Matsumura, Y; Yamada, T; Tanaka, H; Nakamori, S; Arimoto, A; Kawada, N; Fujikawa, M; Fujishima, H; Sugawara, Y; Tanaka, S; Toyokawa, H; Kuwae, Y; Ohsawa, M; Uehara, S; Sato, KK; Hayashi, T; Endo, G. (2014c). Case series of 17 patients with cholangiocarcinoma among young adult workers of a printing company in Japan. J Hepatobiliary Pancreat Sci 21: 479-488. http://dx.doi.org/10.1002/jhbp.86

Kumagai, S; Kurumatani, N; Arimoto, A; Ichihara, G. (2013). Cholangiocarcinoma among offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. Occup Environ Med 70: 508-510. http://dx.doi.org/10.1136/oemed-2012-101246

Kumagai, S; Kurumatani, N; Arimoto, A; Ichihara, G. (2014). Time course of blood parameters in printing workers with cholangiocarcinoma. J Occup Health 56: 279-284. http://dx.doi.org/10.1539/joh.13-0263-OA

Kumagai, S; Sobue, T; Makiuchi, T; Kubo, S; Uehara, S; Hayashi, T; Sato, KK; Endo, G. (2016). Relationship between cumulative exposure to 1,2-dichloropropane and incidence risk of cholangiocarcinoma among offset printing workers. Occup Environ Med 73: 545-552. http://dx.doi.org/10.1136/oemed-2015-103427

Lucantoni, C; Grottoli, S; Gaetti, R. (1992). 1,2-Dichloropropane is a renal and liver toxicant [Letter]. Toxicol Appl Pharmacol 117: 133.

Matsumoto, M; Umeda, Y; Take, M; Nishizawa, T; Fukushima, S. (2013). Subchronic toxicity and carcinogenicity studies of 1,2-dichloropropane inhalation to mice. Inhal Toxicol 25: 435-443. http://dx.doi.org/10.3109/08958378.2013.800618

Matsumoto, T; Okura, Y; Okawa, Y; Mikami, T; Nagase, T; Hashimoto, K; Suzuki, M; Sugai, N; Suzuki, S. (1982). Acute toxicity testing of some chlorinated lower hydro carbons dichloromethane 1 2 dichloropropane and 1 3 dichloropropane [Abstract]. JJTHE 28: P-31.

Matsumoto, T; Okura, Y; Okawa, Y; Mikami, T; Nagase, T; Hashimoto, K; Suzuki, S; Suzuki, M; Sugai, N. (1983). Toxicity test of dichloromethane and 1,2-dichloropropane and 1,3-dichloropropane. JJTHE 29: P38-P38.

Mellon Institute of Industrial Research. (1947a). Recalculation of liver and kidney weights previously reported with revised conclusions on the toxicity of eight chlorinated hydrocarbons. (TSCATS/308694. OTS0515561. EPA Doc I.D.86-870001399). Houston, TX: Union Carbide Corporation.

Mellon Institute of Industrial Research. (1947b). Repeated exposure of rats and dogs to vapors of eight chlorinated hydrocarbons. (TSCATS/308690. OTS0515559. EPA Doc I.D.86-870001397). Pittsburgh, PA: Carbide and Carbon Chemicals Corporation.

Myhr, BC; Caspary, WJ. (1991). Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: Results for 31 coded compounds in the National Toxicology Program. Environ Mol Mutagen 18: 51-83. http://dx.doi.org/10.1002/em.2850180109

NIOSH (National Institute for Occupational Safety and Health). (1994). Immediately dangerous to life or health concentrations (IDHL). Propylene dichloride. Atlanta, GA: Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/idlh/78875.html

NIOSH (National Institute for Occupational Safety and Health). (2011). NIOSH Pocket guide to chemical hazards. Propylene dichloride. Atlanta, GA: Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/npg/npgd0534.html

NIOSH (National Institute for Occupational Safety and Health). (2015). NIOSH pocket guide to chemical hazards. Introduction. Atlanta, GA: Center for Disease Control and Prevention. http://www.cdc.gov/niosh/npg/pgintrod.html

NTP (National Toxicology Program). (1986). Toxicology and carcinogenesis studies of 1,2-dichloropropane (propylene dichloride) (CAS no. 78-87-5) in F344/N rats and B6C3F1 mice (gavage studies) (pp. 182 PP). (NTP TR 263). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service.

NTP (National Toxicology Program). (2014). Report on carcinogens. Thirteenth edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html

OECD (Organisation for Economic Co-operation and Development). (2003). SIDS Initial Assessment Report from SIAM 17. Arona, Italy, 11-15 November 2003. 1,2-dichloropropane. http://www.chem.unep.ch/irptc/sids/OECDSIDS/78875.pdf

OSHA (Occupational Safety & Health Administration). (2006a). Safety and health regulations for construction: Occupational health and environmental controls - Gases, vapors, fumes, dusts, and mists. (1926.55 App A). Washington, DC: U.S. Department of Labor. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10629

OSHA (Occupational Safety & Health Administration). (2006b). 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

OSHA (Occupational Safety & Health Administration). (2011). 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

Perbellini, L; Zedde, A; Schiavon, R; Franchi, GL. (1985). [Disseminated intravascular coagulation (DIC) caused by 1,2-dichloropropane (commercial trielin). Description of 2 cases]. Med Lav 76: 412-417.

Perocco, P; Bolognesi, S; Alberghini, W. (1983). Toxic activity of seventeen industrial solvents and halogenated compounds on human lymphocytes cultured in vitro. Toxicol Lett 16: 69-75. http://dx.doi.org/10.1016/0378-4274(83)90012-7

Pozzi, C; Marai, P; Ponti, R; Dell'Oro, C; Sala, C; Zedda, S; Locatelli, F. (1985). Toxicity in man due to stain removers containing 1,2-dichloropropane. Br J Ind Med 42: 770-772. http://dx.doi.org/10.1136/oem.42.11.770

Principe, P; Dogliotti, E; Bignami, M; Crebelli, R; Falcone, E; Fabrizi, M; Conti, G; Comba, P. (1981). Mutagenicity of chemicals of industry and agricultural relevance in Salmonella, Streptomyces and Aspergillus. J Sci Food Agric 32: 826-832. http://dx.doi.org/10.1002/jsfa.2740320812

Prival, MJ; Dunkel, VC. (1989). Reevaluation of the mutagenicity and carcinogenicity of chemicals previously identified as "false positives" in the Salmonella typhimurium mutagenicity assay. Environ Mol Mutagen 13: 1-24. http://dx.doi.org/10.1002/em.2850130102

Sato, Y; Kubo, S; Takemura, S; Sugawara, Y; Tanaka, S; Fujikawa, M; Arimoto, A; Harada, K; Sasaki, M; Nakanuma, Y. (2014). Different carcinogenic process in cholangiocarcinoma cases epidemically developing among workers of a printing company in Japan. Int J Clin Exp Pathol 7: 4745-4754.

Sekiguchi, S; Suda, M; Zhai, YL; Honma, T. (2002). Effects of 1-bromopropane, 2-bromopropane, and 1,2-dichloropropane on the estrous cycle and ovulation in F344 rats. Toxicol Lett 126: 41-49.

Shell Oil Co (Shell Oil Company). (1982). Toxicology of fine chemicals: The acute oral and percutaneous toxicity, skin and eye irritancy and skin sensitizing potential of 1,2-dichloropropane (light ends). (TSCATS/016752. OTS0205965. EPA I.D. 878212009). Houston, TX.

Sidorenko, GI; Tsulaya, VR; Bonashevskaya, TI; Shaipak, VM. (1979). Study of the combined action of a group of chlorine derivatives of hydrocarbons entering the organism by inhalation. Environ Health Perspect 30: 13-18.

Sobue, T; Utada, M; Makiuchi, T; Ohno, Y; Uehara, S; Hayashi, T; Sato, KK; Endo, G. (2015). Risk of bile duct cancer among printing workers exposed to 1,2-dichloropropane and/or dichloromethane. J Occup Health 57: 230-236. http://dx.doi.org/10.1539/joh.14-0116-OA

SRI (Stanford Research Institute). (1975). In vitro microbiological mutagenicity studies of ethyl compounds. (86870001694). Midland, MI: Dow Chemical Company.

Stolzenberg, SJ; Hine, CH. (1980). Mutagenicity of 2- and 3-carbon halogenated compounds in the Salmonella/mammalian-microsome test. Environ Mutagen 2: 59-66. http://dx.doi.org/10.1002/em.2860020109

Suzuki, T; Yanagiba, Y; Suda, M; Wang, RS. (2014). Assessment of the genotoxicity of 1,2-dichloropropane and dichloromethane after individual and co-exposure by inhalation in mice. J Occup Health 56: 205-214.

Take, M; Matsumoto, M; Takeuchi, T; Haresaku, M; Kondo, H; Senoh, H; Umeda, Y; Takamura-Enya, T; Fukushima, S. (2014). Inhalation exposure to 1,2-dichloropropane: Distribution of blood and tissue concentrations of 1,2-dichloropropane in rats during and after exposure. J Environ Sci Health A Tox Hazard Subst Environ Eng 49: 1341-1348. http://dx.doi.org/10.1080/10934529.2014.928193

Thorel, JM; Bercoff, E; Massari, P; Droy, JM; Chassagne, P; Proust, B; Hemet, J; Bourreille, J. (1986). [Toxicity of 1,2 dichloropropane. A case with portal hypertension]. J Toxicol Clin Exp 6: 247-252.

Timchalk, C; Dryzga, MD; Smith, FA; Bartels, MJ. (1991). Disposition and metabolism of [14C]1,2-dichloropropane following oral and inhalation exposure in Fischer 344 rats. Toxicology 68: 291-306. http://dx.doi.org/10.1016/0300-483X(91)90076-D

Tomimaru, Y; Kobayashi, S; Wada, H; Hama, N; Kawamoto, K; Eguchi, H; Kira, T; Morii, E; Doki, Y; Mori, M; Nagano, H. (2014). Intrahepatic cholangiocarcinoma in a worker at an offset color proof-printing company: An autopsy case report. Hepatology Research Jun: 488-493. http://dx.doi.org/10.1111/hepr.12363

Trevisan, A; Rizzi, E; Bungaro, A; Pozzobon, L; Gioffre, F; Scapinello, A; Valeri, A; Chiesura, P. (1988). Proximal tubule brush border angiotensin converting enzyme behaviour and nephrotoxicity due to 1,2-dichloropropane. Arch Toxicol 12: 190-192. http://dx.doi.org/10.1007/978-3-642-73113-6_31

Trevisan, A; Rizzi, E; Scapinello, A; Gioffre, F; Chiesura, P. (1989). Liver toxicity due to 1,2-dichloropropane in the rat. Arch Toxicol 63: 445-449. http://dx.doi.org/10.1007/BF00316446

Trevisan, A; Troso, O; Maso, S. (1991). Recovery of biochemical changes induced by 1, 2-dichloro propane in rat liver and kidney. Hum Exp Toxicol 10: 241-244.

U.S. Congress. (1990). Clean Air Act as amended in 1990, Sect. 112 (b) (1) Hazardous air pollutants. Public Law 101-549 Nov. 15, 1990.

U.S. EPA (U.S. Environmental Protection Agency). (1987). Health effects assessment for 1,2-dichloropropane [EPA Report]. (EPA/600/8-88/029). Cincinnati, OH: Environmental Criteria and Assessment Ofiice.

U.S. EPA (U.S. Environmental Protection Agency). (1988). Recommendations for and documentation of biological values for use in risk assessment (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). (1991). Guidelines for developmental toxicity risk assessment (pp. 1-71). (EPA/600/FR-91/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162

U.S. EPA (U.S. Environmental Protection Agency). (1992). Dermal exposure assessment: Principles and applications (interim report) [EPA Report]. (EPA/600/8-91/011B). Washington, DC: Office of Health and Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12188

U.S. EPA (U.S. Environmental Protection Agency). (1994a). Chemical assessments and related activities (CARA) [EPA Report]. (600/R-94/904; OHEA-I-127). Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=60001G8L.txt

U.S. EPA (U.S. Environmental Protection Agency). (1994b). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report] (pp. 1-409). (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). (1998). Reregistration eligibility decision (RED). 1,3-Dichloropropene. Washington, DC: Office Prevention, Pesticides and Toxic Substances. http://www.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-029001_1-Sep-98.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2002a). IRIS summary for 1,2-dichloropropane; CASRN 78-87-5. Washington, DC: U.S. Environmental Protection Agency, Integrated Risk Information System. http://www.epa.gov/iris/subst/0601.htm

U.S. EPA (U.S. Environmental Protection Agency). (2002b). A review of the reference dose and reference concentration processes (pp. 1-192). (EPA/630/P-02/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/osa/review-reference-dose-and-reference-concentration-processes

U.S. EPA (U.S. Environmental Protection Agency). (2005). Guidelines for carcinogen risk assessment [EPA Report] (pp. 1-166). (EPA/630/P-03/001F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www2.epa.gov/osa/guidelines-carcinogen-risk-assessment

U.S. EPA (U.S. Environmental Protection Agency). (2011a). Dichloropropane, 1,2- (CASRN 78-87-5). Health Effects Assessment Summary Tables for Superfund (HEAST). Washington, DC: Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response. http://epa-heast.ornl.gov/heast.php?chemical=Dichloropropane%2C+1%2C2-

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/R11/0001). 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). (2012a). 1,2-Dichloropropane. Exposure assessment tools and models: Estimation program interface (EPI) suite. Version 4.11 [Fact Sheet]. Washington, DC: Office of Prevention, Pesticides and Toxic Substances. http://www.epa.gov/oppt/exposure/pubs/episuite.htm

U.S. EPA (U.S. Environmental Protection Agency). (2012b). 2012 Edition of the drinking water standards and health advisories [EPA Report]. (EPA/822/S-12/001). Washington, DC: Office of Water. http://www.epa.gov/sites/production/files/2015-09/documents/dwstandards2012.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2012c). Benchmark dose technical guidance (pp. 1-99). (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). (2012d). Chemical data access toll (CDAT). 2012 Chemical data reporting (CDR). CAS 78-87-5, propane, 1,2-dichloro. Available online at http://www.epa.gov/oppt/cdr/index.html

Umeda, Y; Matsumoto, M; Aiso, S; Nishizawa, T; Nagano, K; Arito, H; Fukushima, S. (2010). Inhalation carcinogenicity and toxicity of 1,2-dichloropropane in rats. Inhal Toxicol 22: 1116-1126. http://dx.doi.org/10.3109/08958378.2010.526973

Utsumi, H; Hakoda, M; Kiyoshige, K; Manabe, H; Mitade, C; Murayama, J; Han, SK; Hamada, A. (1992). Cytotoxicity and mutagenicity of micropollutants in drinking water. Water Sci Technol 25: 325-332.

von der Hude, W; Behm, C; Gürtler, R; Basler, A. (1988). Evaluation of the SOS chromotest. Mutat Res 203: 81-94. http://dx.doi.org/10.1016/0165-1161(88)90023-4

Von Der Hude, W; Scheutwinkel, M; Gramlich, U; Fissler, B; Basler, A. (1987). Genotoxicity of three-carbon compounds evaluated in the SCE test in vitro. Environ Mol Mutagen 9: 401-410. http://dx.doi.org/10.1002/em.2860090406

WHO (World Health Organization). (2016). Online catalog for the Environmental Health Criteria (EHC) monographs. Available online at http://www.who.int/ipcs/publications/ehc/en/

Woodruff, RC; Mason, JM; Valencia, R; Zimmering, S. (1985). Chemical mutagenesis testing in Drosophila. V. Results of 53 coded compounds tested for the National Toxicology Program. Environ Mutagen 7: 677-702. http://dx.doi.org/10.1002/em.2860070507

Yamada, K; Kumagai, S; Nagoya, T; Endo, G. (2014). Chemical exposure levels in printing workers with cholangiocarcinoma. J Occup Health 56: 332-338. http://dx.doi.org/10.1539/joh.14-0073-OA

Zedda, S; Sala, C; Pozzi, C; Locatelli, F. (1900). Human acute poisoning due to 1,2-dichloropropane. (NIOSH/00145827). Zedda, S; Sala, C; Pozzi, C; Locatelli, F.

Zhang, L; Zong, C; Ichihara, S; Naito, H; Toyokuni, S; Kumagai, S; Ichihara, G. (2015). A trial to find appropriate animal models of dichloropropane-induced cholangiocarcinoma based on the hepatic distribution of glutathione S-transferases. J Occup Health 57: 548-554. http://dx.doi.org/10.1539/joh.15-0085-OA