

Provisional Peer-Reviewed Toxicity Values for

Dicyclopentadiene
(CASRN 77-73-6)

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
LOAEL _{ADJ}	LOAEL adjusted to continuous exposure duration
LOAEL _{HEC}	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
NOAEL _{ADJ}	NOAEL adjusted to continuous exposure duration
NOAEL _{HEC}	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF _A	interspecies uncertainty factor
UF _C	composite uncertainty factor
UF _D	database uncertainty factor
UF _H	intraspecies uncertainty factor
UF _L	LOAEL-to-NOAEL uncertainty factor
UF _S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PEER-REVIEWED PROVISIONAL TOXICITY VALUES FOR DICYCLOPENTADIENE (CASRN 77-73-6)

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 (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

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

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

QUESTIONS REGARDING PPRTVs

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

INTRODUCTION

Dicyclopentadiene (DCPD), CAS No. 77-73-6, is a flammable, colorless, crystalline solid (structure provided in Figure 1) with an unpleasant, camphor-like odor (NIOSH, 2010). DCPD has a high vapor pressure at ambient temperatures, indicating volatility. DCPD, with a molecular formula of $C_{10}H_{12}$, is the dimer of cyclopentadiene (CPD) formed by a Diels-Alder addition reaction. DCPD is a highly reactive intermediate product originated from high temperature cracking of petroleum fractions. DCPD is used for a wide range of resins including aromatic hydrocarbons, unsaturated polyesters, phenolics, and epoxies; it is also used as a chemical intermediate in the manufacture of insecticides, paints, varnishes, and flame retardants for plastics. Table 1 provides basic physicochemical properties for DCPD.

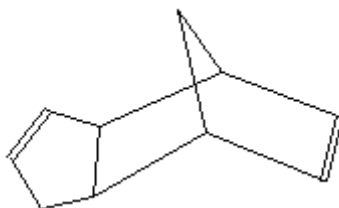


Figure 1. DCPD Structure

Table 1. Physicochemical Properties of DCPD (CASRN 77-73-6)^a	
Property (unit)	Value
Boiling point (°C)	172
Melting point (°C)	32–34
Density (g/cm ³)	0.98
Vapor pressure (mmHg at 20°C)	1.4
pH (unitless)	ND
Solubility in water (% by weight, g/100 mL at 20°C)	0.02
Relative vapor density (air = 1)	4.6–4.7
Molecular weight (g/mol)	132.2

^aSource: NIOSH (2010); IPCS (2005).

ND = no data.

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

Table 2. Summary of Available Toxicity Values for DCPD (CASRN 77-73-6)				
Source/Parameter^a	Value (Applicability)	Notes	Reference	Date Accessed
Noncancer				
ACGIH	8-hr TLV-TWA: 5 ppm	Based on upper respiratory tract, lower respiratory tract, and eye irritation.	ACGIH (2013)	NA
ATSDR	NV	NA	ATSDR (2012)	NA
Cal/EPA	NV	NA	Cal/EPA (2009) ^b	8-1-2013 ^b
NIOSH	8-TWA: 5 ppm	NA	NIOSH (2010)	NA
OSHA	NV	NA	OSHA (2006, 2011)	NA
IRIS	NV	NA	U.S. EPA	8-2-2013
Drinking water	NV	NA	U.S. EPA (2011a)	NA
HEAST	NV	NA	U.S. EPA (2011b)	NA
CARA HEEP	NV	NA	U.S. EPA (1994a)	NA
WHO	NV	NA	WHO	8-5-2013
Cancer				
ACGIH	NV	NA	ACGIH (2013)	NA
IRIS	NV	NA	U.S. EPA	8-2-2013
HEAST	NV	NA	U.S. EPA (2011b)	NA
IARC	NV	NA	IARC	NA
NTP	NV	NA	NTP (2011)	NA
Cal/EPA	NV	NA	Cal/EPA (2009)	NA

^aSources: American Conference of Governmental Industrial Hygienists (ACGIH); Agency for Toxic Substances and Disease Registry (ATSDR); California Environmental Protection Agency (Cal/EPA); National Institute for Occupational Safety and Health (NIOSH); Occupational Safety and Health Administration (OSHA); Chemical Assessments and Related Activities (CARA); Health and Environmental Effects Profile (HEEP); World Health Organization (WHO); Integrated Risk Information System (IRIS); Health Effects Assessment Summary Tables (HEAST); International Agency for Research on Cancer (IARC); National Toxicology Program (NTP).

^bThe Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) Toxicity Criteria Database (<http://oehha.ca.gov/tcdb/index.asp>) was also reviewed and found to contain no information on DCPD.

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

Literature searches were conducted on sources published from 1900 through November 2013 for studies relevant to the derivation of provisional toxicity values for DCPD, CAS No. 77-73-6. The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for relevant health information: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 3 provides an overview of the relevant database for DCPD and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. The phrase “statistical significance,” used throughout the document, indicates a *p*-value of <0.05.

Table 3. Summary of Potentially Relevant Data for DCPD (CASRN 77-73-6)

Category	Number Of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry ^a	Critical Effects	NOAEL ^a	BMDL/BMCL ^a	LOAEL ^a	Reference (Comments)	Notes ^b
Human								
1. Oral								
Acute ^c	ND							
Short-term ^d	ND							
Long-term ^e	ND							
Chronic ^f	ND							
2. Inhalation (mg/m³)^a								
Acute ^c	ND							
Short-term ^d	ND							
Long-term ^e	ND							
Chronic ^f	15/0 workers in plastic products and DCPD recovery, retrospective, evaluated births 1980–1997	No exposure measures but generally exposed to DCPD, CPD, epoxy resin, bisphenol A, and epichlorohydrin	Statistically significant excess of female births (6 males and 18 females, binomial test; $p < 0.01$)	NDr	NDr	NDr	Okubo et al. (2000)	PR
Animal								
1. Oral (mg/kg-d)^a								
Subchronic	30/30, S-D rat, diet, 7 d/wk, 90 d	Males: 0, 6.3, 19.2, or 57.4 Females: 0, 7.2, 22.6, or 68.1 (Adjusted)	No biologically significant effects	M: 57.4 F: 68.1	DU	NDr	Hart (1976)	NPR ^g

Table 3. Summary of Potentially Relevant Data for DCPD (CASRN 77-73-6)

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	32/32, Swiss albino mouse, diet, 7 d/wk, 90 d	Males: 0, 5.6, 17.0, or 49.5 Females: 0, 8.1, 22.7, or 68.4 (Adjusted)	No biologically significant effects	M: 49.5 F: 68.4	DU	NDr	Hart (1976)	NPR ^g
	4/4, Beagle dog, diet, 7 d/wk, 13 wk	Males: 0, 2.7, 8.4, or 28.2 Females: 0, 2.7, 8.6, or 28.8 (Adjusted)	No biologically significant effects	M: 28.2 F: 28.8	DU	NDr	Hart (1980)	NPR ^g
Chronic	ND							
Developmental	0/20 CRL:COBS CD (SD) BR rats diet, GDs 6–15	0, 6.2, 21, or 63	No biologically significant effects	63	DU	NDr	Hart (1980)	NPR ^g

Table 3. Summary of Potentially Relevant Data for DCPD (CASRN 77-73-6)

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	10/20 CRL:COB (SD) BR rat, diet, 3-generation reproductive study	F0 generation parents: Males: 0, 3.6, or 34.2 Females: 0, 4.8, or 48.1 (Adjusted) F1 generation parents: Males: 0, 4.3, or 39.9 Females: 0, 7.8, or 60.7 (Adjusted) F2 generation parents: Males: 0, 4.6, or 44.1 Females: 0, 8.1, or 73.1 (Adjusted)	F0 generation: no compound-related effects in F1 litter of pups; no dose-related changes following gross necropsy of F0 parents F1 generation: no compound-related effects in F2 litter of pups; no dose-related changes following gross necropsy of F1 parents F2 generation: statistically significant reduction in mean pup weight at weaning (but not at birth) in F3b litter of pups at highest exposure; no compound-related effects in F3 litter of pups; no dose-related changes following gross necropsy of F2 parents	M: 34.2 F: 48.1	DU	NDr	Hart (1980)	NPR ^g

Table 3. Summary of Potentially Relevant Data for DCPD (CASRN 77-73-6)

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	20/20, S-D rat, gavage, continuous breeding protocol, select weanlings dosed identically to parents and bred	0, 10, 30, or 100 (Adjusted)	28% fewer F1 pups born live, 8% lower adjusted live F1 pup weights, higher F1 pup mortality, increased cumulative days to litter, and decreased F1 pup survival in high-dose F0 females; slight decrease in pup weight in F2 at 30 mg/kg and in crossover mating in DCPD-treated females; increased liver and kidney weights in both F1 and F2 generations; histopathological changes in liver in F2 at 30 and 100 mg/kg-d	10	DU	30	Jamieson et al. (1995) (abstract only)	NPR
	6/24, mink, diet, 1-generation reproductive study (12 mo)	0, 23.6, 42.4, 85.0, or 169.9 (Adjusted)	Statistically significant, dose-related reduction in kit weight (absolute) during lactation at 42.4, 85.0, and 169.9 mg/kg-d	23.6	DU	42.4	Aulerich et al. (1979)	NPR, PS ^g
Carcinogenic	ND							
2. Inhalation (mg/m³)^a								
Subchronic	51/51, F344 rat, 6 hr/d, 5 d/wk, 13 wk	0, 0.97, 4.9, or 49	Increased formation of hyaline droplets in proximal convoluted tubules of the kidneys in male rats	M: 0.97 F: 49	DU	M: 4.9 F: NDr	Exxon (1980); Dodd et al. (1982); Bevan et al. (1992)	NPR, PS

Table 3. Summary of Potentially Relevant Data for DCPD (CASRN 77-73-6)

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	12/12, Harlan-Wistar rat, 7 hr/d, 5 d/wk, 89 d	0, 22.2, 39.7, or 83.1	Histologic lesions in the kidneys (i.e., round cell accumulations, dilated tubules, casts, and tubular degeneration) in both sexes at concentrations ≥ 39.7 mg/m ³ ; effects were more severe and frequent in males as compared to females	22.2	DU	39.7	Kinkead et al. (1971)	PR
	45/45, B6C3F ₁ mouse, vapor, 6 hr/d, 5 d/wk, 13 wk	0, 0.97, 4.9, or 49	Increased mortality reported at 49 mg/m ³	4.9	NDR	49 (FEL)	Exxon (1980); Dodd et al. (1982)	NPR
	3, male Beagle dog, 7 hr/d, 5 d/wk, 89 d	0, 10.0, 26.5, or 36.5	Increased absolute kidney weight in male dogs	10	DU	26.5	Kinkead et al. (1971)	PR
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

^aDosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m³) for inhalation noncancer effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous exposure. Values from animal developmental studies are not adjusted to a continuous exposure M= males, F= females.

^bNotes: PS = principal study, PR = peer reviewed, NPR = not peer reviewed.

^cAcute = Exposure for 24 hr or less (U.S. EPA, 2002).

^dShort-term = Repeated exposure for >24 hr \leq 30 d (U.S. EPA, 2002).

^eLong-term = Repeated exposure for >30 d \leq 10% lifespan (based on 70-yr typical lifespan) (U.S. EPA, 2002).

^fChronic = Repeated exposure for \geq 10% lifespan (U.S. EPA, 2002).

^gStudy evaluated by IRIS for the assessment of the related compound diisopropyl methylphosphonate (DIMP).

DU = data unsuitable; GD = Gestational Day; ND = no data; NDR = not determined; S-D = Sprague-Dawley.

HUMAN STUDIES

Oral Exposures

No studies were identified.

Inhalation Exposures

The effects of inhalation exposure of humans to DCPD have been evaluated in one chronic-duration epidemiologic retrospective study looking at reproductive endpoints (Okubo et al., 2000).

Acute, Short-Term, and Long-Term Studies

No studies were identified.

Chronic-Duration Studies

Okubo et al. (2000)

Okubo et al. (2000) is a published, peer-reviewed retrospective epidemiologic study characterizing the offspring of 15 male Japanese workers (mean age of 36.1 ± 7.3 years) in a plastic products and DCPC recovery facility. The workers were engaged in the same type of work and exposed to a mixture of epoxy resin, DCPD, cyclopentadiene, bisphenol A, and epichlorohydrin throughout the observation period (1980–1997). No concentration information for this mixture was provided. Individual interviews were conducted with the workers in March 1998 to determine the sex of offspring, birth year, paternal age at start of tenure with the company, and working period until the birth of offspring.

Results showed that the average age at start of tenure with the company was 19.3 ± 1.1 years (ranging from 19 to 22 years), and the average working period until the birth of offspring was 9.5 ± 3.7 years (Okubo et al., 2000). A statistically significant excess of female births (6 males and 18 females, binomial test; $p < 0.01$) were fathered by the workers for the observation period; however, the study authors reported no statistically significant relationship between the sex ratio and birth year, paternal age at the birth of offspring, paternal age at start of tenure with company, or the working period until the birth of offspring. Due to the small number of cases (15) and the exposure to a mixture of chemicals (of which DCPD was one of many chemicals used in the facility), the determination of a NOAEL or LOAEL is precluded.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to DCPD have been evaluated in three subchronic-duration studies (Hart, 1976 [rat and mouse], 1980), one developmental toxicity study (Hart, 1980) and three reproductive toxicity studies (Aulerich et al., 1979; Hart, 1980; Jamieson et al., 1995) studies.

Subchronic-Duration Studies

Hart (1976)

Hart (1976) conducted a subchronic-duration (90-day) oral toxicity study of DCPD administered through the diet of rats for Litton Bionetics, Inc. Concentrations of 80-, 250-, and 50-ppm DCPD (purity 98–99%) to 30 male and 30 female Sprague-Dawley (S-D) rats per

treatment group in a Purina Rat Chow diet, 7 days/week for 90 days. Average daily doses¹ of 0, 6.3, 19.2, or 57.4 mg/kg-day for male rats and 0, 7.2, 22.6, or 68.1 mg/kg-day for female rats have been calculated using time-weighted average body weights and food consumption calculated on a weekly basis. The control group (30 male and 30 female) received standard feed without DCPD. Body weights and food consumption were recorded on a weekly basis as were animal appearance, behavior, and overt signs of toxicity or pharmacologic effects. Mortality was assessed daily. Prior to the administration of the compound and again during the final week of exposure, a veterinarian performed an ophthalmoscopic examination on each animal. Clinical laboratory measurements were conducted on five rats per sex per group at Weeks 4 and 13 postdosing. These measurements included hemocytology (i.e., erythrocyte count, cell packed volume, hemoglobin, and total and differential leukocyte counts), blood biochemistry (i.e., glucose, blood urea nitrogen [BUN], serum glutamic oxaloacetic transaminase [SGOT], alkaline phosphatase, serum glutamic pyruvic transaminase [SGPT], sodium, potassium, and chloride), and urinalysis (i.e., color, specific gravity, pH, sugar, protein [albumin], ketones [acetone], and microscopic examination of sediment). At study termination, animals were necropsied. The following organs were removed and weighed: brain, thyroid, heart, liver, spleen, kidneys, adrenal glands, testes (male), and ovaries (female). This study was not peer-reviewed and did not report Good Laboratory Practice (GLP) compliance.

Results of the hemocytology and blood biochemistry analysis at the 4- and 13-week interval show no treatment-related effects (Hart, 1976); the few instances of statistically significant differences from control values are scattered, and the study author reported them as having “no toxicological importance.” Additionally, no deviations from normal baseline values were obtained in the urinalysis results at either Week 4 or at the termination of the study (Week 13). The absolute weights of various organs collected during necropsy were recorded and presented as original data (see Tables B.1 for males and B.2 for females); calculations of the relative organ weights were also made (see Table B.3 for male rats and Table B.4 for female rats). The study author did not provide statistical analyses of organ-weight data. An independent statistical analysis performed for the purposes of this review revealed no dose-dependent changes in absolute and relative organ-weights. In females, the few statistically significant differences that were observed were not $\geq 10\%$ change and do not meet the criterion of biological significance. For male rats, a significant increase in thyroid weight was observed that exceeded 10% compared to control. This increase was noted at all doses for both relative and absolute thyroid weight but was statistically significant only in the low- and mid-dose groups for absolute weight. Also, a biologically and statistically significant increase in absolute spleen and adrenal weight at the mid dose only (i.e., no dose response) was observed. The results of the histopathological examination show the presence of microscopic lesions. These lesions appeared in all dose groups and were synonymous with those routinely encountered in rats (as reported by the veterinary pathologist that examined the animals). Thus, it is difficult to interpret the sporadic changes observed in organ weight. No other abnormalities were reported. The study author did not define a NOAEL or LOAEL; however, based on the lack of observed toxicity at any of the DCPD concentrations measured, the highest concentration (57.4 mg/kg-day for males and 68.1 mg/kg-day for females) is considered the NOAEL. A LOAEL is precluded.

¹Average daily dose = dose in ppm \times (food consumption \div body weight) \times (days dosed \div total days). Average daily dose = 80 ppm \times (17.23 \div 190.6) \times (7 \div 7) = 7.2 mg/kg-day.

Hart (1976)

Hart (1976) also conducted a subchronic-duration (90-day) oral toxicity study of DCPD on mice for Litton Bionetics, Inc. Swiss Albino mice, 32 male and 32 female, (64 mice per exposure group) were exposed to 28-, 91-, or 273-ppm DCPD (purity 98–99%) in feed 7 days/week for 90 days. The control group (32 mice per sex) was fed a standard rodent chow with no addition of DCPD. Average daily doses of 0, 5.6, 17.0, or 49.5 mg/kg-day for male mice and 0, 8.1, 22.7, or 68.4 mg/kg-day for female mice were calculated using time-weighted average body weights and weekly food consumption. The mice were housed in groups of five in solid-bottom cages throughout the experiment. Body weights and food consumption were recorded on a weekly basis, daily observations for mortality were made, and daily records for appearance, behavior, and signs of toxic or pharmacologic effects were kept. Although a recovery period of 2 and 4 weeks had been initially planned, this was later eliminated by agreement with the project officer when no effects were observed; all surviving mice at the termination of the experiment were sacrificed. Following sacrifice, each animal was subjected to a gross necropsy where any abnormalities observed were recorded. The heart, liver, spleen, kidneys, gonads, and adrenals and thyroid (both after fixation) were removed and weighed. The following organ samples were also collected and preserved in 10% neutral formalin: brain, pituitary, thyroid, lung, heart, liver, spleen, kidneys, adrenals, stomach, pancreas, small and large intestine, mesenteric lymph node, nerve with muscle, testes with epididymis, seminal vesicles, ovaries, uterus, bone marrow, urinary bladder, thoracic spinal cord, eye, rib junction, and any additional organ structures showing lesions. A histopathologic examination was also performed on five male and five female mice from both the control and highest (68.4 mg/kg-day) treatment groups; tissues showing any abnormalities in the highest treatment group were subsequently also examined in the lower dose groups. Tissues examined included brain, pituitary, thyroid, heart, liver, spleen, kidneys, adrenals, stomach, pancreas, small and large intestine, mesenteric lymph node, testes or ovaries, uterus or prostate, bone marrow, urinary bladder, and any other tissues showing unusual lesions.

All mice but one survived until planned sacrifice (Hart, 1976). Because the mice were housed as a group during the exposure ($n = 5/\text{group}$), the weights of the group, and not individual mice, were recorded. The average body weight for each group was not found to be statistically different; the author reported similar growth in all treatment groups. Food consumption values were also calculated as averages for five mice per cage at each exposure concentration. The author reported that no differences in food consumption were observed between the treatment and control groups. No signs of toxicity were noted in any of the groups of mice throughout the experiment. The study author did not provide statistical analyses of organ-weight data. An independent statistical analysis revealed a statistically significant decrease in absolute and relative thyroid weights in female mice at the mid dose but this decrease was not dose dependent (see Tables B.5 and B.7). In male mice, sporadic differences in both absolute and relative organ weights were observed (see Tables B.6 and B.8). In male mice, the only statistically significant changes in absolute organ weight occurred at the mid dose and included decreases of >10% for spleen and testes and 9% for kidney. Relative liver weight was also statistically significantly decreased in male mice at all doses, but the decrease did not reach biological significance (i.e. change was <10%). Relative spleen weight was statistically and biologically (i.e., >10%) significantly decreased in the low and mid dose groups, but not in the high dose group. Relative kidney weights were statistically significantly decreased at all doses, but only the mid dose was biologically significant. Relative testes weights were statistically and biologically significantly depressed at all doses, but no dose-response trend was observed. Following a histopathologic

examination by a veterinary pathologist, all lesions observed in the study were those routinely encountered in unexposed mice. These lesions were found in all dose groups and were not different than those reported in controls. Thus, it is difficult to interpret the sporadic changes in organ weights. No additional abnormalities were noted, and the study author concluded that no evidence of toxicity occurred during the 13-week study following dietary administration of 0-, 5.6-, 17.0-, or 49.5- and 0-, 8.1-, 22.6-, or 68.4-mg/kg-day DCPD in male and female mice, respectively. The study author did not define a NOAEL or LOAEL; however, based on the lack of biologically significant effects at any of the DCPD concentrations measured, the highest concentration (49.5 mg/kg-day in males and 68.4 mg/kg-day in females) is considered the NOAEL. Identification of a LOAEL is precluded.

Hart (1980)

Hart (1980) conducted a subchronic-duration (90-day) oral toxicity study of DCPD on dogs for Litton Bionetics, Inc. Thirty-two purebred beagle dogs (16 male and 16 females, 5 to 6 months old) were received and housed individually in stainless steel cages. Prior to the initiation of the study, all animals were subjected to a preliminary health screening, which included clinical, biochemical, hematological, ophthalmological, and parasitological examinations. Protozoan parasites (*Giardia canis*, *Isopora* and *Trichomonas* species) were found in 16 (50%) of the dogs. The study author considered the parasites to be nonpathogenic and cleared the dogs for use in the study. Eight dogs in each group (four male and four female) were randomly assigned to treatment groups and exposed to 0-, 100-, 300-, and 1,000-ppm DCPD (purity 98–99%). The doses were prepared in corn oil and blended into dog meal. All dogs were given daily administrations of the compound through feed, 7 days/week, for 13 weeks; based on reported time-weighted average body weight and food consumption data, average daily doses of 0, 2.7, 8.4, or 28.2 mg/kg-day for males and 0, 2.7, 8.6, or 28.8 mg/kg-day for females were calculated. Water was provided ad libitum. Animals were observed daily for general appearance, behavior, food consumption, and fecal consistency. Body weights were recorded weekly for each animal, and blood samples were collected from each dog at the initiation of the study, as well as at Weeks 4, 8, and 13 for pathological determinations. Dogs were fasted overnight prior to the collection of each sample. The study author did not report GLP compliance status.

Blood collected from each animal was used for hematology (i.e., hemoglobin, erythrocytes, leukocytes, differential count, and packed cell volume) and blood chemistry (i.e., glucose, calcium, urea nitrogen, SGPT, SGOT, uric acid, alkaline phosphatase, total protein, albumin, cholesterol, lactic dehydrogenase, phosphorus, and bilirubin). Following overnight fasting, urinalysis was also performed on all animals at study initiation and at 8 and 13 weeks of exposure to measure specific gravity, pH, color, sugar, albumin, ketones, occult blood, bilirubin, and a microscopic examination of sediment. Additionally, a veterinary ophthalmologist performed examinations on each animal initially and again prior to study termination. Animals were sacrificed at 94–97 days of exposure. Following termination, the animals were weighed and subjected to a complete necropsy, with the following organs and tissues weighed and preserved for analysis: brain, pituitary, spinal cord, eye, stomach, small and large intestine, testes with epididymis, thyroid, pancreas, lung, heart, rib junction, gall bladder, liver, spleen, kidneys, adrenal glands, prostate, ovary, uterus, bone marrow, skeletal muscle and nerve, urinary bladder, mammary gland, mesenteric lymph node, and any other unusual lesions. A veterinarian completed pathological evaluations of the tissues from dogs, representing both the control and high-dose groups.

No mortality was observed in any of the treatment groups throughout the duration of the study (Hart, 1980). The recorded clinical observations showed no remarkable differences between treated and control groups with the possible exception of a slightly higher frequency of vomiting and soft stools among the treated dogs, especially those from the highest treatment group (28.2 mg/kg-day for males and 28.8 mg/kg-day for females). However, similar observations were made in some of the control animals and these effects (i.e., vomiting and soft stools) were considered minor in all groups. Therefore, the biological significance of these findings is not clear. No other dose-dependent effects were reported.

The study author concluded that the treatment concentrations produced no significant toxicity with only minor intestinal distress (i.e., vomiting and soft stools) observed in dogs from all treatment groups but also occasionally observed in the control animals. The author did not report a NOAEL or LOAEL for the study. Due to a lack of treatment-related effects observed at the highest dose administered, a NOAEL of 28.2 mg/kg-day for males and 28.8 mg/kg-day for females is identified. Identification of a LOAEL is precluded because the highest dose tested is considered a NOAEL.

Chronic-Duration Studies

No chronic-duration studies were identified.

Developmental Studies

Hart (1980)

Hart (1980) administered DCPD (purity >98%) daily at 0, 80, 250, and 750 ppm to groups of 20 CRL:COBS CD (SD) BR pregnant rats in food on Gestational Days (GDs) 6–15. Average doses of 0, 6.2, 21, and 63 mg/kg-day were calculated using time-weighted average body weights and weekly food consumption. The study author examined the animals daily for mortality and signs of toxicity and recorded body weights on GDs 0, 6, 9, 15, and 19. Food consumption was measured during GDs 0–6, 6–16, and 16–19. The animals were sacrificed on GD 19, and the visceral and thoracic organs (not otherwise specified) were examined. The uterus was removed and examined. The number of implantations sites and their placement in the uterine horns, live and dead fetuses, and resorption sites were recorded.

One third of the fetuses of each litter were fixed in Bouin's fluid and later examined for changes to the soft tissues of the head and thoracic and visceral organs. The remaining fetuses were examined for skeletal abnormalities. Statistical analysis of data used the litter as the basic sampling unit. Dunnett's *t*-test was applied to body weights, food consumption, and litter averages of pup weight; ratios were analyzed using a 2 × 2 contingency table with Yates' correction; and discontinuous parameters were analyzed using the Wilcoxon Rank Sum method.

No deaths were observed in the control or treatment groups. One female rat in the low-dose group appeared sick and emaciated, but examination at necropsy indicated that this was not treatment related. No statistically significant differences were observed between any of the treated groups and the control group with respect to mean body weight and food consumption. Examination of the uterine contents at GD 19 revealed no effect from the treatment with DCPD at any dose (see Table B.9). Fetuses in all treatment and control groups had subcutaneous hematomas that were not considered to be treatment related.

The sex ratio in the treated groups was not statistically different from the control group (see Table B.10), and the results of the skeletal examination revealed common abnormalities that were not treatment related (see Table B.11). Based on these findings, the study author identified a NOAEL of 63 mg/kg-day for maternal and fetal effects. A LOAEL for either maternal or fetal toxicity was not identified for DCPD.

Reproductive Studies

Hart (1980)

Hart (1980) conducted a three-generation reproductive and developmental study in which groups of 10 male and 20 female CRL:COB (SD) BR rats (Charles River Breeding Laboratories, Inc., Portage, MI) were administered 0, 80, or 750 ppm (0, 87, and 92% of the desired concentration, equivalent to 0, 69, or 690 ppm) DCPD (purity 98–99%; in corn oil) in diets prepared weekly. The F0 generation was administered DCPD starting at 7 weeks prior to mating. The length of treatment for each of the generations is not specified in the study report. Parental rats in each generation were mated twice to produce “a” and “b” sets of offspring. Adjusted daily doses for the male and female rats were calculated utilizing measured food consumption and body-weight data. The adjusted daily doses for the F0 generation were 0, 3.6, or 34.2 and 0, 4.8, or 48.1 mg/kg-day for male and female rats, respectively; 0, 4.3, or 39.9 and 0, 7.8, or 60.7 mg/kg-day for male and female rats in the F1 generation, respectively; and 0, 4.6, or 44.1 and 0, 8.1, or 73.1 mg/kg-day for male and female rats in the F2 generation, respectively. The F3 generation did not receive direct dietary treatment. Hereafter, the treatment groups are referred to as “low” and “high,” including in the data tables in Appendix B. Food (Purina laboratory chow) and water were provided to the animals ad libitum. This study was not peer-reviewed but a portion of the Hart (1980) study in which diisopropyl methylphosphonate (DIMP) was administered with identical methodology as DCPD was evaluated by IRIS and employed as the principal study for their assessment of DIMP (U.S. EPA, 1993). It is unclear if this study was conducted according to GLP; no certificate is supplied in the report.

Mating began 7 weeks after administration initiation. At the end of the mating, females were returned to individual cages for the gestation and lactation periods. One week following the weaning of the first litter of pups (F1a), the F0 parental animals were remated, each male with a different pair of females in the same exposure group. One week after weaning the second litter (F1b), the F0 parents were sacrificed and necropsied. One male and two female F1b pups from each litter became the parents for the next generation (F2). These animals were maintained and treated identically to the F0 parental animals. When the F1b rats were approximately 100 days old, they were mated to produce F2a and F2b litters. The same procedure was used to produce the F3a and F3b pups.

At Week 4 and during Weeks 8–9, the body weight and food consumption of the parent rats were measured. These parameters were estimated and recorded prior to each mating. Rats were observed daily for mortality and general toxicity, as well as any gross abnormalities in pups, number of live and dead pups, pup mean body weight by sex at birth, number of animals per sex at Day 4 of lactation, and number per sex and body weights at Day 21 (weaning). At Day 4, each litter was reduced to eight total pups (four/sex when possible). For each generation, gross necropsies were performed on one-third of the first litters at weaning.

Results from the first generation (including the F0 parents and F1a and F1b offspring) show that mortality occurred in one F0 female at the low dose; all other animals survived the study, and the study author reported them as being in “generally good condition.” No statistically significant changes in body weight or food consumption were observed between control and treatment groups in the F0 generation. No dose-related changes were reported following the gross necropsy of the F0 parents. Observation revealed that one pup in the low exposure litter had an opaque left eye, and one pup in the high treatment group had a crooked tail. The author reported that such observations were not treatment related and therefore “not meaningful.” Similar results were reported in the F1b generation, with the control and treatment group being comparable with respect to both litter data and pup observations. One instance of an abnormality (a deformed hind foot) was reported in a pup exposed at the low level, but again, the author did not consider this effect related to treatment.

In the second generation (comprising the F1b parents and F2a and F2b offspring), no difference in body weights between the control and treatment-related groups was observed, with the exception of a slight reduction (which was not statistically significant) in body weight in the low-dose parental females at Week 20 and just prior to mating. Food consumption followed a similar trend, with statistically significant reduced food consumption in both the males and females in the high exposure group at Week 20. The F2a (see Table B.12) and F2b (see Table B.13) litter data showed no biologically significant differences between the control and exposure groups. Fertility was reduced (25% and 15% of controls, respectively) in the high female exposure group in both litters (F2a and F2b), but these reductions were not statistically significant. The study author noted that one male in the 39.9-mg/kg-day treatment group in each litter failed to sire a litter and that this may have been the cause of the decreased fertility in the high-dose females. Although a statistically significant decrease in pup viability was observed in the low-dose F2a litter, it is not considered biologically significant because no similar change was observed in the high-dose F2a litter, and no toxicologically relevant changes were observed in any of the F2b litters either. No gross lesions were found in the F1b parents during necropsy.

Both general and necropsy observations in the F3a and F3b offspring as well as gross necropsy findings in the F2b parents did not yield any compound-related effects. A slight, but statistically significant, reduction in mean pup weight at weaning was observed in the treatment groups when compared to the controls in the high-dose group (see Table B.14). The study author indicated that this decrease in pup weight was not biologically significant due to the lack of weight changes seen in the other litter (F3a) of this generation (see Table B.15) or in prior generations. However, there are no indications that this finding was caused by reduced palatability (food consumption was not decreased in parents or offspring) or reductions in maternal body weight (female F2 parental body weight was comparable to controls). Furthermore, pup viability was not decreased compared to controls (in a statistically or biologically significant manner), so the statistically significant decrease in body weight was not likely affected by sample size. An overall reduction in female fertility compared to males was observed in the F3a offspring (80 and 83% in the low and high treatment groups, respectively); however, the fertility in the female control group was only 65%, and therefore, changes were deemed not related to compound administration (see Table B.15). This lower overall fertility also carried over to the F3b offspring, where fertility was 80 and 83% for low and high treatment groups, respectively, but was not statistically significantly different from controls, which had a fertility index of 85% (see Table B.14).

The study author concluded that dietary administration of DCPD to three successive generations of male and female rats resulted in no deleterious effects in either general condition or reproductive performance of the animals when compared to control rats. Based on the lack of reproductive effects, NOAELs of 34.2 and 48.1 mg/kg-day for males and females, respectively, are identified. Identification of a LOAEL is precluded.

Jamieson et al. (1995)

In a study conducted by Jamieson et al. (1995) and published as a Society of Toxicology conference abstract, the reproductive effect of DCPD on S-D rats was assessed. Because the study was published as a conference abstract, the study methods were not completely reported; however, the following details were available. DCPD (purity not specified) was administered by gavage (using corn oil as a vehicle control) at dose levels of 0, 10, 30, and 100 mg/kg-day to male and female animals housed individually and then housed together for 16 weeks (20 animals/sex/group). Newborn litters were sacrificed on Postnatal Day (PND) 1 following evaluation, and litters born on Week 17 or later were reared to PND 21. At this time, selected weanlings (F1) were administered the same dose levels as their parents. On PND 81 ± 10, F1 animals were housed together within groups for 1 week and necropsied after the delivery of a litter (F2). The abstract did not report GLP compliance during the study, and the statistical tests used for comparison of control and treatment groups were not stated.

Females exposed to 100 mg/kg-day exhibited higher F1 pup mortality, 28% fewer live pups, 8% lower adjusted live F1 pup weight, and increased cumulative days to litter. At 30 mg/kg-day, female pup weight was decreased approximately 4%. In a crossover mating study, pup weight was reduced (9%) in litters born to the DCPD-treated females; this effect was not observed in litters produced from DCPD-treated males. Treatment with DCPD also affected organ weight in F1 rats, with increases of 2, 7, and 17% in liver weight and increases of 16, 15, and 16% in kidney weight in males treated with 10, 30, and 100 mg/kg-day, respectively (data not shown). When the livers of rats exposed to 30 and 100 mg/kg-day were evaluated microscopically, an increase in clear cell foci was reported (data not shown). In the second (F2) litter, exposure to 100 mg/kg-day DCPD caused a 12% reduction in pup weight when liver and kidney weights were increased in the F1 generation (data not shown).

The study authors concluded that, although reproductive effects were observed in both generations, the effects were greater in the first generation than the second generation. The doses which increased liver and kidney weights in the parents also produced systemic toxicity in newborns, suggesting that DCPD is not selectively a reproductive toxicant. The authors did not identify a NOAEL or LOAEL from the study results; however, based on the reduction in pup survival and weight at birth observed during the study, a NOAEL of 10 mg/kg-day and a LOAEL of 30 mg/kg-day are identified.

Aulerich et al. (1979)

Aulerich et al. (1979) is selected as the principal study for the derivation of the subchronic and chronic p-RfDs. This report is not peer-reviewed but was evaluated by IRIS for the assessment of DIMP (U.S. EPA, 1993). In this one-generation reproductive study, 30 (6 males and 24 females per dose group), 3-month old, dark variety minks were administered 0-, 100-, 200-, 400-, or 800-ppm (estimated as 0, 23.6, 42.4, 85.0, or 169.9 mg/kg-day for combined male and female minks by the study authors through measured food consumption and body-weight data; see Table B.16) DCPD (purity >99%) in the diet for 12 months, equivalent to

one reproductive season. The life span of a mink in captivity has been estimated to be up to 8 years (Basu, 2013); therefore, this 12-month reproductive study represents a chronic exposure duration for the F0 animals as the treatment with DCPD occurred for greater than 10% of the total mink life span. Mortality and other signs of toxic stress were recorded throughout the duration of the experiment, although the frequency was not recorded. Body weight and feed consumption were measured every 2 weeks, with the exception of the gestation period. Blood samples (for packed cell volume and hemoglobin) and blood smears (for differential leukocyte counts) were collected prior to the study initiation, at 3-month intervals through the study, and at the conclusion of the study. All parameters were evaluated utilizing analysis of variance and Dunnett's *t*-test. The authors did not report GLP compliance status.

Mating began on March 1, 1978, and continued for approximately 20 days, during which females were introduced into the males' cages every fourth day for up to an hour (or until a positive mating confirmation was made). Whenever possible, mating pairs in the same treatment group were used. After successful breeding, the females were transferred to individual cages with a nest box and provided with shredded wood, used for both insulation and nesting material during whelping. During whelping (April 20–May 15), the nest boxes were checked daily for evidence of kits; when found, newborn kits were sexed, and both mother and kit were weighed at whelping and when kits were 1 month of age. Gestation length, litter size, sex ratio, kit mortality, increase in kit biomass during lactation, and changes in the weight of the lactating female were recorded. At study termination, all minks were weighed, blood samples collected via cardiac puncture, and the animals sacrificed. The following whole organs were removed during necropsy, weighed, and evaluated for pathomorphological changes: brain, liver, kidneys, spleen, gonads, lungs, heart, and adrenal glands as well as portions of the intestine, stomach, skeletal muscle, adipose tissue, and integument.

Chronic ingestion of DCPD in the diet of minks at concentrations up to 169.9 mg/kg-day for 12 months did not result in treatment-related mortality in any of the groups (Aulerich et al., 1979). Changes in body weight showed no dose-related trend, although in a few instances, animals in the highest exposure group (169.9 mg/kg-day) were reported to have reduced body weights compared to the control animals; however, when analyzed as a change in body-weight percentage over the course of compound administration, these changes were not apparent (see Table B.17). Feed consumption in the high dose group was initially reduced compared to controls but was reported as greater than controls by study termination (although this change was not reported as statistically significant). Changes in hematological values (including packed cell volume, hemoglobin, and differential leukocyte counts) were equally inconsistent and not found to be dose dependent.

No treatment-related effects on reproductive performance were reported in male or female minks following exposure to DCPD. Whelping rates, gestation length, fecundity, kit weight at birth, and secondary sex ratios were also unaffected. Although kit mortality was not altered by DCPD, the absolute weight of kits during lactation was statistically significantly depressed at Week 4 for animals in the 42.4-, 85.0-, or 169.9-mg/kg-day treatment groups (see Table B.18). The study authors hypothesized that the reduced absolute weight was attributable to either a toxicological effect on the kits through direct ingestion of the chemical in milk or indirectly through a perturbation in maternal metabolism, which affected lactation. When the organs were evaluated following study termination, the only statistically significant changes reported between the treatment and control samples were a reduction in spleen weight in the

85.0-mg/kg-day group (2.4 ± 0.16 vs. 3.3 ± 0.29 g, respectively) and a reduction in the weight of the testes in the 169.9-mg/kg-day group (1.1 ± 0.1 vs. 1.8 ± 0.1 g, respectively; see Table B.19). Although a reduction in spleen weight was reported at 85.0 mg/kg-day, this effect was not observed in the highest dose group, and therefore, the study authors explained the reduction as occurring from chance variation or sampling error. Likewise, the study authors explained the reduction in testes weight observed in the high dose group as the normal seasonal reduction that occurs in this species.

The study authors concluded that chronic ingestion of DCPD in the diet of minks had no adverse effect on growth, survival, or reproductive performance. However, the absolute weight of neonates from lactating dams fed 42.4-, 85.0-, or 169.9 mg/kg day DCPD was statistically decreased in a dose-dependent manner compared to that of neonates for dams in the control or low-dose group. Spleen weight was reduced at 85.0 mg/kg-day, and testes weight was reduced at 169.9 mg/kg-day, respectively, but the study authors did not consider these reductions to be treatment related. No NOAEL or LOAEL was reported in the study, but based on reductions in the kit weight following 4 weeks of nursing at the three highest concentrations, a LOAEL of 42.4 mg/kg-day and a NOAEL of 23.6 mg/kg-day are identified.

Inhalation Exposures

The effects of inhalation exposure of animals to DCPD have been evaluated in four subchronic-duration studies (Exxon, 1980 [rat and mouse]; Dodd et al., 1982 [rat and mouse]; Bevan et al., 1992 [rat]; Kinkead et al., 1971 [rat and dog]).

Subchronic-Duration Studies

Exxon (1980); Dodd et al. (1982); Bevan et al. (1992)

Exxon (1980) is selected as the principal study for the derivation of the screening subchronic and chronic p-RfCs. In a non-peer-reviewed subchronic-duration (90-day) inhalation study performed by Exxon (1980) and reported in Dodd et al. (1982), Fischer 344 (F344) rats (51 male and 51 female rats per exposure concentration) were exposed to target concentrations of 0-, 1-, 5-, or 50-ppm in air; actual air concentrations were 0-, 1.0-, 5.1-, or 51.0-ppm DCPD (purity 95%) for 6 hours/day, 5 days/week, for 13 weeks. The corresponding HECs are calculated as 0, 0.97, 4.9, and 49 mg/m³. Nine animals/sex/concentration were sacrificed at Weeks 3, 7, 14, 18, and 27 of the study, with Weeks 18 and 27 corresponding to Weeks 4 and 13 postexposure. These sacrifice periods were identified as Groups A, B, C, D, and E, respectively, throughout the remainder of the study report.

All animals were weighed the morning before the first exposure (reference weight), and this value was subtracted from each subsequent weight measurement to obtain the change in body weight throughout the course of the experiment. Body-weight measurements were taken weekly for the first 4 weeks and then every 2 weeks for the remainder of the exposure. The animals' weights were collected again prior to sacrifice. Mean food (see Table B.20) and water consumption (see Table B.21) were measured during urine collection periods and standardized to 24-hour rates (Group B rats only), allowing comparisons to be made between measurement periods for each exposure group. Each animal also underwent an ophthalmologic examination (prior to sacrifice interval). Other tests included blood chemistry (prior to sacrifice interval), histopathology of kidneys and urinary bladder following necropsy, and electron microscopy of kidney tissue at the sacrifice intervals at Weeks 14 and 17. Additionally, upon sacrifice, a

necropsy of the animal was performed, and the following organs removed and weighed: kidney (left and right, weighed individually), lung, liver, and testes (males). The study authors did not report GLP compliance status.

One male rat died accidentally following the 16th exposure (reason not reported); no other rat mortality was observed in the study. Observation of the rats during the 6-hour exposure period indicated normal appearance of all rats. Several conditions recorded in the exposure groups were also recorded in the control group including urogenital area wetness (females), lacrimation, and alopecia (males). However, during the recovery period, these observations were recorded only in exposed rats, not in control rats. No statistically significant changes in body weight occurred in either the control or exposed rats throughout the study duration. Changes in food consumption results were observed in male and female rats; however, the differences were not related to the DCPD concentration or the number of exposures. A decrease in food consumption was reported at 92 days postexposure in all DCPD exposure groups and was accompanied by a depression in body weight at the 4.9-mg/m³ concentration level. However, the biological significance of these findings was not assessed by the study authors.

Although concentration-related differences were observed with respect to blood analysis, they were not found to be biologically significant. The following differences were observed: hematology (e.g., depression in red blood cells of male rats at the highest exposure concentration), serum chemistry (e.g., an increase in serum calcium and a decrease in alanine aminotransferase in males exposed to 4.9 and 49 mg/m³ DCPD), and the ophthalmologic examination (mild conjunctivitis with lacrimation in the eyes of male rats at both 4.9 and 49 mg/m³ in Group B; a nonreactive dilated pupil was observed in one control [Group C] and one 49-mg/m³ female rat [Group D]; and two female rats exposed to 0.97 and one to 4.9 mg/m³ developed conjunctivitis with lacrimation in Group E).

The urinalysis results showed that the majority of male rats exposed to 49 mg/m³ and many of the rats exposed to 4.9 mg/m³ DCPD had a decrease in urine specific gravity and osmolality, which was concentration dependent and related to the number of DCPD exposures and the concentration of DCPD (see Table B.22). Analysis of the urinary sediment content in male rats showed evidence of toxic renal damage, with epithelial cells and epithelial cell casts being found in rats from 8 completed exposures and after as much as 29 days of recovery (see Table B.22). The presence of the epithelial cells and casts was reported as dependent on the DCPD concentration. Trends in urinary excretion rates were also reported, including a statistically significant decrease in calcium and sodium and an increase in potassium in the latter part of the exposure regimen (in the 49-mg/m³ group; a similar trend was observed in the 4.9-mg/m³ group, although the values were not statistically significant). It is important to note that these findings were solely identified in males, as no abnormal urinary findings were reported in female rats.

The results of the gross necropsy showed an increased incidence of tubular hyperplasia and a reticular pattern in the kidneys of males exposed to 49-mg/m³ DCPD. A similar reticular pattern, accompanied by a generalized color change of the kidney, was observed in Group A male rats exposed to 4.9 and 49 mg/m³ DCPD at an earlier sacrifice period. The study authors reported no statistically significant differences in the gross lesions between exposed and control groups and that these effects were reversible and no longer apparent at the end of the exposure regimen or at recovery sacrifice. Organ weights followed a similar pattern, with a statistically

significant increase in relative liver weights in male rats exposed to the highest concentration of DCPD (Groups A, B, and C). However, the increases at 49 mg/m³ were not greater than 10% over controls (9.9, 4.8, and 6.9 in the A, B, and C groups, respectively). Although male rats exposed to 0.97 mg/m³ also exhibited increased absolute liver weights, the body weights of the animals exposed to 0.97 mg/m³ were greater than the body weights of control animals, so changes in relative liver weight were minimal. A statistically significant increase in both relative and absolute kidney weight for the left and/or right kidney was also found in male rats from Groups A, B, and C exposed to 49 mg/m³ when compared to controls. However, these differences were not consistently greater than 10% for all three groups, were reversible [not observed by postexposure Day 29 (see Table B.23)]. Group E female rats exposed to 0.97- and 49-mg/m³ DCPD had a statistically significant decrease in the relative weight of the left kidney only. Due to these decreases being slight and not observed in the right kidney, Exxon (1980) and Dodd (1982) attributed the observation to body-weight gain throughout the course of the experiment. No other instances of organ-weight differences were reported among DCPD-exposed female rats.

Exxon (1980) and Dodd (1982) hypothesized that the kidney lesions, which progressively worsened throughout the exposure and recovery phase of the study, were due to chronic glomerulonephrosis, a common syndrome in F344 rats. This syndrome occurs in conjunction with advancing age in both male and female rats. However, the presence of epithelial cells and casts, regenerative epithelium (tubular hyperplasia), and dilation of the tubule in the kidneys, coupled with the most severe effects being observed in male species, could be indicative of an alpha 2u-globulin pathway. Although staining for hyaline droplets was not reported by Exxon (1980) or Dodd (1982), Bevan et al. (1992) used data from Exxon (1980) to examine hyaline droplets and quantify severity indices.

The histological examination of the kidneys from rats exposed to 4.9 and 49 mg/m³ by Bevan et al. (1992) showed the formation of hyaline droplets in the proximal convoluted tubules at a much greater level than the control rats (see Table B.24). The formation of these droplets was concentration dependent in nature and later confirmed through electron microscopy. By Week 13 of exposure, male rats exposed to 49 mg/m³ DCPD developed tubular proteinosis, which persisted after the recovery period. Similar results were observed in the regenerative epithelium, which increased in severity throughout the exposure (see Table B.25) and lessened only minimally throughout the recovery. No liver or kidney changes were observed or reported in female rats. A study by Hamamura et al. (2006), which performed immunohistochemical analysis, suggests that hyaline droplets forming in male rats following DCPD exposure are composed of alpha 2u-globulin. However, the Hamamura et al. (2006) study was short term, exposed animals only through the oral route, and utilized a small sample size. Additionally, the subchronic-duration oral rat study by Hart (1976) utilized a larger sample size and higher DCPD concentrations than Hamamura et al. (2006) but did not report any kidney effects. Taken together, these data suggest that the relevance of the rat kidney lesions observed in the Exxon (1980) study to humans cannot be discounted. Hence, the increased formation of hyaline droplets in the kidneys of male rats is considered the critical effect, with a LOAEL of 4.9 mg/m³ and a NOAEL of 0.97 mg/m³. No biologically significant toxicity was observed in female rats at any concentration tested (NOAEL of 49 mg/m³, the highest concentration tested).

Kinkead et al. (1971)

In a peer-reviewed and published subchronic-duration inhalation toxicity study conducted by Kinkead et al. (1971), groups of 12 male and 12 female Harlan-Wistar rats were exposed to mean measured concentrations of 0-, 19.7-, 35.2-, and 73.8-ppm DCPD (isomeric mixture of endo/exo DCPD in a 95:5 ratio, purity 96.7%) vapor in air for 7 hours/day, 5 days/week, for 89 days. The corresponding HECs are calculated as 0, 22.2, 39.7, and 83.1 mg/m³. Changes in body weight after the 4th, 13th, 31st, 55th, 75th, and 89th days of the study, liver and kidney weights, and gross and microscopic pathology were measured and reported. Twenty samples from the thoracic and abdominal cavities were also collected for microscopic examination following necropsy. The study authors did not report the GLP compliance status.

No deaths were reported in any animals throughout the study duration. Reported results show that convulsions were observed in one female at 22.2 and 83.1 mg/m³ on Exposure Days 45 and 19, respectively. Another female rat exposed to 22.2 mg/m³, likewise, exhibited convulsions for 5 minutes on Day 45. The study authors reported no other exposure-related clinical signs of toxicity. The mean body weight of both sexes was reduced in the 83.1-mg/m³ groups after 4 days, but no statistically significant changes in body weight were reported at the end of the 89-day exposure. Male rats exhibited increased absolute and relative liver and kidney weights at all exposure concentrations, ranging from 14–20% for the liver and 20–25% for the kidney (see Table B.26). However, the authors noted that body weights in exposed animals were consistently higher (6–25%) compared to the control group, thus explaining the increase in liver and kidney weights reported in the exposed groups. As further support, the study authors also stated that these changes in organ and body weights were not concentration dependent and that similar effects were not found in females. Concentration-related histologic kidney lesions were reported in both sexes at concentrations ≥ 39.7 mg/m³. The kidney lesions were described as “round cell accumulations, dilated tubules, casts and tubular degeneration” and were reported in the 39.7- and 83.1-mg/m³ exposure groups. The study authors also noted that the kidney lesions were more severe and frequent in males than in females, although severity scores were not presented in the study results. Additionally, chronic pneumonia and bronchiectasis were reported in three male rats from the highest exposure group, and although this was not considered a biologically significant finding, it represents injury to the lung after repeated inhalation of DCPD at this concentration. Other pathologic effects in the lung were not concentration related, and no other effects were reported in the organs and tissues.

Based on concentration-related histologic kidney lesions (i.e., round cell accumulations, dilated tubules, casts and tubular degeneration) that were reported in both sexes at concentrations ≥ 39.7 mg/m³, the low concentration 22.2 mg/m³ is identified as a NOAEL, and the mid concentration of 39.7 mg/m³ is identified as a LOAEL.

Exxon (1980); Dodd et al. (1982)

In a non-peer-reviewed subchronic-duration (90-day) inhalation study performed by Exxon (1980) and reported in Dodd et al. (1982), B6C3F₁ mice (45 male and 45 female mice per exposure concentration) were exposed to target concentrations of 0-, 1-, 5-, or 50-ppm in air; actual air concentrations were 0-, 1.0-, 5.1-, or 51.0-ppm DCPD (purity 95%) for 6 hours/day, 5 days/week, for 13 weeks. The corresponding HECs are calculated as 0, 0.97, 4.9, and 49 mg/m³. Nine animals/sex/concentration were sacrificed after Weeks 2, 6, and 13 of exposure and at Weeks 4 and 13 postexposure. These sacrifice periods were identified as Groups A, B, C, D, and E, respectively, throughout the remainder of the report. All animals were housed

individually and weighed the morning before the first exposure (reference weight); this value was subtracted from each subsequent weight measurement to obtain a change in body weight throughout the course of the experiment. Body-weight measurements were taken weekly for the first 5 weeks and then every 2 weeks for the remainder of the exposure. The animals were weighed again prior to sacrifice. Food and water consumption rates were not reported in the study. Each animal also underwent an ophthalmologic examination (prior to sacrifice interval; a protocol deviation), blood chemistry (prior to sacrifice interval), and histopathology of kidneys and urinary bladder following necropsy. Additionally, upon sacrifice of the animal, a necropsy was performed, and the following organs removed and weighed: kidney (left and right, weighed individually), lung, liver, and testes (males). The study authors did not report GLP compliance status.

Mortality was high (approximately 20%) across all groups exposed to 49-mg/m³ DCPD; 10 male and 9 female mice died during the course of the study. The authors speculated that this mortality may have been indicative of an exposure-related effect, as no more than two mice died at any other DCPD exposure concentration. No clinical observation of changes in body weight was reported prior to the mortality, although the probable cause of death could be attributed to pulmonary congestion with some cases of renal failure. It is important to note that similar lung lesions were not reported in animals from other exposure groups sacrificed during the course of the study. All mice had a normal appearance after the 6-hour exposure period. Observations recorded in the exposure groups were also recorded in the control group and included urogenital area wetness (females), lacrimation, and alopecia. Mice of both sexes exhibited alopecia throughout the study duration, which was as common in controls as in exposure groups. Scattered incidences of statistically significant changes in body weight were reported for female mice (see Table B.27) during both the exposure (Group C) and postexposure period (Group E) at 4.9 and 49 mg/m³. However, these changes were not concentration dependent and were not observed in males.

Results from the blood analysis of the mice showed variability in serum data because an insufficient quantity of blood was collected from many of the mice, prohibiting the establishment of unequivocal results. Two toxic serum effects potentially related to DCPD exposure included an elevated serum glucose level among male mice (see Table B.28) exposed to 49 mg/m³ DCPD and a reduced serum albumin content (7% from control mean) in female mice (see Table B.29) exposed to 4.9 and 49 mg/m³. The authors hypothesized that reduced serum albumin content accompanied by an increase in the absolute liver weights of the 4.9-mg/m³ exposed females may have indicated some liver dysfunction. However, increases in liver weight only occurred in Group C females and were not concentration dependent. No biologically significant effects as a result of DCPD exposure were found during the hematologic analysis in either sex. Only one male mouse from the highest exposure group was found to have a mild case of conjunctivitis during the ophthalmologic examination.

The results of the necropsy showed no gross findings in mice of either sex. Statistically significant changes in liver and kidney organ weights were observed in Group C female mice exposed to 4.9 mg/m³ DCPD (see Table B.30); however, no relationship between DCPD exposure concentrations or the number of exposures was apparent. The study authors reported no biologically significant histopathologic results for either male or female mice nor

morphological changes associated with DCPD exposure. Because of the high mortality reported following exposure to 49 mg/m³ DCPD, this concentration is considered a frank effect level (FEL). The intermediate concentration of 4.9 mg/m³ is identified as the NOAEL.

Kinkead et al. (1971)

In this peer-reviewed subchronic-duration inhalation toxicity study, Kinkead et al. (1971) exposed groups of three young male beagle dogs to 0-, 8.9-, 23.5-, or 32.4-ppm DCPD (isomeric mixture of endo/exo DCPD in a 95:5 ratio, purity 96.7%) in air for 7 hours/day, 5 days/week, for 89 days. The corresponding HECs are calculated as 0, 10.0, 26.5, and 36.5 mg/m³. Observed parameters of toxicity included clinical signs, hematocrit, total and differential white blood cell counts, BUN, alanine transaminase (ALT), aspartate transaminase (AST), serum acid phosphatase, and serum alkaline phosphatase values. Following sacrifice, the animals were necropsied and body, liver, and kidney weights, as well as gross pathology measures were recorded. Electrocardiograms and 28 samples of various tissues from the cranial, thoracic, and abdominal cavities (including portions of the lung, liver, kidney, heart, spleen, adrenal, thyroid, parathyroid, esophagus, diaphragm, lymph node, gall bladder, maxillary gland, tongue, stomach, duodenum, pancreas, ileum, jejunum, colon, urinary bladder, prostate, testis, epididymis, brain, pituitary, skin, and eye) were collected for microscopic examination. Hematologic and blood chemistry tests were performed 6 days prior to the start of the study and on Exposure Days 20, 37, 65, and 85. Urine was collected for analysis 5 days prior to the initiation of the study and after Days 21, 38, 68, and 87 of the study. This study was performed before GLP guidelines were established.

The only exposure-related changes reported in any of the measurements consisted of minimal changes in biochemical parameters (Kinkead et al., 1971); a slight increase in BUN and acid phosphatase values was reported at Day 20 in the 36.5-mg/m³ exposure group, while alkaline phosphatase values were increased at the same concentration after 85 days of exposure. At 26.5 mg/m³, SGOT and acid phosphatase values increased after 20 days and were accompanied by a minimal decrease in neutrophils noted on Day 85 of exposure at the same DCPD concentration. Due to the inconsistency of observed biochemical changes, the study authors reported that these findings were only isolated and, therefore, had no “physiological significance.” No biochemical changes were noted in dogs exposed to the lowest (10.0 mg/m³) concentration, and no statistically significant deviations in body weight were reported. Concentration-dependent increases in absolute liver and kidney organ weights (see Table B.31) were observed, which reached 10% at ≥ 26.5 mg/m³ for the kidneys and 36.5 mg/m³ for the liver when compared to controls.

No concentration-related pathological changes were observed in any of the exposure groups. Splenic infarcts were present but were discounted as related to the exposure because they are common in dogs and were not concentration related. Electrocardiograms performed on all dogs at the conclusion of the study were also found to be normal. A NOAEL of 10.0 mg/m³ and a LOAEL of 26.5 mg/m³ is identified based on increased kidney weight in male dogs.

Chronic-Duration Studies

No studies were identified.

Developmental Studies

No studies were identified.

Reproductive Studies

No studies were identified.

OTHER DATA

Table 4 summarizes studies examining the genotoxicity and mutagenicity of DCPD. The data demonstrate that DCPD is negative for genotoxic activity.

Table 4. Summary of DCPD Genotoxicity and Mutagenicity						
Endpoint	Test System	Dose Concentration^a	Results^b		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	Ames assay; <i>Salmonella typhimurium</i> strains TA 98, 100, 1535, 1537 and/or 1538 in the presence or absence of S9.	5.0 µL/plate	–	–	Study was conducted in duplicate with strains derived from the same parental strain; same results observed on both occasions.	Hart (1980)
		333 µg/plate	–	–	DCPD tested negative in all tests; highest ineffective dose level tested without clearing of the background colonies in a <i>Salmonella</i> test strain was 100 µg/plate.	Zeiger et al. (1987)
SOS repair induction	ND					
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	<i>Saccharomyces cerevisiae</i> strain D4 in the presence or absence of S9.	5.0 µL/plate	–	–	Study was conducted in duplicate with strains derived from the same parental strain; same results observed on both occasions.	Hart and Dacre (1978)
Recombination induction	ND					
Chromosomal abberation	ND					
Chromosomal malsegregation	ND					

Table 4. Summary of DCPD Genotoxicity and Mutagenicity

Endpoint	Test System	Dose Concentration ^a	Results ^b		Comments	References
			Without Activation	With Activation		
Mitotic arrest	ND					
Genotoxicity studies in mammalian cells—in vitro						
Mutation	ND					
Chromosomal aberrations	Chinese hamster lung cells (CHL/IU)	0.057 mg/mL (continuous treatment)	–	–	DCPD marginally induced chromosomal aberrations at the highest concentration (0.057 mg/mL) after 24-hr continuous treatment; however, these aberrations were confirmed to be negative in the in vitro micronucleus test.	OECD (2002)
		0.057 mg/mL (short-term treatment)	–	–	Cytogenetic effects not reported under the conditions of this test.	OECD (2002)
		0.1 mg/mL (short-term treatment)	–	–	Cytogenetic effects not reported under the conditions of this test.	OECD (2002)
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Genotoxicity studies in mammals—in vivo						
Chromosomal aberrations	ND					
SCE	ND					
DNA damage	ND					

Table 4. Summary of DCPD Genotoxicity and Mutagenicity

Endpoint	Test System	Dose Concentration ^a	Results ^b		Comments	References
			Without Activation	With Activation		
DNA adducts	ND					
Mouse biochemical or visible specific locus test	ND					
Dominant lethal	ND					
Genotoxicity studies in subcellular systems						
DNA binding	ND					

^aLowest effective dose for positive results, highest dose tested for negative results.

^b – = negative; ND = no data.

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

All of the genotoxicity and mutagenicity studies for DCPD were negative or equivocal (see Table 4). DCPD was negative for mutagenicity in both bacteria (*Salmonella typhimurium*) (Hart, 1980; Zeiger et al., 1987) and yeast (*Saccharomyces cerevisiae*) (Hart and Dacre, 1978). DCPD also tested negative in the chromosomal aberration test using Chinese hamster lung (CHL/IU) cells. Both short-term and continuous treatments were administered in the presence and absence of metabolic activation with no cytogenic effects. DCPD marginally induced structural chromosomal aberrations at the highest concentration tested (0.057 mg/mL) following 24 hours of continuous treatment but was later confirmed to be negative in the in vitro micronucleus test (OECD, 2002).

DERIVATION OF PROVISIONAL VALUES

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

Table 5. Summary of Noncancer Reference Values for DCPD (CASRN 77-73-6)							
Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Mink/M+F	Reduced kit weight (absolute) following 4 wk of nursing.	2×10^{-1}	NOAEL	23.6	100	Aulerich et al. (1979)
Chronic p-RfD (mg/kg-d)	Mink/M+F	Reduced kit weight (absolute) following 4 wk of nursing.	8×10^{-2}	NOAEL	23.6	300	Aulerich et al. (1979)
Screening Subchronic p-RfC (mg/m ³) ^a	Rat/M	Increased formation of hyaline droplets in proximal convoluted tubules in male rat kidneys.	3×10^{-3}	NOAEL	0.97	300	Exxon (1980); Dodd et al. (1982); Bevan et al. (1992)
Screening Chronic p-RfC (mg/m ³) ^a	Rat/M	Increased formation of hyaline droplets in proximal convoluted tubules in male rat kidneys.	3×10^{-4}	NOAEL	0.97	3,000	Exxon (1980); Dodd et al. (1982); Bevan et al. (1992)

^aA screening value is provided in Appendix A to this document.

Table 6. Summary of Cancer Values for DCPD (CASRN 77-73-6)				
Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	NDr			
p-IUR	NDr			

NDr = not determined.

DERIVATION OF ORAL REFERENCE DOSES

The database for DCPD oral toxicity studies includes three subchronic-duration studies, conducted on rats, mice, and dogs (Hart, 1976 [rat and mouse]; Hart 1980 [dog]), one developmental study on rats (Hart, 1980), and three reproductive studies, conducted on rats (Hart, 1980 and Jamieson et al., 1995) and mink (Aulerich et al., 1979). The subchronic-duration studies examined a variety of hematology, hemocytology, serum biochemistry, clinical chemistry, histopathology, and ophthalmologic effects. The results of the three studies showed no clear biologically significant effects at the tested doses (ranging from 2.7 to 68.4 mg/kg-day). The studies by Hart (1979 and 1980) and Aulerich et al. (1979) were previously evaluated by IRIS for the assessment of DIMP (U.S. EPA, 1993) and are therefore considered adequate for the derivation of p-RfDs. Also, each study utilized an appropriate number of animals and was conducted under sound experimental guidelines.

Among two rat reproductive studies, the dietary study by Hart (1980) identified NOAELs of 34.2 and 48.1 mg/kg-day for males and females, respectively, based on no observed toxicological effects at the highest dose. The gavage study (Jamieson et al., 1995) reported a NOAEL of 10 mg/kg-day and a LOAEL of 30 mg/kg-day based on the reduction in pup survival and weight at birth. However, the utility of the Jamieson et al. (1995) study is limited because it is only available as a meeting abstract, and the specific details of observations could not be reviewed. The reproductive study in minks by Aulerich et al. (1979) identified a NOAEL of 23.6 mg/kg-day and a LOAEL of 42.4 mg/kg-day based on reduction in kit weight following nursing from females exposed to 42.4 mg/kg-day (LOAEL) DCPD in the diet, indicating either a toxicological effect on neonates through direct ingestion of DCPD in milk or indirectly through a perturbation in the maternal metabolism that affects lactation. The developmental study by Hart (1980) reported no treatment-related effects up to 63 mg/kg-day (the highest dose tested).

From the available database of oral exposure to DCPD, Aulerich et al. (1979) is the only study that is reported in sufficient detail that exhibits a toxicological effect (i.e. reduced kit weight) in animals exposed to DCPD. A lower NOAEL from this study compared to the NOAELs ≥ 28.2 mg/kg-day from subchronic-duration studies by Hart (1980) also suggests that reproductive toxicity in minks is more sensitive than any potential subchronic systemic toxicity. Furthermore, findings by Aulerich et al. (1979) are supported by the Jamieson et al. (1995) study (although available only as a meeting abstract). Therefore, Aulerich et al. (1979) is selected as the principal study for derivation of the p-RfD. Based on this study, a NOAEL of 23.6 mg/kg-day is identified as the point of departure (POD). Benchmark dose (BMD) analysis is not possible because the original report only provided mean and standard error without the sample size, and individual kit response data were not provided (see Table B.18).

The U.S. EPA endorses a hierarchy of approaches to derive human equivalent oral exposures from laboratory animal data, including body-weight scaling to the $3/4$ power (i.e., $BW^{3/4}$) (U.S. EPA, 2011c). The use of $BW^{3/4}$ scaling for deriving an RfD is specifically recommended when the observed effects are systemic and associated with the parent compound or a stable metabolite. In the present case, however, $BW^{3/4}$ scaling is not recommended because there are developmental/neonatal effects (i.e., reduced kit weight following 4 weeks of nursing) in which neonatal animals are directly exposed to DCPD, and empirical data are currently lacking on whether $BW^{3/4}$ scaling is appropriate for extrapolating from neonates or juveniles across species (i.e., minks to humans).

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The subchronic p-RfD for DCPD, based on the NOAEL_{ADJ} of 23.6 mg/kg-day (Aulerich et al., 1979), is derived as follows:

$$\begin{aligned} \text{Subchronic p-RfD} &= \text{NOAEL}_{\text{ADJ}} \div \text{UF}_C \\ &= 23.6 \text{ mg/kg-day} \div 100 \\ &= 2 \times 10^{-1} \text{ mg/kg-day} \end{aligned}$$

The composite uncertainty factor (UF_C) for the subchronic p-RfD is 100, as explained in Table 7.

Table 7. UFs for Subchronic p-RfD of DCPD		
UF	Value	Justification
UF _A	10	A UF _A of 10 has been applied for interspecies extrapolation to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability) because information was unavailable to quantitatively assess toxicokinetic or toxicodynamic differences between animals and humans for DCPD.
UF _D	1	A UF _D of 1 has been applied because the database includes two acceptable multi-generation reproductive toxicity studies in rats and minks (Hart, 1980; Aulerich et al., 1979), and one acceptable developmental toxicity study in rats (Hart, 1980) via the oral route.
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 DCPD in humans.
UF _L	1	A UF _L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF _S	1	A UF _S of 1 has been applied because developmental/neonatal toxicity was used as the critical effect (i.e., reduced kit weight). The developmental/neonatal period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of effects than lifetime exposure (U.S. EPA, 1991).
UF _C	100	

The confidence of the subchronic p-RfD for DCPD is medium as explained in Table 8 below.

Table 8. Confidence Descriptors for Subchronic p-RfD for DCPD

Confidence Categories	Designation^a	Discussion
Confidence in study	M	Confidence in the key study is medium. The Aulerich et al. (1979) study has a sound experimental design for a reproductive study in minks. Although this study (Aulerich et al., 1979) is not peer reviewed, it was previously evaluated by IRIS and considered adequate for the derivation of a p-RfD. Also, experiments were performed according to GLP guidelines. The reported effects were also supported by a rat gavage study (Jamieson et al., 1995).
Confidence in database	M	The database includes subchronic-duration studies on rats, mice, and dogs (Hart, 1976 [rat and mouse]; Hart, 1980 [dog]) and reproductive studies on rats and mink (Hart, 1980; Jamieson, 1995; Aulerich et al., 1979). Of the available studies on oral exposure, all three subchronic-duration oral studies (Hart, 1976 [rat and mouse]; Hart, 1980 [dog]), and three reproductive studies (Hart, 1980; Jamieson et al., 1995; Aulerich et al., 1979) reported similar effects following treatment with DCPD, which increases the confidence in the database.
Confidence in subchronic p-RfD ^b	M	The overall confidence in the subchronic p-RfD is medium.

^aL = low, M = medium, H = high.

^bThe overall confidence cannot be greater than lowest entry in table.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

Based on the same database and similar considerations, the chronic p-RfD for DCPD, based on the NOAEL_{ADJ} of 23.6 mg/kg-day (Aulerich et al., 1979), is derived as follows:

$$\begin{aligned} \text{Chronic p-RfD} &= \text{NOAEL}_{\text{ADJ}} \div \text{UF}_C \\ &= 23.6 \text{ mg/kg-day} \div 300 \\ &= 8 \times 10^{-2} \text{ mg/kg-day} \end{aligned}$$

The UF_C for the chronic p-RfD is 300, as explained in Table 9.

UF	Value	Justification
UF _A	10	A UF _A of 10 has been applied for interspecies extrapolation to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability) because information was unavailable to quantitatively assess toxicokinetic or toxicodynamic differences between animals and humans for DCPD.
UF _D	1	A UF _D of 1 has been applied because the database includes two acceptable multi-generation reproductive toxicity studies in rats and minks (Hart, 1980; Aulerich et al., 1979), and one acceptable developmental toxicity study in rats (Hart, 1980) via the oral route.
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 DCPD in humans.
UF _L	1	A UF _L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF _S	3	A UF _S of 3 is applied to account for duration extrapolation. The study by Aulerich et al. (1979) on minks is a reproductive study but also contains a chronic-duration portion on adult animals. However, this study does not comprehensively evaluate chronic systemic toxicity endpoints (e.g., no detailed biochemistry measurements). Therefore, a partial UF _S of 3 is warranted.
UF _C	300	

The confidence of the chronic p-RfD for DCPD is medium as explained in Table 10 below.

Table 10. Confidence Descriptors for Chronic p-RfD for DCPD

Confidence Categories	Designation ^a	Discussion
Confidence in study	M	Confidence in the key study is medium. The Aulerich et al. (1979) study has a sound experimental design for a reproductive study in minks. Although this study (Aulerich et al., 1979) is not peer reviewed, it was previously evaluated by IRIS and considered adequate for the derivation of a p-RfD. Also, experiments were performed according to GLP guidelines. The reported effects were also supported by a rat gavage study (Jamieson, 1995).
Confidence in database	M	The database includes subchronic-duration studies on rats, mice, and dogs (Hart, 1976 [rat and mouse]; Hart, 1980 [dog]) and reproductive studies on rats and minks (Hart, 1980; Jamieson, 1995; Aulerich et al., 1979). Of the available studies on oral exposure, all three subchronic-duration oral studies (Hart, 1976 [rat and mouse]; Hart, 1980 [dog]), and three reproductive studies (Hart, 1980; Jamieson et al., 1995; Aulerich et al., 1979) reported similar effects following treatment with DCPD, which increases the confidence in the database. However, the database lacks chronic toxicity studies.
Confidence in chronic p-RfD ^b	M	The overall confidence in the chronic p-RfD is medium.

^aL = low, M = medium, H = high.

^bThe overall confidence cannot be greater than lowest entry in table.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

One human case study (Okubo et al., 2000) reported a statistically significant increase in female births among the workers in a plastic products and DCPD recovery facility; however, the study is limited by the small sample size and exposure to a mixture of chemicals including DCPD. There are four subchronic-duration inhalation animal studies (Exxon, 1980 [rat and mouse]; Kinkead et al., 1971 [rat and dog]) available for the development of subchronic and chronic p-RfCs. Two of these studies were conducted in two different strains of rats (F344 and Harlan Wistar strains), and the other two studies were conducted in mice and dogs. Each of these studies examined a variety of serum chemical, clinical chemical, histopathologic, and ophthalmologic parameters. Kidney lesions (e.g., tubule degeneration, the presence of epithelial cells and casts, and increased formation of hyaline droplets in proximal convoluted tubules) were reported at many of the exposure concentrations in both male and female rats. The study in F344 rats (Exxon, 1980) reported kidney lesions only in males, but a similar study in Harlan-Wistar rats (Kinkead et al., 1971) reported these responses in both males and females. However, the kidney lesions in males were more severe than those in females. Although these rat studies did not confirm the presence of alpha 2u-globulin in the kidneys of male rats exposed to DCPD, an additional study by Hamamura et al. (2006) showed accumulation of alpha 2u-globulin in the kidneys of male rats following exposure to DCPD, but only through the oral route. However, the Hamamura et al. (2006) study is limited by its short duration (10 days), small sample size (4/sex), and conflicting findings when compared to a larger oral study by Hart (1976), which did not find any kidney effects in rats of the same strain exposed to DCPD. Hence, the lack of clear evidence directly associating alpha 2u-globulin with renal lesions following DCPD inhalation precludes ruling out the relevance of these rat kidney lesions to

humans. Furthermore, kidney effects were also observed in the dog study by Kinkead et al. (1971), which showed concentration-dependent increases in kidney weight that reached 10% at concentrations $\geq 26.5 \text{ mg/m}^3$.

In addition to kidney effects, Exxon (1980) reported reduced serum albumin accompanied by increased absolute and relative liver weights in female mice after exposure to 4.9 mg/m^3 . However, these liver changes were not concentration dependent. In rats, liver weights were increased but did not consistently reach 10% when compared to controls. Liver weights in dogs increased by more than 10% but occurred at concentrations higher than the kidney effects (Kinkead et al., 1971; Exxon, 1980).

The increased formation of hyaline droplets in proximal convoluted tubules in the kidneys of male F344 rats (Exxon, 1980) is supported by concentration-related histologic kidney lesions (i.e., round cell accumulations, dilated tubules, casts, and tubular degeneration) in both sexes of Harlan-Wistar rats (Kinkead et al., 1971) at concentrations $\geq 39.7 \text{ mg/m}^3$ (35.2 ppm). Additional kidney effects such as concentration-dependent increases in kidney weight were also observed in dogs at $\geq 26.5 \text{ mg/m}^3$ (Kinkead et al., 1971). Because rats are more sensitive than mice and beagle dogs (Kinkead et al., 1971; Exxon, 1980), the Exxon (1980) report on rats is selected as the principal study with increased formation of hyaline droplets in the proximal convoluted tubules of the kidneys in male rats as the critical effect. The Exxon (1980) study is considered inadequate for p-RfC derivation because it is not peer reviewed nor does it indicate the use of GLP guidelines. However, this study is suitable for the derivation of screening p-RfCs in accordance with U.S. EPA practice (see Appendix A).

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 11 identifies the cancer WOE descriptor for DCPD.

Table 11. Cancer WOE Descriptor for DCPD			
Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
<i>“Carcinogenic to Humans”</i>	NS	NA	No human carcinogenicity data were identified.
<i>“Likely to Be Carcinogenic to Humans”</i>	NS	NA	No animal carcinogenicity studies were identified.
<i>“Suggestive Evidence of Carcinogenic Potential”</i>	NS	NA	No animal carcinogenicity studies were identified.
<i>“Inadequate Information to Assess Carcinogenic Potential”</i>	Selected	Both	Selected due to the lack of any information on carcinogenicity.
<i>“Not Likely to Be Carcinogenic to Humans”</i>	NS	NA	There are no data to indicate that DCPD is not carcinogenic.

NA = not applicable; NS = not selected.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of any data on the carcinogenicity of DCPD precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A. PROVISIONAL SCREENING VALUES

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional subchronic and chronic RfCs for DCPD. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an appendix and develops a “screening value.” Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

DERIVATION OF SCREENING PROVISIONAL INHALATION REFERENCE CONCENTRATIONS

Derivation of Screening Subchronic Provisional RfC (Screening Subchronic p-RfC)

One human study (Okubo et al., 2000) examining the effects of chronic inhalation of DCPD is available in the literature. However, the small number of cases assessed and the exposure to a mixture of chemicals prevents the use of this study for the derivation of p-RfCs. No animal studies examining the effects of chronic inhalation of DCPD are available in the literature; therefore, subchronic-duration studies are used for the development of the screening chronic p-RfC value. The principal study (Exxon, 1980) identified a NOAEL of 0.97 mg/m³ with increased formation of hyaline droplets in the proximal convoluted tubules of the kidneys in male rats selected as the critical effect. Kidney effects were also seen at higher exposure levels in rats and beagle dogs (Kinkead et al., 1971). Because the data on formation of hyaline droplets in renal tubules of male rats (see Table B.22, epithelial cell casts) are considered semiquantitative measurements and are presented as median and quantile deviation without a sample size, they are not amenable to benchmark dose (BMD) modeling. Therefore, the NOAEL of 0.97 mg/m³ is used as the POD for derivation of screening subchronic and chronic p-RfCs.

To determine the POD for derivation of the screening subchronic p-RfC, exposure concentrations are first adjusted for continuous exposure (Conc_{ADJ}) followed by HEC conversions (Conc_{HEC}) based on Conc_{ADJ} (calculated for extrarrespiratory effects – increased formation of hyaline droplets in proximal convoluted tubules in the kidneys of male rats) as specified in the RfC guidelines (U.S. EPA, 1994b). Example calculations are presented below. The Exxon (1980) study did not observe any portal of entry/respiratory effects.

Exposure concentration adjustment for continuous exposure:

$$\begin{aligned} \text{Conc}_{\text{ADJ}} &= \text{Conc}_{\text{Exxon (1980)}} \times (\text{MW} \div 24.45) \times (\text{hours exposed} \div 24) \times \\ &\quad (\text{days exposed} \div 7 \text{ days per week}) \\ &= 1 \times (132.2 \div 24.45) \times (6 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days}) \\ &= 0.97 \text{ mg/m}^3 \end{aligned}$$

HEC conversion for extrarespiratory effects:

$$\text{Conc}_{\text{HEC}} = \text{Conc}_{\text{ADJ}} \times \text{DAF};$$

DAF (dosimetric adjustment factor for the specific site of effects such as respiratory and extrarespiratory tract regions).

The DAF_r for gases/vapors with toxicity effects at sites remote of the respiratory tract (extrarespiratory effects) is based on the ratio of the animal blood:gas partition coefficient ($\text{H}_{\text{b/g-animal}}$) and the human blood:gas partition coefficient ($\text{H}_{\text{b/g-human}}$). See below:

$$\begin{aligned} \text{DAF} &= ([\text{H}_{\text{b/g}}]_{\text{A}} \div [\text{H}_{\text{b/g}}]_{\text{H}}) = \text{the ratio of the blood:gas (air) partition coefficient of the chemical for the rat to the human. The value of 1.0 is used for the ratio of } (\text{H}_{\text{b/g}})_{\text{A}} \div (\text{H}_{\text{b/g}})_{\text{H}} \text{ or as a default gas partition coefficient of 1.0 when one or both of the partition coefficients are not available, as recommended by U.S. EPA (1994b).} \\ &= 1.0 \end{aligned}$$

$$\begin{aligned} \text{Conc}_{\text{HEC}} &= \text{Conc}_{\text{ADJ}} \times \text{DAF} \\ &= 0.97 \times 1.0 \\ &= 0.97 \text{ mg/m}^3 \end{aligned}$$

The screening subchronic p-RfC for DCPD is derived as follows:

$$\begin{aligned} \text{Screening Subchronic p-RfC} &= \text{NOAEL}_{\text{HEC}} \div \text{UF}_C \\ &= 0.97 \text{ mg/m}^3 \div 300 \\ &= 3 \times 10^{-3} \text{ mg/m}^3 \end{aligned}$$

The UF_C for the subchronic p-RfD is 300, as explained in Table A.1.

Table A.1. UFs for Screening Subchronic p-RfC of DCPD		
UF	Value	Justification
UF _A	3	A UF _A of 3 (10 ^{0.5}) has been applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following inhalation exposure to DCPD. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent concentration (HEC) as described in the RfC methodology (U.S. EPA, 1994b).
UF _D	10	A UF _D of 10 has been applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies via the inhalation route.
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 DCPD in humans.
UF _L	1	A UF _L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF _S	1	A UF _S of 1 is applied because a subchronic-duration study was selected as the principal study.
UF _C	300	

Derivation of Screening Chronic Provisional RfC (Screening Chronic p-RfC)

The screening chronic p-RfC is derived based on the same principal study (Exxon, 1980) and POD (0.97 mg/m³) as used to derive the screening subchronic RfC.

The screening chronic p-RfC for DCPD is derived as follows:

$$\begin{aligned}
 \text{Screening Chronic p-RfC} &= \text{NOAEL}_{\text{HEC}} \div \text{UF}_C \\
 &= 0.97 \text{ mg/m}^3 \div 3,000 \\
 &= 3 \times 10^{-4} \text{ mg/m}^3
 \end{aligned}$$

The UF_C for the chronic p-RfD is 3,000, as explained in Table A.2.

Table A.2. UFs for Screening Chronic p-RfC of DCPD		
UF	Value	Justification
UF _A	3	A UF _A of 3 (10 ^{0.5}) has been applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following inhalation exposure to DCPD. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent concentration (HEC) as described in the RfC methodology (U.S. EPA, 1994b).
UF _D	10	A UF _D of 10 has been applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies via the inhalation route.
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 DCPD in humans.
UF _L	1	A UF _L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF _S	10	A UF _S of 10 is applied to account for the extrapolation from less than chronic exposure.
UF _C	3,000	

APPENDIX B. DATA TABLES

Table B.1. Average Absolute Body and Organ Weights (g) in Male S-D Rats Exposed to DCPD in Food for 13 Weeks^{a,b}									
	Body Weight	Brain	Thyroid	Heart	Liver	Spleen	Kidneys	Adrenals	Testes
Controls									
Mean	351.8	1.7038	0.0200	1.3098	15.7852	0.6630	3.2419	0.0548	4.7420
SD	42.4	0.0925	0.0053	0.1673	2.5732	0.0990	0.4082	0.0083	0.7157
SE	8.3	0.0185	0.0011	0.0328	0.5046	0.0198	0.0801	0.0017	0.1404
<i>N</i>	26	25	25	26	26	25	26	24	26
6.3 mg/kg-d									
Mean	371.4	1.7005	0.0240*	1.3004	15.9446	0.6559	3.3816	0.0590	4.8376
SD	40.6	0.1634	0.0056	0.1858	2.8713	0.0800	0.4277	0.0104	0.5220
SE	7.8	0.0320	0.0011	0.0358	0.5526	0.0157	0.0823	0.0021	0.1005
<i>N</i>	27	26	27	27	27	26	27	25	27
19.2 mg/kg-d									
Mean	361.1	1.7098	0.0266*	1.3177	15.2345	0.6965*	3.4018	0.0647*	4.8663
SD	52.5	0.0690	0.0057	0.1892	3.6048	0.1155	0.3887	0.0089	0.5082
SE	10.9	0.0147	0.0012	0.0394	0.7516	0.0241	0.0811	0.0019	0.1060
<i>N</i>	23	22	22	23	23	23	23	22	23
57.4 mg/kg-d									
Mean	347.3	1.6562	0.0226	1.2093*	14.6744	0.6403	3.3712	0.0589	4.6509
SD	55.4	0.1086	0.0036	0.1727	3.2639	0.1087	0.4972	0.0079	0.7680
SE	10.9	0.0213	0.0007	0.0339	0.6401	0.0213	0.0975	0.0017	0.1506
<i>N</i>	26	26	24	26	26	26	26	22	26

^aSource: Hart (1976).

^bStatistical analysis and significance data not presented by study author.

*Statistically significant by Student's *t*-test, $p < 0.05$, conducted independently for this review.

Table B.2. Average Absolute Organ and Body Weights (g) of Female S-D Rats Exposed to DCPD in Food for 13 Weeks^{a,b}

	Body Weight	Brain	Thyroid	Heart	Liver	Spleen	Kidneys	Adrenals	Ovaries
Controls									
Mean	227.2	1.6212	0.0204	0.9114	9.0666	0.5195	2.0271	0.0723	0.1134
SD	26.1	0.1024	0.0052	0.1320	1.5696	0.1228	0.2280	0.0112	0.0339
SE	4.9	0.0194	0.0010	0.0249	0.2966	0.0232	0.0431	0.0023	0.0064
N	28	28	27	28	28	28	28	24	28
7.2 mg/kg-d									
Mean	230.9	1.5343	0.0202*	0.8713	9.2143	0.5108	2.0120	0.0737	0.1071
SD	17.5	0.1443	0.0071	0.0746	0.9725	0.0845	0.1235	0.0123	0.0331
SE	3.2	0.0268	0.0014	0.0138	0.1806	0.0157	0.0229	0.0025	0.0061
N	29	29	28	29	29	29	29	25	29
22.6 mg/kg-d									
Mean	230.4	1.5834	0.0198	0.8838	8.7616	0.5128	2.0054	0.0725	0.1162
SD	24.4	0.1291	0.0034	0.1306	1.2906	0.0748	0.2216	0.0090	0.0323
SE	4.6	0.0248	0.0006	0.0247	0.2439	0.0141	0.0419	0.0018	0.0061
N	28	27	28	28	28	28	28	25	28
68.1 mg/kg-d									
Mean	233.4	1.5877	0.0205	0.8768	8.5947	0.5042	1.9281	0.0732	0.1238
SD	14.5	0.1335	0.0045	0.1804	1.5838	0.0758	0.3560	0.0093	0.0374
SE ^c	(2.6) NR	(0.02) NR	(0.0008) NR	(0.03) NR	(0.29) NR	(0.01) NR	(0.06) NR	(0.002) NR	(0.007) NR
N	30	29	30	30	30	30	30	30	30

^aSource: Hart (1976).

^bStatistical analysis and significance data not presented by study author.

^cValues in parentheses independently calculated for this review based on reported SD and N.

*Statistically significant by Student's *t*-test, $p < 0.05$, conducted independently for this review.

NR = not reported.

Table B.3. Average Relative Organ/Body-Weight Percentages of Male S-D Rats Exposed to DCPD in Food for 13 Weeks^{a,b}

	Brain	Thyroid	Heart	Liver	Spleen	Kidneys	Adrenals	Testes
Controls								
Mean	0.4892	0.0057	0.3744	4.4932	0.1902	0.9236	0.0157	1.3520
SD	0.0560	0.0014	0.0442	0.5863	0.0270	0.0694	0.0029	0.1700
SE	0.0112	0.0003	0.0087	0.1150	0.0054	0.0136	0.0006	0.0333
N	25	25	26	26	25	26	24	26
6.3 mg/kg-d								
Mean	0.4627	0.0065	0.3522	4.3061	0.1793	0.9122	0.0161	1.3091
SD	0.0633	0.0016	0.0526	0.7433	0.0302	0.0764	0.0030	0.1324
SE	0.0124	0.0003	0.0101	0.1431	0.0059	0.0147	0.0006	0.0255
N	26	27	27	27	26	27	25	27
19.2 mg/kg-d								
Mean	0.4876	0.0077*	0.3682	4.1992	0.1946	0.9488	0.0183*	1.3616
SD	0.0910	0.0030	0.0473	0.7536	0.0307	0.0695	0.0045	0.1333
SE	0.0194	0.0006	0.0099	0.1571	0.0064	0.0145	0.0010	0.0278
N	22	22	23	23	23	23	22	23
57.4 mg/kg-d								
Mean	0.4929	0.0068*	0.3517	4.2057	0.1864	0.9768*	0.0176	1.3405
SD	0.1131	0.0017	0.0569	0.5494	0.0329	0.0826	0.0053	0.1187
SE	0.0222	0.0008	0.0112	0.1077	0.0064	0.0162	0.0011	0.0233
N	26	24	26	26	26	26	22	26

^aSource: Hart (1976).

^bStatistical analysis and significance data not presented by study author.

*Statistically significant by Student's *t*-test, $p < 0.05$, conducted independently for this review.

Table B.4. Average Relative Organ Weight Percentages of Female S-D Rats Exposed to DCPD in Food for 13 Weeks^{a,b}

	Brain	Thyroid	Heart	Liver	Spleen	Kidneys	Adrenals	Ovaries
Controls								
Mean	0.7240	0.0088	0.4079	3.9851	0.2282	0.8952	0.0329	0.0502
SD	0.1117	0.0034	0.0928	0.5587	0.0494	0.0657	0.0081	0.0142
SE	0.0211	0.0007	0.0172	0.1056	0.0093	0.0124	0.0017	0.0027
N	28	27	28	28	28	28	24	28
7.2 mg/kg-d								
Mean	0.6681*	0.0088	0.3788	3.9941	0.2221	0.8742	0.0320	0.0466
SD	0.0800	0.0032	0.0384	0.3414	0.0376	0.0607	0.0048	0.0144
SE	0.0149	0.0006	0.0071	0.0634	0.0070	0.0113	0.0010	0.0027
N	29	28	29	29	29	29	25	29
22.6 mg/kg-d								
Mean	0.6952	0.0087	0.3844	3.8021	0.2230	0.8730	0.0317	0.0503
SD	0.0841	0.0018	0.0428	0.3940	0.0263	0.0747	0.0033	0.0126
SE	0.0162	0.0003	0.0081	0.0745	0.0050	0.0141	0.0007	0.0024
N	27	28	28	28	28	28	25	28
57.4 mg/kg-d								
Mean	0.6831	0.0088	0.3767	3.6890	0.2165	0.8266*	0.0314	0.0535
SD	0.0688	0.0019	0.0775	0.6555	0.0329	0.1432	0.0036	0.0176
SE	Illegible	Illegible	Illegible	Illegible	0.0060	0.0261	0.0007	0.0032
N	29	30	30	30	30	30	30	30

^aSource: Hart (1976).

^bStatistical analysis and significance data not presented by study author.

*Statistically significant by Student's *t*-test, $p < 0.05$, conducted independently for this review.

Table B.5. Average Absolute Organ Weights (g) of Female Swiss Albino Mice Exposed to DCPD in Food for 13 Weeks^{a,b}								
	Body Weight	Thyroid	Heart	Liver	Spleen	Kidneys	Adrenals	Ovaries
Controls								
Mean	28.9	0.0056	0.2013	1.8839	0.1345	0.4676	0.0104	0.0458
SD	2.7	0.0033	0.0773	0.3554	0.0774	0.1054	0.0032	0.0612
SE	0.5	0.0007	0.0139	0.0638	0.0139	0.0189	0.0006	0.0110
<i>N</i>	31	26	31	31	31	31	26	31
8.1 mg/kg-d								
Mean	28.9	0.0054	0.2122	1.8816	0.1448	0.4808	0.0111	0.0438
SD	3.5	0.0014	0.0990	0.3415	0.0818	0.1031	0.0015	0.515
SE	0.6	0.0003	0.0178	0.0613	0.0147	0.0185	0.0003	0.0092
<i>N</i>	31	24	31	31	31	31	22	31
22.7 mg/kg-d								
Mean	28.8	0.0036*	0.1907	1.7801	0.1241	0.4524	0.0098	0.0326
SD	2.3	0.0010	0.0310	0.2553	0.0350	0.0569	0.0017	0.0178
SE	0.4	0.0002	0.0055	0.0451	0.0062	0.0101	0.0003	0.0031
<i>N</i>	32	26	32	32	32	32	28	32
68.4 mg/kg-d								
Mean	29.5	0.0049	0.1886	1.8644	0.1333	0.4778	0.0111	0.0391
SD	2.1	0.0025	0.0573	0.2426	0.0654	0.0695	0.0041	0.0570
SE	0.4	0.0005	0.0101	0.0429	0.0116	0.0123	0.0008	0.0101
<i>N</i>	32	30	32	32	32	32	27	32

^aSource: Hart (1976).

^bStatistical analysis and significance data not presented by study author.

*Statistically significant by Student's *t*-test, $p < 0.05$ compared to control, conducted independently for this review.

Table B.6. Average Absolute Organ Weights (g) of Male Swiss Albino Mice Exposed to DCPD in Food for 13 Weeks^{a,b}

	Body Weight	Thyroid	Heart	Liver	Spleen	Kidneys	Adrenals	Testes
Controls								
Mean	36.0	0.0048	0.2481	2.5269	0.1560	0.7341	0.0073	0.5130
SD	4.0	0.0024	0.0869	0.4153	0.0937	0.1274	0.0023	0.2474
SE	0.7	0.0006	0.0154	0.0734	0.0166	0.0225	0.0005	0.0459
N	32	18	32	32	32	32	21	29
5.6 mg/kg-d								
Mean	37.7*	0.0040	0.2706	2.5562	0.1221	0.7232	0.0078	0.4311
SD	3.8	0.0011	0.0607	0.4303	0.0279	0.1068	0.0021	0.0601
SE	0.7	0.0002	0.0107	0.0761	0.0049	0.0189	0.0006	0.0106
N	32	23	32	32	32	32	14	32
17.0 mg/kg-d								
Mean	37.4	0.0051	0.2747	2.3727	0.1208*	0.6671*	0.0072	0.4216*
SD	7.5	0.0013	0.0463	0.3711	0.0318	0.1218	0.0022	0.0565
SE	1.3	0.0003	0.0082	0.0656	0.0056	0.0215	0.0005	0.0100
N	32	25	32	32	32	32	19	32
49.5 mg/kg-d								
Mean	36.7	0.0057	0.2413	2.3936	0.1362	0.6922	0.0075	0.4205
SD	3.5	0.0037	0.0473	0.3625	0.0490	0.1097	0.0035	0.0655
SE	0.5	0.0008	0.0086	0.0662	0.0091	0.0200	0.0007	0.0120
N	30	23	30	30	29	30	26	30

^aSource: Hart (1976).

^bStatistical analysis and significance data not presented by study author.

*Statistically significant by Student's *t*-test, $p < 0.05$, conducted independently for this review.

Table B.7. Average Relative Organ/Body-Weight Percentages of Female Swiss Albino Mice Exposed to DCPD in Food for 13 Weeks^{a,b}

	Thyroid	Heart	Liver	Spleen	Kidneys	Adrenals	Ovaries
Controls							
Mean	0.0190	0.6929	6.4711	0.4566	1.6074	0.0361	0.1510
SD	0.0114	0.2264	0.7119	0.2267	0.2533	0.0110	0.1824
SE	0.0022	0.0407	0.1279	0.0407	0.0455	0.0022	0.0328
<i>N</i>	26	31	31	31	31	26	31
8.1 mg/kg-d							
Mean	0.0190	0.7332	6.5076	0.4983	1.6635	0.0392	0.1527
SD	0.0050	0.3253	0.8117	0.2723	0.2884	0.0055	0.1776
SE	0.0010	0.0584	0.1458	0.0489	0.0518	0.0012	0.0319
<i>N</i>	24	31	31	31	31	22	31
22.7 mg/kg-d							
Mean	0.0128*	0.6644	6.1703	0.4280	1.5713	0.0340	0.1132
SD	0.0037	0.1064	0.5692	0.1056	0.1430	0.0058	0.0602
SE	0.0007	0.0188	0.1006	0.0187	0.0253	0.0011	0.0106
<i>N</i>	25	32	32	32	32	28	32
68.4 mg/kg-d							
Mean	0.0170	0.6421	6.3346	0.4515	1.6202	0.0376	0.1330
SD	0.0097	0.2025	0.7743	0.2152	0.2073	0.0134	0.1908
SE	0.0018	0.0358	0.1369	0.0380	0.0366	0.0026	0.0337
<i>N</i>	30	32	32	32	32	27	32

^aSource: Hart (1976).

^bStatistical analysis and significance data not presented by study author.

*Statistically significant by Student's *t*-test, $p < 0.05$ compared to control, conducted independently for this review.

Table B.8. Average Relative Organ/Body-Weight Percentages of Male Swiss Albino Mice Exposed to DCPD in Food for 13 Weeks^{a,b}							
	Thyroid	Heart	Liver	Spleen	Kidneys	Adrenals	Testes
Controls							
Mean	0.0130	0.6935	7.0208	0.4315	2.0435	0.0201	1.4114
SD	0.0060	0.2397	0.7822	0.2548	0.2871	0.0056	0.6606
SE	0.0014	0.0424	0.1383	0.0450	0.0507	0.0012	0.1227
<i>N</i>	18	32	32	32	32	21	29
5.6 mg/kg-d							
Mean	0.0107	0.7168	6.4650*	0.3264*	1.9191*	0.0203	1.1537*
SD	0.0029	0.1313	0.7544	0.0814	0.2031	0.0048	0.1865
SE	0.0006	0.0232	0.1334	0.0144	0.0359	0.0013	0.0330
<i>N</i>	23	32	32	32	32	14	32
17.0 mg/kg-d							
Mean	0.0138	0.7529	6.4595*	0.3302*	1.8171*	0.0189	1.1538*
SD	0.0042	0.1517	1.0829	0.0969	0.3361	0.0062	0.2124
SE	0.0008	0.0268	0.1914	0.0171	0.0594	0.0014	0.0375
<i>N</i>	25	32	32	32	32	19	32
49.5 mg/kg-d							
Mean	0.0157	0.6608	6.5150*	0.3660	1.8807*	0.0212	1.1499*
SD	0.0109	0.1289	0.6649	0.1050	0.1949	0.0112	0.1625
SE	0.0023	0.0235	0.1214	0.0195	0.0356	0.0022	0.0297
<i>N</i>	23	30	30	29	30	26	30

^aSource: Hart (1976).

^bStatistical analysis and significance data not presented by study author.

*Statistically significant by Student's *t*-test, $p < 0.05$, conducted independently for this review.

Table B.9. Summary of Reproductive Performance in Female Rats (CRL:COBS CD [SD] BR) Dosed with DCPD in Food on GDs 6–15^{a,b}				
	Dose (ppm)			
Pregnancy ratio (Pregnant/bred)	19/21	20/20	19/20	19/20
Live litter	19/19 (100%)	20/20 (100%)	19/19 (100%)	19/19 (100%)
Implantation sites (left horn/right horn)	154/159	132/168	132/160	134/158
Resorptions	18	22	19	13
Litters with resorptions	14 (74%)	8 (40%)	11 (58%)	8 (42%)
Dead fetuses	0	0	0	0
Litters with dead fetuses	0	0	0	0
Live fetuses/implantation site	295/313 (94%)	278/300 (93%)	273/292 (93%)	279/292 (96%)
Mean live litter size (fetuses)	15.5	13.9	14.4	14.7
Average fetal weight (g)	2.3	2.3	2.4	2.4
Average fetal length (cm)	2.7	2.6	2.7	2.7

^aSource: Hart (1980).

^bStatistical analysis conducted by study author using the litter as the basic statistical unit.

Table B.10. Number and Sex of Fetuses From Female Rats Dosed with DCPD in Food on GDs 6–15^{a,b}		
Dose (ppm)	Males	Females
0 (Control)	48	46
80	40	46
250	47	39
750	40	47

^aSource: Hart (1980).

^bStatistical analysis conducted by study author using the litter is the basic statistical unit.

Table B.11. Skeletal Abnormalities in Fetuses from Female Rats Dosed with DCPD in Food on GDs 6–15^{a,b,c}

Dose (ppm)	Number Fetuses Examined	Number Fetuses Normal	Fetuses with Commonly Encountered Changes Only	Fetuses with Unusual Skeletal Variations
0 (Control)	199 (19)	106	91 (17)	2 (2)
80	192 (20)	85	103 (19)	4 (3)
250	187 (19)	92	95 (13)	0 (0)
750	192 (19)	91	98 (17)	3 (2)

^aSource: Hart (1980).

^bNumber of litters in parentheses.

^cStatistical analysis conducted by study author using the litter as the basic statistical unit.

Table B.12. Summary of F1b Generation—First Mating (F2a)^a

Parameter	Exposure Group ^b		
	Control	Low	High
Indices ^c			
Male fertility (males producing litter/mated)	10/10 (100)	10/10 (100)	9/10 (90)
Female fertility (females producing litter/mated)	19/20 (95)	18/20 (90)	14/20 (70)
Gestation (females live litter/pregnant)	19/19 (100)	18/18 (100)	14/14 (100)
Newborn viability (live pups/total pups)	241/242 (100)	209/216 (97)	162/162 (100)
Pup viability (pups Day 4/pups Day 0)	237/241 (98)	196/209 (94)*	159/162 (98)
Lactation (pups Day 21/pups Day 4)	147/150 (98)	135/139 (97)	107/109 (98)
Pup weight (g) ^d			
Day 0 Males	6 ± 0.90 (100)	6 ± 0.84 (100)	6 ± 0.83 (100)
Day 0 Females	6 ± 0.79 (100)	6 ± 0.92 (100)	6 ± 0.95 (100)
Day 21 Males	44 ± 5.9 (100)	46 ± 6.4 (105)	44 ± 5.5 (100)
Day 21 Females	41 ± 5.3	43 ± 6.6 (105)	42 ± 5.3 (102)
Sex ratio offspring (M/F) Day 0 ^e	111/131 (46) ^f	94/122 (44) ^f	84/78 (52) ^f
Live pups per litter (Mean ± SD) ^d	13 ± 2.6	12 ± 2.7 (92)	12 ± 2.7 (92)

^aSource: Hart (1980); subscripts a and b distinguish the results in pups from the first (a) or second (b) mating of the F1b generation.

^bAverage daily doses were calculated for each generation and sex by the study author; for the F1b generation males, doses were 0, 4.3, or 39.9 mg/kg-d and for females doses were 0, 7.8, or 60.7 mg/kg-d; for the F2b generation, male doses were 0, 4.6, or 44.1 mg/kg-d and female doses were 0, 8.1, or 73.1 mg/kg-d.

^cIndex data presented as ratio (percent).

^dData presented as mean ± SD (% of controls); % calculated for this review.

^eData presented as number of males/number of females (% males).

^fSome pups missexed.

*Statistically significant ($p < 0.05$). Calculated independently for this review.

Table B.13. Summary of F1b Generation—Second Mating (F2b)^a

Parameter	Exposure Group ^b		
	Control	Low	High
Indices ^c			
Male fertility (males producing litter/mated)	10/10 (100)	10/10 (100)	9/10 (90)
Female fertility (females producing litter/mated)	19/20 (95)	19/20 (95)	17/20 (85)
Gestation (females live litter/pregnant)	19/19 (100)	19/19 (100)	17/17 (100)
Newborn viability (live pups/total pups)	263/263 (99)	286/287 (100)	230/235 (98)
Pup viability (pups Day 4/pups Day 0)	250/263 (95)	280/286 (98)	214/230 (93)
Lactation (pups Day 21/pups Day 4)	149/151 (99)	149/152 (98)	127/128 (99)
Pup weight (g) ^d			
Day 0 Males	6 ± 0.84	6 ± 0.63 (100)	6 ± 0.54 (100)
Day 0 Females	6 ± 0.75	6 ± 0.52 (100)	6 ± 0.66 (100)
Day 21 Males	45 ± 6.8	48 ± 7.2 (107)	51 ± 6.6 (113)
Day 21 Females	43 ± 7.4	46 ± 6.6 (107)	48 ± 6.6 (112)
Sex ratio offspring (M/F) Day 0 ^e	121/145 (45)	146/141 (51)	119/116 (51)
Live pups per litter (Mean ± SD)	14 ± 2.5	15 ± 1.6 (107)	14 ± 1.4 (100)

^aSource: Hart (1980); subscripts a and b distinguish the results in pups from the first (a) or second (b) mating of the F1b generation.

^bAverage daily doses were calculated for each generation and sex by the author; for the F1b generation males doses were 0, 4.3, or 39.9 mg/kg-d and for females doses were 0, 7.8, or 60.7 mg/kg-d; for the F2b generation, male doses were 0, 4.6, or 44.1 mg/kg-d and female doses were 0, 8.1, or 73.1 mg/kg-d.

^cIndex data presented as ratio (percent).

^dData presented as mean ± SD (% of controls); % calculated for this review.

^eData presented as number of males/number of females (% males).

Table B.14. Summary of F2b Generation—Second Mating (F3b)^a

Parameter	Exposure Group ^b		
	Control	Low	High
Indices ^c			
Male fertility (males producing litter/mated)	9/10 (90)	10/10 (100)	9/9 (100)
Female fertility (females producing litter/mated)	17/20 (85)	16/20 (80)	15/18 (83)
Gestation (females live litter/pregnant)	17/17 (100)	16/16 (100)	15/15 (100)
Newborn viability (live pups/total pups)	211/215 (98)	206/213 (97)	188/191 (98)
Pup viability (pups Day 4/pups Day 0)	207/211 (98)	206/206 (100)	185/188 (98)
Lactation (pups Day 21/pups Day 4)	134/135 (99)	127/128 (99)	114/117 (97)
Pup weight (g) ^d			
Day 0 Males	6 ± 0.79	7 ± 0.98 (117)	7 ± 0.83 (117)
Day 0 Females	6 ± 0.64	6 ± 0.87 (100)	6 ± 0.83 (100)
Day 21 Males	49 ± 10	44 ± 11 (90)	43 ± 11 (88)
Day 21 Females	48 ± 9.3	41 ± 12 (85)	41 ± 9.5* (85)
Sex ratio offspring (M/F) Day 0 ^e	93/122 (43)	107/106 (50)	93/98 (49)
Live pups per litter ^d	12 ± 2.7	13 ± 2.5	13 ± 2.8

^aSource: Hart (1980); subscripts a and b distinguish the results in pups from the first (a) or second (b) mating of the F2b generation.

^bAverage daily doses were calculated for each generation and sex by the author; for the F2b generation, male doses were 0, 4.6, or 44.1 mg/kg-d, and female doses were 0, 8.1, or 73.1 mg/kg-d; author did not calculate F3 doses.

^cIndex data presented as ratio (percent).

^dData presented as mean ± SD (% of controls); % calculated for this review.

^eData presented as number of males/number of females (% males).

*Statistically significant at $p < 0.05$ compared to control; Student's t -test.

Table B.15. Summary of F2b Generation—First Mating (F3a)^a			
Parameter	Exposure Group^b		
	Control	Low	High
Indices ^c			
Male fertility (males producing litter/mated)	9/10 (90)	10/10 (100)	8/9 (89)
Female fertility (females producing litter/mated)	13/20 (65)	16/20 (80)	15/18 (83)
Gestation (females live litter/pregnant)	13/13 (100)	16/16 (100)	15/15 (100)
Newborn viability (live pups/total pups)	162/163 (99)	195/196 (99)	204/206 (99)
Pup viability (pups Day 4/pups Day 0)	156/162 (96)	187/195 (96)	201/204 (99)
Lactation (pups Day 21/pups Day 4)	92/100 (92)	118/118 (100)	117/120 (98)
Pup Weight (g) ^d			
Day 0 Males	6 ± 0.77	6 ± 1.3 (100)	7 ± 0.82 (117)
Day 0 Females	7 ± 0.80	5 ± 1.2 (71)	6 ± 0.80 (86)
Day 21 Males	46 ± 5.8	46 ± 4.7 (100)	48 ± 6.1 (104)
Day 21 Females	45 ± 7.6	42 ± 4.2 (93)	45 ± 5.7 (100)
Sex ratio offspring (M/F) Day 0 ^e	81/82 (50)	103/93 (53)	108/98 (52)
Live pups per litter (Mean ± SD) ^d	12 ± 3.3	12 ± 3.9	14 ± 2.0

^aSource: Hart (1980); subscripts a and b distinguish the results in pups from the first (a) or second (b) mating of the F2b generation.

^bAverage daily doses were calculated for each generation and sex by the author; for the F2b generation, male doses were 0, 4.6, or 44.1 mg/kg-d, and female doses were 0, 8.1, or 73.1 mg/kg-d; author did not calculate F3 doses.

^cIndex data presented as ratio (percent).

^dData presented as mean ± SD (% of controls); % calculated for this review.

^eData presented as number of males/number of females (% males).

Table B.16. Calculation of Estimated Daily Intake by Minks Fed DCPD at Various Dose Levels for 12 Months^a				
DCPD Level in Diet (ppm)	Mean Daily Feed Consumption (g)^b	Mg DCPD Ingested/d	Mean Body Weight (g)^c	Daily Ingested Dose (mg/kg-d)
0	230	0	1,071	0
100	245	24.5	1,038	23.6
200	222	44.4	1,047	42.4
400	217	86.8	1,021	85.0
800	210	168.0	989	169.9

^aSource: Aulerich et al. (1979).

^bRepresents mean feed consumption for eight measurements taken over 4 months.

^cRepresents mean body weight for 18 measurements taken over 12 months.

Table B.17. Summary of Body-Weight Changes in Minks fed DCPD at Three Doses for 12 Months^a					
DCPD Level in Diet, ppm (ADD^b, mg/kg-d)	N	Body Weight at Study Initiation, 07/22/1977	N	Body Weight at Study Termination, 06/30/1978	Change in Body Weight (%)
Males					
0 (0)	6	1,083 ± 56	6	1,640 ± 62	51.4
100 (23.6)	6	1,133 ± 47	5	1,573 ± 69	38.8
200 (42.4)	6	1,029 ± 55	5	1,508 ± 92*	46.6
400 (85.0)	6	1,150 ± 40*	6	1,722 ± 70	49.7
800 (169.9)	6	1,054 ± 42	6	1,538 ± 43*	45.9
Females					
0 (0)	24	760 ± 16	19	811 ± 26	6.7
100 (23.6)	24	739 ± 14*	21	746 ± 25*	0.9
200 (42.4)	24	739 ± 16*	21	837 ± 27*	13.3
400 (85.0)	24	731 ± 18*	23	837 ± 25*	14.5
800 (169.9)	24	731 ± 18*	21	771 ± 20*	5.5
Combined Males and Females					
0 (0)	30	825 ± 29	25	1,010 ± 75	22.4
100 (23.6)	30	818 ± 32	26	905 ± 68*	10.6
200 (42.4)	30	796 ± 27*	26	966 ± 59*	21.4
400 (85.0)	30	815 ± 35	29	1020 ± 71	25.2
800 (169.9)	30	796 ± 29*	27	941 ± 64*	18.2

^aSource: Aulerich et al. (1979).

^bAdjusted daily dose.

*Statistically significant ($p < 0.05$, Fisher's Exact test). Calculated independently for this review.

Table B.18. Performance of Nursing Offspring and Dams fed DCPD^a							
DCPD Level, ppm (ADD^b, mg/kg-d)	Whelping Females Lactating at 4 Wk (%)	Kit Mortality to 4 Wk (%)	Number of Kits per Lactating Female (± SE)	Average Absolute Weight of Kits at 4 Wk (g ± SE)	Kit Biomass^c	Average Weight of Whelping Dam (g ± SE)	Average Weight of Lactating Females 4 Wk Postpartum (g ± SE)
0.0 (0.0)	79	21.7	4.91 ± 0.51	165 ± 2.6	810.2	978 ± 27.4	878 ± 38.2
100 (23.6)	89	22.9	4.63 ± 0.51	158 ± 2.7	732.5	1,000 ± 27.6	867 ± 23.1
200 (42.4)	93	33.8	3.92 ± 0.54	146 ± 5.2*	571.9	981 ± 42.4	900 ± 44.4
400 (85.0)	100	14.7	4.76 ± 0.38	147 ± 2.6*	701.1	995 ± 25.1	913 ± 29.1
800 (169.9)	100	15.6	4.50 ± 0.41	128 ± 3.1*	576.0	939 ± 20.2	843 ± 20.5

^aSource: Aulerich et al. (1979).

^bAdjusted Daily Dose.

^cBiomass = average kit body-weight gain between birth and 4 wk of age × the average number of kits raised per lactating female.

*Statistically significant ($p < 0.05$; Dunnett's t -test); calculated by study authors.

Table B.19. Effect of Chronic Administration of DCPD to Minks on Mean Organ Weights (g ± SE) at Necropsy^a

Organs	DCPD Treatment, ppm (Adjusted Daily Dose, mg/kg-d) ^b				
	0 (0.0)	100 (23.6)	200 (42.4)	400 (85.0)	800 (169.9)
Liver	27 ± 1.5	24 ± 1.4	26 ± 1.0	28 ± 1.6	32 ± 2.0
Spleen	3.3 ± 0.29	2.5 ± 0.20	2.6 ± 0.21	2.4 ± 0.16*	2.5 ± 0.24
Kidney	4.8 ± 0.22	4.5 ± 0.22	4.4 ± 0.18	4.7 ± 0.21	4.7 ± 0.23
Lungs	7.8 ± 0.42	7.0 ± 0.35	7.6 ± 0.41	8.1 ± 0.43	7.3 ± 0.31
Adrenals	0.10 ± 0.015	0.11 ± 0.007	0.10 ± 0.011	0.12 ± 0.011	0.13 ± 0.012
Heart	6.0 ± 0.30	5.8 ± 0.28	5.5 ± 0.27	5.9 ± 0.26	5.6 ± 0.24
Testes	1.8 ± 0.1	1.6 ± 0.3	1.8 ± 0.2	1.8 ± 0.2	1.1 ± 0.1*
Ovaries	0.10 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01
Brain	8.1 ± 0.18	7.8 ± 0.15	7.9 ± 0.20	7.9 ± 0.13	7.9 ± 0.13

^aSource: Aulerich et al. (1979).

^bCalculated from average body weights and food consumption provided in study using the following equation

$$\text{Dose}_{\text{ADJ}} = \text{Dose}_{\text{ppm}} \times \text{Food Consumption per Day} \times (1 \div \text{Body Weight}) \times (\text{Days Dosed} \div \text{Total Days}).$$

*Statistically significant ($p < 0.05$; Dunnett's t -test); calculated by study authors.

Table B.20. Mean Food Consumption of Male and Female Fischer 344 Rats Exposed to DCPD Vapor During a 90-Day Inhalation Study^a

Completed Exposures (days)	Mean Chamber Concentration, ppm (HECs, mg/m ³)				
	Group	Control (0.0)	1.0 (0.97)	5.1 (4.9)	51.0 (49)
Male Rats					
4	B	30.7 ± 6.9 ^b	35.0 ± 6.6	36.1 ± 5.1	31.8 ± 3.0
8	B	27.4 ± 2.0	28.0 ± 1.8	32.0 ± 3.0**	27.8 ± 2.8
10	A	28.6 ± 2.5	25.6 ± 3.8	29.9 ± 6.2	26.9 ± 2.1
13	B	27.5 ± 3.4	26.7 ± 2.9	27.8 ± 2.3	28.6 ± 2.9
19	B	22.7 ± 1.7	23.4 ± 2.0	22.1 ± 2.0	24.6 ± 1.4
30	B	27.4 ± 2.2	26.9 ± 2.6	26.5 ± 2.4	28.1 ± 2.8
65	C	22.6 ± 3.9	22.9 ± 2.1	25.0 ± 2.6	25.6 ± 3.0
64 (29) ^c	D	17.5 ± 5.6	21.3 ± 1.7	17.2 ± 6.0	20.9 ± 3.7
64 (92)	E	20.6 ± 2.2	20.1 ± 4.4	19.5 ± 3.4	22.8 ± 2.5
Female Rats					
4	B	17.3 ± 2.3 ^b	16.5 ± 1.4	17.0 ± 0.9	18.3 ± 4.6
8	B	19.3 ± 2.4	19.2 ± 2.7	19.7 ± 3.2	19.4 ± 1.3
10	A	17.4 ± 1.7	17.4 ± 3.9	16.8 ± 2.2	18.2 ± 1.9
13	B	18.0 ± 2.5	19.7 ± 1.9	18.9 ± 1.8	20.4 ± 1.5
19	B	17.0 ± 1.7	15.4 ± 2.5	16.7 ± 3.8	19.0 ± 1.4
30	B	17.6 ± 3.0	18.4 ± 2.1	18.6 ± 3.2	19.2 ± 1.9
65	C	17.8 ± 1.6	16.7 ± 1.8	18.0 ± 1.9	18.4 ± 1.2
64 (29) ^c	D	15.2 ± 1.3	16.2 ± 1.6	15.4 ± 1.1	17.2 ± 2.2*
64 (92)	E	19.0 ± 2.4	16.6 ± 1.5*	13.9 ± 5.8*	16.9 ± 1.8*

^aSource: Exxon (1980).

^bValues represent mean ± SD for *N* = 7–9 animals; units are mg/rat/24 hr.

^c() Indicates the number of postexposure days for Groups D and E.

*Statistically significant (*p* < 0.05, analysis of variance [ANOVA]) compared to control.

**Statistically significant (*p* < 0.01, ANOVA) compared to control.

Table B.21. Mean Water Consumption of Male and Female Fischer 344 Rats Exposed to DCPD Vapor During a 90-Day Inhalation Study^a					
Completed Exposures (days)	Mean Chamber Concentration, ppm (HECs, mg/m³)				
	Group	Control (0.0)	1.0 (0.97)	5.1 (4.9)	51.0 (49)
Male Rats					
4	B	37.1 ± 4.4 ^b	43.2 ± 4.4*	40.4 ± 5.1	46.0 ± 5.5***
8	B	42.7 ± 5.2	42.4 ± 3.0	43.1 ± 2.0	46.2 ± 2.9
10	A	37.3 ± 3.0	34.2 ± 6.6	38.8 ± 4.3	42.9 ± 5.3*
13	B	43.2 ± 3.8	43.1 ± 4.0	42.3 ± 4.5	49.0 ± 5.2**
19	B	38.1 ± 3.5	39.4 ± 3.7	38.2 ± 3.6	43.9 ± 4.6**
30	B	41.0 ± 4.1	42.9 ± 4.0	38.9 ± 5.2	50.0 ± 4.5***
65	C	35.2 ± 3.6	42.9 ± 3.0***	30.2 ± 5.1*	33.1 ± 3.5
64 (29) ^c	D	26.1 ± 9.5	28.7 ± 3.9	23.5 ± 10.9	34.1 ± 5.0*
64 (92)	E	29.7 ± 3.0	27.1 ± 10.4	26.8 ± 8.5	33.1 ± 4.8
Female Rats					
4	B	31.3 ± 5.5 ^b	28.3 ± 3.8	29.1 ± 3.0	32.6 ± 3.6
8	B	32.4 ± 6.9	29.3 ± 3.3	29.6 ± 5.6	32.9 ± 4.3
10	A	27.8 ± 2.7	30.6 ± 2.7	30.0 ± 5.2	30.1 ± 3.8
13	B	34.5 ± 4.4	34.8 ± 5.7	32.9 ± 2.4	40.5 ± 4.5*
19	B	32.0 ± 2.3	30.2 ± 4.5	28.1 ± 10.3	37.0 ± 4.3*
30	B	32.2 ± 4.4	33.8 ± 6.8	31.6 ± 4.4	37.5 ± 5.0
65	C	29.9 ± 3.2	30.7 ± 3.1	34.2 ± 4.4*	32.8 ± 2.6
64 (29) ^c	D	28.5 ± 2.0	28.5 ± 3.4	31.3 ± 4.7	26.7 ± 2.0
64 (92)	E	27.6 ± 4.7	24.9 ± 5.5	21.8 ± 8.7	26.1 ± 4.9

^aSource: Exxon (1980).

^bValues represent mean ± SD for *N* = 7–9 animals; units are ml/rat/24 hr.

^c() Indicates the number of postexposure days for Groups D and E.

Statistically significant by ANOVA, at *p* < 0.05*, *p* < 0.01**, and *p* < 0.001*** compared to control.

Table B.22. Mean and Median Results of Urinary Determinations from Male Fischer 344 Rats Exposed to DCPD Vapor During a 90-Day Inhalation Study^a

Exposure Concentration, ppm (HECs, mg/m ³)	Urine Volume (ml) ^b	Specific Gravity (g/ml) ^b	Osmolality (mOsm/kg) ^b	Urine Sediment Examination ^d	
				Epithelial Cells ^c	Epithelial Cell Casts ^c
Group B^c—4 completed exposures^f					
Control (0.0)	7.3 ± 1.3	1.056 ± 0.004	2118 ± 178	0 ± 0	0 ± 0
1.0 (0.97)	7.6 ± 1.1	1.053 ± 0.004	2130 ± 172	0 ± 0	0 ± 0
5.1 (4.9)	6.9 ± 1.3	1.055 ± 0.004	2155 ± 183	0 ± 0.2	0 ± 0
51.0 (49)	8.0 ± 1.6	1.047 ± 0.007**	1811 ± 268**	0 ± 0	0 ± 0
Group B^c—8 completed exposures^f					
Control (0.0)	7.3 ± 1.5	1.054 ± 0.005	1998 ± 194	0 ± 0.2	0 ± 0
1.0 (0.97)	7.6 ± 1.2	1.055 ± 0.004	2055 ± 165	1 ± 0.3	0 ± 0
5.1 (4.9)	6.9 ± 1.9	1.056 ± 0.004	2074 ± 191	2 ± 0***	0 ± 0.5
51.0 (49)	7.9 ± 1.5	1.048 ± 0.005*	1762 ± 182*	3 ± 0***	1 ± 0.5**
Group A^c—10 completed exposures^f					
Control (0.0)	6.6 ± 0.7	1.055 ± 0.004	2143 ± 157	0 ± 0	0 ± 0
1.0 (0.97)	6.0 ± 1.6	1.056 ± 0.005	2213 ± 242	1 ± 0.8*	0 ± 0
5.1 (4.9)	7.0 ± 0.8	1.053 ± 0.003	2108 ± 150	1 ± 0.5	0 ± 0
51.0 (49)	8.3 ± 1.6*	1.045 ± 0.004***	1753 ± 220***	1 ± 0**	0 ± 0.2
Group B^c—13 completed exposures^f					
Control (0.0)	7.8 ± 1.3	1.055 ± 0.005	2082 ± 195	0 ± 0.5	0 ± 0
1.0 (0.97)	7.2 ± 1.8	1.055 ± 0.007	2097 ± 294	1 ± 0.5	0 ± 0
5.1 (4.9)	7.5 ± 1.5	1.055 ± 0.003	2103 ± 113	1 ± 0.5	0 ± 0.5
51.0 (49)	8.6 ± 2.3	1.046 ± 0.005**	1754 ± 254	2 ± 0.2**	0 ± 0.5
Group B^c—19 completed exposures^f					
Control (0.0)	7.2 ± 1.1	1.058 ± 0.004	2269 ± 217	0 ± 0.4	0 ± 0
1.0 (0.97)	6.6 ± 1.2	1.058 ± 0.004	2257 ± 203	1 ± 0.2	1 ± 0.5
5.1 (4.9)	6.2 ± 2.1	1.056 ± 0.005	2159 ± 188	2 ± 0.5**	1 ± 0.8
51.0 (49)	7.5 ± 1.5	1.050 ± 0.004**	1966 ± 240*	3 ± 0***	2 ± 1**
Group B^c—30 completed exposures^f					
Control (0.0)	6.8 ± 1.6	1.060 ± 0.004	2350 ± 147	0 ± 0	0 ± 0
1.0 (0.97)	7.3 ± 1.7	1.059 ± 0.004	2290 ± 154	1 ± 0.5	0 ± 0.2
5.1 (4.9)	6.9 ± 0.9	1.056 ± 0.003	2156 ± 120**	2 ± 0.5**	1 ± 0*
51.0 (49)	9.0 ± 1.9**	1.047 ± 0.005***	1768 ± 208***	3 ± 0***	1 ± 1

Table B.22. Mean and Median Results of Urinary Determinations from Male Fischer 344 Rats Exposed to DCPD Vapor During a 90-Day Inhalation Study^a

Exposure Concentration, ppm (HECs, mg/m ³)	Urine Volume (ml) ^b	Specific Gravity (g/ml) ^b	Osmolality (mOsm/kg) ^b	Urine Sediment Examination ^d	
				Epithelial Cells ^c	Epithelial Cell Casts ^c
Group C^c—64 completed exposures^f					
Control (0.0)	4.6 ± 1.1	1.064 ± 0.002	2447 ± 160	0 ± 0.5	0 ± 0
1.0 (0.97)	4.1 ± 0.8	1.062 ± 0.002	2328 ± 87	1 ± 1	0 ± 0
5.1 (4.9)	5.1 ± 1.5	1.057 ± 0.004***	2099 ± 155***	2 ± 0.5	0 ± 0
51.0 (49)	6.8 ± 1.5**	1.046 ± 0.002***	1656 ± 106***	3 ± 0.5***	0 ± 0.5
Group D^c—64 completed exposures/29 postexposure days^f					
Control (0.0)	4.2 ± 2.0	1.064 ± 0.005	2379 ± 270	0 ± 0	0 ± 0
1.0 (0.97)	4.2 ± 0.6	1.066 ± 0.002	2497 ± 65	1 ± 0.5	0 ± 0
5.1 (4.9)	4.6 ± 1.7	1.060 ± 0.008	2202 ± 362	1 ± 0.2	0 ± 0
51.0 (49)	6.7 ± 1.1	1.054 ± 0.003***	1994 ± 191**	2 ± 0.5***	0 ± 0
Group E^c—64 completed exposures/92 postexposure days^f					
Control (0.0)	5.2 ± 1.6	1.064 ± 0.006	2389 ± 253	0 ± 0.2	0 ± 0
1.0 (0.97)	4.5 ± 1.1	1.065 ± 0.004	2405 ± 142	0 ± 0.2	0 ± 0
5.1 (4.9)	4.9 ± 1.0	1.065 ± 0.003	2399 ± 139	0 ± 0.5	0 ± 0
51.0 (49)	6.5 ± 1.0*	1.056 ± 0.003***	2056 ± 115***	0 ± 0.5	0 ± 0

^aSource: Exxon (1980).

^bValues represent mean ± SD.

^cValues represent median ± quartile deviation.

^dUrine sediment examination results; 0 = negative; 1+ = a few; 2+ = moderate amount; 3+ = numerous.

^eGroups A, B, C, D, and E correspond to sacrifice weeks 3, 7, 14, 18, and 27, respectively. Exposure started at the end of Week 1 for each group.

^fInterim data collection time.

*Statistically significant ($0.05 < p < 0.01$, Bartlett's test for the homogeneity of variance).

**Statistically significant ($0.01 < p < 0.001$, Bartlett's test for the homogeneity of variance).

***Statistically significant ($p < 0.001$, Bartlett's test for the homogeneity of variance).

Table B.23. Mean Absolute and Relative Liver and Kidney Weights for Male Fischer 344 Rats Exposed to DCPD Vapor During a 90-Day Inhalation Study^a

Parameter	Mean Chamber Concentration, ppm (HECs, mg/m ³)			
	Control (0.0)	1.0 (0.97)	5.1 (4.9)	51.0 (49)
Male Rats—Group A				
Body weight (g) at sacrifice	237.4 ± 13.1 ^b	241.7 ± 12.8	238.0 ± 11.4	241.8 ± 10.3
Liver weight, absolute, g	9.502 ± 0.730	9.939 ± 0.918	9.990 ± 0.896	10.675 ± 0.976
Liver weight, % body weight	4.002 ± 0.197	4.107 ± 0.206	4.189 ± 0.240	4.408 ± 0.248***
Right kidney weight, absolute, g	0.883 ± 0.068	0.907 ± 0.051	0.911 ± 0.071	0.977 ± 0.049**
Right kidney weight, % body weight	0.372 ± 0.023	0.376 ± 0.018	0.383 ± 0.024	0.405 ± 0.018**
Left kidney weight, absolute, g	0.887 ± 0.073	0.901 ± 0.078	0.907 ± 0.044	1.010 ± 0.079**
Left kidney weight, % body weight	0.374 ± 0.020	0.373 ± 0.023	0.382 ± 0.015	0.418 ± 0.026***
Male Rats—Group B				
Body weight (g) at sacrifice	289.5 ± 10.0 ^b	305.5 ± 17.7	288.8 ± 10.2	290.9 ± 12.9
Liver weight, absolute, g	10.668 ± 0.558	11.477 ± 0.918*	10.583 ± 0.757	11.258 ± 0.660
Liver weight, % body weight	3.684 ± 0.112	3.754 ± 0.154	3.662 ± 0.177	3.869 ± 0.107*
Right kidney weight, absolute, g	1.041 ± 0.061	1.151 ± 0.065**	1.068 ± 0.083	1.180 ± 0.078***
Right kidney weight, % body weight	0.359 ± 0.012	0.377 ± 0.023	0.370 ± 0.024	0.406 ± 0.021***
Left kidney weight, absolute, g	1.042 ± 0.063	1.144 ± 0.066**	1.085 ± 0.064	1.155 ± 0.077**
Left kidney weight, % body weight	0.360 ± 0.019	0.375 ± 0.020	0.376 ± 0.019	0.397 ± 0.021***
Male Rats—Group C				
Body weight (g) at sacrifice	340.0 ± 15.8 ^b	341.2 ± 24.8	341.7 ± 15.1	343.0 ± 16.9
Liver weight, absolute, g	11.171 ± 0.617	11.243 ± 1.004	11.228 ± 0.839	12.059 ± 0.685
Liver weight, % body weight	3.287 ± 0.124	3.294 ± 0.144	3.284 ± 0.134	3.517 ± 0.134***
Right kidney weight, absolute, g	1.291 ± 0.195	1.249 ± 0.211	1.148 ± 0.074	1.311 ± 0.081
Right kidney weight, % body weight	0.381 ± 0.062	0.366 ± 0.056	0.336 ± 0.020	0.383 ± 0.019
Left kidney weight, absolute, g	1.196 ± 0.111	1.243 ± 0.184	1.149 ± 0.053	1.319 ± 0.088*
Left kidney weight, % body weight	0.352 ± 0.027	0.365 ± 0.049	0.337 ± 0.016	0.385 ± 0.022*

Table B.23. Mean Absolute and Relative Liver and Kidney Weights for Male Fischer 344 Rats Exposed to DCPD Vapor During a 90-Day Inhalation Study^a

Parameter	Mean Chamber Concentration, ppm (HECs, mg/m ³)			
	Control (0.0)	1.0 (0.97)	5.1 (4.9)	51.0 (49)
Male Rats—Group D				
Body weight (g) at sacrifice	355.0 ± 23.7 ^b	359.5 ± 12.4	374.0 ± 27.5	376.2 ± 12.9
Liver weight, absolute, g	11.271 ± 0.965	11.668 ± 0.583	11.712 ± 1.425	12.444 ± 0.870
Liver weight, % body weight	3.173 ± 0.115	3.246 ± 0.124	3.125 ± 0.214	3.306 ± 0.157
Right kidney weight, absolute, g	1.237 ± 0.144	1.224 ± 0.061	1.279 ± 0.109	1.281 ± 0.062
Right kidney weight, % body weight	0.348 ± 0.022	0.341 ± 0.014	0.342 ± 0.018	0.341 ± 0.015
Left kidney weight, absolute, g	1.228 ± 0.112	1.222 ± 0.079	1.252 ± 0.082	1.290 ± 0.061
Left kidney weight, % body weight	0.346 ± 0.015	0.340 ± 0.018	0.335 ± 0.017	0.343 ± 0.014
Male Rats—Group E				
Body weight (g) at sacrifice	403.5 ± 17.0 ^b	394.9 ± 24.0	397.9 ± 14.5	407.8 ± 19.1
Liver weight, absolute, g	13.058 ± 1.433	11.905 ± 1.247	12.137 ± 1.040	12.825 ± 0.889
Liver weight, % body weight	3.238 ± 0.347	3.009 ± 0.192	3.049 ± 0.219	3.144 ± 0.152
Right kidney weight, absolute, g	1.409 ± 0.097	1.441 ± 0.231	1.402 ± 0.205	1.367 ± 0.127
Right kidney weight, % body weight	0.350 ± 0.028	0.364 ± 0.038	0.353 ± 0.054	0.335 ± 0.023
Left kidney weight, absolute, g	1.401 ± 0.080	1.431 ± 0.135	1.431 ± 0.167	1.397 ± 0.115
Left kidney weight, % body weight	0.347 ± 0.018	0.363 ± 0.028	0.360 ± 0.042	0.342 ± 0.016

^aSource: Exxon (1980).

^bValues represent mean ± SD for *N* = 9 animals.

*Statistically significant (*p* < 0.05, ANOVA) compared to control.

**Statistically significant (*p* < 0.01, ANOVA) compared to control.

***Statistically significant (*p* < 0.001, ANOVA) compared to control.

Table B.24. Incidence and Severity of Hyaline Droplets in Proximal Tubules of Male Rats Exposed to DCPD for 13 Weeks^a

Severity ^b	Week 6 Exposure Group, ppm (Human Equivalency Concentration, mg/m ³) ^c			
	Control (0)	1.0 (0.97)	5.1 (4.9)	51.0 (49)
Mild	0/9 (0)	5/9 (55.6)	4/9 (44.4)	0/9 (0)
Moderate	0/9 (0)	2/9 (22.2)	1/9 (11.1)	6/9 (66.7)
Marked	0/9 (0)	0/9 (0)	0/9 (0)	1/9 (11.1)
Severity ^b	Week 13 Exposure Group, ppm (Human Equivalency Concentration, mg/m ³) ^c			
	Control (0)	1.0 (0.97)	5.1 (4.9)	51.0 (49)
Mild	0/9 (0)	0/9 (0)	8/9 (88.9)	0/9 (0)
Moderate	0/9 (0)	0/9 (0)	0/9 (0)	3/9 (33.3)
Marked	0/9 (0)	0/9 (0)	0/9 (0)	6/9 (66.7)

^aSource: Bevan et al. (1992).

^bValues represent the incidence of the structural change at the respective degree of severity.

^cNumber of animals with endpoint/number of animals exposed, () = percent of total.

Table B.25. Incidence and Severity of Regenerative Epithelium in Proximal Tubules of Male Rats Exposed to DCPD for 13 Weeks with a 13-Week Recovery Period^a

Severity ^b	Week 6 Exposure Group, ppm (Human Equivalency Concentration, mg/m ³) ^c			
	Control (0)	1.0 (0.97)	5.1 (4.9)	51.0 (49)
Males				
Minimal	1/8 (12.5)	2/9 (22.2)	3/9 (33.3)	0/9 (0)
Mild	2/8 (25)	3/9 (33.3)	4/9 (44.4)	7/9 (77.8)
Moderate	0/8 (0)	0/9 (0)	2/9 (22.2)	2/9 (22.2)
Severe	0/8 (0)	0/9 (0)	0/9 (0)	0/9 (0)
Females				
Mild only	0/9 (0)	0/9 (0)	0/9 (0)	0/9 (0)
Severity ^b	Week 13 Exposure Group, ppm (Human Equivalency Concentration, mg/m ³) ^c			
	Control (0)	1.0 (0.97)	5.1 (4.9)	51.0 (49)
Males				
Minimal	0/9 (0)	1/9 (11.1)	0/9 (0)	0/9 (0)
Mild	9/9 (100)	7/9 (77.8)	0/9 (0)	0/9 (0)
Moderate	0/9 (0)	1/9 (11.1)	8/9 (88.9)	1/9 (11.1)
Severe	0/9 (0)	0/9 (0)	1/9 (11.1)	8/9 (88.9)
Females				
Mild only	1/9 (11.1)	1/9 (11.1)	0/9 (0.0)	0/9 (0.0)
Severity ^b	Week 13 Recovery Group, ppm (Human Equivalency Concentration, mg/m ³) ^{c,d}			
	Control (0)	1.0 (0.97)	5.1 (4.9)	51.0 (49)
Males				
Minimal	3/9 (33.3)	2/9 (22.2)	2/9 (22.2)	1/9 (11.1)
Mild	6/9 (66.7)	7/9 (77.8)	6/9 (66.7)	6/9 (66.7)
Moderate	0/9 (0)	0/9 (0)	0/9 (0)	2/9 (22.2)
Severe	0/9 (0)	0/9 (0)	0/9 (0)	0/9 (0)
Females				
Mild only	2/9 (22.2)	3/9 (33.3)	3/9 (33.3)	1/9 (11.1)

^aSource: Bevan et al. (1992)

^bValues represent the incidence of the structural change at the respective degree of severity. Animals having a grade of <1 are not listed.

^cNumber of animals with endpoint/number of animals exposed, () = percent of total.

^dFollowing 13 weeks of exposure, animals were maintained 13 weeks without exposure.

Table B.26. Summary of Responses of Groups of 12 Rats of Each Sex that Inhaled DCPD Vapor for 89 Days^a								
Parameter	Males				Females			
Mean concentration, ppm (mg/m ³)	0.0 (0.0)	19.7 (22.2)	35.2 (39.7)	73.8 (83.1)	0.0 (0.0)	19.7 (22.2)	35.2 (39.7)	73.8 (83.1)
Initial body weight (g)	219.6	232.8	217.3	225.1	175.3	177.9	178.7	176.8
Final body weight (g)	526.8	568.7	569.6	559.6	355.3	348.9	356.5	345.7
Mean body weight gain (g)	307.3	335.8	352.3	333.9 ^b	179.9	169.9	177.8	168.1
Mean liver weight (g)	16.54	19.57**	18.82*	19.83**	11.10	10.86	12.33	11.60
Mean liver weight (% of body weight)	3.13	3.45**	3.30	3.55***	3.16	3.12	3.48	3.36
Mean kidney weight (g)	3.23	3.89***	4.05***	3.95***	2.21	2.14	2.26	2.19
Mean kidney weight (% of body weight)	0.62	0.68***	0.71***	0.70***	0.62	0.62	0.64	0.63
Number of sets of tissues examined microscopically	12	12	12	12	12	11	12	12

^aSource: Kinkead et al. (1971).

^bOne male rat given 73.8 ppm did not gain weight normally due to an unnoticed excessive incisor growth, which prevented the obtainment of a normal food intake. Therefore, the remaining 11 rats were used for statistical analysis.

*Statistically significant ($< 0.05 < p < 0.01$, ANOVA).

**Statistically significant ($< 0.01 < p < 0.001$, ANOVA).

***Statistically significant ($p < 0.001$, ANOVA).

Table B.27. Mean Body Weight in B6C3F₁ Mice Exposed to DCPD Vapor During a 90-Day Inhalation Study^a				
Group Identification	Mean Chamber Concentration (ppm) (HEC equivalent, mg/m³)			
	Control	1.0 (0.97)	5.1 (4.9)	51.0 (49)
	Body weight (g)^b			
Male				
A	25.8 ± 2.1	25.1 ± 2.1	27.0 ± 2.6	26.7 ± 1.4
B	28.4 ± 2.2	28.6 ± 2.8	29.4 ± 2.1	29.3 ± 2.3
C	31.8 ± 3.1	31.3 ± 2.2	30.4 ± 2.6	32.0 ± 2.5
D	30.0 ± 2.0	30.5 ± 1.8	30.9 ± 2.3	31.8 ± 3.0
E	32.8 ± 4.6	32.7 ± 1.7	31.3 ± 2.0	34.3 ± 3.2
Female				
A	22.9 ± 0.9	21.3 ± 1.4	22.0 ± 1.1	21.9 ± 1.0
B	25.0 ± 0.8	24.2 ± 0.9	25.0 ± 1.8	25.4 ± 1.7
C	26.2 ± 1.5	25.6 ± 1.6	28.2 ± 1.4*	28.1 ± 2.2*
D	26.9 ± 1.3	27.2 ± 1.7	27.6 ± 1.9	28.1 ± 2.3
E	32.0 ± 2.8	29.5 ± 1.0*	27.6 ± 1.5*	29.7 ± 2.3*

^aSource: Exxon (1980).

^bValues represent mean ± SD, units are in grams.

*Statistically significant ($p < 0.05$, ANOVA) compared to control.

Table B.28. Mean Serum Glucose Concentrations for Male B6C3F₁ Mice Exposed to DCPD Vapor During a 90-Day Inhalation Study^a	
Chamber concentration (ppm) (HEC equivalent, mg/m³)	Glucose (g/L)^b
Group A—10 completed exposures	
Control (0.0)	1.96 ± 0.20
1.0 (0.97)	1.97 ± 0.23
5.1 (4.9)	2.02 ± 0.16
51.0 (49)	2.19 ± 0.27
Group B—30 completed exposures	
Control (0.0)	2.41 ± 0.50
1.0 (0.97)	2.22 ± 0.37
5.1 (4.9)	2.20 ± 0.16
51.0 (49)	2.41 ± 0.42
Group C—64 completed exposures	
Control (0.0)	2.27 ± 0.34
1.0 (0.97)	2.56 ± 0.37
5.1 (4.9)	2.53 ± 0.27
51.0 (49)	2.92 ± 0.34*

^aSource: Exxon (1980).

^bValues represent mean ± SD.

*Statistically significant ($0.01 < p < 0.001$, Bartlett's test for the homogeneity of variance).

Table B.29. Mean Serum Albumin Concentrations for Female B6C3F₁ Mice Exposed to DCPD Vapor During a 90-Day Inhalation Study^a

Chamber concentration (ppm) (HEC equivalent, mg/m ³)	Albumin (g/L) ^c
Group A—10 completed exposures^b	
Control (0.0)	
1.0 (0.97)	
5.1 (4.9)	
51.0 (49)	
Group B—30 completed exposures	
Control (0.0)	34.9 ± 2.4
1.0 (0.97)	36.7 ± 1.3
5.1 (4.9)	35.1 ± 2.3
51.0 (49)	33.5 ± 2.1
Group C—64 completed exposures	
Control (0.0)	31.5 ± 1.0
1.0 (0.97)	30.8 ± 1.5
5.1 (4.9)	29.2 ± 1.0*
51.0 (49)	29.3 ± 0.9*

^aSource: Exxon (1980).

^bInsufficient sample collected.

^cValues represent mean ± SD.

*Statistically significant ($0.01 < p < 0.001$, Bartlett's test for the homogeneity of variance).

Table B.30. Mean Absolute Liver and Kidney Weights in B6C3F₁ Mice Exposed to DCPD Vapor During a 90-Day Inhalation Study^a

Group Identification	Mean Chamber Concentration (ppm) (HEC equivalent, mg/m ³)			
	Control	1.0 (0.97)	5.1 (4.9)	51.0 (49)
	Absolute Liver weight (g) ^b			
Male				
A	1.506 ± 0.101	1.512 ± 0.140	1.665 ± 0.182	1.597 ± 0.197
B	1.605 ± 0.087	1.602 ± 0.187	1.628 ± 0.167	1.717 ± 0.301
C	1.642 ± 0.265	1.775 ± 0.108	1.688 ± 0.194	1.745 ± 0.169
D	1.553 ± 0.118	1.594 ± 0.083	1.633 ± 0.136	1.648 ± 0.113
E	1.770 ± 0.196	1.735 ± 0.140	1.634 ± 0.158	1.809 ± 0.126
Female				
A	1.413 ± 0.091	1.256 ± 0.088*	1.341 ± 0.095	1.340 ± 0.139
B	1.427 ± 0.108	1.410 ± 0.099	1.613 ± 0.493	1.454 ± 0.138
C	1.537 ± 0.184	1.464 ± 0.184	1.795 ± 0.147*	1.644 ± 0.122
D	1.530 ± 0.114	1.632 ± 0.107	1.650 ± 0.126	1.652 ± 0.134
E	1.743 ± 0.143	1.676 ± 0.073	1.490 ± 0.135*	1.652 ± 0.121
Absolute Right Kidney weight (g)^b				
Male				
A	0.266 ± 0.042	0.248 ± 0.027	0.274 ± 0.033	0.257 ± 0.028
B	0.292 ± 0.025	0.298 ± 0.048	0.291 ± 0.037	0.290 ± 0.044
C	0.345 ± 0.029	0.349 ± 0.035	0.331 ± 0.034	0.335 ± 0.031
D	0.338 ± 0.032	0.328 ± 0.047	0.339 ± 0.026	0.336 ± 0.044
E	0.365 ± 0.058	0.353 ± 0.044	0.355 ± 0.036	0.358 ± 0.049
Female				
A	0.190 ± 0.019	0.167 ± 0.021	0.174 ± 0.016	0.183 ± 0.015
B	0.188 ± 0.015	0.185 ± 0.028	0.203 ± 0.028	0.210 ± 0.027
C	0.233 ± 0.021	0.235 ± 0.012	0.265 ± 0.033*	0.250 ± 0.023
D	0.255 ± 0.017	0.254 ± 0.024	0.244 ± 0.024	0.272 ± 0.018
E	0.274 ± 0.034	0.262 ± 0.026	0.259 ± 0.022	0.273 ± 0.027

^aSource: Exxon (1980).

^bValues represent mean ± SD, units are in grams.

*Statistically significant ($p < 0.05$, ANOVA) compared to control.

Table B.31. Summary of Responses of Groups of Three Male Beagles that Inhaled DCPD Vapor for 89 Days^a				
Parameter	Mean concentration (ppm) (Human Equivalency Concentration, mg/m³)^b			
	0 (0)	8.9 (10.0)	23.5 (26.5)	32.4 (36.5)
Mean body weight at end (kg)	11.2	10.0	11.2	10.9
Mean body weight gain at end (kg)	1.60	1.23	1.93	2.67
Mean liver weight (g)	317.0	328.7 (104)	339.0 (107)	393.3 (124)
Mean liver weight (% of body weight)	2.85	3.35 (116)	3.04 (107)	3.61 (127)
Mean kidney weight (g)	42.7	46.0 (108)	51.0 (119)	53.3 (125)
Mean kidney weight (% of body weight)	0.38	0.47 (124)	0.45 (118)	0.49 (129)

^aSource: Kinkead et al. (1971).

^b(): % of control.

APPENDIX C. BMD MODELING OUTPUTS FOR DCPD

There are no BMD modeling outputs for DCPD.

APPENDIX D. REFERENCES

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