United States
Environmental Protection
Agency

EPA/690/R-14/009F
Final
9-16-2014

Provisional Peer-Reviewed Toxicity Values for

Isopropanol
(CASRN 67-63-0)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS AND ACRONYMS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR ISOPROPANOL (CASRN 67-63-0)

BACKGROUND

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

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

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

DISCLAIMERS

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

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

QUESTIONS REGARDING PPRTVs

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

INTRODUCTION

Isopropanol (also known as isopropyl alcohol and 2-propanol) is a colorless, volatile liquid. It has a sharp, musty alcohol smell, with an odor threshold of about 1 ppm. It is commonly sold and used as a disinfectant in a 70% aqueous solution (rubbing alcohol). Isopropanol is also used as a fuel drier/de-icer, as an intermediate in the synthesis of organic chemicals, as a solvent for oils and resins, and in cosmetics, skin and hair preparations, pharmaceuticals, perfumes, lacquer formulations, dye solutions, soaps, and window cleaners. It is miscible in water. The empirical formula for isopropanol is C_3H_8O (see Figure 1). A list of physicochemical properties is provided in Table 1.

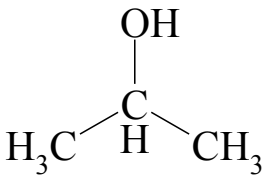

Figure 1. Isopropanol Structure

Table 1. Physicochemical Properties of Isopropanol (CASRN 67-63-0)[a]

Property (unit)	Value
Boiling point (°C)	82
Melting point (°C)	-89.5
Density (g/cm^3 at 25°C)	0.785
Vapor pressure (Pa at 25°C)	4,400
pH (unitless)	NA
Solubility in water (g/100 mL at 25°C)	Miscible
Relative vapor density (air = 1)	2.1
Molecular weight (g/mol)	60.09
Flash point (°C)	11.7
Octanol/water partition coefficient (unitless)	NA

[a]Values from IARC (1999) and from ChemicalBook (2008).

NA = not available.

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

Table 2. Summary of Available Toxicity Values for Isopropanol (CASRN 67-63-0)				
Source/ Parameter[a]	**Value (Applicability)**	**Notes**	**Reference**	**Date Accessed**
Noncancer				
ACGIH	8-h TLV-TWA: 200 ppm (490 mg/m^3) 15-min TLV-STEL: 400 ppm (980 mg/m^3) BEI: 40 mg/L	TLV based on eye and upper respiratory tract irritation and central nervous system effects (i.e., changes in postural sway). Determinant for the BEI was acetone in urine.	ACGIH (2013)	NA
ATSDR	NV	NA	ATSDR (2013)	NA
Cal/EPA	Acute REL: 3.2 × 10^3 µg/m^3 (3.2 mg/m^3) Chronic REL: 7.0 × 10^3 µg/m^3 (7.0 mg/m^3)	The acute REL hazard index targets are eyes and respiratory system. The chronic REL hazard index targets are development and kidney.	Cal/EPA (2014)	NA
NIOSH	10-h REL-TWA: 400 ppm (980 mg/m^3) 15-min REL-TWA: 500 ppm (1,225 mg/m^3) IDLH: 2,000 ppm	The IDLH is set at 2,000 ppm, based on 10% of the lower explosive limit, even though the relevant toxicological data indicates irreversible health effects or impairment of escape exists only at higher concentrations.	NIOSH (2010)	NA
OSHA	8-h PEL-TWA: 400 ppm (980 mg/m^3)	NA	OSHA (2011)	NA
IRIS	NV	NA	U.S. EPA	9-12-2014
Drinking water	NV	NA	U.S. EPA (2012a)	NA
HEAST	NV	NA	U.S. EPA (2011a)	NA
CARA HEEP	NV	NA	U.S. EPA (1994a, 1985)	NA
WHO	NV	NA	WHO	9-12-2014
Cancer				
IRIS	NV	NA	U.S. EPA	9-12-2014
HEAST	NV	NA	U.S. EPA (2011a)	NA
IARC	"*Not Classifiable as to its Carcinogenicity to Humans (Group 3)*"	Selection made due to inadequate evidence in humans and experimental animals.	IARC (1999)	NA

Table 2. Summary of Available Toxicity Values for Isopropanol (CASRN 67-63-0)				
Source/ Parameter[a]	**Value (Applicability)**	**Notes**	**Reference**	**Date Accessed**
NTP	NA	NV	NTP (2011)	NA
Cal/EPA	NA	NV	Cal/EPA (2012)	NA
ACGIH	"*Not Classifiable as a Human Carcinogen* (A4)"	NA	ACGIH (2013)	NA

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

BEI = biological exposure index; IDLH = immediately dangerous to life or health; NA = not applicable; NV = not available; PEL-TWA = permissible exposure level-time weighted average; REL = reference exposure levels; REL-TWA = recommended exposure level-time weighted average; TLV-STEL = threshold limit value-short-term exposure limit; TLV-TWA = threshold limit value-time weighted average.

Literature searches were conducted on sources published from 1900 through March 26, 2014 for studies relevant to the derivation of provisional toxicity values for isopropanol, CASRN 67-63-0. Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for relevant health information: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, 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 isopropanol and includes all potentially relevant repeat-dose short-term-, subchronic-, and chronic-duration studies. Reference to "statistical significance" used throughout the document indicates a *p*-value of <0.05.

Table 3. Summary of Potentially Relevant Data for Isopropanol (CASRN 67-63-0)								
Category	**Number of Male/Female, Strain Species, Study Type, Study Duration**	**Dosimetry[a]**	**Observed Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (Comments)**	**Notes[b]**
Human								
1. Oral (mg/kg-d)[a]								
Acute[c]	ND							
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
2. Inhalation (mg/m^3)[a]								
Acute[c]	ND							
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
Animal								
1. Oral (mg/kg-d)[a]								
Subchronic	22/0, Wistar SPF rat, drinking water, 12 wk	0; 870, 1,280, 1,680, 2,520 (Adjusted)	Increased relative liver weight at ≥1,680 mg/kg-d, increased relative kidney weight at ≥1,280 mg/kg-d, increased relative adrenal weight at ≥1,680 mg/kg-d, and increased relative testes weight at 2,520 mg/kg-d.	870 (Adjusted)	554 for increased relative kidney weight	1,280 (Adjusted)	Pilegaard and Ladefoged (1993)	PR

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Category	**Number of Male/Female, Strain Species, Study Type, Study Duration**	**Dosimetry[a]**	**Observed Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (Comments)**	**Notes[b]**
Chronic	ND							
Developmental	0/20, Wistar-derived rat, drinking water, GDs 6−16, sacrificed on GD 20	0, 596, 1,242, 1,605	F0: Decreased maternal food consumption at ≥1,242 mg/kg-d and decreased water intake at ≥596 mg/kg-d. F1: Decreased male and female fetal body weight at 1,605 mg/kg-d and decreased number of fetuses with the fourth sacral arch at ≥596 mg/kg-d.	Maternal: NDr Developmental: NDr	847 for decreased fetal body weight in male and female rats	Maternal: 596 Developmental: 596	BIBRA (1987)	PR
Developmental	0/64, CD(S-D)BR rat, gavage, GD 6−PND 21	0, 200, 700, 1,200	F0: One 1,200-mg/kg-d dam died on PND 15. F1: No observed effects.	Maternal: 700 Developmental: 1,200	DU	Maternal: 1,200 (FEL) Developmental: NDr	Bates et al. (1994)	PR
Developmental	0/25, CD(S-D) rat, gavage (aqueous), GDs 6−15, sacrificed on GD 20	0, 400, 800, 1,200	F0: Dam mortality at ≥800 mg/kg-d. F1: Decreased fetal body weight in males and females at ≥800 mg/kg-d and males and females combined at 1,200 mg/kg-d.	Maternal: 400 Developmental: 400	513 for decreased fetal body weight in female rats	Maternal: 800 (FEL) Developmental: 800	Tyl et al. (1994)	PR

Table 3. Summary of Potentially Relevant Data for Isopropanol (CASRN 67-63-0)								
Category	**Number of Male/Female, Strain Species, Study Type, Study Duration**	**Dosimetry[a]**	**Observed Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (Comments)**	**Notes[b]**
Developmental	**0/15, NZW rabbit, gavage (aqueous), GDs 6−18, sacrificed on GD 30**	**0, 120, 240, 480**	**F0: Dam mortality at 480 mg/kg-d and decreased maternal food consumption at 480 mg/kg-d.** **F1: Decreased fetal body weight in males only and males and females combined at 480 mg/kg-d and in females only at ≥240 mg/kg-d.**	**Maternal: 240** **Developmental: 120**	**120 for decreased fetal body weight in female rabbits**	**Maternal: 480 (FEL)** **Developmental: 240**	**Tyl et al. (1994)**	**PR, PS**
Reproductive (one-generation)	10/10, Wistar-derived rat, drinking water, treatment initiated 70 d (male) and 21 d (female) prior to mating with dosing continued through weaning of F1 litters on PND 21. The premating phase refers to treatment of F0 females for 21 d prior to mating. The postpartum phase refers to treatment of F0 females from PND 1 to PND 21. Each F0 male treatment group received the same doses throughout the duration of the study.	F0 male average: 0, 317, 711, 1,001, 1,176 (Adjusted) F0 female average (Adjusted for postpartum phase): 0, 1,167, 2,645, 2,825, 2,724	F0 (parental): Decreased body weight in dams on PND 21 at 2,825 and 2,724 mg/kg-d; decreased food consumption and water intake in dams on PND 21 at 2,825 and 2,724 mg/kg-d; decreased food consumption and water intake in males at ≥711 mg/kg-d; increased absolute liver and kidney weights in males at 1,176 mg/kg-d; increased relative liver and kidney weights in males at ≥ 1,001 mg/kg-d; increased absolute liver weight in females at ≥2,645 mg/kg-d; increased absolute kidney weight and relative liver and kidney weights in females at 2,825 and 2,724 mg/kg-d. F1: Decreased pup weight in both sexes at ≥1,167 mg/kg-d.	Parental: 317 (F0 males) Postpartum phase: NDr (F1 pups, both sexes)	606 for increased absolute liver weight in F0 males	Parental: 711 (F0 males) Postpartum phase: 1,167 (F1 pups, both sexes)	BIBRA (1986)	NPR; pilot study

Table 3. Summary of Potentially Relevant Data for Isopropanol (CASRN 67-63-0)								
Category	**Number of Male/Female, Strain Species, Study Type, Study Duration**	**Dosimetry[a]**	**Observed Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (Comments)**	**Notes[b]**
Reproductive (one-generation)	10/30, (10 females for embryotoxicity; 20 females for single-generation [littering]), Wistar-derived rat, drinking water, treatment initiated 70 d (male) and 21 d (female) prior to mating with dosing continued through weaning of F1 litters on PND 21. The premating phase refers to treatment of F0 females for 21 d prior to mating. The postpartum phase refers to treatment of F0 females from PND 1 to PND 21.	F0 male average (Days –3 to 126 Adjusted): 0, 347, 625, 1,030 F0 Female average (Adjusted for premating phase): 0, 456, 835, 1,206 (Adjusted for postpartum phase): 0, 1,053, 1,948, 2,768	F0 (parental): Decreased water intake in males at ≥625 mg/kg-d; decreased water intake in females at 1,206 mg/kg-d; decreased food consumption in males at ≥347 mg/kg-d; decreased food consumption in females at 1,206 (premating) and 1,902 (gestation) mg/kg-d; increased relative liver, spleen, and kidney weights in males at 1,030 mg/kg-d; increased relative and absolute liver weight in females at 2,768 mg/kg-d; increased absolute kidney weights in males at 1,030 mg/kg-d.	Parental: NDr (F0 males)	663 for increased relative liver weight in F0 males	Parental: 347	BIBRA (1988)	PR; parental (F0) component of the BIBRA (1988) study.

Table 3. Summary of Potentially Relevant Data for Isopropanol (CASRN 67-63-0)								
Category	**Number of Male/Female, Strain Species, Study Type, Study Duration**	**Dosimetry[a]**	**Observed Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (Comments)**	**Notes[b]**
Reproductive (one-generation)		0, 668, 1,330, 1,902	F0 (parental): Deceased food consumption in females at 1,902 mg/kg-d. F1: Decreased pup body weight in both sexes on PND 4 at ≥1,330 mg/kg-d; decreased fetal body weight at 1,902 mg/kg-d; increased number of preimplantation losses at 1,902 mg/kg-d.	Parental: 1,330 (F0 females) F1 pups: 668 (both sexes)	613 for decreased pup body weight in both sexes on PND 4	Parental: 1,902 (F0 females) F1 pups: 1,330 (both sexes)	BIBRA (1988)	PR; gestational component of the BIBRA (1988) study. Doses for F1 pups are presented assuming that they received 100% of the dose given to dams.
Reproductive (one-generation)		0, 1,053, 1,948, 2,768	F1 pups: Decreased pup body weight in both sexes on PND 21 at ≥1,053 mg/kg-d; increased relative liver weight in males and females at 2,768 mg/kg-d at ~31 d postweaning; increased relative testes weight in males at 2,768 mg/kg-d at ~31 d postweaning.	NDr	580.9 for decreased pup body weight in both sexes on PND 21	1,053	BIBRA (1988)	PR; postpartum component of the BIBRA (1988) study. Doses for F1 pups are presented assuming that they received 100% of the dose given to dams.

Table 3. Summary of Potentially Relevant Data for Isopropanol (CASRN 67-63-0)								
Category	**Number of Male/Female, Strain Species, Study Type, Study Duration**	**Dosimetry[a]**	**Observed Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (Comments)**	**Notes[b]**
Reproductive (two-generation)	30/30, S-D rat, gavage, treatment began 10−13 wk before mating and continued through lactation (female) and until the last litter was sired (male)	0, 100, 500, 1,000 (Adjusted)	F0: Increased absolute and relative liver weight in males and increased relative liver weight in females at 1,000 mg/kg-d. F1: Increased relative liver weight in adult males at ≥500 mg/kg-d; increased relative liver weight in adult females at 1,000 mg/kg-d; decreased male mating index at 1,000 mg/kg-d; decreased live birth index at 1,000 mg/kg-d; decreased Day 1 (1,000 mg/kg-d) and Day 4 (≥500 mg/kg-d) survival indices. F2: Decreased Day 1 (≥500 mg/kg-d), Day 4 (1,000 mg/kg-d), and Day 7 (≥500 mg/kg-d) survival indices; decreased lactation index at ≥500 mg/kg-d; decreased male pup body weight at 1,000 mg/kg-d.	Parental: 100 (Adjusted) Reproductive: 500 (Adjusted) Developmental: 100	197 for increased relative liver weight in F1 adult males	Parental: 500 (Adjusted) Reproductive: 1,000 (Adjusted) Developmental: 500	Bevan et al. (1995)	PR; mortality was also observed but does not appear to be dose related.
Carcinogenic	ND							

Table 3. Summary of Potentially Relevant Data for Isopropanol (CASRN 67-63-0)								
Category	**Number of Male/Female, Strain Species, Study Type, Study Duration**	**Dosimetry[a]**	**Observed Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (Comments)**	**Notes[b]**
2. Inhalation (mg/m^3)[a]								
Subchronic	**25/25, F344 rat, vapor inhalation for 13 wk, 6 h/d, 5 d/wk (10/10 for systemic toxicity, and 15/15 for neurobehavioral assessment)**	**0, 43.9, 222, 661.8, 2,198**	Mean cumulative motor activity was increased in females at 2,198 mg/m^3 in neurobehavioral assessment.	**661.8**	**DU**	**2,198**	**Burleigh-Flayer et al. (1994)**	**PR, PS**
Subchronic	0/30, F344 rat, vapor inhalation, 9 wk or 13 wk, 6 h/d, 5 d/wk	0, 2,199	Mean cumulative motor activity was increased.	NDr	DU	2,199	Burleigh-Flayer et al. (1998)	PR; the study was specifically designed to test neurotoxicity
Subchronic	10/10, CD-1 mouse, vapor inhalation for 13 wk, 6 h/d, 5 d/wk	0, 43.9, 222, 661.8, 2,198	Increased relative liver weight in females at ≥661.8 mg/m^3.	222	DU	661.8	Burleigh-Flayer et al. (1994)	PR
Chronic	ND							
Developmental	0/9−15, S-D rat, vapor inhalation, GDs 1−19, 7 h/d, 7 d/wk	0, 2,516, 5,048, 7,185	F0: No observed effects. F1: decreased fetal body weight in males and females at ≥5,048 mg/m^3; decreased number of implants and live implants at 7,185 mg/m^3; increased resorptions at 7,185 mg/m^3; increased malformations at ≥5,048 mg/m^3.	Maternal: 7,185 Developmental: 2,516	1,907 for decreased fetal body weight in male rats	Maternal: NDr Developmental: 5,048	Nelson et al. (1988)	PR
Reproductive	ND							

Table 3. Summary of Potentially Relevant Data for Isopropanol (CASRN 67-63-0)

Category	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry[a]	Observed Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Carcinogenic/ Chronic	75/75, F344 rat, vapor inhalation, exposed for at least 104 wk, 6 h/d, 5 d/wk; interim sacrifice of 10 animals/sex/concentration group at Wk 72	0, 221, 1,101, 2,211	Increased mortality in males at 2,211 mg/m^3; increased relative liver weight in males at 1,101 mg/m^3; increased relative liver weight in females at 2,211 mg/m^3; increased incidence of microscopic kidney damage in males and females at 2,211 mg/m^3.	Systemic: 221	262 for increased relative liver weight in male rats	Systemic: 1,101	Burleigh-Flayer et al. (1997)	PR, PS
Carcinogenic/ Chronic	**75/75, CD-1 mouse vapor inhalation, exposed for at least 78 wk, 6 h/d, 5 d/wk; interim sacrifice of 10 animals/sex/concentration group at Wk 54** **Additional recovery group (10 animals/sex/concentration group) not exposed after Wk 53, sacrificed at Wk 78**	**0, 221, 1,101, 2,211**	**Increased relative liver weight in females at 2,211 mg/m^3; decreased absolute and relative testes weights in males at ≥221 mg/m^3; increased incidence of seminal vesicle enlargement in males at 2,211 mg/m^3; increased incidences of adrenal gland congestion, mucosal cell hyperplasia in the stomach, splenic hematopoiesis, and hemosiderosis in females at 2,211 mg/m^3.**	**Systemic: NDr**	**1,181 for increased relative liver weight in female mice**	**Systemic: 221**	**Burleigh-Flayer et al. (1997)**	**PR**

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer and carcinogenic effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous exposure. Values from animal developmental studies are not adjusted to a continuous exposure.

HED = animal dose (mg/kg-d) × $(BW_a \div BW_h)^{1/4}$

HEC_{EXRESP} = ppm × (MW ÷ 24.45) × (h per d exposed ÷ 24) × (d per wk exposed ÷ 7) × blood gas partition coefficient.

[b]Notes: IRIS = Utilized by IRIS; date of last update; NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

[c]Acute = Exposure for 24 h or less (U.S. EPA, 2002).

[d]Short-term = Repeated exposure for > 24 h ≤ 30 d (U.S. EPA, 2002).

[e]Long-term = Repeated exposure for > 30 d ≤ 10% lifespan (based on 70 yr typical lifespan) (U.S. EPA, 2002).

[f]Chronic = Repeated exposure for ≥10% lifespan (U.S. EPA, 2002).

DU = data unsuitable; FEL = frank effect level; GD = Gestation Day; ND = no data; NDr = not determined; NS = not selected; NZW = New Zealand White; PND = Postnatal Day; S-D = Sprague-Dawley.

HUMAN STUDIES

Oral Exposures, Inhalation Exposures, and Other Exposures

Although there were no human studies suitable for reference value derivation, there are several published case reports that are briefly summarized in Table 5 below.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposures to isopropanol in animals have been evaluated in one subchronic-duration neurotoxicity study (Pilegaard and Ladefoged, 1993), four developmental studies (Bates et al., 1994; Tyl et al., 1994; BIBRA, 1987), and three reproductive studies (BIBRA, 1988, 1986) [pilot study]; (Bevan et al., 1995). These study reports are articles published in peer-reviewed journals and/or performed in compliance with Good Laboratory Practice (GLP) requirements. Chronic-duration and carcinogenicity oral studies with isopropanol have not been identified. Tyl et al. (1994) is a journal article containing studies performed on two different species (rat and rabbit).

Subchronic-duration Studies

Pilegaard and Ladefoged (1993)

Pilegaard and Ladefoged (1993) reported on an investigation of the subchronic toxicity and neurotoxicity of isopropanol in rats after administration in drinking water. Male Wistar SPF rats were separated into five groups of 22 rats each. Isopropanol in drinking water was administered at 0 (control), 1, 2, 3, or 5% (0, 870, 1,280, 1,680, and 2,520 mg/kg-day) for 12 weeks. Purity and formulated dose stability were not reported. In the high-dose group (2,520 mg/kg-day), water intake was low during Week 1; the amount of isopropanol was reduced to 4% during Week 2 and returned to 5% for the remainder of the study. Animals were sacrificed on Day 90. Twelve animals per group were decapitated and submitted for pathological examination. The liver, heart, spleen, testes, kidneys, and adrenals were weighed, and organ specimens were prepared and stained appropriately for histopathological examination. The remaining 10 animals per group were transcardially perfused with 4% neutral buffered formaldehyde and submitted for brain tissue densitometry. A section of the right hemisphere containing the dorsal hippocampus was removed, embedded in paraffin, and cut into serial sections. Random sections were selected for immunohistochemical staining for glial fibrillary acidic protein (GFAP). Densitometric measurements in several regions of each section (CA1, CA3, and hilar), as well as section thickness measurements, were performed.

Pilegaard and Ladefoged (1993) noted statistically significant decreases in body weight in the 1,680- and 2,520-mg/kg-day isopropanol groups, and body weight was increased in the 870-mg/kg-day group compared to control (numerical body-weight data and level of significance were not reported). Relative water intake was lower (statistical significance unknown) in the 1,280-, 1,680-, and 2,520-mg/kg-day isopropanol groups initially, and one rat died in the 2,520-mg/kg-day group. Statistically significant dose-dependent increases were observed in relative (to body) liver weight in the 1,280-mg/kg-day group (9%), the 1,680-mg/kg-day group (11%), and the 2,520-mg/kg-day group (12%); in relative kidney weight in the 1,280- to 2,520-mg/kg-day groups (20−35%), and in relative adrenal weight in the 1,680 and 2,520 mg/kg-day groups (27−34%). Relative testes weight was also statistically significantly increased at 2,520 mg/kg-day (13%) (see Table B-1). The study authors reported dose-related increases in hyaline cast and hyaline droplet formation in the renal proximal tubules in the males

at ≥1,280 mg/kg-day; however, no incidence or severity data were provided. No abnormalities were observed in the other examined organs. No differences in absorbance in the CA1, CA3, and hilar regions of the dorsal hippocampus due to isopropanol exposure were observed (see Table B-1). No neurotoxic effect of isopropanol on the dorsal hippocampus was observed in this study according to the densitometric method used. A LOAEL of 1,280 mg/kg-day is identified from this study based on increased relative kidney weight with a corresponding NOAEL of 870 mg/kg-day.

Chronic-duration Studies

No studies were identified.

Developmental Studies

BIBRA (1987)

The non-peer-reviewed technical report by BIBRA (1987) was not publically available; however, limited results from the report were published in a peer-reviewed journal (Faber et al., 2008). BIBRA (1987) conducted a GLP-compliant developmental study in rats as part of a series of studies for the Feed and Drink Federation IPA Steering Group (London, UK). Virgin male and female Wistar-derived rats were obtained from Olac 1976 Ltd. and acclimated for at least 1 week prior to study initiation. Animals were maintained on a 12:12 hour light:dark cycle at a temperature and humidity of 20−24ºC and 45−65%. Prior to mating, the animals were group housed, by sex, in polypropylene cages with stainless steel tops and grid floors; animals had access to Certified Rat and Mouse No. 3 feed (Special Diet Services) and domestic mains tap water ad libitum. Female and male rats, 11−12 weeks of age, were paired overnight until successful mating occurred: the presence of sperm in the vagina or a vaginal plug defined Gestation Day (GD) 0. Mated females were housed singly, as previously described, and randomly assigned to one of the four dose groups (n = 20/group).

The isopropanol utilized in the BIBRA (1987) study was provided by Shell Chemicals UK Ltd. (batch 1A1/41.3/84 GB1/260) and had a purity of 99.89% according to gas-liquid chromatography (GLC). Drinking water formulations were prepared with domestic mains tap water at intervals of 2 weeks or less and analyzed by GLC to confirm isopropanol concentration and stability. All formulations were within ±10% of nominal concentrations and stable for at least 28 days. Isopropanol drinking water concentrations presented to dams in the developmental study were 0%, 0.5%, 1.25%, or 2.5% (0, 596, 1,242, or 1,605 mg/kg-day) on GDs 6−16. Isopropanol intake was calculated from body weight and water intake data, and the actual dose concentrations. General observations were made daily, with thorough clinical observations conducted weekly. Maternal body weights, food consumption, and water intake were determined daily (GDs 0−20), and dams were euthanized on GD 20. The abdominal and thoracic contents were examined for abnormalities. The ovaries were examined and the number of corpora lutea recorded. The uterus was examined, and the numbers and locations of viable and nonviable fetuses, early and late resorptions, total implantations, and pre- and postimplantation losses were recorded. Live fetuses were weighed and examined for gross abnormalities. Approximately 50% of all of the fetuses (including all with gross abnormalities) were preserved in ethanol, eviscerated, and processed for skeletal examination after staining with Alizarin Red S. The stained preparations were examined for skeletal abnormalities, variants, and variations in the degree of ossification. The remaining fetuses were preserved in Bouin's solution; the high-dose and control groups were examined by freehand sectioning of the head and palate and dissection of the abdomen and thorax. The sex was determined and recorded.

Continuous variables (maternal and fetal weights, intakes, and the total number of resorptions, pre- and postimplantation losses, and live fetuses) were compared with analysis of variance (ANOVA) and least-square difference and Student's *t*-test procedures. Incidences of maternal abnormalities, and fetal skeletal and visceral abnormalities (accounting for both between and within litter variation), were compared with Fisher's Exact tests.

The BIBRA (1987) study reported no deaths, abortions, or early deliveries for the females, and the numbers of nonpregnant females were distributed across the dose groups in a nontreatment-related manner. Food consumption was statistically significantly reduced relative to control levels in the 1,242- and 1,605-mg/kg-day groups during the dosing period (high dose, GDs 6−16; mid dose, GDs 6−9). Water intake was statistically significantly decreased at ≥596 mg/kg-day. Food consumption and water intake in these groups rebounded after GD 16 to levels greater than or similar to control; intake levels in the low-dose group (596 mg/kg-day) were similar to the control throughout the study. Dams in the high-dose group lost weight (GDs 6–8) and had a lower rate of body-weight gain through GD 16; body-weight gain was greater than control during GDs 17−20 in the high-dose dams, but overall body weights remained lower through GD 20. Table B-2 summarizes the litter parameters and fetal weights, including endpoints for events that occurred prior to isopropanol exposure (pregnancy rate, total number of corpora lutea, and total numbers of preimplantation loss). No effects related to isopropanol exposure in postimplantation loss, mean number of implantation sites, or live fetuses were observed. Findings included a slight dose-dependent decrease in mean litter weight (not statistically significant) and a statistically significant decrease in mean fetal weight in the 1,242 and 1,605 mg/kg-day dose groups. Mean fetal body weight was statistically significantly decreased at 1,605 mg/kg-day. No gross abnormalities were observed; the only skeletal malformation was an absence of caudal vertebrae and short forelimb and hindlimb bones in a single control fetus. Statistically significant increases in skeletal variations were indicative of a lower degree of ossification in the treated animals. The study noted dose-dependent decreases in the number of fetuses with the fourth sacral arch and dose-dependent increases in the number of fetuses with less than two caudal arches. Increased numbers of fetuses with small, absent, or incompletely ossified sternebrae also indicated statistically significantly reduced ossification at 1,605 mg/kg-day. Other statistically significant skeletal findings were not dose dependent. No abnormalities were noted in the viscera of offspring in the 1,605-mg/kg-day dose group compared to the control group. A maternal LOAEL of 596 mg/kg-day is identified based on decreased water intake. A developmental LOAEL of 596 mg/kg-day is identified based on decreased number of fetuses with the fourth sacral arch. Because 596 mg/kg-day is the lowest dose tested, neither a maternal nor developmental NOAEL can be identified.

Bates et al. (1994)

In a developmental neurotoxicity study, Bates et al. (1994) administered isopropanol via gavage to CD (S-D)BR rats. Aqueous dosing solutions of isopropanol were formulated at 0, 40, 140, or 240 mg/mL (0, 200, 700, or 1,200 mg/kg-day in a dose volume of 5 mL/kg). Two hundred fifty-six sperm-positive female animals were randomized into four groups (64 rats per group). Doses were administered from GD 6 through Postnatal Day (PND) 21. Pups were counted, weighed, and sexed on PNDs 0 and 4, after which standard litter sizes were achieved (4:4 or 5:3) through culling, with other animals removed from the study. Offspring were weighed through PND 68 and randomized into male:female pairs for behavioral testing or neuropathological assessment. Three pairs of pups/litter were evaluated for motor activity

(figure-eight maze), auditory startle response (120-dB tone), or learning/memory (active avoidance test) in one pair per test on PNDs 13, 17, 21, 47, and 58. Body, liver, and kidney weight, and implantation site evaluations were performed on all dams after sacrifice on PND 22. On PNDs 22 and 68, a male and a female pup from each litter (n = 12) were sacrificed and weighed, and central and peripheral nervous system tissues were prepared for histopathological evaluation. Brains of all remaining animals were removed after euthanization, weighed, and examined.

Bates et al. (1994) noted that all pregnant dams gave birth to litters, and the majority of litters within each dose group had a sufficiently balanced pup sex ratio (n = 26−31). Although only approximately one-half of the mated animals became pregnant, the study authors did not attribute this to a treatment effect because treatment began after mating had occurred. In addition, no treatment-related effects were observed in maternal weight or weight gain, gestation duration, or food consumption, and no effects were noted in pup weight, weight gain, sex ratio, development, or survival. Finally, no treatment-related effects were observed in the pup behavioral tests, maternal organ weights, brain region weights, or in the nervous system histopathological examinations. The only treatment-related effect of note was death of a single dam in the 1,200-mg/kg-day group on PND 15. The maternal NOAEL is 700 mg/kg-day. A maternal LOAEL could not be determined because the next highest dose (1,200 mg/kg-day) resulted in death. Therefore, 1,200 mg/kg-day is considered a frank effect level (FEL). A developmental NOAEL of 1,200 mg/kg-day is identified based on a lack of observed developmental effects; identification of a developmental LOAEL is precluded.

Tyl et al. (1994)

In a developmental toxicity study in the rat, Tyl et al. (1994) examined the developmental toxicity of isopropanol in orally dosed timed-pregnant female CD (S-D) rats (Charles River Laboratories, Inc.). Dosing solutions of isopropanol (99.95 ± 0.01% pure) were formulated in deionized/distilled water at 0, 80, 160, and 240 mg/mL (0, 400, 800, and 1,200 mg/kg-day at a dose volume of 5 mL/kg) with stability determined for at least 49 days refrigerated. One hundred sperm-positive female animals (214−275 g in weight and 10 weeks old at GD 0) were used. The animals were housed singly in polycarbonate cages with stainless steel wire lids and purified cage litter. Food and deionized/filtered water were available ad libitum, and a 12:12 hour light:dark cycle was maintained. Animals were randomized into one of four groups (three treatment and a deionized/distilled water vehicle control, 25 per group) to achieve uniform mean body weight across groups. Aqueous solutions of test article or vehicle alone were administered by gavage from GDs 6−15. Clinical observations were conducted at least once daily prior to dosing initiation (GDs 0−5) and post-treatment (GDs 16−20) and twice daily during the dosing period (GDs 6−15). Body weights and food consumption were recorded on GDs 0, 6, 9, 12, 15, 18, and 20. Maternal animals were euthanized by CO_2 asphyxiation on GD 20, and thoracic and abdominal organs and cavities were examined. Body, liver, and uterine weights were recorded, ovarian corpora lutea were counted, and uterine implantation site status was recorded. Rat fetuses were weighed, sexed, and examined for external alterations. Half of the fetuses in each litter were decapitated and further examined for visceral alterations, with the heads examined for soft tissue craniofacial alterations. Fetuses were also examined for skeletal malformations and variations.

Tyl et al. (1994) reported that pregnancy rate in the rat was high (96%). The three deaths that occurred after the dosing period (GDs 16 to 18) were considered to be treatment related by the study authors (1/25[4%] and 2/25 [8%] in the 800-mg/kg-day and 1,200-mg/kg-day dose groups). Maternal body and liver weights and food consumption were statistically equivalent across all groups at all time points measured, except for a statistically significant reduction in maternal weight gain in the 1,200-mg/kg-day group for GDs 0−20 (89.9% of control). This decrease may be accounted for by reduced fetal body weights in this group. No maternal necropsy observations appeared treatment related. All pregnant animals had one or more live fetuses (no resorptions), and all gestational parameters were equivalent across all groups with no late fetal deaths. The number and sex ratio of live fetuses were also equivalent.

Body weights per litter were statistically significantly reduced at ≥800 mg/kg-day in male and female fetuses (see Table B-3). Fetal body weights per litter in all rats (males and females combined) were statistically significantly decreased at 1,200 mg/kg-day. Fetal variations were distributed across all groups, with no treatment-related changes observed during external, visceral, or skeletal examinations. The study authors concluded that isopropanol was not teratogenic after gavage administration during major organogenesis in the CD rat. A maternal LOAEL is not determined because of mortality in the dams at the two highest doses. Thus, a maternal FEL of 800 mg/kg-day with a corresponding NOAEL of 400 mg/kg-day are identified. A developmental LOAEL of 800 mg/kg-day is identified based on decreased male and female fetal body weight (>5% change compared to control values) with a corresponding NOAEL of 400 mg/kg-day.

Tyl et al. (1994)

The developmental study in rabbits conducted by Tyl et al. (1994) is selected as the principal study for deriving the subchronic provisional reference dose (p-RfD) and chronic p-RfD. This study was conducted according to GLP regulations (RTI, 1990) and examined the developmental toxicity of isopropanol in the New Zealand White (NZW) rabbit (Hazleton Research Products, Inc.). Dosing solutions of isopropanol (99.95 ± 0.01% pure) were formulated in deionized/distilled water at 0, 60, 120, or 240 mg/mL (0, 120, 240, or 480 mg/kg-day at a dose volume of 2 mL/kg), with stability determined to be least 49 days under refrigeration. Measured nominal concentrations of dose formulations ranged from 97−106%. Sixty artificially inseminated female animals (2,750 to 3,800 g in weight and approximately 5.5 months old at GD 0) were used. The animals were housed singly in stainless steel cages with mesh flooring. Food and deionized/filtered water were available ad libitum, and a 12:12 hour light:dark cycle was maintained. Animals were randomized into one of four groups (three treatment and a deionized/distilled water vehicle control, 15 per group) to achieve uniform mean body weight across groups. The dosing solutions were administered by gavage from GDs 6−18. Clinical observations were recorded once daily prior to initiation of treatment (GDs 0−5) and following the treatment period (GDs 19−30) and twice daily during treatment (GDs 6−18). Body weights and food consumption were recorded on GDs 0, 6, 9, 12, 15, 18, 21, 24, and 30. Maternal animals were euthanized on GD 30, and thoracic and abdominal organs and cavities were examined. Body, liver, uterine weights, and uterine implantation site status (implantations, resorptions, and live and dead fetuses) were recorded, and ovarian corpora lutea were counted. Fetuses were weighed and examined for external alterations. Fifty percent of the fetuses were then sacrificed, sexed internally, and examined for visceral alterations. Fetuses were also examined for skeletal malformations, and heads were examined for soft tissue craniofacial

alterations. General linear models (GLM) procedures were used to test for significant linear trends for all analyses of variance; significant effects were further examined by William's and/or Dunnett's multiple comparison tests. Nominal scale measures were analyzed by χ^2 test for independence, with significant differences examined with a one-tailed Fisher's exact probability test.

Tyl et al. (1994) reported that the pregnancy rate in the rabbit was high (96.7%) in this study. The four deaths that occurred during or immediately after the dosing period (GDs 11−19) were considered treatment related (4/15, 27%, in the 480-mg/kg-day group); however, the study authors provided no further details regarding the cause(s) of the deaths. Maternal body weights were statistically equivalent across all groups at all time points measured, although body-weight change was statistically significantly reduced in the 480-mg/kg-day group during the treatment period (GDs 6−18, 45%). This decrease was associated with a statistically significant reduction in maternal food consumption during the same period. Gravid uterine and liver weights were equivalent across all groups. General treatment-related clinical observations were noted at 480 mg/kg-day, including flushed ears, and various nonspecific indicators of stress. No maternal necropsy observations appeared treatment related. All pregnant animals had one or more live fetuses (no resorptions), and all gestational parameters were equivalent across all groups. The number and sex ratio of live fetuses were equivalent between groups, with only slight weight reductions noted (not statistically significant). There were also decreases in fetal body weight per litter, albeit not statistically significant (see Table B-4). Female fetal body weight was decreased (>5% change compared to control values) at ≥240 mg/kg-day. Fetal body weight in all rabbits (males and females combined) and male rabbits alone was decreased (>5% change compared to control values) at 480 mg/kg-day. Fetal variations were distributed across all groups, with no treatment-related changes observed during external, visceral, or skeletal examinations; therefore, the study authors concluded that isopropanol was not teratogenic after gavage administration during major organogenesis in the NZW rabbit. A maternal LOAEL is not available because the 480 mg/kg-day dose is an FEL in the dams with a corresponding NOAEL of 240 mg/kg-day. A developmental LOAEL of 240 mg/kg-day is identified based on decreased female fetal body weight (>5% change compared to control values) with a corresponding NOAEL of 120 mg/kg-day.

Reproductive Studies

BIBRA (1986)

A one-generation reproductive toxicity pilot study with isopropanol was conducted according to international GLP regulations by (BIBRA, 1986) in response to the U.S. Toxic Substances Control Act (TSCA) (not peer reviewed). Dosing solutions of isopropanol were formulated in domestic tap water at concentrations of 0 (control), 0.5, 1.25, 2.0, and 2.5%. This study used the Wistar-derived rat (10 male and 10 female animals/group), aged 7−8 weeks. The test solutions were administered over the following periods: males were administered the test article 70 days before mating, during mating, and up until sacrifice; females received the test article 21 days before and during mating, during gestation, rearing of offspring, and up until sacrifice; and offspring were administered the test article during rearing and up until sacrifice. The overall intake of isopropanol for male animals over the 18 weeks of treatment was 317, 711, 1,001, or 1,176 mg/kg-day. The intake values for females in the 3-week premating phase were 517, 1,131, 1,330, and 1,335 mg/kg-day, and 1,167, 2,645, 2,825, and 2,724 mg/kg-day in the 3-week postpartum phase of the study. Isopropanol intake during the premating and postpartum phases was calculated by the study authors using body weight data, water intake data, and the

nominal dose concentrations. However, isopropanol intake, food consumption, and water intake were not determined for either sex during the mating period, nor were they determined during the gestational period for the female rats. The animals' weights were recorded throughout the study, and food consumption and water intake was monitored by weight during the study. At Day 70 (male) or Day 21 (female) after treatment initiation, one female was housed with one male from the same treatment group for 15 days. Litters were examined on PND 1 (the morning after birth) for any stillborn or abnormal young and examined on PNDs 4, 7, 10, 14, 17, and 21 for number of survivors and abnormalities. Each litter was observed daily; the sex of each pup was recorded on PND 21. Within 7 days of rearing of the last litter, each adult animal was fasted overnight and sacrificed by exsanguination under anesthesia, and a postmortem examination for macroscopic abnormalities was performed. The weights of the liver and kidneys were recorded. Blood was taken from the aorta and analyzed for total erythrocyte and leukocyte counts, hemoglobin concentration, and mean cell volume. The hematocrit value also was calculated. All pups were sacrificed at PND 21, but no further information was reported.

BIBRA (1986) reported that body weights of male animals administered 1,001 and 1,176 mg/kg-day isopropanol in the drinking water were statistically significantly decreased by 6% compared to control animals during the first week of treatment. No significant difference in male body weights were observed for the remainder of the study. Rats administered isopropanol at concentrations of ≥711 mg/kg-day in males, and 1,330/1,335 mg/kg-day (premating) and 2,825/2,724 mg/kg-day (postpartum) in females, had statistically significantly reduced food consumption immediately following administration of the test article, with reductions statistically significantly lower in both sexes intermittently during treatment. The administration of drinking water containing ≥711 mg/kg-day in males, and ≥1,131 mg/kg-day (premating) and 2,724 mg/kg-day (postpartum) in females, resulted in an immediate statistically significant and dose-related decrease in water intake. Generally, the water intake during the scheduled assessments for males and premating females was statistically significantly reduced, as were overall mean values. Postpartum observations in female animals indicated generally statistically significant reductions in body weight (5−13% and 13−20% in the 2,825- and 2,724-mg/kg-day dose groups, respectively) (see Table B-5). Food consumption and water intake were statistically significantly decreased in females administered isopropanol at concentrations of 2,825 and 2,724 mg/kg-day, with occasional decreases in the 2,645-mg/kg-day group (see Table B-5). Although fertility (100%) and the number of litters were not adversely affected by isopropanol treatment, the mean number of pups per litter and mean pup survival per litter were decreased (statistical significance unknown) at isopropanol concentrations of 1,330 and 1,335 mg/kg-day (premating) and 2,825 and 2,724 mg/kg-day (postpartum) in females; (see Table B-6). Mean pup weight was decreased (>5% change compared to control values) at ≥1,167 mg/kg-day and statistically significantly decreased at ≥2,645 mg/kg-day. Females administered 1,330 and 1,335 mg/kg-day (premating) and 2,825 and 2,724 mg/kg-day (postpartum) had dose-related decreases in red blood cell number (statistically significant), hematocrit, and hemoglobin concentration, although significant differences varied between parameters (and decreases in the high-dose concentration group were only 9 to 12% less than control values). Male animals had a small, not dose-dependent, statistically significant increase (3−5%) in mean cell volume in groups receiving ≥711 mg/kg-day isopropanol. Mean absolute liver and kidney weights (and organ weights relative to body weight) were generally statistically significantly increased for both sexes in the two highest dose groups (see Table B-7), although no differences in terminal body weight due to treatment were noted. Absolute liver and kidney

weights were statistically significantly increased in males at 1,176 mg/kg-day. Absolute liver weight was statistically significantly increased in females at ≥2,645 mg/kg-day and absolute kidney weight was statistically significantly increased in females at 2,825 and 2,724 mg/kg-day. Statistically significant increases in relative liver weight in the two high-dose isopropanol treatment groups in males are calculated as 12 and 14%, respectively, and 25 and 21% in females, respectively. Statistically significant increases in relative kidney weight in the two high-dose isopropanol treatment groups in males are calculated as 13 and 15%, respectively, and 25 and 21% in females, respectively. No histopathological examination of these organs was conducted. A parental (F0) LOAEL of 711 mg/kg-day based on decreased food consumption and water intake is identified in male rats with a corresponding NOAEL of 317 mg/kg-day. During the postpartum period, a LOAEL of 1,167 mg/kg-day is identified based on decreased F1 pup body weight (>5% change compared to control values). Identification of a NOAEL is precluded because 1,167 mg/kg-day is the lowest dose tested during the postpartum period.

BIBRA (1988)

As part of a series of studies conducted for the Feed and Drink Federation IPA Steering Group (London, UK), BIBRA (1988) conducted a non-peer-reviewed, one-generation reproduction/embryotoxicity study. This study complied with GLP regulations and was reported in a peer-reviewed article by Faber et al. (2008). Virgin male and female Wistar-derived rats were obtained from Olac 1976 Ltd. and acclimated for at least 1 week prior to study initiation. Animals were maintained on a 12:12 hour-light:dark cycle at a temperature and humidity of 20−24ºC and 45−65%. Prior to mating, the animals were group housed, by sex, in polypropylene cages with stainless steel tops and grid floors; animals had access to Certified Rat and Mouse No. 3 feed (Special Diet Services) and domestic mains tap water ad libitum. Each dose group consisted of 10 males and 30 females (10 females for embryotoxicity determinations and 20 females for the littering/reproduction phase). Treatment was initiated 70 days (male, 7−8 weeks of age) and 21 days (female, 10−11 weeks of age) prior to mating. During the mating period, two females from animals assigned to the littering phase and one female assigned to the embryotoxicity phase were housed with one male from the same treatment group for up to 15 days. The females were examined every morning until successful mating occurred: the presence of sperm in the vagina or a vaginal plug defined GD 0. Mated females were housed singly, as previously described, except for females assigned to the littering phase that had cages with solid floors with sawdust and nesting materials as needed.

The isopropanol utilized in the BIBRA (1988) was provided by Shell Chemicals UK Ltd. (batch 1A1/41.3/84 GB1/260), with a purity of 99.89% according to GLC. Drinking water formulations were prepared with domestic tap water at intervals of ≤2 weeks and were analyzed by GLC to confirm isopropanol concentration and stability. All formulations were within ±10% of nominal concentrations, and stable for at least 28 days. Isopropanol drinking water concentrations presented to dams in the one-generation reproduction/embryotoxicity study were 0%, 0.5%, 1.0%, or 2.0% (males: 0, 383, 686, or 1,107 mg/kg-day during premating and 0, 347, 625, or 1,030 mg/kg-day for the full study period (Days −3 to 126); females: 0, 456, 835, or 1,206 mg/kg-day during premating; 0, 668, 1,330, or 1,902 mg/kg-day during gestation; and 0, 1,053, 1,948, or 2,768 mg/kg-day during the postpartum period). Isopropanol intake was calculated by the study authors from body weight and water intake data with the nominal dose concentrations.

General observations were made daily during the BIBRA (1988) study, with more thorough examinations conducted weekly. Body weights of male rats were recorded 3 days prior to and 4 days after the initiation of treatment, and then twice weekly throughout the study. Females were weighed daily 3 days prior to and 4 days after treatment was started, and then twice weekly for 3 weeks. During gestation, females were weighed on GD 0 and every day until they littered or were euthanized. During lactation, the weight of the female and the total litter weight were recorded on PNDs 1, 4, 7, and 14. On PND 21, the dams and each of the pups were weighed individually. Food consumption and water intake were determined at the same intervals as the body-weight measurements, except for the females during the postpartum period when consumption/intake of food and water was measured twice weekly. Males were euthanized on Day 126 of the study, and dams assigned to the embryotoxicity phase of the study were euthanized on GD 19. The abdominal and thoracic regions were examined for abnormalities, the ovaries were examined, and the number of corpora lutea were recorded. The uterus was examined, and the numbers and locations of viable and nonviable fetuses, early and late resorptions, total implantations, and pre- and postimplantation losses were recorded. Live fetuses were weighed and examined for gross abnormalities. All fetuses from the embryotoxicity phase were preserved in ethanol. The viscera of fetuses, and littermates, which showed evidence of edema in the embryotoxicity study, were examined by evisceration under a dissecting microscope, and the sex of each fetus was recorded. The remaining females were allowed to litter. Litters were examined on PND 1 for stillborn or abnormal young, and then daily for any subsequent deaths. Survivors and additional abnormalities were recorded on PNDs 4, 7, 10, 14, 17, and 21, after which pups were weaned and removed from the dams. Approximately 21 days after weaning the last litter, each adult animal and one pup/sex/litter were fasted overnight and euthanized by exsanguination under anesthesia. Blood was collected from the aorta of each adult for analysis of total erythrocyte and leukocyte counts, hemoglobin concentration, and mean cell volume. Twelve females (five controls, three in the mid-dose group, and four in the high-dose group) that failed to litter were euthanized 24 days after the last day of pairing. Adrenal glands, brain, cecum, gonads, heart, liver, kidney, and spleen weights were recorded. The following tissues were preserved in 10% neutral buffered formalin for histopathologic examination in the control and high-dose adult animals: bladder, cervix and uteri, epididymides, ovaries, pituitary, prostate, seminal vesicles, testes, uterine horns, and vagina. Approximately 10 days later, the remaining pups (F1 generation) were euthanized by carbon dioxide inhalation and examined for gross, external abnormalities. The liver and kidneys were weighed, and tissue samples were preserved in formalin. Statistical analyses were similar to those described previously for the developmental study by BIBRA (1987).

The BIBRA (1988) study reported that no deaths, abortions, or early deliveries occurred during the study, and the numbers of nonpregnant females were distributed across the dose groups in a nontreatment-related manner. Mean water intake was statistically significantly decreased in males at ≥625 mg/kg-day, and food consumption was statistically significantly decreased in males at ≥347 mg/kg-day. Mean water intake volumes in the high-dose females were statistically significantly decreased during premating (31%), gestation (23%), and postpartum (37%). Water intake levels in the low- and mid-dose females were similar to control values during premating and postpartum phases but were statistically significantly increased 14% and 10%, respectively, during gestation. Similar decreases in food consumption were noted in female rats, with statistically significant reductions noted in the high-dose females during premating (13%) and gestation (6%); apparent reductions in food consumption in the 2,768-mg/kg-day females during postpartum were not statistically significant due to increased

variability across all dose groups. All treated females exhibited immediate weight loss during the premating period, with a recovery of weight gain after 1 week. Body weights and weight gain were similar to control during the gestation period and at the beginning of the postpartum period, but weight gain and weights in the 2,768-mg/kg-day females were statistically significantly lower after PND 4. No statistically significant effects on male or female fertility due to isopropanol treatment were observed in the BIBRA (1988) study, although the number of pups/litter on PND 1 and pup survival/litter were decreased in the high-dose females (see Table B-8). Additionally, the body weights of pups were statistically significantly decreased (>5%) on PND 21 at ≥668 mg/kg-day.

No macroscopic abnormalities were observed at necropsy in females from either phase of the present study, and no treatment-related histopathological effects were noted in reproductive system tissues from high-dose parental animals. In the embryotoxicity study, the authors reported that preimplantation loss was statistically significantly increased at 1,902 mg/kg-day (1.0 ± 1.31) compared to controls (0.1 ± 0.33) (see Table B-9). Additionally, whole body edema was observed in 40% of the fetuses in 3/8 litters in 1,902 mg/kg-day dams. Statistically significant increases were observed in absolute kidney weight (10%) as well as relative kidney (16%), liver (11%), and spleen (11%) weights in the 1,030 mg/kg-day F0 generation males. The high-dose F0 generation females had significantly increased absolute and relative liver weights (19% and 14%, respectively) and absolute kidney (8%) weights (see Table B-10). Statistically significantly increased relative liver weights were observed in all dose groups for F1 generation males and females (>10% change compared to control values in only the high-dose male and female pups). High-dose F1 males also had higher (not statistically significant) relative kidney weights (5%), and high-dose males and females had brain-weight decreases (statistically significant for absolute weight) of less than 10%. For the parental component of the study, a LOAEL of 347 mg/kg-day is identified based on decreased food consumption in male F0 rats; because 347 mg/kg-day is the lowest dose tested in male F0 rats, a parental NOAEL cannot be determined. During the gestational component of the study, a paternal LOAEL of 1,902 mg/kg-day is identified based on decreased food consumption in F0 dams with a corresponding NOAEL of 1,330 mg/kg-day. For F1 pups, a gestational LOAEL of 1,330 mg/kg-day is identified based on decreased body weight in both sexes on PND 4 with a corresponding NOAEL of 668 mg/kg-day. During the postpartum component of the study, a LOAEL of 1,053 mg/kg-day is identified based on decreased F1 pup body weight on PND 21 in both sexes; because 1,053 mg/kg-day is the lowest dose tested in F1 pups during the postpartum phase, a NOAEL cannot be determined.

Bevan et al. (1995)

Bevan et al. (1995) reported on a two-generation reproductive toxicity study with isopropanol. Four groups of male and female Sprague-Dawley (S-D) rats (30 per sex), designated as the P generation by the study authors but referred to as the F0 generation in this document, were given isopropanol solutions in water at a volume of 5 mL/kg by gavage at doses of 0 (control), 100, 500, or 1,000 mg/kg-day for at least 10 weeks prior to mating. Dosing was continued in parental females during mating, gestation, and lactation through the day prior to euthanasia (following weaning). Parental males were dosed until the day prior to euthanasia, after delivery of their last sired litter. The date on which birth was recorded was designated as PND 0, and offspring of the F0 generation were designated as the F1 generation. At weaning on PND 21, two pups of each sex per litter were selected at random to become a pool of animals from which the F1 parents would be chosen for each treatment group. The selected

F1 populations consisted of 30 neonates of each sex from the control, 100-, and 500-mg/kg-day groups. The selected F1 population from the 1,000-mg/kg-day group consisted of only 26 pups of each sex due to mortality encountered in that group. The F1 adult generation (designated as P2 by the study authors) began receiving treatment on PND 21 according to the same treatment, mating, and disposition procedures described for the F0 generation. Viability and clinical examinations were performed, and body weight and food consumption were recorded throughout the study. Litters were examined periodically for viability, number of offspring, and sex determination. Gross postmortem examinations were performed on selected pups on PND 21 (5 per sex) and on all adult animals used for mating. Liver and kidney weights were recorded for all mated adults that survived to scheduled termination. The pituitary, testes and epididymides, prostate and seminal vesicles, vagina, uterus, and ovaries were checked for gross lesions, prepared and stained appropriately, and then examined microscopically for all parental animals in the control and 1,000-mg/kg-day groups; liver and kidneys from all F0 and F1 parents were examined histopathologically.

Bevan et al. (1995) reported that a total of seven treatment-related parental deaths occurred during the study (two F0 females and two F1 females in the 1,000-mg/kg-day group; one F1 female in the 500-mg/kg-day group; and two F1 males in the 100-mg/kg-day group); no other treatment-related clinical signs of toxicity were observed during the study. No details were provided by the study authors regarding the cause(s) of the deaths. Body weights of the treated and control F0 and F1 adult male animals were similar during the study (see Table B-11). When compared to the control group, statistically significantly increased body-weight gain in the postpartum female rats was noted in the 500-mg/kg-day dose groups (F1, 3.1 ± 17.5 g vs. 19.2 ± 15.9 g [520%]) and 1,000-mg/kg-day dose groups (F0, 15.1 ± 30.5 g vs. 40.4 ± 24.4 g [170%] and F1, 3.1 ± 17.5 g vs. 25.3 ± 23.2g [720%]). No treatment-related effects on food consumption in males or females in either parental generation were observed. Absolute and relative liver weights of F0 males dosed with 1,000 mg/kg-day were statistically significantly increased compared to control (10% increase in relative liver weight, see Table B-11). In the F1 adult males, the absolute liver weights were increased in the 500-mg/kg-day group, and relative liver weights were increased in the 500- and 1,000-mg/kg-day groups compared with the control group (11% and 14%, respectively). Relative kidney weights were also increased in the adult F1 males dosed with 1,000 mg/kg-day (7%). Absolute liver weights of the adult F1 females were increased in the 1,000-mg/kg-day group compared with control, and relative liver weights were increased in the F0 and adult F1 females dosed with 500 and 1,000 mg/kg-day (F0, 5% and 10%, respectively; and F1, 8% and 18%, respectively) (see Table B-11). Relative kidney weights were also increased in the F0 and adult F1 females dosed with 1,000 mg/kg-day (6% and 8%, respectively).

Bevan et al. (1995) reported that no adverse effects of treatment were evident from gross postmortem examinations of surviving males and females from either parental generation. The study authors also noted that the histopathological effects in kidneys (increases in number of hyaline droplets in the epithelial cells of the proximal convoluted tubules, incidence and severity of epithelial degeneration and hyperplasia, incidence of proteinaceous casts in the renal tubules, and incidence of focal interstitial mononuclear cell infiltration) in the 500- and 1,000-mg/kg-day F0 male rats and all treated adult F1 males were likely associated with alpha 2u-globulin nephropathy. Centrilobular hepatocyte hypertrophy was observed in one quarter of the adult F1 male animals dosed with 1,000 mg/kg-day. No other treatment-related microscopic changes

were observed in the reproductive tissues, liver, kidneys, or other tissues. The only statistically significant difference between treated and control groups for any reproductive parameter was a decrease in the male mating index in the adult F1 generation at 1,000 mg/kg-day (see Table B-12). The study authors also reported a statistically significant decrease in the live birth index in F1 rats at 1,000 mg/kg-day. The survival index was also statistically significantly decreased in F1 and F2 rats on PNDs 1 (at 1,000 mg/kg-day for F1 and at ≥500 mg/kg-day for F2) and 4 (at ≥500 mg/kg-day for F1 and 1,000 mg/kg-day for F2). The survival index in F2 rats was also statistically significantly decreased on PND 7 at ≥500 mg/kg-day, and the lactation index was statistically significantly decreased in F2 rats at ≥500 mg/kg-day (see Table B-13). Although there were 18 offspring deaths in the 1,000-mg/kg-day group during the postweaning period (PNDs 21−41) prior to selection of the F2 generation (number of animals in this group reduced to 26), the F1 and F2 offspring that survived to scheduled termination were free of treatment-related abnormalities. Body weight was statistically significantly decreased in F1 males on PNDs 0 and 1 at 1,000 mg/kg-day, and increased on PND 21 at 100 mg/kg-day (see Table B-14). In F1 females, body weight was statistically significantly increased on PNDs 14 and 21 at 100 mg/kg-day. In F2 males and females, body weight was statistically significantly decreased on PNDs 0, 1, and 4 at 1,000 mg/kg-day. A parental LOAEL of 500 mg/kg-day is identified based on increased relative liver weight in F1 adult males with a corresponding NOAEL of 100 mg/kg-day. A reproductive LOAEL of 1,000 mg/kg-day is identified based on decreased mating index in F1 adult males with a corresponding NOAEL of 500 mg/kg-day. A developmental LOAEL of 500 mg/kg-day is identified based on decreased survival index in F1 and F2 offspring with a corresponding NOAEL of 100 mg/kg-day.

Carcinogenicity Studies

No studies were identified.

Inhalation Exposures

The effects of inhalation exposure of animals to isopropanol have been evaluated in three subchronic-duration studies (Burleigh-Flayer et al., 1998; Burleigh-Flayer et al., 1994), one developmental study (Nelson et al., 1988), and two chronic-duration/carcinogenic (Burleigh-Flayer et al., 1997) studies. These study reports are articles published in peer-reviewed journals or correspond to studies performed in compliance with GLP requirements. Burleigh-Flayer et al. (1994) is a journal article containing studies performed on two different species (rat and mouse). To differentiate between the studies, the designation of Burleigh-Flayer et al. (1994) is used for the rat study and Burleigh-Flayer et al. (1994) is used for the mouse study. Similarly, Burleigh-Flayer et al. (1997) is also a journal article containing studies conducted with the rat (Burleigh-Flayer et al., 1997) and the mouse (Burleigh-Flayer et al., 1997).

Subchronic-duration Studies

Burleigh-Flayer et al. (1994)

The subchronic-duration study in rats by Burleigh-Flayer et al. (1994) is selected as the principal study for the derivation of the subchronic p-RfC. Although the GLP status of this study was not specifically stated, other research studies and reports from this author and facility maintain GLP standards, and it is assumed that this study was conducted similarly. This study used the F344 rat (Harlan Sprague Dawley, Inc.). Animals were housed individually in stainless steel, wire-mesh cages throughout the study. The animals were maintained under standard temperature and humidity conditions on a 12-hour light/dark cycle, with access to

municipal water and powdered food (certified Rodent Chow® 5002) ad libitum, except during exposure periods and neurobehavioral evaluations. Initial body-weight ranges for the male and female rats (8 weeks of age) were 140−165 and 112−130 g, respectively. Nominal vapor concentrations of isopropanol of 0 (control), 100, 500, 1,500, or 5,000 ppm were used for this study. Ten rats/sex were randomly assigned to each exposure group for the purposes of evaluating systemic toxicity, with an additional 15 rats/sex assigned to each exposure group for assessment of neurobehavioral function. Rats were exposed for 6 hours/day, 5 days/week, for 13 weeks, and were sacrificed the morning after their last exposure day. The animals were exposed to air (control) or isopropanol vapor in individual cages within a stainless steel and glass chamber (1,330 L vol) with an airflow of approximately 300 L/min. The purity of the isopropanol prior to vaporization was determined to be 99.9% (stability not reported). The mean (±SD) isopropanol chamber concentrations were 100 ± 5, 506 ± 12, 1,508 ± 53, and 5,008 ± 120 ppm (human equivalent concentrations [HECs] of 0, 43.9, 222, 661.8, or 2,198 mg/m^3, respectively). The rats were observed daily on an individual and group basis for clinical signs of toxicity. Direct ophthalmoscopy examinations were performed on all rats prior to study initiation and at Week 12. Ten of the 15 rats/sex designated for neurobehavioral function assessments were evaluated with the functional observational battery (FOB) prior to study initiation and after Weeks 1, 2, 4, 9, and 13 (approximately 42 hours after the most recent exposure). FOB testing was performed by trained technicians blind with respect to exposure status and included numerous physical and neurological assessments. Motor activity evaluations for the tested rats were done prior to initial exposure, and after 4, 9, and 13 weeks of exposure. Body weight data were collected throughout the study period. Motor activity data were collected for individual animals with an automated photocell-recording apparatus during 90-minute test sessions for subsequent analysis. During Study Week 6, hematologic evaluations were done with blood samples collected from 10 rats/sex/group, and hematologic and serum clinical chemistry evaluations were performed on blood samples collected from 10 rats/sex/group at study termination. All rats were anesthetized and sacrificed at the end of the study. A complete necropsy was performed on each rat, and the brain, liver, lungs, kidneys, adrenals, testes, and ovaries from all surviving animals were weighed. Tissues were prepared and stained as appropriate, and an exhaustive list of tissues was examined from the control animals and animals exposed to 2,198 mg/m^3 isopropanol. Neuroanatomic pathology evaluation was conducted on 10/15 rats/sex/group used for the motor activity assessments after the brain was weighed and measured.

Burleigh-Flayer et al. (1994) reported that no exposure-related mortality was observed in any exposure group during the study. No clinical signs of toxicity were noted during exposures for male and female rats in the 43.9- and 222-mg/m^3 exposure groups. Ataxia, narcosis (absent after Week 2), hypoactivity, and a lack of a startle reflex were observed in some rats after exposure to 2,198 mg/m^3, with only hypoactivity observed immediately after exposure to 661.8 mg/m^3. Ataxia and/or hypoactivity also were observed in some animals in the 2,198-mg/m^3 group immediately after exposure. Clinical signs observed following exposures included swollen periocular tissue in females (at 2,198 mg/m^3) and perinasal encrustation in males (at ≥222 mg/m^3). No exposure-related clinical signs were observed after exposure to 43.9 mg/m^3. Isopropanol exposure did not affect any of the FOB parameters. Statistically significantly increased motor activity was observed in the females in the 2,198-mg/m^3 exposure group after Weeks 9 (57% increase) and 13 (26% increase), with no changes noted in the males. Body weight and/or body-weight gain were statistically significantly lower after Week 1 for all rats in

the 2,198-mg/m^3 group and the females in the 661.8-mg/m^3 group (tabular, numerical data not reported). However, decreases in body weight and/or body-weight gain were not present after Week 2. In general, these parameters were significantly increased by Week 5 and after in the 661.8- and 2,198-mg/m^3 exposure groups (end of study percentage increases in body-weight gain were 12 and 16% at 2,198 mg/m^3, and 7 and 8% at 661.8 mg/m^3, in the males and female, respectively). An initial significant decrease in food consumption in the females in the 2,198-mg/m^3 exposure group reversed after Week 1 (tabular, numerical data and significance level were not reported), and significant increases in food consumption were observed in the 2,198-mg/m^3 group by Weeks 4−5. Percentage increases in food consumption at the end of the study in the 2,198-mg/m^3 groups were 5 and 13%, in the males and females, respectively. Increased water intake was observed beginning at Week 2 in the 661.8- and 2,198-mg/m^3 groups. Changes in hematologic parameters generally observed at 2,198 mg/m^3 in male and female rats were suggestive of a slight, but transient, anemia (present at Week 6 but resolved by Week 14); no exposure-related changes in serum clinical chemistry parameters occurred in the rats at Week 14. Relative (to body) liver weight was increased at 2,198 mg/m^3 (8 and 5% in male and female rats, respectively). The only exposure-related change observed following histological examination was the presence of increased number and size of hyaline droplets within the kidneys in the exposed male rats (not clearly concentration-dependent). Initial decreases in body weight and food consumption, and the presence of anemia, were transient and minor. A LOAEL of 2,198 mg/m^3 is identified for increased motor activity in female rats with a corresponding NOAEL of 661.8 mg/m^3.

Burleigh-Flayer et al. (1998)

Burleigh-Flayer et al. (1998) reported a subchronic inhalation toxicity follow-up study with isopropanol conducted according to U.S. TSCA GLP standards (BushyRun, 1994). The BushyRun (1994) report is a subchronic-duration, 13-week study submitted to the EPA and later published as part of Burleigh-Flayer et al. (1998). Female F344 rats were assigned randomly to the control or exposure groups (30/group) and exposed to target concentrations of 0 (control) or 5,000 ppm of isopropanol vapor for 6 hours/day, 5 days/week. The actual concentration of isopropanol vapor for the exposed group was 5,011 (±105) ppm (HEC = 2,199 mg/m^3). Fifteen rats in each group were exposed to isopropanol for 9 weeks, and the other 15 were exposed for 13 weeks. Motor activity was evaluated during the exposure periods, as well as for 1 week after the end of exposure for the 9-week subgroup and for 6 weeks after the end of exposure for the 13-week subgroup to assess the potential for reversibility. Observations for clinical signs of toxicity, including ataxia and hypoactivity, were made on an individual and group basis. Motor activity evaluations were done prior to initial exposure, and after 4, 7, and 9 weeks of exposure (9-week subgroup) and 4, 7, 9, 11, and 13 weeks of exposure (13-week subgroup). Reversibility of potential effects was evaluated at 2, 4, and 7 days after the final exposure in the 9-week subgroup and at 2, 4, 7, 14, 21, 28, 35, and 42 days after final exposure in the 13-week subgroup. Motor activity measurements were conducted in an isolated room under controlled conditions (sound and light level, and odor). Weight data were collected throughout the study. Data for ambulatory activity, fine motor activity, rearing activity, and the sum of these individual types of activity were collected for individual animals with an automated photocell-recording apparatus in nine consecutive 10-minute intervals (90-minute test session) for subsequent analysis. Statistical significance was assessed but significance levels are not reported for any parameter. The animals were sacrificed by carbon dioxide overdose after the final motor activity evaluation; necropsies were not performed.

Burleigh-Flayer et al. (1998) reported that no exposure-related mortality was observed during the study, and clinical signs during exposure were minimal (i.e., apparent decreased movement within the enclosures and diminished startle response). Swollen periocular tissue was observed during the nonexposure periods. Although body weight and body-weight gain were decreased for the exposed rats after the first week of exposure, statistically significant increases in these parameters were observed for exposed rats by Week 3. Significant increases in body weight continued to be observed for isopropanol-exposed rats throughout the remainder of the study (mean body weight and body-weight gain for the 9-week subgroup rats were increased by 6% and 17%, respectively, relative to control; for the 13-week subgroup rats, these increases were 5% and 13%, respectively, relative to control). Weight increases were maintained for isopropanol-exposed rats during the recovery period, with mean body weight and body-weight gain for the 13-week subgroup rats increased by 3% and 9%, respectively, after Week 19. Increases in mean cumulative motor activity (the sum of total activity across a 90-minute test session) were observed at all of the evaluation time points during each exposure regimen and Postexposure Day 1 (4, 7, and 9 weeks, and 4, 7, 9, 11, and 13 weeks, respectively) (see Table B-15). In the 9-week exposure group, cumulative test session activity was not different from control values by Postexposure Day 2. In contrast, cumulative test session activity remained increased compared to control values through Postexposure Day 7 in the 14-week exposure group, was not significantly different from control on Postexposure Days 14 and 21, and then showed a statistically significant increase on Postexposure Day 28. Repeated measures analysis of motor activity habituation curves indicated significant differences between the isopropanol exposure and control groups during some study weeks (Week 7 for the 9-week exposure group, and Weeks 4, 9, and 11 for the 13-week group). Additionally, some significant differences were noted in postexposure habituation curves. A LOAEL of 2,199 mg/m^3 is identified from this study for increased motor activity in female rats. Because 2,199 mg/m^3 is the only concentration tested, a NOAEL cannot be determined.

Burleigh-Flayer et al. (1994)

In another subchronic-duration inhalation study, Burleigh-Flayer et al. (1994) exposed CD-1 mice to isopropanol vapor for up to 13 weeks. Animal husbandry and target vapor concentrations were as described previously Burleigh-Flayer et al. (1994). Ten animals/sex were randomly assigned to each exposure group, with exposure parameters and system as described previously. A complete necropsy was performed on each animal. The mean (±SD) isopropanol concentrations were 100 ± 5, 506 ± 12, 1,508 ± 53, or 5,008 ± 120 ppm (HECs of 0, 43.9, 222, 661.8, and 2,198 mg/m^3).

Burleigh-Flayer et al. (1994) reported that no exposure-related mortality was observed in any exposure group during the study. No clinical signs were noted during exposures for mice in the 43.9- and 222-mg/m^3 groups. During exposure, ataxia, narcosis, and hypoactivity were observed in the 661.8- and 2,198-mg/m^3 groups, and lack of a startle reflex was noted at 2,198 mg/m^3. Ataxia and/or hypoactivity also were observed in some animals in the 2,198-mg/m^3 group immediately after exposure. Significantly increased body weight and body-weight gain were observed in the females in the 2,198-mg/m^3 group by Week 3 (end of study percentage increases in body weight and body-weight gain were 13 and 71%, respectively; no significance level reported), with no exposure-related effects on weight noted in the males. There were no exposure-related effects on food consumption in any group. Increased water intake was observed in the males in the 661.8- and 2,198-mg/m^3 groups (during Weeks 1 and 2),

and in the females (2,198-mg/m^3 group) throughout the study. Although there were no exposure-related changes in hematologic or serum clinical chemistry parameters for the males (2,198 mg/m^3) at Week 14, the study authors suggested that changes in these parameters (present in the females in this exposure group) were indicative of slight dehydration. Relative (to body) liver weight was increased in the females in the 661.8- and 2,198-mg/m^3 groups (>10% change compared to control values at both concentrations). No exposure-related changes were observed following histological examination in the exposed mice. A LOAEL of 661.8 mg/m^3 is identified for increased relative liver weight) in female mice with a corresponding NOAEL of 222 mg/m^3.

Developmental Studies

Nelson et al. (1988)

Nelson et al. (1988) reported a developmental inhalation toxicity study in the S-D rat with isopropanol; a subsequent peer-reviewed published journal article by Nelson et al. (1990) included summarized data from this study as well as similar investigations with 12 other alcohols. Females were placed individually with breeder males for mating. Pregnant animals (n = 15, 14, 13, and 9) were assigned to 0, 3,500, 7,000, or 10,000 ppm exposure groups. Measured isopropanol vapor exposures throughout the study (Nelson et al., 1988) were similar to target concentrations (generally within 10%, HECs of 0, 2,516, 5,048, and 7,185 mg/m^3). Maternal weight data were collected throughout the study periods, and food consumption and water intake were determined weekly. Pregnant females were exposed to isopropanol vapors on GDs 1−19 for 7 hours per day in 0.5-m^3 Hinner-type exposure chambers; control animals were exposed to filtered air. Females were weighed and sacrificed by CO_2 asphyxiation on GD 20. Uteri with ovaries were removed and examined for corpora lutea, resorptions, and live fetuses. Half of the fetuses underwent visceral examination, and the remaining fetuses were examined for skeletal defects. Additionally, nonpregnant adult female rats were exposed to isopropanol vapors for 1, 10, or 19 days (exposure conditions identical to pregnant animals). A separate group of young females (n = 8, approximately 90 g) were exposed to the high concentration of isopropanol (7,185 mg/m^3) for a single 7-hour period to assess toxicity in younger animals. Blood was collected after CO_2 overdose at the end of each exposure period (1, 10, or 19 days), and isopropanol concentrations were determined by an appropriate gas chromatographic method.

Dams exposed to 7,185 and 5,048 mg/m^3 exhibited narcosis and unsteady gait, early in the exposure protocol, but these signs diminished in both groups after 19 days of exposure; no effects were observed in the 2,516-mg/m^3 exposure group. Isopropanol concentrations in blood tended to decrease over time (Days 1−19), and isopropanol concentrations in the younger females were higher than in the nonpregnant adults. Animals receiving 7,185- and 5,048-mg/m^3 isopropanol vapor showed reductions in food consumption during the first 2 weeks of exposure, and decreased weight gain across the 19-day exposure period; these effects were not statistically significant. Six of the 15 females at the highest concentration were not pregnant, which the study authors suggested as a failure of implantation. In addition, dams in the high-concentration group had statistically significant decreases in mean number of implants per dam and implants alive per litter (embryotoxicity), with a concomitant statistically significant increase in the number of resorptions per litter (see Table B-16). Concentration-dependent, statistically significant reductions in fetal body weight occurred after maternal exposure in all groups; this effect only reached a 5% or greater reduction level at ≥5,048 mg/m^3. The number of skeletal malformations was statistically significantly increased in the two highest concentration groups (5,048 and 7,185 mg/m^3), primarily attributed to rudimentary cervical ribs; no other malformation rates were affected. The study authors noted that teratogenic effects at these two

concentrations may have been secondary to maternal toxicity. A maternal NOAEL of 7,185 mg/m^3 is identified based on the lack of significant effects observed. No maternal LOAEL can be determined. A developmental LOAEL of 5,048 mg/m^3 is identified based on decreased fetal body weight (>5% change compared to control values) and increased skeletal malformations in males and females with a corresponding NOAEL of 2,516 mg/m^3.

Reproductive Studies

No studies were identified.

Carcinogenicity/Chronic-duration Studies

Burleigh-Flayer et al. (1997)

The study conducted by Burleigh-Flayer et al. (1997) is selected as the principal study for deriving the chronic p-RfC. This chronic-duration inhalation carcinogenicity study was conducted according to GLP standards and submitted previously to the EPA as BushyRun (1994). This study was conducted with F344 rats (Harlan Sprague Dawley, Inc.). The animals were housed two per cage for 2 weeks, then individually for the remainder of the study in stainless steel, wire-mesh cages. The animals were maintained under standard temperature and humidity conditions on a 12-hour light/dark cycle, with access to municipal water and pelleted food (Agway Prolab Animal Diet 3000) ad libitum, except during exposure periods. Initial body-weight ranges for males and females (7 weeks of age) were 121−165 and 93−124 g, respectively. Target isopropanol vapor concentrations were 0 (control); 500, 2,500, or 5,000 ppm. Actual isopropanol concentrations were determined to be within 2% of nominal (HECs of 0, 221, 1,101, or 2,211 mg/m^3). Seventy-five animals/sex were randomly assigned to each exposure group. A core group (65/sex/group) was exposed for 6 hours/day, 5 days/week, for at least 104 weeks, with an additional 10 animals/sex/group designated for interim sacrifice at 72 weeks. Animals were exposed to either air (control) or isopropanol vapor in stainless steel and glass chambers (4,320 L vol) with an airflow of approximately 900 L/min. The purity of the isopropanol prior to vaporization was determined to be 99.9%, and purity/stability was evaluated at 6-month intervals. Observations were made daily for individual clinical signs of toxicity, with group observations made during exposures. Indirect ophthalmoscopic examinations were made initially and at 17 months, 19 months, and at terminal sacrifice. All animals were weighed initially, weekly through Week 14, and then every other week. Blood smears were obtained from core animals at approximately 13 and 19 months, with differential leukocyte count evaluations for all control and high-concentration animals. Full hematologic evaluations were performed on blood samples collected at terminal sacrifice. Urinalysis, urine chemistries, and osmolality determinations were performed at selected time points (Weeks 57 and 58, Week 74, and terminal sacrifice). Animals were euthanized at the interim and terminal time points, and the brain, liver, lungs, kidneys, heart, spleen, and testes from all surviving animals were weighed. A complete necropsy was performed on each animal; tissues were prepared and stained as appropriate, and numerous tissues were evaluated in the control and high-concentration animals. In the low and intermediate concentration-groups, only the kidneys, testes, and gross lesions were microscopically evaluated. Continuous, parametric data were compared with Levene's test for homogeneity of variance, by ANOVA, and by *t*-tests. Incidence data were compared with Fisher's Exact test. Nonparametric data were evaluated with the Kruskal-Wallis test, and the Wilcoxon rank sum test as modified by Mann-Whitney.

Burleigh-Flayer et al. (1997) reported that 100% mortality occurred for males at 2,211 mg/m^3, with a significantly decreased mean survival time noted for males in this group (577 days) compared to controls (631 days). No differences in mean survival time were noted for the females. Transient clinical signs noted at 1,101 and 2,211 mg/m^3 during exposure included hypoactivity, lack of a startle reflex, ataxia, prostration, and narcosis, with no clinical signs observed at 221 mg/m^3 during or after exposure. Clinical signs noted during nonexposure periods included emaciation and dehydration in the 2,211-mg/m^3 males, urine stains in both sexes at ≥1,101 mg/m^3 and swollen periocular tissue in the 2,211-mg/m^3 females. There was no notable increase in the incidence of eye lesions. Decreased mean body weight and/or body-weight gain was observed initially at 2,211 mg/m^3 (through Week 2 of exposure). From this point, body weight increased, and increased body weight and body-weight gain were noted by the end of Week 6. At Week 52, body weight and body-weight gain were increased 5 and 7%, respectively (2,211-mg/m^3 males), and 4 and 6%, respectively (1,101-mg/m^3 males). Concentration-related increases in body weight and body-weight gain were observed in the female rats after Week 5. At Week 52, body weight and body-weight gain were increased 6 and 10%, respectively, in 2,211-mg/m^3 females and 4 and 7%, respectively, in 1,101-mg/m^3 females, with a slight (1% or less) increase in the 221-mg/m^3 female rats. No exposure-related changes in hematologic parameters were observed in the rats in this study. Statistically significant changes were generally observed in urinalysis and urine chemistry parameters in the 2,211-mg/m^3 rats (see Table B-17). Osmolality was decreased in males at 13 months, decreased in males and females at 17 months, and decreased in females at 24 months. Total protein was increased in males at 13 months, and increased in males and females at 17 months. Total volume was increased in females at 13 months, increased in males and females at 17 months, and increased in females at 24 months. Glucose was decreased in females at 13 months, decreased in males at 17 months, and decreased in females at 24 months.

Burleigh-Flayer et al. (1997) reported increased liver weight (2,211-mg/m^3 males) and a concentration-related increase in testes weight at the interim sacrifice (Week 73) but not in the terminal experimental group (see Table B-18). No effects were noted in kidney or brain weights in male or female rats at Week 73. Organ-weight changes in rats at Week 104 included decreased kidney weight (221- and 1,101-mg/m^3 females), increased liver weight (1,101-mg/m^3 males and 2,211-mg/m^3 females), and decreased brain weight (all exposed females). Microscopic evaluation of male rats at the interim sacrifice indicated increased atrophy of seminiferous tubules and increased severity of renal lesions. At the interim and terminal sacrifice of rats at ≥1,101 mg/m^3, increased severity of renal lesions in all rats (including those found dead or moribund) and the incidence of these lesions were observed, with incidence and severity greater in males compared to females (see Tables B-19 and B-20). Rats found dead or moribund displayed increased organ mineralization, and a variety of other nonneoplastic lesions. No increased frequencies of neoplastic lesions were observed in the females. In the males, concentration-dependent increases in testicular interstitial (Leydig) cell adenomas were seen in all exposure groups among the animals euthanized or found dead (57.7−94.7% exposed vs. 64.9% in concurrent controls) and when considering all animals (77.3−94.7% exposed vs. 64.9% concurrent controls). The study authors concluded that although the incidence was substantially increased in a concentration-dependent manner, the controls in this study were lower than historical controls. Furthermore, this tumor has been identified as the most frequently observed spontaneous tumor in the male F344 rat (Haseman et al., 1990; Takaki et al., 1989). A review of the incidence of Leydig cell adenomas in male F344 controls from 2-year NTP studies reported a

mean incidence of 88% in control (unexposed) males. Additionally, Leydig cell adenoma incidences of 86 and 91% were reported in male F344 control rats from two studies conducted previously at the facility used in the Burleigh-Flayer et al. (1997) study, similar to the range of incidence for this tumor in the exposed males in this study (77.3−94.7%). Therefore, the study authors suggested that this increase was a study artifact. Furthermore, due to the common occurrence of these tumors in male rats, the biological significance of an increased incidence of Leydig cell adenomas in male F344 rats is unclear. Chronic renal disease was identified as the main cause of death in female rats in the 2,211-mg/m^3 group and male rats in the 1,101-mg/m^3 group, as well as for early mortality in males in the 2,211-mg/m^3 group. A LOAEL of 1,101 mg/m^3 is identified based on increased relative liver weight in male rats with a corresponding NOAEL of 221 mg/m^3.

Burleigh-Flayer et al. (1997)

Burleigh-Flayer et al. (1997) also conducted a chronic-duration inhalation carcinogenicity study in the CD-1 mouse (Charles River Breeding Laboratories, Inc.). These data were also reported in a non-peer-reviewed technical report by the BushyRun (1994). Initial weight ranges for the male and female mice (7 weeks of age) were 22−35 and 19−28 g, respectively. Animal husbandry conditions were as described previously for the rat study (Burleigh-Flayer et al., 1997). Target isopropanol vapor concentrations were 0 (control); 500, 2,500, or 5,000 ppm and the actual concentrations were within 2% of nominal (HECs of 0, 221, 1,101, or 2,211 mg/m^3). Seventy-five mice/sex were randomly assigned to each exposure group, with a core group (55/sex/group) exposed for 6 hours/day, 5 days/week, for at least 78 weeks, and an additional 10 mice/sex/group were designated for an interim sacrifice at 54 weeks. The remaining 10 mice/sex/group were assigned to a recovery group, exposed for 54 weeks, but sacrificed at Week 78. Isopropanol vapor exposure was conducted as described previously. Observations were made daily for individual clinical signs of toxicity, with group observations made during exposures. All mice were weighed initially, weekly through Week 14, and then every other week. Blood smears were obtained from the core group of animals at approximately 12 months, with differential leukocyte count evaluations for all control and high concentration group animals, and full hematologic evaluations were performed on blood samples collected at terminal sacrifice. Animals were sacrificed at the interim and terminal time points, with organ and tissue treatments as described previously. Kidneys, liver, testes, and gross lesions from animals in the low and intermediate groups also were evaluated. Statistical analyses were conducted as described previously.

Burleigh-Flayer et al. (1997) reported that there were no differences in mean survival time for the interim, core, or recovery groups. Transient clinical signs noted at ≥1,101 mg/m^3 during exposure included hypoactivity, lack of a startle reflex, ataxia, prostration (2,211 mg/m^3 only), and narcosis, with no clinical signs observed at 221 mg/m^3 during or after exposure. Ataxia also was noted at 2,211 mg/m^3 immediately following exposure, but this effect was absent the following morning. Concentration-related increases in mean body weight and body-weight gain were observed in the core group of mice throughout the study as follows: 2 and 6%, respectively (221-mg/m^3 males), 5 and 23%, respectively (1,101-mg/m^3 males), 7 and 30%, respectively (2,211-mg/m^3 males), and 5 and 30%, respectively (2,211-mg/m^3 females). A 15% increase in body-weight gain only was observed in 1,101-mg/m^3 females. Additionally, in the recovery group, increases were observed in mean body weight and body-weight gain in the 2,211 mg/m^3 male mice (6 and 30%, respectively) and in body-weight gain only in the

1,101-mg/m^3 males (20%) and ≥1,101-mg/m^3 females (approximately 10−20%). No exposure-related changes in hematologic parameters were observed in the mice in this study.

Statistically significant relative (to body) organ-weight changes in the interim group (Week 54 termination) were limited to increased liver and decreased brain weights in the 2,211-mg/m^3 males and females and concentration-related increases in liver weight in males in the recovery group (where there were no exposure-related effects on brain weight) (see Table B-21). Statistically significant effects noted in the core group at terminal sacrifice (Week 78) included increased liver weight in the 2,211-mg/m^3 females, decreased brain weight in the 2,211-mg/m^3 males and females, and a decrease in testes weight in males in all concentration groups. In the recovery group, liver weight in males was statistically significantly and concentration-dependently increased by 10−30% in all exposed groups. There were also changes in absolute organ weights in the different exposure duration groups (see Table B-22). Absolute liver weight in males and females was statistically significantly increased at 2,211 mg/m^3 at the interim sacrifice. The following changes were observed at the terminal sacrifice: absolute liver weight in males was statistically significantly increased at ≥1,101 mg/m^3 and absolute testes weight was statistically significantly decreased at 221 mg/m^3; absolute brain weight was statistically significantly decreased in females at 2,211 mg/m^3. In the recovery group, absolute liver weight was statistically significantly increased in males at ≥1,101 mg/m^3. Microscopic evaluation revealed statistically significant, seminal vesicle ectasia (2,211-mg/m^3 males), tubular proteinosis/dilation (221-mg/m^3 males and females, 1,101-mg/m^3 males, and 2,211-mg/m^3 females), increased adrenal congestion, mucosal cell hyperplasia in the stomach, and extramedullary hematopoiesis and hemosiderosis in the spleen (2,211-mg/m^3 females) (see Table B-23). However, none of these effects were determined to be concentration-related. No increased frequencies of neoplastic lesions were observed in any animals. A LOAEL of 221 mg/m^3 is identified for decreased absolute and relative testes weights in male mice. Because 221 mg/m^3 is the lowest exposure tested, a NOAEL cannot be determined.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Table 4A contains summary data from genotoxicity studies with isopropanol, and Table 4B contains summary data from other types of studies with isopropanol (e.g., pharmaco/toxicokinetics, acute human exposure, occupational). Brief study summaries are included after the tables.

Table 4A. Summary of Isopropanol (CASRN 67-63-0) Genotoxicity and Mutagenicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium*, TA98, 100, 1535, 1537, 1538	2,500 µg/mL	–	–	NA	IARC (1999); Zeiger et al. (1992)
Reverse mutation	*S. typhimurium*, TA97, 98, 100, 1535, 1537	5,000 µg/mL	–	–	NA	IARC (1999); Zeiger et al. (1992)
Reverse mutation	*Escherichia coli* WP2 *uvr*A	2,500 µg/mL	–	–	NA	IARC (1999)
SOS repair induction	ND					
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	ND					
Recombination induction	ND					
Chromosomal abberation	ND					
Meiotic nondisjunction, aneuploidy	*Neurospora crassa*	NR	–	–	NA	IARC (1999)
Mitotic arrest	ND					
Genotoxicity studies in mammalian cells—in vitro						
Mutation	Chinese hamster ovary (CHO) cells, *hrpt* locus	5,000 µg/mL	–	–	NA	IARC (1999)
Chromosomal aberrations	ND					
Sister chromatid exchange (SCE)	Chinese hamster V79 cells	6,000 µg/mL	–	–	NA	IARC (1999)
DNA damage	ND					

Table 4A. Summary of Isopropanol (CASRN 67-63-0) Genotoxicity and Mutagenicity Studies						
			Results[b]			
Endpoint	Test System	Dose Concentration[a]	Without Activation	With Activation	Comments	References
DNA adducts	ND					
Genotoxicity studies in mammals—in vivo						
Chromosomal aberrations	ICR mouse bone marrow cells	2,500 µg/mL ip × 1	–	ND	NA	IARC (1999)
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Mouse biochemical or visible specific locus test	ND					
Dominant lethal	ND					
Genotoxicity studies in subcellular systems						
DNA binding	ND					

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive; ± = equivocal or weakly positive; – = negative; T = cytotoxicity; DU = data unsuitable; NA = not applicable; NV = not available; ND = no data; NDr = not determined; NI = not identified; NP = not provided; NR = not reported; NR/Dr = not reported but determined from data; NS = not selected.

Table 4B. Summary of Other Isopropanol (CASRN 67-63-0) Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Dermal Absorption and Pharmacokinetics	Isopropanol (70% w/w) aqueous solution was applied to the shaved backs of male and female F344 rats for 4 h. Absorption, elimination, and total recovery of ^{14}C-isopropanol after dermal (4 h and 5 min) and intravenous (iv) administration to rats were determined. Dermal absorption rates and permeability coefficients were calculated.	Maximum isopropanol blood concentrations were achieved at 4 h (exposure limit) and decreased to below quantifiable limit (BQL) by 8 h. Acetone blood levels increased and peaked at 4.5 h (male) and 5 h (female) and were BQL by 24 h. After iv administration, approximately 50−55% of the dose was eliminated as CO_2, with an additional 20−26% eliminated as expired volatiles and 5−6% eliminated in the urine.	Calculated dermal absorption rates were approximately 0.8 mg/cm^2/h, and calculated permeability coefficients suggested rapid dermal absorption.	Eastman Kodak (1995)
Dermal Toxicity	Study in rabbits; best available copy is not legible.	None	None	OTS (1987)
Pharmacokinetics	A physiologically based pharmacokinetic (PBPK) model for isopropanol and its major metabolite, acetone, is described. The subsequent reports (Gentry et al., 2003; Gentry et al., 2002) utilized this PBPK model to derive putative toxicity values for acetone and isopropanol.	The robustness and validity of the model were demonstrated by its ability to fit existing exposure data (various species and routes of administration). Putative toxicity values were generated for acetone and isopropanol with existing peer-reviewed data and compared to toxicity values derived with EPA default methodologies.	The authors reported that this model provided a validated framework for chemical-specific route-to-route extrapolation and cross-species dosimetry that could potentially be used in support of isopropanol and acetone risk assessment.	Clewell et al. (2001); Gentry et al. (2002); Gentry et al. (2003)
Metabolism	The potentiation of carbon tetrachloride (CCl_4) hepatotoxicity was investigated in fresh microsomes isolated after oral administration of isopropanol or acetone in the male S-D rat.	Isopropanol and acetone administration at 16 or 24 h prior to microsome isolation increased covalent binding of $^{14}CCl_4$ and *N*-demethylation of dimethylnitrosamine but did not increase CYP450 or cytochrome c reductase content in the microsomes. In vitro addition of isopropanol and acetone to microsomes was inhibitory.	Due to the lack of CYP450 or cytochrome c reductase content effects, the mechanism for increased covalent binding of $^{14}CCl_4$ and *N*-demethylation of dimethylnitrosamine by isopropanol and acetone was not determined.	Sipes et al. (1973)

Table 4B. Summary of Other Isopropanol (CASRN 67-63-0) Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Immunotoxicity	The immunosuppressive potential of isopropanol was investigated in vitro in human T lymphocytes and NK cells (up to 1.2% w/v) by various methods (CFSE staining, Western blot and luciferase assay, cytokine analysis, ELISA-based transcription factor activation assay, and cytotoxicity assays) and in vivo (2 g/kg i.p. to generate a blood alcohol concentration of 200 mg/dL [0.2% or 33 mM] after 30 min) with sepsis-induced female BALB/c mice.	Treatment was detrimental to human T lymphocyte and NK cell activity (at IPA concentrations as low as 0.08% [13 mM] as measured by IFN-release in NK cells and 0.16% [26 mM] as measured by IL-2 and IFN-release in T cells) and reduced the ability to release IL-2 and IFN-gamma in the serum in response to staphylococcal enterotoxin B (SEB), in vivo. Animals injected with SEB after presensitization with D-galactosamine developed a fulminating toxic shock syndrome with a median survival of 9 h. The syndrome did not occur or had its development delayed in all mice treated with isopropanol, and the majority of mice survived.	The data suggest that acute isopropanol exposure reduces the ability of lymphocytes to produce proinflammatory cytokines and may compromise the immune system. These results may be relevant in the context of acute intoxication considering a significant effect in vitro with isopropanol concentrations as low as 0.08−0.16% (13−26 mM) was observed, and the potential for skin application at higher concentrations (even in a hypothetical situation assuming poor dermal absorption).	Désy et al. (2008)
Occupational	Retrospective analysis of 434 workers involved in isopropanol manufacture by the decreased sulfuric acid method. Exact exposure routes and/or exposure levels were not determined (length of service ranged from 6 mo to 17 yr). Cancer deaths in the cohort were compared to expected cancer deaths.	A slight excess in all cancer deaths (9 vs. 7.28) and in respiratory cancer (4 vs. 2.96) for workers exposed to isopropanol during manufacture after 20+ yr was observed. Approximately one third of the workers in the isopropanol cohort also were involved in the manufacture of epichlorhydrin, which is a confounding factor.	No clear evidence that exposure during isopropanol manufacture at this site caused or increased the risk of cancer.	Shell Oil Co (2000)

Table 4B. Summary of Other Isopropanol (CASRN 67-63-0) Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Occupational	Retrospective analysis of 335 workers involved in ethanol and isopropanol manufacture, and a second cohort with an additional 408 employees (n = 743 total). Cancer deaths in the cohort were compared to expected cancer deaths.	The incidence of laryngeal cancer was 5-fold higher than expected. Other disproportionate cancer values were excluded due to low case numbers (n = 1).	The increased incidence of laryngeal cancer is associated with the high acid ethanol process (exposure to diethyl sulfate) and not associated with the low acid isopropanol process.	Lynch et al. (1979)
Acute Human Exposure	Five male and 7 female adult subjects, occupationally-exposed and control groups, vapor inhalation, 0 or 164 mg/m^3, 4 h. Subjects rated symptoms during exposure with respect to odor intensity, sensory irritation, and annoyance. Objective endpoints obtained before, during, and after exposure included ocular hyperemia, nasal congestion and secretion, and respiration. Isopropanol exposure was compared to phenylethyl alcohol (negative control) and clean air.	Higher intensity ratings for odor, irritation, and annoyance were noted by occupationally-exposed subjects, but overall sensory irritation was rated low. Respiration frequency was increased during exposure to isopropanol in both groups.	Increased respiration frequency may be a result of a voluntary change in breathing due to odor instead of a reflexive change due to a sensory irritant.	Smeets et al. (2002)
Acute Human Exposure	Twenty-eight male and28 female adults, vapor inhalation, 0 and 31 mg/m^3, 2 h (at rest). Subjects rated symptoms on a visual analog scale before, during, and after exposure, and blinking frequency was measured during exposure. Pulmonary function, nasal swelling, inflammatory markers in nasal lavage, and color vision were measured before, and at 0 and 3 h after exposure.	Discomfort in throat and airways as well as fatigue were reported, with no significant effects on pulmonary function due to isopropanol exposure.	Women were reported to be slightly more sensitive than men to the acute irritant effects of isopropanol.	Ernstgård et al. (2002)

Table 4B. Summary of Other Isopropanol (CASRN 67-63-0) Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Acute Human Exposure/Toxicokinetics	Eight male and 9 female subjects, human adult, vapor inhalation, 0 and 350 mg/m^3, 2 h (during light physical exercise),. Isopropanol and acetone were monitored up to 24 h after exposure in exhaled air, blood, saliva, and urine, and the toxicokinetic profile in blood was determined. Genotypes were determined by PCR-based assays for ADH and CYP2E1. The CYP2E1 phenotype was assessed by the in vivo 2 h plasma 6-hydroxychlorzoxazone/chlorzoxazone metabolic ratio.	Sex differences were observed, and females exhibited lower respiratory uptake, smaller volume of distribution, shorter half-life of isopropanol in blood, and a higher apparent total clearance when corrected for body composition. Isopropanol levels in exhaled air at 10 min postexposure and later were increased approximately 4-fold, and acetone in blood was slightly higher in women. Marked sex differences included an approximately 100-fold increase in salivary acetone in women (no increase in men)and a 10-fold higher blood:breath ratio in men, suggestive of sex differences in isopropanol lung metabolism. There was no significant difference in toxicokinetics between subjects of different metabolic genotypes or phenotypes.	Although most of the sex differences are consistent with anatomical differences between men and women, body build does not explain the differences in isopropanol levels in expired air and acetone in saliva.	Ernstgård et al. (2003)

Genotoxicity and/or Mutagenicity Studies

Several published, peer-reviewed journal articles have examined the genotoxic potential of isopropanol in a variety of test systems including reverse mutation in *S. typhimurium* TA100, TA1535, TA1537, TA1538, TA98, and E. coli WP2 *uvr*A (IARC, 1999), reverse mutation in *S. typhimurium* TA100, TA1535, TA1537, TA98, and TA97 (Zeiger et al., 1992), meiotic nondisjunction and aneuploidy in *N. crassa* (IARC, 1999), gene mutation in Chinese hamster ovary (CHO) cells, *hprt* locus in vitro and micronucleus test in ICR mouse bone marrow cells in vivo (IARC, 1999), and sister chromatid exchange in Chinese hamster V79 cells in vitro (IARC, 1999). The results of all tests (with or without an exogenous metabolic system) were negative, and isopropanol was not genotoxic under these test systems and conditions.

Dermal Absorption, Metabolism, and Pharmacokinetic Studies

A study examining the dermal absorption and pharmacokinetics of isopropanol was conducted according to EPA and TSCA GLP standards by the Eastman Kodak Company and submitted to the EPA (Eastman Kodak, 1995). Isopropanol (greater than 99% purity) was prepared as a 70% (w/w) aqueous solution (0.3 mL) and applied under occlusion to the shaved backs of male and female Fischer 344 rats for a 4-hour period. Mass balance determinations were also conducted after dermal and intravenous (iv) administration of ^{14}C-isopropanol (purity not reported). Dermal exposures (4 hours and 5 minutes) were performed similar to administration of the nonradiolabeled material, and iv administration of ^{14}C-isopropanol in isotonic saline at a concentration of 24 mg/g (6 mg/rat) was given as a bolus injection in a lateral tail vein (0.25 mL).

Maximal blood concentrations of isopropanol (approximately 0.2 µmol/g) were achieved by 4 hours in the dermal study (Eastman Kodak, 1995); concentrations declined after 4 hours (removal of material) and were below quantifiable limits (BQL) at 8 hours. Concentrations of acetone (a primary metabolite) increased until 4.5 (males) or 5 hours (females), achieving peak concentrations of 0.79 and 1.17 µmol/g, respectively, with acetone concentrations BQL by 24 hours. First-order elimination half-life estimates were similar in both sexes, with mean values of approximately 0.8 (isopropanol) and 2.6 hours (acetone). Total recovery after iv administration was approximately 83% in the rat, with 50−55% of the total dose recovered as CO_2, with a further 20−26% recovered as expired volatiles, and 5−6% recovered in urine. Recovery from the application site after dermal exposure was similar after both 4-hour and 5-minute periods, with 84−86% and 86−87%, respectively, recovered. The study authors concluded that isopropanol underwent rapid dermal absorption in this study.

There are five peer-reviewed and published studies that described the development of a physiologically based pharmacokinetic (PBPK) model for isopropanol and its major metabolite, acetone. The model by Clewell et al. (2001) evaluated the kinetics of isopropanol and acetone, and was developed for oral and inhalation routes for both rats and humans. Models for rats and humans were parameterized according to values available in the peer-reviewed literature. Oral uptake rates and metabolic parameters were obtained using model optimization procedures to fit rates against in vivo pharmacokinetic data in the peer-reviewed literature for oral and inhalation studies in rats and humans exposed to isopropanol and acetone. Model structure included compartments for tissues representing major functions including liver (for metabolism) and brain (for CNS effects). Acetone metabolism parameters for the human were evaluated by comparison of predictions to observations of a) venous blood isopropanol and acetone concentrations

following oral exposure to unspecified doses (0.6 ml/kg 70% isopropanol in 240 ml water and 0.4 ml/kg 70% isopropanol in 201 ml apple juice), and b) expired air concentrations of isopropanol and acetone during inhalation exposure to an unspecified concentration for 10 minutes. This PBPK model described by Clewell et al. (2001) was later evaluated by Clark et al. (2004) as described below.

The manuscript by Gentry et al. (2002) presented an extension of the previous model (Clewell et al., 2001) to include physiological/anatomic changes associated with pregnancy in rats and humans. The base model of Clewell et al. (2001) was used to simulate non-developmental toxicities in adult rats and extrapolate point of departure (POD) values to humans. The study authors applied the PBPK model to translate rat neurological NOAEL values identified from (Burleigh-Flayer et al. (1998); Burleigh-Flayer et al. (1994)), to corresponding human equivalent exposures and then onto putative toxicity values. The study authors concluded that isopropanol and acetone may each contribute to CNS effects following isopropanol exposure. This PBPK model described by Gentry et al. (2002) was also later evaluated by Clark et al. (2004) as described below.

Gentry et al. (2003) investigated the utilization of the PBPK models for isopropanol and acetone described by Clewell et al. (2001) and Gentry et al. (2002) to examine several factors including the extent to which the formation of acetone following isopropanol exposure may contribute to hematologic and reproductive/developmental toxicity of isopropanol. A comparison of the combined AUC values for isopropanol and acetone following isopropanol exposure to the AUC values for acetone alone for acetone-exposed animals led to the conclusion that the AUC values for acetone alone were unable to account for the developmental toxicity observed in isopropanol-exposed animals. This suggests that the developmental toxicity in these animals resulted from combined exposure to isopropanol and acetone. The same was shown to be true for hematological effects. No neurological data were presented or discussed.

The study by Clark et al. (2004) evaluated the PBPK models for isopropanol and acetone described earlier by Clewell et al. (2001) and Gentry et al. (2002) based on the following parameters: model purpose, model structure and biological characterizations, mathematical descriptions, computer implementation, parameter analysis and model fit, and assessment of specialized areas. Based on this evaluation, the study authors concluded that the PBPK models by Clewell et al. (2001) and Gentry et al. (2002) were valid for risk assessment for neurological and systemic toxicity but not developmental and reproductive effects.

In a study by Huizer et al. (2012), the study authors implemented a PBPK model to test the influence of variability in human physiological parameters on the blood concentrations of isopropanol and acetone during and following a simulated 4-hour inhalation exposure to isopropanol. The analysis concluded that variability for blood concentrations approximated 2- to 3-fold during and following exposure, that uncertainty approximated variability during exposure, but that uncertainty following exposure may range up to 100-fold at 16 hours following cessation of the exposure. This study was designed for purposes other than risk assessment, with the primary goal to highlight the importance of parameter value estimation when evaluating human interindividual variability.

In a metabolism study by Sipes et al. (1973), the potentiation of carbon tetrachloride (CCl_4) hepatotoxicity was investigated in fresh microsomes that were isolated after oral administration of isopropanol or acetone in the male S-D rat. Isopropanol or acetone was administered at 16 or 24 hours prior to sacrifice and microsome isolation. Pre-exposure in vivo to isopropanol or acetone increased covalent binding of $^{14}CCl_4$ and *N*-demethylation of dimethylnitrosamine in rat microsomes but did not increase CYP450 or cytochrome c reductase content or the amount of microsomal protein. In vitro addition of isopropanol and acetone to microsomes was inhibitory in the covalent binding and *N*-demethylation experiments. Due to the lack of treatment effect on CYP450 or cytochrome c reductase microsomal content, the mechanism for increased covalent binding of $^{14}CCl_4$ and *N*-demethylation of dimethylnitrosamine by isopropanol and acetone was not determined in this study.

Immunotoxicity Study

The immunosuppressive effects of isopropanol were investigated by Désy et al. (2008) in a series of in vitro and in vivo experiments. In vitro, isopropanol (≥0.16%) interfered with the production of interleukin (IL)-2 in human peripheral lymphocytes and inhibited IL-2 transcription at a concentration of 0.3% and higher. Isopropanol also inhibited interferon (IFN)-γ release in human peripheral T lymphocytes and natural killer (NK) cells, with virtually complete inhibition at isopropanol concentrations of 1.2% and 0.6−1.2%, respectively. Inhibition of IL-2 and IFN-γ in vivo in the mouse was demonstrated by delay or protection from staphylococcal enterotoxin B-induced toxic shock, and reduced cytokine production, after administration of isopropanol. The study authors noted that a potential implication of these findings may be immunosuppression after acute isopropanol intoxication; a hypothetical situation of exposure to isopropanol concentrations of 60−95% in hand sanitizer products that were 500- to 1,000-fold more concentrated than the in vitro effective concentration illustrated the potential for limited and transitory immunosuppressive effects even if poor dermal absorption were assumed.

Occupational Exposure Studies

Limited information is available regarding occupational exposure of humans to isopropanol. Shell Oil Co (2000) performed a retrospective study of male workers who were involved in the manufacture of isopropanol by the low sulfuric acid method (67 to 80% acid) and exposed for 6 months to 18 years in Deer Park, TX, between 1943 and 1965. The study evaluated cancer deaths in this cohort relative to cancer incidence in workers potentially exposed to isopropyl oil generated by isopropanol manufacture with the high sulfuric acid method (98 to 99% acid). Although a slight excess in all cancer deaths (9 vs. 7.28) and in respiratory cancer (4 vs. 2.96) was observed for workers exposed over 20 years to isopropanol during the manufacturing process, there was no clear evidence that isopropanol exposure at this site was causal to or increased the risk of cancer. A confounding factor in this exposure assessment was that approximately one-third of the workers in the isopropanol cohort were also involved in the manufacture of epichlorhydrin.

Another occupational exposure study (Lynch et al., 1979) conducted a retrospective analysis of 335 workers involved in ethanol and isopropanol manufacture, as well as a second cohort with an additional 408 employees (n = 743 total). The incidences of cancer deaths in the cohorts were compared to expected cancer deaths in white males listed in the Third U.S. National Cancer Survey conducted in 1975. The incidence of laryngeal cancer was 5-fold

higher than expected, but other disproportionate cancer values were excluded due to low case numbers (n = 1). The increased incidence of laryngeal cancer was reported as being solely associated with the high acid ethanol process (worker exposure to diethyl sulfate) and was not associated with the low acid isopropanol process.

Short-term Studies

Short-term exposure of human subjects to isopropanol in a scientifically controlled environment has been examined in three inhalation studies. In a peer-reviewed published journal article study by Smeets et al. (2002), groups of 12 adults (5 males and 7 females, with prior occupational exposure or control) were administered a single exposure to 0 (control) or 164 mg/m^3 isopropanol vapor for 4 hours. Approval for human exposure in this study was obtained from an Institutional Review Board for the University of Pennsylvania. This exposure was below the recommended exposure limit of 490 mg/m^3 for an 8-hour TWA (ACGIH, 2013). Overall, sensory irritation was rated as low and weak, although respiration frequency increased in both groups (possibly the result of a voluntary, not reflexive, change in breathing due to an unpleasant odor). No differences were noted between the control group and adults with prior occupational exposure to isopropanol.

Two related peer-reviewed articles of human inhalation studies by Ernstgård et al. (2002) investigated sex differences due to isopropanol vapor inhalation. Both studies were approved by the regional ethical committee at the Karolinska Institute. Discomfort in the throat and airways and fatigue were reported after a single 2-hour exposure to 31 mg/m^3 of isopropanol vapor at rest, with no significant effects on pulmonary function (Ernstgård et al., 2002). This exposure was below the recommended exposure limit of 490 mg/m^3 for an 8-hour TWA (ACGIH, 2013). Women were reported to be slightly more sensitive than men to the acute irritant effects of isopropanol. After a single 2-hour exposure to 350 mg/m^3 during light physical activity (Ernstgård et al., 2003), sex differences observed in females included lower respiratory uptake, smaller volume of distribution, slightly shorter half-life of isopropanol in blood, and a higher apparent total clearance when corrected for body composition. This exposure was below the recommended exposure limit of 490 mg/m^3 for an 8-hour TWA and the short-term exposure limit of 980 mg/m^3 (ACGIH, 2013). Isopropanol levels in exhaled air at 10 minutes postexposure and times later were increased approximately 4-fold, and acetone blood concentrations were slightly higher in women. The most marked sex difference was an approximately 100-fold increase in salivary acetone concentration in women, with no increase in men. Another marked sex difference was a 10-fold higher in vivo blood:breath ratio in men, suggestive of sex differences in isopropanol lung metabolism. There was no significant difference in toxicokinetics between subjects with different genotypes or phenotypes for metabolic enzymes (i.e., alcohol dehydrogenase and CYP2E1). The study indicated several sex differences in the inhalation toxicokinetics of isopropanol, and although most of these differences were consistent with anatomical differences between women and men, differences in isopropanol concentrations in expired air and acetone in saliva were not correlated to differences in body build.

Case Reports

Additionally, various case report studies have been published describing the hospitalization (primarily Emergency Department) and treatment of subjects after various conditions of exposure (Shetty et al., 2013; Blow et al., 2012; Rehman, 2012; Killeen et al.,

2011; Clark, 2010; Krieg, 2008; Leeper et al., 2000; Vivier et al., 1994; Parker and Lera, 1992; Rich et al., 1990; Gaudet and Fraser, 1989; Natowicz et al., 1985; Daniel et al., 1981; Mcfadden and Haddow, 1969). These studies are briefly summarized in Table 5. Isopropanol intoxication is well documented because isopropanol is inexpensive, readily available, and commonly used in cleaning and several home remedies/therapies. General symptoms of isopropanol intoxication included ataxia, lethargy, hypotonia, hyporeflexia, unresponsiveness to pain, and coma. While symptoms usually resolved after 2−3 days of supportive management, central nervous system and respiratory depression can result in deep coma. Blood concentrations of isopropanol and acetone were often determined and followed throughout the course of medical treatment. The pharmacokinetics of isopropanol and acetone generally were consistent with accepted values. Of note, the half-life of acetone in one child (<1 year) was approximately half of the accepted adult value (consistent with 2-fold greater ketone clearance in children) (Parker and Lera, 1992). Reported cases of intoxication in humans via dermal exposure are likely due to vapor inhalation and/or compromised skin integrity. In one adult case, intoxication resulted from applying isopropanol-soaked towels to the face and shoulders during sleep to reduce pain (Leeper et al., 2000), and in two cases in children, intoxication resulted from isopropanol application to the umbilical cord (Vivier et al., 1994) or to whole body/nightclothes to aid fever reduction (Mcfadden and Haddow, 1969).

Table 5. Summary of Case Reports of Human Exposure To Isopropanol					
Reference	**Number of cases**	**Exposure**	**Effects Observed**	**Comments**	**Setting/Purpose**
Mcfadden and Haddow (1969)	One infant male	Topical application of 2 quarts of 70% isopropanol	Coma	Whether the isopropanol was absorbed through the skin or inhaled could not be determined.	Medical use
Daniel et al. (1981)	One adult male and one adult female	Ingestion of unknown amount of 70% isopropanol in male and 1 pint in female.	Specific effects not reported for male; mental confusion reported for female.	Isopropanol disappeared from the blood at a rate following first-order kinetics in both cases; blood half-lives were estimated at 155 and 187 min in the male and female patients, respectively.	Intentional abuse
Natowicz et al. (1985)	One adult female	Ingestion of unknown amount of 70% isopropanol	Coma	Pharmacokinetic analysis showed that the elimination of both isopropanol and its major metabolite acetone obeyed apparent first-order kinetics with half-lives of 6.4 and 22.4 h, respectively	Intentional abuse
Gaudet and Fraser (1989)	One adult female	Ingestion of unknown amount of 70% isopropanol	Unresponsiveness, slurred speech, and disorientation.	The calculated half-life of isopropanol was 7.3 h	Intentional abuse
Rich et al. (1990)	Three adult males	Ingestion of unknown amount of 70% isopropanol	Apathy, mental confusion, ataxia, hyperreflexia, and encephalopathy.	No comments	Intentional abuse
Parker and Lera (1992)	One infant female	Ingestion of ~4 ounces of isopropanol (concentration unknown)	Vomiting, lethargic, and hyporeflexia.	Isopropanol (half-life = 5.8 h) clearance was similar to values reported for adults; acetone (half-life = 10.8 h) was eliminated twice as rapidly as in adults	Accidental use
Vivier et al. (1994)	One infant male	Topical application of 175 mL of 70% isopropanol	Hypotonia, lethargy, and unresponsiveness.	None	Medical use
Leeper et al. (2000)	One adult female	Topical application with an unknown amount of 70% isopropanol	Syncope and multiple neurological deficits.	None	Medical use

Table 5. Summary of Case Reports of Human Exposure To Isopropanol					
Reference	**Number of cases**	**Exposure**	**Effects Observed**	**Comments**	**Setting/Purpose**
Blow et al. (2012)	One adult female	Inhalation of unknown concentration of isopropanol	Respiratory failure, lung infiltrates, and hemoptysis.	None	Intentional abuse
Rehman et al. (2012)	One adult female	Ingestion of unknown amount of isopropanol (concentration unknown)	Ketoacidosis, abdominal pain, and vomiting.	None	Intentional abuse
Clark (2010)	One adult male	Ingestion of ~24 ounces of 70% isopropanol	Coma, poor respiratory effort, dilated pupils, and significant hypotension.	None	Intentional abuse
Shetty et al. (2013)	One adult male	Ingestion of unknown amount of isopropanol-based sanitizer (concentration unknown)	Cardiac arrest	Sanitizer contained glycerin and perfume	Intentional abuse
Krieg (2008)	One male child	Transcutaneous absorption of 24 to 32 oz (0.7 to 0.95 L) of 70% isopropanol	Coma	None	Medical use
Killeen et al. (2011)	One adult female	Ingestion of unknown amount of 70% isopropanol	Unresponsiveness and pseudorenal insufficiency.	None	Intentional abuse

DERIVATION OF PROVISIONAL VALUES

Table 6 presents a summary of noncancer reference values. Table 7 presents a summary of cancer values.

Table 6. Summary of Noncancer Reference Values for Isopropanol (CASRN 67-63-0)

Toxicity Type (Units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rabbit/F	Decreased fetal body weight	2×10^0	$BMDL_{05HED}$	55.2	30	Tyl et al. (1994)
Chronic p-RfD (mg/kg-d)	Rabbit/F	Decreased fetal body weight	2×10^0	$BMDL_{05HED}$	55.2	30	Tyl et al. (1994)
Subchronic p-RfC (mg/m^3)	Rat/F	Increased mean cumulative motor activity	7×10^0	$NOAEL_{HEC}$	661.8	100	Burleigh-Flayer et al. (1994)
Chronic p-RfC (mg/m^3)	Mice/M	Decreased absolute and relative testes weights	2×10^{-1}	$LOAEL_{HEC}$	221	1,000	Burleigh-Flayer et al. (1997)

Table 7. Summary of Cancer Reference Values for Isopropanol (CASRN 67-63-0)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	NDr			
p-IUR	NDr			

NDr = Not determined.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The developmental study in rabbits by Tyl et al. (1994) is selected as the principal study for derivation of the subchronic p-RfD. This study was presented in a peer-reviewed journal, was performed according to good laboratory practice (GLP), and otherwise meets the standards of study design and performance with regard to numbers of animals, examination of potential toxicity endpoints, and presentation of information. Details of the study are provided in the "Review of Potentially Relevant Data" section.

Justification

The effects of oral exposures to isopropanol in animals have been evaluated in one subchronic-duration study, four developmental toxicity studies, and three reproductive toxicity studies (see Table 3). As described above, these studies identified a variety of effects on the liver, kidney, adrenals, spleen, body weight, developing fetus, and reproductive system, with NOAELs ranging from 120 and 1,948 mg/kg-day and LOAELs ranging from 240 and 2,768 mg/kg-day (Bevan et al., 1995; Bates et al., 1994; Tyl et al., 1994; Pilegaard and Ladefoged, 1993; BIBRA, 1991, 1988, 1986). These studies were considered for the selection of the principal study and are described below. Because all of these studies were considered adequate for the derivation of the subchronic p-RfD and they identified sensitive effects in the low-dose range, benchmark dose (BMD) modeling was performed on several of the endpoints (where the data are amenable) and these results are presented below and discussed in detail in Appendix C. The results of the BMD modeling were then used to identify potential PODs (see Table 8) for the selection of the principal study and critical effect and derivation of the subchronic p-RfD.

It is important to note that several studies observed concomitant decreases in water intake and food consumption (see Table 3). With respect to decreased food consumption, treatment with alcohol is a known contributor to caloric intake. It is possible that isopropanol treatment was delivering calories and resulted in a decrease in food consumption, suggesting that this endpoint is not a direct toxicological effect of isopropanol and therefore not an appropriate critical effect for reference value derivation. The decrease in water intake is most likely due to taste aversion, which may also have contributed to a decrease in food consumption. Based on these reasons, these particular endpoints were not considered for reference value derivation.

In a study by Pilegaard and Ladefoged (1993), 22 male Wistar rats per group were treated to 0, 870, 1,280, 1,680, and 2,520 mg/kg-day of isopropanol in the drinking water. Increases in organ weights were observed at various doses: relative liver and adrenal weight at ≥1,680 mg/kg-day and relative kidney weight at ≥1,280 mg/kg-day. The data for these organ weight changes were subjected to BMD modeling, and the study was considered further for selection as the principal study for derivation of the subchronic p-RfD. The results of the BMD modeling are presented below.

BIBRA (1987) reported decreased fetal body weight in male and female fetal rats at 1,605 mg/kg-day as well as a decreased number of fetuses with the fourth sacral arch at ≥596 mg/kg-day. For the decreased number of fetuses with the fourth sacral arch in Wistar rats (BIBRA, 1987), the biological significance of this effect is unknown. Furthermore, the most common skeletal variations (e.g., poorly ossified frontal bone and supraoccipital bone, etc.)

observed in other developmental toxicity studies were not observed in the BIBRA (1987) study. These data suggest that a decreased number of fetuses with the fourth sacral arch in Wistar rats (BIBRA, 1987) is not a relevant toxicological endpoint and was therefore not considered for derivation of the subchronic p-RfD for isopropanol. However, the data for decreased fetal body weight were subjected to BMD modeling, and the study was considered further for selection as the principal study for derivation of the subchronic p-RfD.

In a developmental toxicity study by Bates et al. (1994), maternal CD rats were gavaged with 0, 200, 700, or 1,200 mg/kg-day of isopropanol from GD 6 to PND 21. The study authors reported that one dam died in the high-dose group on PND 15, identifying an FEL of 1,200 mg/kg-day with a corresponding NOAEL of 700 mg/kg-day. Because there is no benchmark response (BMR) for increased mortality in adult animals, these data from Bates et al. (1994) were not subjected to BMD modeling, nor were mortality data from any other study. Thus, the Bates et al. (1994) study was not considered further for selection as the principal study for derivation of the subchronic p-RfD.

Tyl et al. (1994) performed a developmental toxicity study in which dose groups of 25 maternal CD rats were treated by gavage to 0, 400, 800, and 1,200 mg/kg-day of isopropanol from GDs 6–15. The study authors observed mortality in dams and decreased fetal body weight; both at ≥800 mg/kg-day. The data for decreased fetal body weight were subjected to BMD modeling, and the study was considered further for selection as the principal study for derivation of the subchronic p-RfD.

In a developmental toxicity study by Tyl et al. (1994), maternal NZW rabbits (15 per dose group) were gavaged with isopropanol (0, 120, 240, or 480 mg/kg-day) from GDs 6–18. The study authors reported decreased food consumption and increased mortality in dams at 480 mg/kg-day. Decreased fetal body weight was observed at ≥240 mg/kg-day. The data for decreased fetal body weight from this study were subjected to BMD modeling, and the study was considered further for selection as the principal study for derivation of the subchronic p-RfD.

In a one-generation reproductive toxicity pilot study (BIBRA, 1986), male and female Wistar rats were treated with isopropanol in the drinking water. The study authors reported effects in both F0 and F1 rats. In F0 dams, body weight and food consumption were decreased at both 2,825 and 2,724 mg/kg-day on PND 21. Absolute kidney and relative liver and kidney weights were increased in dams at both 2,825 and 2,724 mg/kg-day. Also in dams, absolute liver weight was increased at ≥2,645 mg/kg-day. In F0 males, food consumption and water intake were decreased at ≥711 mg/kg-day. Increased absolute liver and kidney weights were also observed in males at 1,176 mg/kg-day as well as increased relative liver and kidney weights at ≥1,001 mg/kg-day. In F1 rats, decreased pup weight was reported at ≥1,167 mg/kg-day.

For the BIBRA (1986) study, BMD modeling was not conducted for effects occurring at a LOAEL 10-fold greater than 240 mg/kg-day, which is the most sensitive, relevant LOAEL identified in Table 3 (for decreased fetal body weight in female rabbits in Tyl et al., 1994). With respect to the endpoint of decreased pup weight in Wistar rats observed in BIBRA (1986), this study is considered a pilot study (i.e., range-finding study) for the later study by BIBRA (1988). Compared to the BIBRA (1986) study, the BIBRA (1988) study is considered more complete because the study authors treated a larger number of dams which resulted in a larger number of

pups. Additionally, the dosimetry could not be calculated for the full duration of the BIBRA (1986) pilot study because isopropanol intake, food consumption, and water intake were not determined for either sex during the mating period, nor were these parameters determined for the dams during the gestational period. The endpoint of decreased pup weight in Wistar rats that was observed in both the BIBRA (1988), BIBRA (1986) studies could be BMD modeled using data from the more complete BIBRA (1988) study. The resulting BMDL serves as the potential POD for decreased pup weight from both the BIBRA (1988), BIBRA (1986) studies. Effects occurring in F0 adult male rats from this study (e.g., liver weight changes) were not considered for the derivation of the subchronic p-RfD because the adult male rats were treated longer than 13 weeks. These data were considered in the derivation of the chronic p-RfD as discussed below. Based on the reasons described here, this study was not considered further for selection as the principal study for derivation of the subchronic p-RfD.

In an additional one-generation reproductive toxicity study in male and female rats by BIBRA (1988), similar effects to those observed in the BIBRA (1986) study were noted in F0 and F1 rats. In F0 rats, decreased water intake was reported in males at ≥625 mg/kg-day and in females at 1,206 mg/kg-day. Decreased food consumption was observed in F0 males at ≥347 mg/kg-day and in females at 1,206 mg/kg-day. Increased relative liver, spleen, and kidney weights and increased absolute kidney weight were reported in males at 1,030 mg/kg-day. Increased relative and absolute liver weight in females was observed at 2,768 mg/kg-day. In F1 rats, decreased pup body weight was reported at ≥668 mg/kg-day. At a dose of 1,902 mg/kg-day, the study authors reported decreased fetal body weight and an increased number of preimplantation losses in F1 rats. Increased relative liver weight was reported in adult male and female F1 rats at 2,768 mg/kg-day. As discussed above, effects with LOAELs 10-fold greater than 240 mg/kg-day were not BMD modeled. Effects occurring in F0 adult male rats from this study (i.e., liver weight changes) were not considered in the derivation of the subchronic p-RfD because the adult rats were treated longer than 13 weeks. These data were considered in the derivation of the chronic p-RfD as discussed below. For all other effects occurring at lower doses, the data were BMD modeled and the study was considered further for selection as the principal study for derivation of the subchronic p-RfD.

In a two-generation reproductive toxicity study, Bevan et al. (1995) reported gavage administration of isopropanol (0, 100, 500, or 1,000 mg/kg-day) to groups of 30 male and 30 female S-D rats for 10−13 weeks before mating and continued through lactation (females) and until the last litter was sired (males). The study authors noted effects in the F0, F1, and F2 generations. In F0 rats, the study authors reported increased absolute and relative liver weight in males and increased relative liver weight in females (all at 1,000 mg/kg-day). In F1 rats, increased relative liver weight was reported in adult males at ≥500 mg/kg-day and increased relative liver weight in adult females at 1,000 mg/kg-day. The following reproductive and developmental effects were noted in F1 rats: decreased male mating index at 1,000 mg/kg-day; decreased live birth index at 1,000 mg/kg-day; decreased Day 1 (1,000 mg/kg-day) and Day 4 (≥500 mg/kg-day) survival indices. Similar reproductive and developmental effects were also reported in F2 rats. The study authors reported decreased Day 1 (≥500 mg/kg-day), Day 4 (1,000 mg/kg-day), and Day 7 (≥500 mg/kg-day) survival indices as well as decreased lactation index at ≥500 mg/kg-day in F2 rats. Decreased male pup body weight was observed in F2 rats at 1,000 mg/kg-day. Effects occurring in F0 and F1 adult rats (e.g., liver weight changes and decreased male mating index) from this study were not

considered in the derivation of the subchronic p-RfD because the adult rats were treated longer than 13 weeks. These data were considered in the derivation of the chronic p-RfD as discussed below. Finally, with respect to decreased survival index, lactation index, and live birth index in F1 and/or F2 rats (Bevan et al., 1995), BMD modeling could not be performed due to a lack of individual pup survival data and variance data. However, Allen et al. (1998) reported BMD modeling results for the F1 and F2 survival data using a nested logistic model and these data were considered as potential PODs to derive the subchronic p-RfD for isopropanol. The data for decreased pup weight in F2 male rats were BMD modeled, and the study was considered further for selection as the principal study for derivation of the subchronic p-RfD.

Based on the results of the dose-response analysis, the most sensitive effect identified is decreased fetal body weight in rabbits (Tyl et al., 1994). As described in Appendix C, all available continuous models in the EPA Benchmark Dose Software (BMDS version 2.1.2) (U.S. EPA, 2010) were fit to the number of litters with decreased fetal body weight in rabbits following treatment with isopropanol on GDs 6–18. Although use of a 10% BMR is the standard practice, in this case, a 5% BMR is used because the developmental effect (i.e., decreased fetal body weight) was observed during a potentially sensitive life stage. For male rabbits and males and females combined, the data for decreased fetal body weight were not amenable to BMD modeling; a NOAEL/LOAEL approach was employed to identify a potential POD. For decreased fetal body weight in males and males and females combined, the LOAEL is 480 mg/kg-day based on a ≥5% decrease in rabbits, with a corresponding NOAEL of 240 mg/kg-day. For decreased fetal body weight in female rabbits, BMD modeling resulted in a $BMDL_{05}$ of 120 mg/kg-day. Decreased fetal body weight is a common toxicological effect following oral exposure to isopropanol as observed in four studies in rats. **Thus, decreased fetal body weight in female rabbits is chosen as the critical effect with a $BMDL_{05}$ of 120 mg/kg-day.**

Table 8. Potential PODs for Subchronic p-RfD Derivation for Isopropanol (CASRN 67-63-0)

Study	Species/Study	Sex	Critical Effect	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	BMD[a] (mg/kg-d)	BMDL[a] (mg/kg-d)
Pilegaard and Ladefoged (1993)	Rat/Subchronic	M	↑ Relative kidney weight	870	1,280	666[b]	554[b]
BIBRA (1987)	Rat/Developmental	M/F	↓ Fetal weight	1,242	1,605	1,348[c]	847[c]
Tyl et al. (1994)	**Rabbit/Developmental**	**F**	**↓ Fetal weight**	**120**	**240**	**284[c]**	**120[c]**
Tyl et al. (1994)	Rat/Developmental	F	↓ Fetal weight	400	800	719[c]	513[c]
BIBRA (1988)	Rat/One-Gen Reproductive	M/F	↓ Pup weight	NDr	668	563[c]	402[c]
Bevan et al. (1995)	Rat/Two-Gen Reproductive	M/F	↓ Survival index on PND 4 in F2 rats	500	1,000	804[c]	418[c] as determined by Allen et al. (1998)

[a]Column contains lowest BMD(L) values among all endpoints modeled in the respective studies.
[b]BMR of 10% relative risk.
[c]BMR of 5% relative risk.

NDr = not determined.

Dosimetric Adjustments:

No duration dosimetric adjustments are made because developmental toxicity studies are not adjusted for continuous exposure.

In EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based pharmacokinetic (PBPK) modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, the U.S. EPA endorses body weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a standard method to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving a RfD under certain exposure conditions, including when extrapolating from developmental effects in laboratory animals to humans in those situations where exposure to the chemical of interest occurred in utero (i.e., dams were administered the chemical of interest during gestation with effects observed subsequently in the offspring). The use of $BW^{3/4}$ scaling for deriving a RfD is also recommended when the observed effects are associated with the parent compound or a stable metabolite, but not for portal-of-entry effects. A validated human PBPK model for isopropanol is not available for use in extrapolating doses from rabbits to humans. The selected critical effect of decreased fetal body weight is associated with the parent

compound or a stable metabolite. Furthermore, this fetal effect is not a portal-of-entry effect. Therefore, scaling by $BW^{3/4}$ is relevant for deriving human equivalent doses (HEDs) for this effect.

Following U.S. EPA (2011b) guidance, the POD for decreased fetal body weight in female rabbits is converted to a HED through application of a dosimetric adjustment factor (DAF^1) derived as follows:

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

where

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

Using a BW_a of 3.10 kg for female rabbits (U.S. EPA, 1994b) and a BW_h of 70 kg for humans (U.S. EPA, 1988) the resulting DAF is 0.46. Applying this DAF to the $BMDL_{05}$ identified for the critical effect in fetal rabbits yields a $BMDL_{05HED}$ as follows:

$$\begin{aligned} BMDL_{05HED} &= 120 \text{ mg/kg-day} \times DAF \\ &= 120 \text{ mg/kg-day} \times 0.46 \\ &= 55.2 \text{ mg/kg-day} \end{aligned}$$

The subchronic p-RfD for isopropanol, based on the $BMDL_{05HED}$ of 55.2 mg/kg-day (POD) in female fetal rabbits (Tyl et al., 1994), is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= BMDL_{05HED} \div UF_C \\ &= 55.2 \text{ mg/kg-day} \div 30 \\ &= \mathbf{2 \times 10^0 \text{ mg/kg-day}} \end{aligned}$$

Tables 9 and 10 summarize the uncertainty factors and the confidence descriptors, respectively, for the subchronic p-RfD for isopropanol.

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

Table 9. Uncertainty Factors for Subchronic p-RfD for Isopropanol (CASRN 67-63-0)		
UF	**Value**	**Justification**
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following oral isopropanol exposure. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) through application of a dosimetric adjustment factor (DAF) as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	1	A UF_D of 1 is applied because the database includes one acceptable two-generation reproductive toxicity study in rats (Bevan et al., 1995) and three acceptable developmental toxicity studies in rats and rabbits (Bates et al., 1994; Tyl et al., 1994) via the oral route.
UF_H	10	A UF_H of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of isopropanol in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because the critical effect (i.e., decreased fetal body weight) is a developmental effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	30	Composite Uncertainty Factor ($UF_A \times UF_D \times UF_H \times UF_L \times UF_S$)

Table 10. Confidence Descriptors for Subchronic p-RfD for Isopropanol (CASRN 67-63-0)		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	H	The study by the Tyl et al. (1994) is a well-conducted, peer-reviewed, GLP compliant, and comprehensive study with a sufficient number of animals that examined a variety of endpoints.
Confidence in Database	M	The database is given medium confidence because there is a subchronic-duration study in rats, as well as three developmental toxicity studies in rats and one in rabbits. There are also acceptable one- and two-generation reproductive toxicity studies in rats. However, there are no chronic-duration oral studies performed in animals.
Confidence in Subchronic p-RfD[b]	M	The overall confidence in the subchronic p-RfD is medium.

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

Derivation of Chronic Provisional RfD (Chronic p-RfD)

As described above in the derivation of the subchronic p-RfD, there are three reproductive toxicity studies (with treatmet durations ranging from 126 to 147 days; Bevan et al., 1995; BIBRA, 1988, 1986) showing effects in adult animals that could be considered for derivation of the chronic p-RfD, and the effects observed in these studies were BMD modeled to determine potential PODs.

For the BIBRA (1986) study, the most sensitive effect is increased absolute liver weight in adult male F0 rats with a $BMDL_{10}$ of 606 mg/kg-day. The most sensitive effect from the BIBRA (1988) study is a $BMDL_{10}$ of 663 mg/kg-day for increased relative liver weight in F0 adult male rats. For the Bevan et al. (1995) study, the most sensitive effect is increased relative liver weight in F1 adult male rats with a $BMDL_{10}$ of 197 mg/kg-day. These potential PODs are all less sensitive than the $BMDL_{05}$ of 120 mg/kg-day for decreased fetal body weight in female rabbits identified from the developmental study by Tyl et al. (1994) (see Table 11). Thus, based on the increased sensitivity of decreased fetal body weight in female rabbits compared to the available chronic-duration data in rats and for the reasons detailed above under the derivation of subchronic p-RfD, **decreased fetal body weight in female rabbits from Tyl et al. (1994) is chosen as the critical effect for derivation of the chronic p-RfD, with a $BMDL_{05}$ of 120 mg/kg-day**.

Table 11. Potential PODs for Chronic p-RfD Derivation for Isopropanol (CASRN 67-63-0)

Study	Species/Study	Sex	Critical Effect	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	BMD[a] (mg/kg-d)	BMDL[a] (mg/kg-d)
BIBRA (1986)	Rat/One-Gen Reproductive	M	↑ Absolute liver weight	1,001	1,176	958[b]	606[b]
BIBRA (1988)	Rat/One-Gen Reproductive	M	↑ Relative liver weight	625	1,030	1,049[b]	663[b]
Bevan et al. (1995)	Rat/Two-Gen Reproductive	M	↑ Relative liver weight	100	500	413[b]	197[b]
BIBRA (1987)	Rat/Developmental	M/F	↓ Fetal weight	1,242	1,605	1,348[c]	847[c]
Tyl et al. (1994)	**Rabbit/Developmental**	**F**	**↓ Fetal weight**	**120**	**240**	**284[c]**	**120[c]**
Tyl et al. (1994)	Rat/Developmental	F	↓ Fetal weight	400	800	719[c]	513[c]
BIBRA (1988)	Rat/One-Gen Reproductive	M/F	↓ Pup weight	NDr	668	563[c]	402[c]
Bevan et al. (1995)	Rat/Two-Gen Reproductive	M/F	↓ Survival index on PND 4 in F2 rats	500	1,000	804[c]	418[c] as determined by Allen et al. (1998)

[a]Column contains lowest BMD(L) values among all endpoints modeled in the respective studies.
[b]BMR of 10% relative risk.
[c]BMR of 5% relative risk.

NDr = not determined.

Dosimetric Adjustments:

No duration dosimetric adjustments are made because developmental toxicity studies are not adjusted for continuous exposure.

Following U.S. EPA (2011b) guidance, the POD for decreased fetal body weight in female rabbits is converted to a HED through application of a dosimetric adjustment factor (DAF^2) derived as follows:

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

where

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

Using a BW_a of 3.10 kg for female rabbits (U.S. EPA, 1994b) and a BW_h of 70 kg for humans (U.S. EPA, 1988) the resulting DAF is 0.46. Applying this DAF to the $BMDL_{05}$ identified for the critical effect in fetal rabbits yields a $BMDL_{05HED}$ as follows:

$$\begin{aligned} BMDL_{05HED} &= 120 \text{ mg/kg-day} \times DAF \\ &= 120 \text{ mg/kg-day} \times 0.46 \\ &= 55.2 \text{ mg/kg-day} \end{aligned}$$

The chronic p-RfD for isopropanol, based on the $BMDL_{05HED}$ of 55.2 mg/kg-day (POD) in female fetal rabbits (Tyl et al., 1994), is derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfD} &= BMDL_{05HED} \div UF_C \\ &= 55.2 \text{ mg/kg-day} \div 30 \\ &= \mathbf{2 \times 10^0 \text{ mg/kg-day}} \end{aligned}$$

Tables 12 and 13 summarize the uncertainty factors and the confidence descriptors, respectively, for the chronic p-RfD for isopropanol.

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

Table 12. Uncertainty Factors for the Chronic p-RfD for Isopropanol (CASRN 67-63-0)		
UF	**Value**	**Justification**
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following oral isopropanol exposure. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) through application of a dosimetric adjustment factor (DAF) as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	1	A UF_D of 1 is applied because the database includes one acceptable two-generation reproductive toxicity study in rats (Bevan et al., 1995) and three acceptable developmental toxicity studies in rats and rabbits (Bates et al., 1994; Tyl et al., 1994) via the oral route.
UF_H	10	A UF_H of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of isopropanol in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because the critical effect (i.e., decreased fetal body weight) is a developmental effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	30	Composite Uncertainty Factor ($UF_A \times UF_D \times UF_H \times UF_L \times UF_S$)

Table 13. Confidence Descriptors for Chronic p-RfD for Isopropanol (CASRN 67-63-0)		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	H	The study by the Tyl et al. (1994) is a well-conducted, peer-reviewed, GLP compliant, and comprehensive study with a sufficient number of animals that examined a variety of endpoints.
Confidence in Database	M	The database is given medium confidence because there is one subchronic-duration study in rats, as well as three developmental toxicity studies in rats and one in rabbits. There are also acceptable one- and two-generation reproductive toxicity studies in rats. However, there are no chronic-duration oral studies performed in animals.
Confidence in Chronic p-RfD[b]	M	The overall confidence in the chronic p-RfD is medium.

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

DERIVATION OF INHALATION REFERENCE CONCENTRATION

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

The subchronic-duration study in rats by Burleigh-Flayer et al. (1994) is selected as the principal study for derivation of the subchronic p-RfC. This study was presented in a peer-reviewed journal and was performed according to good laboratory practice (GLP) and otherwise meets the standards of study design and performance with regard to numbers of animals, examination of potential toxicity endpoints, and presentation of information. Details of the study are provided in the "Review of Potentially Relevant Data" section.

Justification

No published studies investigating the effects of subchronic-duration inhalation exposure to isopropanol in humans were identified. However, a developmental toxicity study in rats and three subchronic-duration (13-week) studies in rats or mice utilized inhalation as the route of exposure. Potential PODs evaluated from these studies are presented below in Table 15.

The most sensitive potential POD from the subchronic-duration inhalation studies is a NOAEL of 222 mg/m^3 for increased relative liver weight in female CD-1 mice (Burleigh-Flayer et al., 1994). However, this NOAEL is not consistent with other NOAELs observed for increased relative liver weight in female mice from other inhalation studies. In a chronic-duration study by Burleigh-Flayer et al. (1997), a LOAEL of 2,211 mg/m^3 is identified for increased relative liver weight in female CD-1 mice with a corresponding NOAEL of 1,101 mg/m^3. The NOAEL from the subchronic-duration study by Burleigh-Flayer et al. (1994) is 5-fold lower than that identified from the chronic-duration study by Burleigh-Flayer et al. (1997) for the same liver endpoint in the same sex and strain of mouse. These data suggest that the NOAEL of 222 mg/m^3 may not be reliable because of its inconsistency with other NOAELs identified for the same endpoint following even longer exposure durations. The next most sensitive potential POD is a NOAEL of 661.8 mg/m^3 for increased mean cumulative motor activity in female rats in the chronic study by Burleigh-Flayer et al. (1994). Neither summary (mean ± SD) nor individual data were provided for endpoints other than kidney histopathology; therefore, BMD modeling could not be performed on these endpoints from Burleigh-Flayer et al. (1994). Increased motor activity is a consistently observed effect following inhalation exposure of isopropanol as it was also observed in female rats exposed to 2,199 mg/m^3 for 13 weeks in the subchronic-duration study by Burleigh-Flayer et al. (1998). Furthermore, the selection of the NOAEL of 661.8 mg/m^3 for increased mean cumulative motor activity in female rats would be protective against other less sensitive subchronic-duration and developmental toxicity effects due to isopropanol inhalation listed in Table 14. **Thus, increased mean cumulative motor activity in female rats is chosen as the critical effect with a NOAEL of 661.8 mg/m^3.**

Table 14. Potential PODs for Subchronic p-RfC Derivation for Isopropanol (CASRN 67-63-0)

Study	Species/Study	Sex	Critical Effect	NOAEL (mg/m^3)	LOAEL (mg/m^3)	BMC (mg/m^3)	BMCL (mg/m^3)
Burleigh-Flayer et al. (1994)	Rat/Subchronic	F	↑ Motor activity	661.8	2,198	NDr	NDr
Burleigh-Flayer et al. (1998)	Rat/Subchronic	F	↑ Motor activity	NDr	2,199	NDr	NDr
Burleigh-Flayer et al. (1994)	Mouse/Subchronic	F	↑ Relative liver weight	222	661.8	NDr	NDr
Nelson et al. (1988)	Rat/Developmental	M	↓ Fetal weight	2,516	5,048	2,537[a]	1,907[a]

[a]BMR of 5% relative risk.

NDr = not determined.

Adjusted concentrations for daily exposure:

The following dosimetric adjustments have been made for inhalation exposures. Dosimetric adjustment for the 1,508-ppm group is presented as an example below.

$(EXPOSURE_{HEC,\ EXRESP})$ = [PPM conversion]
× [average daily concentration conversion]
× [blood gas partition coefficients (BGPC)*]
= (PPM) × (MW ÷ 24.45) × (hours exposed ÷ 24)
× (days exposed ÷ total days) × (BGPC)
= 1,508 ppm × (60.09 ÷ 24.45) × (6 ÷ 24) × (65 ÷ 91) × 1
= 661.8 mg/m^3

*BGPC = $[(H_{B/G})_A] \div [(H_{B/G})_H]$
= $(1{,}290)_A \div (848)_H$ as determined by Kaneko et al. (1994)
= 1.5 (therefore, the default value of 1 is used for a BGPC ratio >1). Although there is a valid PBPK model for isopropanol (Clewell et al., 2001) for converting animal concentrations to human, the application of PBPK models is outside of the scope of a PPRTV assessment.

The subchronic p-RfC for isopropanol, based on the $NOAEL_{HEC}$ of 661.8 mg/m^3 is derived as follows:

Subchronic p-RfC = $NOAEL_{HEC} \div UF_C$
= 661.8 $mg/m^3 \div 100$
= **7×10^0 mg/m^3**

Tables 15 and 16 summarize the UFs and the confidence descriptors, respectively, for the subchronic p-RfC for isopropanol.

Table 15. Uncertainty Factors for Subchronic p-RfC for Isopropanol (CASRN 67-63-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following inhalation exposure to isopropanol. 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	3	A UF_D of 3 is applied because the database includes one acceptable developmental toxicity study in rats (Nelson et al., 1988) but no acceptable two-generation reproductive toxicity studies via the inhalation route.
UF_H	10	A UF_H of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of isopropanol in humans.
UF_L	1	A UF_L of 1 is 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	100	Composite Uncertainty Factor ($UF_A \times UF_D \times UF_H \times UF_L \times UF_S$)

Table 16. Confidence Descriptors for Subchronic p-RfC for Isopropanol (CASRN 67-63-0)		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	H	The principal study (Burleigh-Flayer et al., 1994) assessed an acceptable number of endpoints including body weight, motor activity, food consumption and water intake, blood chemistry, organ weights, and histopathology. The exposure duration of 13 weeks is sufficient to determine subchronic-duration toxicity.
Confidence in Database	M	The database includes two subchronic-duration studies in rats and one in mice. There was a single developmental toxicity study in rats. There were also one carcinogenic/chronic study in rats and one in mice. A two-generation reproductive toxicity study is not available.
Confidence in Subchronic p-RfC[b]	M	The overall confidence in the subchronic p-RfC is medium.

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

Derivation of Chronic Provisional RfC (Chronic p-RfC)

The chronic-duration inhalation study in mice by Burleigh-Flayer et al. (1997) is selected as the principal study for derivation of the chronic p-RfC. This study was presented in a peer-reviewed journal and was performed according to good laboratory practice (GLP) and otherwise meets the standards of study design and performance with regard to numbers of animals, examination of potential toxicity endpoints, and presentation of information. Details of the study are provided in the "Review of Potentially Relevant Data" section.

Justification

No published studies investigating the effects of chronic-duration inhalation exposure to isopropanol in humans were identified. A developmental toxicity study in rats (Nelson et al., 1988) and chronic-duration carcinogenicity studies (Burleigh-Flayer et al., 1997) in rats (104 weeks) and mice (78 weeks) utilized inhalation as the route of exposure. For changes in organ weight in rats and mice observed in the Burleigh-Flayer et al. (1997) studies, only those noted at the terminal euthanasia were considered for candidate PODs. For organ weight changes, the EPA Benchmark Dose Software (BMDS version 2.1.2) (U.S. EPA, 2010) continous models were fit to the data. The most sensitive potential POD from these studies is a LOAEL of 221 mg/m^3 for decreased absolute and relative testes weights in male mice following 78 weeks of exposure (Burleigh-Flayer et al., 1997); these data were not amenable to BMD modeling. Testicular effects due to isopropanol treatment were also observed in other studies as indicated in Table 3. Testicular seminiferous tubule atrophy was observed (unknown statistical significance) in F344 rats at 2,211 mg/m^3 at the interim sacrifice in the chronic-duration cancer inhalation study by Burleigh-Flayer et al. (1997). The incidence of seminal vesicle enlargement was also statistically significantly increased at 2,211 mg/m^3 in male mice from this study. Additionally, increased relative testes weight was observed following oral exposure in rats at 2,520 mg/kg-day in the subchronic-duration study by Pilegaard and Ladefoged (1993), and was also observed at 2,768 mg/kg-day in F1 male rats in the reproductive study by BIBRA (1988). In the other oral reproductive studies in rats by BIBRA (1986) and Bevan et al. (1995), testes weight was not measured so it is possible that effects on testes weight could have been observed in those studies.

There were also reproductive effects rats treated with isopropanol. In the oral reproductive study by Bevan et al. (1995), the male mating index was statistically decreased at 1,000 mg/kg-day in S-D rats, and these reproductive effects due to isopropanol exposure could possibly be related to testicular effects also caused by this chemical.

The next most sensitive effect is increased relative liver weight in male rats with a $BMCL_{10}$ of 262 mg/m^3 (Burleigh-Flayer et al., 1997). Absolute liver weight was also statistically significantly increased at the two highest concentrations but there were also concominant increases in body weight that could have contributed to this effect, thus this effect was not modeled.

An increase in the incidence and severity of renal lesions such as tubular proteinosis, glomerulosclerosis, interstitial nephritis, interstitial fibrosis, and transitional cell hyperplasia in mid- and high-concentration rats (both sexes) was also observed following inhalation of isopropanol, with incidence and severity greater in males compared to females (Burleigh-Flayer et al., 1997). However, a potential confounding factor in the biological relevance of some of these renal lesions in both male and female rats may be the high incidence rates (>50%) that occurred in the control animals. For interstitial fibrosis in male rats, the incidence rate in the controls was 64%. For interstitial nephritis in male and female rats, the controls displayed incidences of 76% and 58%, respectively. Due to the high incidence rates in the control groups, these specific lesions were not considered for selection of a POD to derive the chronic p-RfC. All other lesions occurring in male and female rats that were statistically significantly increased, were considered for selection of a POD. The EPA Benchmark Dose Software (BMDS version 2.1.2) (U.S. EPA, 2010) dichotomous models were fit to the data for incidences of these renal lesions in male and female rats. BMC input data for these incidences are presented in Tables B-19 (male rats) and B-20 (female rats). The most sensitive of these renal lesions is transitional cell hyperplasia in the male rat with a $BMCL_{10}$ of 291 mg/m^3.

There were also developmental effects (e.g., decreased fetal body weight, increased malformations, etc.) in rats due to inhalation exposure of isopropanol as reported by Nelson et al. (1988). The most sensitive of these developmental effects is decreased fetal body weight in male rats with a $BMDL_5$ of 1,907 mg/m^3.

Of the potential PODs for derivation of the chronic p-RfC, the most sensitive is a LOAEL of 221 mg/m^3 for decreased absolute and relative testes weights in male mice (Burleigh-Flayer et al., 1997). As described above, there is large support for the testes being a target organ of isopropanol-induced toxicity. Furthermore, the selection of the LOAEL of 221 mg/m^3 for decreased absolute and relative testes weights in male mice would be protective against other less sensitive chronic-duration and developmental effects due to isopropanol inhalation. **Thus, decreased absolute and relative testes weights in male mice is chosen as the critical effect with a LOAEL of 221 mg/m^3.**

Adjusted concentrations for daily exposure:

The following dosimetric adjustments have been made for inhalation exposures. Dosimetric adjustment for the 500-ppm group is presented as an example below.

$(EXPOSURE_{HEC,\ EXRESP})$ = [PPM conversion]
× [average daily concentration conversion]
× [blood gas partition coefficients (BGPC)*]
= (PPM) × (MW ÷ 24.45) × [(hours exposed ÷ 24)
× (days exposed ÷ total days)] × (BGPC)
= 504 ppm × (60.09 ÷ 24.45) × (6 ÷ 24) × (390 ÷ 546) × 1
= 221 mg/m^3

*BGPC = $[(H_{B/G})_A] \div [(H_{B/G})_H]$
= $(1{,}290)_A \div (848)_H$ as determined by Kaneko et al. (1994).
= 1.5 (therefore, the standard value of 1 is used for a BGPC ratio >1). Although there is a valid PBPK model for isopropanol (Clewell et al., 2001) for converting animal concentrations to human, the use of PBPK is outside of the scope of a PPRTV.

The chronic p-RfC for isopropanol, based on the $LOAEL_{HEC}$ of 221 mg/m^3 for decreased absolute and relative testes weights in male mice (Burleigh-Flayer et al., 1997), is derived as follows:

Chronic p-RfC = $LOAEL_{HEC} \div UF_C$
= 221 $mg/m^3 \div 1{,}000$
= **2×10^{-1} mg/m^3**

Tables 17 and 18 summarize the uncertainty factors and the confidence descriptors, respectively, for the chronic p-RfC for isopropanol.

Table 17. Uncertainty Factors for Chronic p-RfC for Isopropanol (CASRN 67-63-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following inhalation exposure to isopropanol. 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	3	A UF_D of 3 is applied because the database includes one acceptable developmental toxicity study in rats (Nelson et al., 1988) but no acceptable two-generation reproductive toxicity studies via the inhalation route.
UF_H	10	A UF_H of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of isopropanol in humans.
UF_L	10	A UF_L of 10 is applied for LOAEL-to-NOAEL extrapolation because the POD is a LOAEL.
UF_S	1	A UF_S of 1 is applied because a chronic-duration study was selected as the principal study.
UF_C	1,000	Composite Uncertainty Factor ($UF_A \times UF_D \times UF_H \times UF_L \times UF_S$)

Table 18. Confidence Descriptors for Chronic p-RfC for Isopropanol (CASRN 67-63-0)		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in Study	H	The principal study (Burleigh-Flayer et al., 1997) assessed an acceptable number of endpoints including survival, body weight, organ weight (kidneys, liver, testes, brain, and lungs), urinalysis and urine chemistry data, and histopathology of numerous tissues. The exposure durations of 104 and 78 wk in the rat and the mouse are considered sufficient to determine chronic toxicity.
Confidence in Database	M	The database includes two subchronic-duration studies in rats and one in mice. There was a single developmental toxicity study in rats. There were also one carcinogenic/chronic study in rats and one in mice. A two-generation reproductive toxicity study is not available.
Confidence in Chronic p-RfC[b]	M	The overall confidence in the chronic p-RfC is medium.

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

CANCER WOE DESCRIPTOR

Table 19 identifies the cancer WOE descriptors for isopropanol. No carcinogenicity studies in humans or animals by the oral route have been found. Human studies do not provide exposure-response data for assessing carcinogenicity of isopropanol following inhalation exposure. Inadequate epidemiology data are available to assess the potential for isopropanol to act as a carcinogen in exposed humans. An association between upper respiratory cancer and strong acid isopropanol processing jobs/factories was noted but was inadequate to assess for isopropanol alone. A peer-reviewed journal article by Burleigh-Flayer et al. (1997) reported a chronic-duration inhalation carcinogenicity study conducted with the F344 rat and the CD-1 mouse. No increases in the frequency of neoplastic lesions were observed in the mouse (both sexes) or the female rat. An increased incidence in testicular interstitial (Leydig) cell adenomas was noted in the male rat, but the finding was discounted as an artifact due to a low incidence in the control group relative to historical incidence for male F344 control animals in the study authors' laboratory and in NTP two-year carcinogenicity studies conducted with this rat strain. The study authors stated that "…interstitial cell adenomas of the testes probably represent foci of marked hyperplasia rather than autonomous growth, because these adenomas originate as multiple foci of hyperplasia, and the transformation from hyperplasia to adenoma represents a continuous spectrum of morphologic change occurring within the testes of aged F344 male rats." Interstitial cell tumors of the testes were also noted as the most frequently observed spontaneous tumor in aged male F344 rats. Taken together, and in the absence of information to indicate otherwise, there is *inadequate information to assess carcinogenic potential* for isopropanol following oral exposure. For inhalation exposure, isopropanol is considered *not likely to be carcinogenic to humans*.

Table 19. Cancer WOE Descriptor for Isopropanol (CASRN 67-63-0)			
Possible WOE Descriptor	**Designation**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	There are no human data to support this.
"Likely to be Carcinogenic to Humans"	NS	NA	There are insufficient data in animals and no data in humans to support this.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There are insufficient animal data to support this.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Oral**	**There is adequate information available to assess the carcinogenic potential of isopropanol in animals following inhalation exposure but no information is available for the oral route.**
"Not Likely to be Carcinogenic to Humans"	**Selected**	**Inhalation**	**Based on two studies (Burleigh-Flayer et al., 1997) which observed no positive association between relevant tumors and isopropanol inhalation exposure in both sexes of rats and mice and an unrelated increase in testes tumors in male rats, isopropanol is considered *not likely to be carcinogenic to humans* for the inhalation route.**

NA = not applicable, NS = not selected.

MODE-OF-ACTION DISCUSSION

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) define mode of action "…as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation." Examples of possible modes of carcinogenic action for any given chemical include "…mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression" (p. 1–10).

Isopropanol tested negative for mutagenicity in Ames assays (IARC, 1999; Zeiger et al., 1992), a meiotic nondisjunction and aneuploidy assay, gene mutation tests in CHO cells, a mouse micronucleus assay, and a sister chromatid exchange assay in Chinese hamster V79 cells (IARC, 1999). In the absence of positive results, isopropanol is not considered to be mutagenic.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

Lack of human and animal data preclude derivation of a p-OSF.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

Because there is no evidence of carcinogenic potential for isopropanol following exposure via the inhalation route and it is considered *not likely to be carcinogenic to humans*, derivation of a p-IUR is precluded.

APPENDIX A. PROVISIONAL SCREENING VALUES

No provisional screening values were derived.

APPENDIX B. DATA TABLES

Table B-1. Relative Organ Weights and Absorbance in the Dorsal Hippocampus in Male Rats Exposed to Isopropanol in Drinking Water for 12 Weeks[a]

Parameter	Isopropanol (mean intake mg/kg-d)				
	0	**870**	**1,280**	**1,680**	**2,520**
Relative Organ Weight g/100 g (± SD)					
Organ					
Liver (% increase)	2.90 ± 0.24	3.02 ± 0.12	3.15 ± 0.24* (↑9)[b]	3.22 ± 0.20** (↑11)	3.26 ± 0.25*** (↑12)
Kidneys (% increase)	0.483 ± 0.033	0.515 ± 0.036	0.582 ± 0.052*** (↑20)	0.601 ± 0.038*** (↑24)	0.654 ± 0.061*** (↑35)
Adrenals (% increase)	10.9 ± 1.5	11.5 ± 1.0	12.5 ± 1.3	13.8 ± 1.9*** (↑27)	14.6 ± 1.7*** (↑34)
Testes (% increase)	0.785 ± 0.086	0.741 ± 0.072	0.736 ± 0.065	0.788 ± 0.091	0.888 ± 0.084** (↑13)
Heart	0.251 ± 0.020	0.251 ± 0.016	0.246 ± 0.013	0.257 ± 0.018	0.259 ± 0.022
Spleen	0.157 ± 0.020	0.163 ± 0.030	0.160 ± 0.015	0.169 ± 0.023	0.153 ± 0.022
Absorbance (Mean ± SD)					
CA1	0.139 ± 0.014	ND	ND	ND	0.127 ± 0.011
CA3	0.149 ± 0.008	ND	ND	ND	0.139 ± 0.014
Hilus	0.186 ± 0.024**[c]	ND	ND	ND	0.163 ± 0.021**[c]

[a]Data were obtained from Tables 1 and 2 on page 329 in Pilegaard and Ladefoged (1993).
[b]Direction of percentage difference from control is included in parentheses.
[c]Difference between the hilar and CA1 regions.

n = 12/group, except for the high-dose group (n = 11).

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

Table B-2. Effects of Daily Gestational Oral Exposures in the Cesarean Section Data from Rats Administered Isopropanol by Gavage on GDs 6−16[a]

Parameter	Exposure Group (mg/kg-d)			
	0	**596**	**1,242**	**1,605**
All litters (*n*)[b]	17	18	18	19
Corpora lutea per dam[c]	13 ± 2.54	14.2 ± 2.23	12.7 ± 1.41	12.2 ± 2.93
Implantation sites per litter[c]	11.9 ± 1.50	11.3 ± 2.19	11.7 ± 1.88	11.1 ± 3.15
Preimplantation losses[c]	1.4 ± 2.83	2.9 ± 4.32	1.0 ± 1.61	1.11 ± 1.52
Live fetuses[c]	11.1 ± 2.34	10.2 ± 3.19	11.0 ± 2.11	10.6 ± 3.31
Early resorptions[c]	0.8 ± 1.20	1.1 ± 1.37	0.6 ± 0.85	0.4 ± 0.6
Late resorptions[c]	0.1 ± 0.24	0.1 ± 0.24	0.1 ± 0.24	0.1 ± 0.32
Postimplantation losses[c]	0.8 ± 1.38	1.2 ± 1.58	0.7 ± 0.84	0.5 ± 0.77
Mean % implantations	92.9	85	93.9	90.8
No. of females with postimplantation losses	7	13	9	6
Litter weight (g)[c]	40.1 ± 8.99	38.7 ± 7.87	37.6 ± 6.77	37.0 ± 6.49
Fetal sex ratio (M:F)	1.05	1.26	1.23	1.35
Mean fetal body weight per litter (g)[c]				
All fetuses	3.59 ± 0.202	3.58 ± 0.252	3.43 ± 0.221* (↓5)	3.35 ± 0.282** (↓7)
Male fetuses	3.71 ± 0.205	3.69 ± 0.180	3.54 ± 0.233	3.44 ± 0.254
Female fetuses	3.47 ± 0.214	3.48 ± 0.260	3.32 ± 0.228	3.24 ± 0.319

[a]Data were obtained from Table 2 on page 464 in Faber et al. (2008).
[b]Includes all dams with litters on GD 20.
[c]Reported as mean ± SD.

*$p < 0.01$.
**$p < 0.001$.

Table B-3. Effects of Daily Gestational Oral Exposures in the Cesarean Section Data from Rats Administered Isopropanol by Gavage on GDs 6−15[a]

Parameter	Exposure Group (mg/kg-d)			
	0	400	800	1,200
All litters (*n*)[b]	(23)	(25)	(23)	(22)
Corpora lutea per dam[c]	14.9 ± 0.4	15.4 ± 0.4	14.6 ± 0.4	14.4 ± 0.4
Implantation sites per litter[c]	14.4 ± 0.4	14.9 ± 0.4	14.2 ± 0.3	14.1 ± 0.4
Percentage preimplantation loss[c]	4.0 ± 1.2	4.2 ± 1.0	4.0 ± 1.0	2.9 ± 0.9
Percentage resorptions per litter[c]	1.5 ± 0.6	1.4 ± 0.6	1.8 ± 1.0	4.1 ± 1.3
No. (%) litters with resorptions	5 (21.7)	5 (20.0)	3 (13.0)	9 (40.9)
Percentage late fetal deaths per litter[c]	0.0	0.0	0.0	0.0
No. litters with late fetal deaths	0	0	0	0
Percentage adversely affected implants per litter[c,d],‡	1.8 ± 0.6	3.8 ± 1.1	2.8 ± 1.1	5.7 ± 1.4
No. (%) litters with adversely affected implants	6 (26.1)	9 (36.0)	6 (26.1)	13 (59.1)
Live litters (*n*)[e]	(23)	(25)	(23)	(22)
Live fetuses per litter[c]	14.0 ± 0.4	14.7 ± 0.4	13.9 ± 0.3	13.5 ± 0.4
Percentage male fetuses per litter[c],†	44.4 ± 2.9	50.2 ± 2.8	56.0 ± 2.2**	46.9 ± 2.4
Average fetal body weight per litter[c]				
All fetuses††, ‡‡‡	3.866 ± 0.051	3.794 ± 0.058	3.682 ± 0.050	3.559 ± 0.075**
Male fetuses††, ‡‡‡	3.972 ± 0.055	3.875 ± 0.052	3.762 ± 0.052*	3.649 ± 0.076**
Female fetuses††, ‡‡‡	3.791 ± 0.050	3.717 ± 0.065	3.574 ± 0.053*	3.487 ± 0.074**

[a]Data were obtained from Table 1 on page 143 in Tyl et al. (1994).
[b]Includes all dams pregnant at sacrifice; litter size = no. implantation sites per dam.
[c]Reported as mean ± standard error of the mean.
[d]Adversely affected = nonlive (late fetal deaths plus resorptions) plus malformed.
[e]Includes only dams with live fetuses; litter size = no. live fetuses per dam.

*$p < 0.05$; Dunnett's test.
**$p < 0.01$; Dunnett's test.
†$p < 0.05$; ANOVA.
††$p < 0.01$; ANOVA.
‡ $p < 0.05$; test for linear trend.
‡‡‡$p < 0.001$; test for linear trend.

Table B-4. Average Fetal Body Weight Per Litter of Rabbits from Dams treated on GDs 6–18[a]

Parameter	Exposure Group (mg/kg-d)			
	0	**120**	**240**	**480**
All litters (*n*)[b]	15	11	15	11
Live litters (*n*)[c]	15	11	15	11
Average fetal body weight per litter[d]				
All fetuses	49.71 ± 1.80	49.71 ± 0.82	47.92 ± 1.56	46.48 ± 3.31
Male fetuses	49.68 ± 2.23	50.42 ± 0.99	48.99 ± 1.6	46.04 ± 2.94
Female fetuses‡	49.75 ± 1.88	48.68 ± 1.06	46.65 ± 1.69	42.79 ± 3.05

[a]Data were obtained from Tyl et al. (1994).
[b]Includes all dams pregnant at sacrifice; litter size = no. implantation sites per dam.
[c]Includes only dams with live fetuses; litter size = no. live fetuses per dam.
[d]Reported as mean ± standard error of the mean.

‡ $p < 0.05$; test for linear trend.

Table B-5. Mean Body Weight (g) and Food (g/rat-day) Consumption and Water (mL/rat-day) Intake in Postpartum Parental (F0) Female Rats Exposed to Isopropanol in Drinking Water[a]

Postpartum Day	Isopropanol (mean intake mg/kg-d[b])				
	0	1,167	2,645	2,825	2,724
Weight (g) in the Female Rat (± SD)					
1 (% change)	242.7 ± 15.26	248.9 ± 24.79	236.3 ± 19.69	236.8 ± 16.18	223.8 ± 21.53
4 (% change)	259.2 ± 14.21	263.4 ± 12.57	259.4 ± 18.65	245.1 ± 15.82* (↓5)[c]	226.0 ± 12.14*** (↓13)
7 (% change)	270.3 ± 15.87	279.1 ± 11.44	269.1 ± 20.81	249.1 ± 12.29** (↓8)	230.1 ± 10.25*** (↓15)
14 (% change)	289.1 ± 20.25	299.4 ± 7.17	287.5 ± 20.00	255.4 ± 13.34*** (↓12)	230.2 ± 20.02*** (↓20)
21 (% change)	282.8 ± 23.00	289.4 ± 12.76	289.9 ± 20.26	244.9 ± 17.93*** (↓13)	226.4 ± 33.93*** (↓20)
Food consumption (g/rat-day) in the Female Rat (± SD)					
Premating	16.2 ± 2.11	15.4 ± 1.65	14.7 ± 1.85	14.0 ± 1.97*	12.7 ± 2.36**
1−4	26.9 ± 7.29	30.6 ± 4.67	30.1 ± 3.73	25.1 ± 6.01	16.5 ± 4.35***
4−7	45.5 ± 12.95	43.5 ± 6.19[d]	39.6 ± 5.31	30.0 ± 6.78***	21.0 ± 7.60***
7−11	47.2 ± 8.38	52.0 ± 9.02	45.8 ± 8.86	34.7 ± 8.85**	24.7 ± 7.85***
11−14	55.5 ± 13.26	57.9 ± 10.38	54.7 ± 7.56	38.7 ± 9.96**	24.7 ± 9.66***
14−18	63.0 ± 12.50	63.1 ± 7.97	58.4 ± 6.13	43.3 ± 12.84***	23.9 ± 6.46***
18−21	75.6 ± 19.00	78.1 ± 10.48	66.1 ± 11.00	43.7 ± 12.28***	25.8 ± 8.65***
Water Intake (mL/rat-day) in the Female Rat (± SD)					
Premating	28.3 ± 2.21	27.7 ± 0.92	24.2 ± 1.87***	17.1 ± 2.24***	14.3 ± 1.61***
1−4	51.6 ± 11.3	52.3 ± 7.33	49.2 ± 6.13	35.2 ± 5.13***	28.5 ± 3.07***
4−7	65.6 ± 16.55	75.0 ± 11.22*	61.0 ± 8.29	40.6 ± 6.12***	30.5 ± 4.59***
7−11	83.6 ± 18.00	90.2 ± 8.84	79.7 ± 15.29	44.5 ± 14.46***	36.1 ± 14.01***
11−14	98.1 ± 26.06	98.0 ± 10.18	87.8 ± 10.49	49.4 ± 12.00***	32.1 ± 6.60***
14−18	96.5 ± 20.33	102.0 ± 12.59	88.5 ± 16.77	54.9 ± 15.47***	32.0 ± 7.44***
18−21	122.9 ± 29.88	122.9 ± 15.66	112.1 ± 15.85	56.4 ± 16.76***	34.7 ± 10.12***

[a]Data were obtained from Tables 8, 9, and 10 on pages 47−49 in BIBRA (1986).
[b]Mean intake conversion data were obtained from Table 12 on page 51 in BIBRA (1986).
[c]Direction of percentage difference from control is included in parentheses.
[d]This number was illegible in the available copy of the document and may have been 43.5 ± 8.19.

n = 9−10/group.
Figures marked with asterisk(s) differ significantly from control by ANOVA and the procedure of Least Significant Difference, and Student's t-test for the mean premating value.

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

Table B-6. Litter Size, Pup Survival, and Pup Weight of F1 Animals Produced by Paired Rats Exposed to Isopropanol in Drinking Water During the Postpartum Period[a]

Parameters	Isopropanol Exposure Group (mean intake mg/kg-d[b])				
	0	**1,167**	**2,645**	**2,825**	**2,724**
No. of litters	9	10	10	10	9
No. pups at Day 1	84	106	92	68	37
Mean no. pups/litter at Day 1	9.3	10.6	9.2	6.8	4.1
No. of pups at Day 21	82	105	90	62	31
Mean no. pups/litter at Day 21	9.1	10.5	9.0	6.2	3.4
Mean pup survival/litter (%)[+]	98.1	98.9	97.8	85.9	63.5
Total pup survival[#]	97.6	99.0	97.8	91.2	83.8
No. litters with 100% survival[##]	3	2	2	5	6
Mean pup weight/litter[c]	48.6 ± 5.42	45.3 ± 2.62	43.4 ± 4.54*	38.4 ± 5.04***	29.8 ± 4.63***

[a]Data were obtained from BIBRA (1986).
[b]Mean intake conversion data were obtained from Table 12 on page 51 in BIBRA (1986).
[c]Mean ± SD.

[+]Calculated from individual data as Mean no. pups Day 21 ÷ Mean no. pups Day 1 × 100.
[#]Calculated as: Total pups Day 21 ÷ Total pups Day 1 × 100.
[##]Including animals with dead pups on Day 1.
*$p < 0.05$.
***$p < 0.001$.

Table B-7. Mean Absolute and Relative Organ Weights in Parental (F0) Rats Exposed to Isopropanol in Drinking Water for a Pilot One-Generation Reproductive Study[a]

Parameter	Isopropanol (mean intake mg/kg-d[b])				
	0	**317**	**711**	**1,001**	**1,176**
Male					
Absolute Weight (g)					
Liver	10.64 ± 0.631	10.74 ± 1.203	10.96 ± 0.912	11.49 ± 1.181	12.00 ± 1.358**
Kidney	2.56 ± 0.119	2.54 ± 0.227	2.59 ± 0.204	2.78 ± 0.213*	2.89 ± 0.234***
Terminal Body Weight (g)	416.8 ± 18.16	427.1 ± 39.02	419.3 ± 22.14	402.5 ± 37.93	412.1 ± 37.11
Relative Weight (g/100 g bw)					
Liver (% change)	2.56 ± 0.158	2.51 ± 0.121	2.62 ± 0.166	2.86 ± 0.142*** (↑12)[b]	2.91 ± 0.185*** (↑14)
Kidney (% change)	0.61 ± 0.031	0.60 ± 0.034	0.62 ± 0.035	0.69 ± 0.055*** (↑13)	0.70 ± 0.039*** (↑15)
Parameter	**Isopropanol (mean intake mg/kg-d[b])**				
	0	**1,167**	**2,645**	**2,825**	**2,724**
Female					
Absolute Weight (g)					
Liver	6.90 ± 0.928	6.96 ± 0.320	7.61 ± 0.657*	8.23 ± 1.072***	7.89 ± 0.645**
Kidney	1.58 ± 0.121	1.63 ± 0.090	1.73 ±0.137	1.92 ± 0.242***	1.83 ± 0.327**
Terminal Body Weight (g)	232.4 ± 17.01	236.3 ± 8.18	241.4 ± 20.19	226.0 ± 13.73	225.0 ± 18.06
Relative Weight (g/100 g bw)					
Liver (% change)	2.93 ± 0.403	2.95 ± 0.135	3.17 ± 0.320	3.66 ± 0.590*** (↑25)	3.54 ± 0.494** (↑21)
Kidney (% change)	0.68 ± 0.061	0.69 ± 0.039	0.72 ± 0.069	0.85 ± 0.136*** (↑25)	0.82 ± 0.169** (↑21)

[a]Data were obtained from Table 16 on page 55 in BIBRA (1986).
[b]Direction of percentage difference from control is included in parentheses.

Figures marked with asterisk(s) differ significantly from control by ANOVA and the procedure of Least Significant Difference.

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

Table B-8. Effects of Daily Oral Exposures to Isopropanol in Rats on Litter Parameters in the Gestational and Postpartum Components of a One-Generation Reproductive Study[a]

Parameter	Exposure Group (mg/kg-d)			
	0	**668/1,053**	**1,330/1,948**	**1,902/2,768**
No. of infertile males	0	0	0	0
Length of gestation (days)[b]	22.1 ± 0.36	22.2 ± 0.49	22.1 ± 0.24	22.3 ± 0.45
No. of females with litters on PND 1	15	20	17	16
No. of pups/litter on PND 1	7.9	9.5	8.3	6.1
Total no. pup survival (%)	84	89.4	89.4	71.4
Pup survival/litter (%)	87.5	85.3	86	58.6
Pup BW on PND 1 (g)[b]	5.9 ± 1.54	5.6 ± 1.09	5.3 ± 1.10	5.7 ± 0.81
Pup BW on PND 4 (g)[b]	8.9 ± 2.07	8.6 ± 1.90	8.3 ± 1.50	8.1 ± 0.92
Pup BW on PND 7 (g)[b]	13.0 ± 2.86	12.4 ± 2.35	12.2 ± 2.04	10.5 ± 1.23** (↓12%)
Pup BW on PND 14 (g)[b]	27.6 ± 5.71	25.7 ± 5.04	26.3 ± 3.74	23.7 ± 2.71
Pup BW on PND 21 (g)[b]	47.4 ± 7.22	44.2 ± 8.08	44.0 ± 5.38	38.3 ± 5.06** (↓19%)
Pup BWG on PND 1−21 (g)[b]	42.3 ± 6.35	38.5 ± 7.14	38.6 ± 4.68	32.7 ± 5.14*** (↓23%)

[a]Data were obtained from Table 5 on page 471 in Faber et al. (2008).
[b]Reported as mean ± SD.

**$p < 0.01$; ANOVA.
***$p < 0.001$; ANOVA.

Table B-9. Effects of Daily Oral Exposures to Isopropanol in Rats in the Gestational and Postpartum Components of a One-Generation Reproductive Study[a]

Parameter	Exposure Group (mg/kg-d)			
	0	**668**	**1,330**	**1,902**
All litters (*n*)[b]	9	9	7	8
Corpora lutea per dam[c]	13.2 ± 1.09	13.8 ± 2.05	12.7 ± 0.76	13.3 ± 1.04
Implantation sites per litter[c]	13.1 ± 0.78	13.3 ± 2.29	13.0 ± 0.82	12.4 ± 1.19
Preimplantation losses[c]	0.1 ± 0.33	0.7 ± 0.73	0.1 ± 0.38	1.0 ± 1.31*
Live fetuses[c]	12.1 ± 1.62	12.4 ± 1.88	12.0 ± 0.82	12.1 ± 1.55
Early resorptions[c]	0.9 ± 1.27	0.8 ± 1.39	1.0 ± 0.82	0.4 ± 0.52
Late resorptions[c]	0.1 ± 0.33	0.1 ± 0.33	0	0
Postimplantation losses[c]	1.0 ± 1.22	0.9 ± 1.36	1.0 ± 0.82	0.4 ± 0.52
Mean % implantations	92.2	94.1	92.4	96.8
Litter weight (g)[c]	25.3 ± 3.34	26.7 ± 3.78	26.5 ± 7.13	22.9 ± 2.04
Fetal body weight (g)[c]	2.09 ± 0.135	2.15 ± 0.095	2.19 ± 0.461	1.90 ± 0.133

[a]Data were obtained from Table 6 on page 471 in Faber et al. (2008).
[b]Number of females with litters on GD 20.
[c]Reported as mean ± SD.

*$p < 0.05$; ANOVA.

Table B-10. Organ Weights in Rats After Continuous Exposure to Isopropanol in Drinking Water for Two-Generations[a,b]

	Exposure Group (mg/kg-d)			
	0	**347**	**625**	**1,030**
F0 Males				
No. in Group	10	10	10	10
Terminal BW (g)	454.5 ± 45.80	459.9 ± 34.35	458.5 ± 52.58	426.4 ± 28.51
Liver (g)	11.64 ± 1.317	11.49 ± 1.137	11.90 ± 1.774	12.20 ± 1.046
(g/100 g BW)	2.57 ± 0.276	2.50 ± 0.137	2.59 ± 0.143	2.86 ± 0.171** (↑11)
Spleen (g)	0.84 ± 0.148	0.87 ± 0.119	0.82 ± 0.124	0.91 ± 0.103
(g/100 g BW)	0.19 ± 0.031	0.19 ± 0.032	0.18 ± 0.013	0.21 ± 0.019* (↑11)
Kidney (g)	2.79 ± 0.279	2.71 ± 0.180	2.85 ± 0.418	3.07 ± 0.187* (↑10)
(g/100 g BW)	0.62 ± 0.059	0.59 ± 0.045	0.62 ± 0.060	0.72 ± 0.030*** (↑16)
	Exposure Group (mg/kg-d)			
	0	**668/1,053[c]**	**1,330/1,948[c]**	**1,902/2,768[c]**
F0 Females				
No. in Group	15	20	17	16
Terminal BW (g)	234.1 ± 11.73	239.8 ± 10.70	237.6 ± 14.50	234.4 ± 20.90
Liver (g)	6.74 ± 0.712	6.77 ± 0.521	7.35 ± 0.928	8.00 ± 1.327*** (↑19%)
(g/100 g BW)	2.88 ± 0.273	2.83 ± 0.249	3.10 ± 0.345	3.29 ± 0.543** (↑14%)
Spleen (g)	0.53 ± 0.071	0.55 ± 0.056	0.58 ± 0.096	0.52 ± 0.078
(g/100 g BW)	0.23 ± 0.027	0.23 ± 0.024	0.24 ± 0.035	0.21 ± 0.023
Kidney (g)	1.54 ± 0.085	1.53 ± 0.092	1.59 ± 0.161	1.66 ± 0.153* (↑8)
(g/100 g BW)	0.66 ± 0.031	0.64 ± 0.035	0.67 ± 0.062	0.68 ± 0.055
F1 Males				
No. in Group	12	17	13	9
Terminal BW (g)	173.3 ± 34.91	179.8 ± 24.46	178.5 ± 31.44	167.0 ± 22.74
Liver (g)	6.68 ± 1.255	7.31 ± 1.022	7.38 ± 1.446	7.28 ± 0.872
(g/100 g BW)	3.87 ± 0.260	4.07 ± 0.182* (↑5)	4.13 ± 0.332** (↑7)	4.37 ± 0.116*** (↑13)
Spleen (g)	0.62 ± 0.131	0.60 ± 0.067	0.63 ± 0.118	0.57 ± 0.107
(g/100 g BW)	0.36 ± 0.041	0.34 ± 0.052	0.36 ± 0.068	0.34 ± 0.039
Kidney (g)	1.51 ± 0.251	1.55 ± 0.186	1.50 ± 0.214	1.54 ± 0.223
(g/100 g BW)	0.88 ± 0.066	0.86 ± 0.067	0.85 ± 0.065	0.92 ± 0.059 (↑5)
F1 Females				
No. in Group	12	18	14	9
Terminal BW (g)	128.4 ± 16.50	128.3 ± 14.45	132.1 ± 17.57	124.4 ± 15.91
Liver (g)	4.84 ± 0.716	5.15 ± 0.621	5.23 ± 0.667	5.40 ± 0.707
(g/100 g BW)	3.73 ± 0.243	4.02 ± 0.252** (↑8)	4.00 ± 0.325* (↑7)	4.48 ± 0.200*** (↑20)

Table B-10. Organ Weights in Rats After Continuous Exposure to Isopropanol in Drinking Water for Two-Generations[a,b]

	Exposure Group (mg/kg-d)			
	0	**347**	**625**	**1,030**
Spleen (g)	0.47 ± 0.071	0.47 ± 0.061	0.46 ± 0.073	0.45 ± 0.094
(g/100 g BW)	0.37 ± 0.039	0.37 ± 0.041	0.35 ± 0.041	0.36 ± 0.050
Kidney (g)	1.15 ± 0.130	1.16 ± 0.170	1.17 ± 0.117	1.14 ± 0.124
(g/100 g BW)	0.90 ± 0.045	0.90 ± 0.060	0.90 ± 0.074	0.92 ± 0.050

[a]Data were obtained from Table 7 on page 472 in Faber et al. (2008).
[b]Direction of percentage difference from control is included in parentheses.
[c]Gestation/lactation doses.

Values are means ± SD.

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

Table B-11. Mean Absolute Organ Weights in Rats Exposed Daily to Isopropanol by Gavage Prior to and During Mating, and During Gestation and Lactation[a]

	Exposure Group (mg/kg-d)			
	0	**100**	**500**	**1,000**
F0 Males				
Body weight (g)	603.8 ± 45.9	583.5 ± 51.9	618.6 ± 42.1	612 ± 59.1
Organ weight (g)				
Liver	23.0 ± 3.1	21.9 ± 3.0	24.0 ± 2.8	25.6 ± 2.8** (↑11)[b]
Kidney	4.7 ± 0.6	4.5 ± 0.4	4.8 ± 0.5	5.0 ± 0.5
Organ weight/Body-weight ratio (%)				
Liver (% increase)	3.8 ± 0.4	3.7 ± 0.3	3.9 ± 0.3	4.2 ± 0.3** (↑10)
Kidney	0.79 ± 0.11	0.76 ± 0.05	0.78 ± 0.06	0.83 ± 0.07
F1 Males				
Body weight (g)	661.2 ± 63.7	678.2 ± 62.7	683.1 ± 66.2	630.2 ± 60.8
Organ weight (g)				
Liver	24.1 ± 3.2	25.2 ± 3.5	27.2 ± 3.8*	25.9 ± 3.9
Kidney	4.6 ± 0.5	4.5 ± 0.4	4.8 ± 0.5	4.7 ± 0.6
Organ weight/Body-weight ratio (%)				
Liver (% increase)	3.6 ± 0.3	3.7 ± 0.3	4.0 ± 0.3** (↑11)	4.1 ± 0.4** (↑14)
Kidney (% increase)	0.7 ± 0.07	0.66 ± 0.06	0.70 ± 0.06	0.75 ± 0.08** (↑7)
F0 Females				
Body weight (g)	331.6 ± 38.4	330.2 ± 30.2	335.2 ± 31.9	328.3 ± 29.4
Organ weight (g)				
Liver	13.2 ± 2.0	13.3 ± 1.7	14.2 ± 2.0	14.4 ± 1.7
Kidney	2.6 ± 0.3	2.6 ± 0.3	2.7 ± 0.2	2.7 ± 0.3
Organ weight/Body-weight ratio (%)				
Liver (% increase)	4.0 ± 0.4	4.0 ± 0.3	4.2 ± 0.4* (↑5)	4.4 ± 0.4** (↑10)
Kidney (% increase)	0.77 ± 0.07	0.79 ± 0.06	0.80 ± 0.06	0.82 ± 0.06* (↑6)
F1 Females				
Body weight (g)	366.8 ± 34.8	369.8 ± 36.9	355.1 ± 46.2	353.5 ± 31.9
Organ weight (g)				
Liver	14.0 ± 1.7	14.3 ± 1.6	14.5 ± 2.6	16.0 ± 1.9** (↑14)
Kidney	2.7 ± 0.3	2.7 ± 0.3	2.7 ± 0.4	2.8 ± 0.2
Organ weight/Body-weight ratio (%)				
Liver (% increase)	3.8 ± 0.3	3.9 ± 0.3	4.1 ± 0.4* (↑8)	4.5 ± 0.6** (↑18)
Kidney (% increase)	0.74 ± 0.06	0.74 ± 0.07	0.77 ± 0.09	0.8 ± 0.08* (↑8)

[a]Data were obtained from Tables 1 and 2 on page 120 in Bevan et al. (1995).
[b]Direction of percentage difference from control is included in parentheses.

Values are means ± SD.
*$p < 0.05$ and **$p < 0.01$.

Table B-12. Summary of Reproductive Data from Parental Rats Exposed Daily to Isopropanol by Gavage[a]

	Exposure group (mg/kg-d)			
	0	**100**	**500**	**1,000**
F0				
Male mating index (%)[b]	86.7	90.0	93.1	96.7
Male fertility index (%)[c]	80.0	83.3	82.8	70.0
Female fertility index (%)[d]	89.7	90.0	93.3	96.7
Female fecundity index (%)[e]	88.5	88.9	85.7	72.4
Gestational index (%)[f]	100	100	100	100
Mean gestational length (days)	22.5	22.5	22.4	22.6
Mean litter size	12.4	13.3	14.2	14.4
Mean live/litter	12.2	13.2	13.7	13.8
Mean dead/litter	0.2	0.1	0.5	0.6
F1				
Male mating index (%)[b]	93.3	96.4	93.1	73.1*
Male fertility index (%)[c]	80.0	82.1	72.4	61.5
Female fertility index (%)[d]	93.3	96.7	93.1	82.6
Female fecundity index (%)[e]	82.1	79.3	77.8	78.9
Gestational index (%)[f]	100	95.8	100	100
Mean gestational length (days)	22.7	22.6	22.7	22.6
Mean litter size	13.2	14.0	14.1	14.4
Mean live/litter	13.0	13.7	13.7	14.0
Mean dead/litter	0.2	0.4	0.4	0.4

[a]Data were obtained from Table 3 on page 121 in Bevan et al. (1995).
[b](No. of confirmed mated males ÷ no. of males used for mating) × 100.
[c](No. of males impregnating females ÷ no. of males used for mating) × 100.
[d](No. of confirmed mated females ÷ no. of females used in mating) × 100.
[e](No. of females pregnant, excluding nonconfirmed mated females ÷ no. of females confirmed mated) × 100.
[f](No. of females with live litters ÷ no. of females pregnant) × 100.

*$p < 0.05$.

Table B-13. Summary of Offspring Survival Data from Parental Rats Exposed Daily to Isopropanol by Gavage[a]

	Exposure Group (mg/kg-d)			
	0	**100**	**500**	**1,000**
F1				
Live birth index (%)[b]	98.3	99.4	96.3	95.7*
Day 1 survival index (%)[c]	98.6	97.6	98.0	84.5**
Day 4 survival index (%)[d]	99.7	98.4	96.7**	91.0**
Day 7 survival index (%)[e]	100	100	99.5	99.2
Day 14 survival index (%)[f]	100	100	99.5	100
Day 21 survival index (%)[g]	100	99.5	100	99.2
Lactation index[h]	99.4	99.5	99.0	92.2
F2				
Live birth index (%)[b]	98.4	97.9	97.0	97.0
Day 1 survival index (%)[c]	99.4	98.8	94.8**	94.2**
Day 4 survival index (%)[d]	99.0	99.1	97.1	96.2*
Day 7 survival index (%)[e]	100	99.4	96.3*	91.0**
Day 14 survival index (%)[f]	100	98.9	98.1	100
Day 21 survival index (%)[g]	100	99.4	100	100
Lactation index[h]	100	97.8	94.4**	91.0**

[a]Data were obtained from Table 4 on page 121 in Bevan et al. (1995).
[b](No. of live pups at birth ÷ no. of pups born) × 100.
[c](No. of live pups at Day 1 ÷ no. of live pups at birth) × 100.
[d][No. of live pups at Day 4(precull) ÷ no. of live pups at Day 1] × 100.
[e][No. of live pups at Day 7 ÷ no. of live pups at Day 4(postcull)] × 100.
[f](No. of live pups at Day 14 ÷ no. of live pups at Day 7) × 100.
[g](No. of live pups at Day 21 ÷ no. of live pups at Day 14) × 100.
[h][No. of live pups at Day 21 ÷ no. of live pups at Day 4(postcull)] × 100.

*$p < 0.05$.
**$p < 0.01$.

Table B-14. Summary of F1 and F2 Offspring Body Weights from Parental Rats Exposed Daily to Isopropanol by Gavage[a]

Postnatal Day	Exposure Group (mg/kg-d)			
	0	100	500	1,000
F1 Males				
0	6.61 ± 0.79	6.68 ± 0.75	6.46 ± 0.70	6.27 ± 0.77* (↓5)[b]
1	7.00 ± 0.79	7.19 ± 0.87	6.77 ± 0.91	6.51 ± 0.86* (↓7)
4	9.47 ± 1.56	9.94 ± 1.54	9.30 ± 1.62	8.94 ± 1.56
7	15.09 ± 2.67	15.96 ± 2.30	14.21 ± 2.74	14.31 ± 2.59
14	30.71 ± 4.18	32.65 ± 3.69	30.46 ± 5.22	30.21 ± 4.71
21	48.01 ± 7.63	52.94 ± 6.59*	48.24 ± 7.83	49.19 ± 6.54
F1 Females				
0	6.22 ± 0.64	6.37 ± 0.72	6.25 ± 0.70	5.98 ± 0.71
1	6.57 ± 0.69	6.84 ± 0.80	6.59 ± 0.93	6.25 ± 0.90
4	9.05 ± 1.41	9.54 ± 1.44	9.09 ± 1.64	8.35 ± 1.79
7	14.21 ± 2.30	15.34 ± 2.33	13.62 ± 2.75	12.97 ± 2.66
14	29.32 ± 3.89	31.89 ± 4.07*	29.77 ± 4.79	28.35 ± 4.78
21	45.56 ± 6.59	50.79 ± 6.06**	46.94 ± 7.03	45.85 ± 6.93
F2 Males				
0	6.66 ± 0.66	6.75 ± 0.71	6.58 ± 0.76	6.33 ± 0.77* (↓5)
1	7.20 ± 0.81	7.21 ± 0.81	7.03 ± 0.94	6.45 ± 0.97** (↓10)
4	10.21 ± 1.68	10.24 ± 1.49	9.72 ± 1.65	9.34 ± 1.94* (↓9)
7	16.34 ± 2.75	16.14 ± 2.96	15.72 ± 2.69	15.39 ± 2.97
14	32.74 ± 3.62	32.66 ± 4.48	32.54 ± 3.80	31.11 ± 4.97
21	50.25 ± 6.74	50.40 ± 7.41	50.74 ± 6.51	47.71 ± 6.15
F2 Females				
0	6.31 ± 0.69	6.35 ± 0.66	6.31 ± 0.62	5.79 ± 0.64** (↓8)
1	6.87 ± 0.89	6.84 ± 0.81	6.67 ± 0.83	6.07 ± 0.79** (↓12)
4	9.70 ± 1.67	9.73 ± 1.43	9.27 ± 1.75	8.50 ± 1.63** (↓12)
7	15.16 ± 3.19	15.56 ± 2.87	14.96 ± 3.13	14.07 ± 2.79
14	30.45 ± 5.30	31.59 ± 4.49	31.14 ± 4.13	28.97 ± 4.81
21	47.17 ± 6.92	48.94 ± 7.06	48.59 ± 6.82	45.15 ± 7.21

[a]Data were obtained from Tables 5 and 6 on page 122 in Bevan et al. (1995).
[b]Direction of percentage difference from control is included in parentheses.
Values are means ± SD.

*$p < 0.05$ and **$p < 0.01$.

Table B-15. Summary of Motor Activity Data (Mean Cumulative Test Session Counts ± SD) in Rats Exposed to Isopropanol by Vapor Inhalation[a]

Time	Group 1 (13-Week Exposure)		Group 2 (9-Week Exposure)	
	Human Equivalent Concentration (HEC, mg/m^3)			
	0	2,199	0	2,199
Pre-exposure	933.4 ± 480.6	965.0 ± 364.57	679.0 ± 175.0	758.3 ± 201.12
Week 4–1 Day Postexposure	956.1 ± 229.21	1,294.5 ± 420.25*	1,034.5 ± 354.32	1,461.5 ± 589.3*
Week 7–1 Day Postexposure	1,121.0 ± 445.09	1,710.7 ± 733.58*	1,028.2 ± 237.0	1,838.9 ± 805.45*
Week 9–1 Day Postexposure	783.3 ± 221.72	1,913.6 ± 693.46**	1,049.6 ± 281.44	1,852.7 ± 613.0**
Week 9–2 Day Postexposure	ND[b]	ND	968.4 ± 342.72	1,180.6 ± 661.17
Week 10–4 Day Postexposure	ND	ND	733.8 ± 261.3	903.5 ± 533.4
Week 10–7 Day Postexposure	ND	ND	678.4 ± 264.04	734.5 ± 309
Week 11–1 Day Postexposure	809.5 ± 371.43	1,646.2 ± 1,024.69**	ND	ND
Week 13–1 Day Postexposure	934.9 ± 328.52	2,020.8 ± 830.73**	ND	ND
Week 13–2 Day Postexposure	685.9 ± 261.93	1,226.7 ± 514.79**	ND	ND
Week 14–4 Day Postexposure	826.9 ± 267.34	1,401.5 ± 451.69**	ND	ND
Week 14–7 Day Postexposure	818.5 ± 215.52	1,128.9 ± 478.5*	ND	ND
Week 15–14 Day Postexposure	1,320.9 ± 558.63	1,393.6 ± 442.13	ND	ND
Week 16–21 Day Postexposure	758.1 ± 425.82	963.3 ± 380.47	ND	ND
Week 17–28 Day Postexposure	955.2 ± 355.22	1,431.3 ± 718.77*	ND	ND
Week 18–35 Day Postexposure	1,266.9 ± 455.41	1,496.6 ± 635.5	ND	ND
Week 19–42 Day Postexposure	1,438.8 ± 626.03	1,510.9 ± 648.44	ND	ND

[a]Data were obtained from Table 1 on pages 98−99 in Burleigh-Flayer et al. (1998).
[b]ND—no value determined; no animals tested from this block at this time.

n = 15/concentration group.
Values are mean ± SD.

*$p < 0.05$.
**$p < 0.01$.

Table B-16. Cesarean Section Observations on GD 20 in Rats Exposed to Isopropanol by Vapor Inhalation from GDs 1−19[a]

Parameter	Human Equivalent Concentration (HEC, mg/m^3)			
	0	2,516	5,048	7,185
No. pregnant per no. bred	15/15	14/15	13/13	9/15
Mean no. of corpora lutea per dam	15.9	15.6	15.6	14.9
Mean no. of implants per dam	14.9	15.5	14.8	13.1* (↓12)
Implants resorbed per litter (%)	6	4	7	59* (↑883)
Implants alive per litter (%)	94	96	93	41* (↓56)
Mean fetal weights ± SD (g)				
Female	3.12 ± 0.29	3.00 ± 0.38* (↓4)[b]	2.63 ± 0.25* (↓16)	1.88 ± 0.45* (↓40)
Male	3.27 ± 0.27	3.13 ± 0.36* (↓4)	2.82 ± 0.30* (↓14)	1.89 ± 0.49* (↓42)

[a]Data were obtained from Table 3 on page 251 in Nelson et al. (1988).
[b]Direction of percentage difference from control is included in parentheses.

*$p < 0.05$; Kruskal-Wallis test for corpora lutea comparisons and ANOVA for fetal data.

Table B-17. Mean (SD) Results of Urinalysis and Urine Chemistry Evaluations in Rats Exposed to Isopropanol by Vapor Inhalation for up to 24 Months[a]

	Human Equivalent Concentration (HEC, mg/m^3)			
	0	**221**	**1,101**	**2,211**
13 Months				
Osmolality (mOsm/kg)				
Male	2,332 ± 217.5	2,113 ± 318.2	2,157 ± 300.7	1,574 ± 182.8**
Female	2,808 ± 280.5	3,036 ± 436.7	2,739 ± 397.1	2,512 ± 258.5
Total Protein (g/L)				
Male	11.426 ± 3.6650	11.534 ± 4.0704	12.768 ± 3.5047	15.926 ± 4.0636*
Female	8.526 ± 4.6510	7.438 ± 3.8735	10.548 ± 5.6097	6.424 ± 1.3920
Total Volume (mL)				
Male	8.3 ± 2.53	7.3 ± 2.59	8.0 ± 2.05	9.9 ± 2.07
Female	4.9 ± 1.54	5.7 ± 2.08	6.4 ± 1.98	7.3 ± 1.77**
Glucose (g/L)				
Male	1.00 ± 0.254	1.09 ± 0.338	0.93 ± 0.392	0.82 ± 0.183
Female	0.71 ± 0.145	0.70 ± 0.136	0.64 ± 0.126	0.54 ± 0.088**
17 Months				
Osmolality (mOsm/kg)				
Male	1,225 ± 401.7	1,491 ± 355.7	942 ± 346.0	605 ± 154.4**
Female	1,973 ± 322.8	1,954 ± 367.8	1,841 ± 413.8	1,254 ± 440.6**
Total Protein (g/L)				
Male	11.821 ± 4.7889	13.243 ± 4.0401	17.306 ± 8.1660	19.382 ± 3.8714**
Female	8.333 ± 3.0904	6.795 ± 2.2485	12.652 ± 7.5233	16.561 ± 7.1626**
Total Volume (mL)				
Male	8.7 ± 2.87	5.9 ± 1.96	11.9 ± 5.68	16.5 ± 4.47**
Female	6.3 ± 1.78	5.0 ± 1.00	7.3 ± 3.32	11.6 ± 6.11*
Glucose (g/L)				
Male	0.43 ± 0.240	0.47 ± 0.227	0.29 ± 0.087	0.21 ± 0.054*
Female	0.54 ± 0.084	0.54 ± 0.127	0.52 ± 0.145	0.41 ± 0.139
24 Months				
Osmolality (mOsm/kg)				
Male	842 ± 405.1	801 ± 314.9	572 ± 128.3	—[b]
Female	1,108 ± 590.1	1,054 ± 328.4	934 ± 347.0	537 ± 256.3*
Total Protein (g/L)				
Male	21.201 ± 6.4667	19.344 ± 3.3613	25.088 ± 6.1684	—[b]
Female	17.020 ± 7.9967	19.931 ± 5.6631	20.213 ± 6.9797	19.507 ± 7.1804

Table B-17. Mean (SD) Results of Urinalysis and Urine Chemistry Evaluations in Rats Exposed to Isopropanol by Vapor Inhalation for up to 24 Months[a]

	Human Equivalent Concentration (HEC, mg/m^3)			
	0	**221**	**1,101**	**2,211**
Total Volume (mL)				
Male	11.7 ± 4.79	13.8 ± 6.16	16.3 ± 7.74	—[b]
Female	11.0 ± 5.66	12.1 ± 4.05	14.8 ± 5.14	23.3 ± 6.92**
Glucose (g/L)				
Male	0.39 ± 0.194	0.36 ± 0.122	0.28 ± 0.087	—[b]
Female	0.51 ± 0.256	0.52 ± 0.095	0.47 ± 0.116	0.33 ± 0.146*

[a]Data were obtained from Table 1 on page 101 in Burleigh-Flayer et al. (1997).
[b]There were no surviving animals at this time point.

Significantly different from control.

*$p < 0.05$.
**$p < 0.01$.

Table B-18. Mean (±SD) Results of Selected Organ Weights as a Percentage of Final Body Weight in Rats Exposed to Isopropanol by Vapor Inhalation for up to 104 Weeks[a]

	Human Equivalent Concentration (HEC, mg/m^3)			
	0	**221**	**1,101**	**2,211**
Interim Euthanasia (Week 73)				
Kidney				
Male	0.742 ± 0.1202	0.706 ± 0.0449	0.722 ± 0.0473	0.821 ± 0.0430
Female	0.779 ± 0.0540	0.767 ± 0.0676	0.757 ± 0.0544	0.800 ± 0.0871
Liver				
Male	3.455 ± 0.6166	3.279 ± 0.1550	3.693 ± 0.5405	4.283 ± 0.6276** (↑24)
Female	3.419 ± 0.3480	3.275 ± 0.2292	3.311 ± 0.2653	3.447 ± 0.3295
Testes				
Male	0.646 ± 0.1394	0.702 ± 0.0773	0.817 ± 0.1719*	0.993 ± 0.1693**(↑53)
Brain				
Male	0.460 ± 0.0549	0.443 ± 0.0273	0.442 ± 0.0287	0.427 ± 0.0151
Female	0.645 ± 0.0368	0.662 ± 0.0584	0.630 ± 0.0307	0.650 ± 0.0594
Lung				
Male	0.442 ± 0.2906	0.374 ± 0.0578	0.404 ± 0.1261	0.384 ± 0.0589
Female	0.389 ± 0.0296	0.409 ± 0.0246	0.397 ± 0.0326	0.426 ± 0.0539
Terminal Euthanasia (Week 104)				
Kidney				
Male	1.017 ± 0.3057	0.914 ± 0.2244	1.140 ± 0.2953	—[b]
Female	1.056 ± 0.3424	0.886 ± 0.1812*	0.875 ± 0.1923*	1.214 ± 0.3391
Liver				
Male	4.693 ± 0.9872	4.603 ± 0.7731	5.855 ± 1.0923*	—[b]
Female	4.363 ± 0.8208	4.202 ± 0.8523	4.342 ± 0.7325	5.394 ± 0.5415** (↑24)
Testes				
Male	1.174 ± 0.5502	1.457 ± 0.6831	1.407 ± 0.5896	—[b]
Brain				
Male	0.560 ± 0.1023	0.525 ± 0.0498	0.554 ± 0.0984	—[b]
Female	0.701 ± 0.1072	0.638 ± 0.0942**	0.604 ± 0.0742**	0.647 ± 0.0942*
Lung				
Male	0.669 ± 0.2875	0.625 ± 0.3170	0.865 ± 0.4844	—[b]
Female	0.536 ± 0.2070	0.458 ± 0.0938	0.492 ± 0.2471	0.573 ± 0.2416

[a]Data were obtained from Table 3 on page 103 in Burleigh-Flayer et al. (1997).
[b]There were no surviving animals at this time point.

Significantly different from control.

*$p < 0.05$.
**$p < 0.01$.

Table B-19. Microscopic Findings in Kidneys of Male Rats Exposed to Isopropanol by Vapor Inhalation[a]

	Human Equivalent Concentration (HEC, mg/m^3)			
	0	**221**	**1,101**	**2,211**
Number of Animals	75	75	75	75
Mineralization	13	11	24	46
Minimal	4	1	2	2
Mild	1	2	3	5
Moderate	4	5	8	21
Marked	4	3	11	18
Glomeruloscerosis	70	68	73	73
Minimal	1	8	6	0
Mild	38	30	22	17
Moderate	18	18	19	10
Marked	12	12	26	43
Severe	1	0	0	3
Interstitial nephritis	57	66	60	70
Minimal	4	9	5	0
Mild	44	41	22	36
Moderate	9	16	33	33
Marked	0	0	0	1
Interstitial fibrosis	48	60	65	67
Minimal	2	10	3	2
Mild	31	33	30	21
Moderate	15	17	27	42
Marked	0	0	5	2
Hydronephrosis	22	23	28	50
Minimal	0	0	1	0
Mild	22	23	27	46
Moderate	0	0	0	4
Transitional cell hyperplasia	12	14	30	39
Minimal	4	4	6	6
Mild	7	9	21	31
Moderate	1	1	2	2
Marked	0	0	1	0

Table B-19. Microscopic Findings in Kidneys of Male Rats Exposed to Isopropanol by Vapor Inhalation[a]

	Human Equivalent Concentration (HEC, mg/m^3)			
	0	**221**	**1,101**	**2,211**
Tubular proteinosis	75	73	75	74
Minimal	1	0	1	0
Mild	24	25	18	10
Moderate	28	25	20	13
Marked	16	16	19	16
Severe	6	7	17	35
Tubular dilation	14	5	27	31
Mild	13	3	13	20
Moderate	0	2	14	11
Marked	1	0	0	0

[a]Data were obtained from Table 5 on page 107 in Burleigh-Flayer et al. (1997).

Table B-20. Microscopic Findings in Kidneys of Female Rats Exposed to Isopropanol by Vapor Inhalation[a]

	Human Equivalent Concentration (HEC, mg/m^3)			
	0	**221**	**1,101**	**2,211**
Number of Animals	75	75	75	75
Mineralization	14	12	21	20
Minimal	7	8	9	1
Mild	2	0	1	2
Moderate	1	2	4	10
Marked	4	2	7	7
Glomeruloscerosis	65	66	64	70
Minimal	8	14	8	3
Mild	34	36	28	21
Moderate	13	12	17	22
Marked	10	4	11	24
Interstitial nephritis	44	50	59	58
Minimal	11	8	15	2
Mild	28	35	40	54
Moderate	5	7	4	2
Interstitial fibrosis	42	40	51	53
Minimal	8	11	10	3
Mild	22	19	26	20
Moderate	12	10	15	30
Hydronephrosis	10	11	14	21
Mild	9	11	13	19
Moderate	1	0	1	2
Transitional cell hyperplasia	4	2	2	8
Minimal	0	1	0	6
Mild	4	1	2	2
Tubular proteinosis	73	73	74	75
Minimal	8	2	6	4
Mild	26	31	18	14
Moderate	25	28	27	23
Marked	12	9	15	23
Severe	2	3	8	11
Tubular dilation	5	7	6	24
Mild	2	5	5	16
Moderate	3	2	1	8

[a]Data were obtained from Table 6 on page 108 in Burleigh-Flayer et al. (1997).

Table B-21. Mean (±SD) Results of Selected Organ Weights as a Percentage of Final Body Weight in Mice Exposed to Isopropanol by Vapor Inhalation for up to 78 Weeks[a]

	Human Equivalent Concentration (HEC, mg/m^3)			
	0	**221**	**1,101**	**2,211**
Interim Euthanasia (Week 54)				
Kidney				
Male	2.306 ± 0.3670	2.192 ± 0.2249	2.307 ± 0.3662	2.304 ± 0.3178
Female	1.464 ± 0.00882	1.582 ± 0.2263	1.622 ± 0.2165	1.444 ± 0.1497
Liver				
Male	5.732 ± 0.5354	5.708 ± 0.4639	5.788 ± 0.6522	6.547 ± 0.8840** (↑14)
Female	5.472 ± 0.2849	5.643 ± 0.4365	5.811 ± 0.4400	5.859 ± 0.9078
Testes				
Male	0.620 ± 0.1319	0.559 ± 0.1489	0.557 ± 0.0704	0.484 ± 0.0843
Brain				
Male	1.380 ± 0.1488	1.333 ± 0.1474	1.268 ± 0.0973	1.267 ± 0.1357
Female	1.491 ± 0.1011	1.591 ± 0.1230	1.490 ± 0.1450	1.360 ± 0.1350*
Lung				
Male	0.788 ± 0.3499	0.671 ± 0.0545	0.643 ± 0.0817	0.640 ± 0.0770
Female	0.686 ± 0.0526	0.695 ± 0.0351	0.713 ± 0.0714	0.667 ± 0.0558
Terminal Euthanasia (Week 78)				
Kidney				
Male	2.150 ± 0.4560	2.243 ± 0.4188	2.149 ± 0.3060	2.057 ± 0.2183
Female	1.577 ± 0.2191	1.548 ± 0.1804	1.558 ± 0.2147	1.573 ± 0.1945
Liver				
Male	5.823 ± 1.2043	5.726 ± 0.9857	6.203 ± 1.4794	6.173 ± 1.6437
Female	5.822 ± 0.7635	5.903 ± 0.7201	6.139 ± 0.8526	6.642 ± 0.6800** (↑14)
Testes				
Male	0.566 ± 0.0896	0.479 ± 0.1335**	0.495 ± 0.0956*	0.496 ± 0.1050**
Brain				
Male	1.387 ± 0.1256	1.366 ± 0.2047	1.323 ± 0.1695	1.240 ± 0.1071**
Female	1.575 ± 0.1724	1.540 ± 0.1392	1.518 ± 0.1400	1.438 ± 0.1348**
Lung				
Male	0.782 ± 0.2325	0.749 ± 0.2014	0.758 ± 0.2289	0.760 ± 0.1672
Female	0.809 ± 0.1548	0.781 ± 0.1165	0.785 ± 0.1447	0.828 ± 0.1427
Recovery Euthanasia (Week 78—only exposed through Week 54)				
Kidney				
Male	2.062 ± 0.2014	1.923 ± 0.1822	2.067 ± 0.3037	2.030 ± 0.3060
Female	1.428 ± 0.2014	1.636 ± 0.2477	1.644 ± 0.2786	1.498 ± 0.2286

Table B-21. Mean (±SD) Results of Selected Organ Weights as a Percentage of Final Body Weight in Mice Exposed to Isopropanol by Vapor Inhalation for up to 78 Weeks[a]

	Human Equivalent Concentration (HEC, mg/m^3)			
	0	**221**	**1,101**	**2,211**
Liver				
Male	4.828 ± 0.3637	5.333 ± 0.4389* (↑10)	5.611 ± 0.8950* (↑16)	6.319 ± 1.2627* (↑30)
Female	5.999 ± 0.5685	6.454 ± 0.4329	8.735 ± 5.2223	6.418 ± 1.7143
Testes				
Male	0.490 ± 0.0854	0.410 ± 0.1531	0.408 ± 0.1069	0.459 ± 0.0416
Brain				
Male	1.240 ± 0.1308	1.213 ± 0.0993	1.195 ± 0.1106	1.152 ± 0.0660
Female	1.390 ± 0.1362	1.432 ± 0.0751	1.414 ± 0.1921	1.316 ± 0.1375
Lung				
Male	0.662 ± 0.0667	0.679 ± 0.0791	0.750 ± 0.1732	0.683 ± 0.0915
Female	0.762 ± 0.0802	0.933 ± 0.2263	0.764 ± 0.0686	0.891 ± 0.2105

[a]Data were obtained from Table 2 on page 102 in Burleigh-Flayer et al. (1997).

Significantly different from control.

*$p < 0.05$.
**$p < 0.01$.

Table B-22. Mean (±SD) Results of Selected Absolute Organ Weights in Mice Exposed to Isopropanol by Vapor Inhalation for up to 78 Weeks[a]

	Human Equivalent Concentration (HEC, mg/m^3)			
	0	**221**	**1,101**	**2,211**
Interim Euthanasia (Week 54)				
Body				
Male	36.8 ± 4.98	38.0 ± 2.78	40.7 ± 4.47 (↑11%)	41.3 ± 5.18 (↑12%)
Female	35.0 ± 2.09	33.9 ± 2.27	35.8 ± 3.13	38.1 ± 3.19*
Kidney				
Male	0.843 ± 0.1395	0.832 ± 0.0841	0.939 ± 0.1784 (↑11%)	0.948 ± 0.1625 (↑12%)
Female	0.513 ± 0.0473	0.535 ± 0.0784	0.579 ± 0.0842 (↑13%)	0.550 ± 0.0674
Liver				
Male	2.098 ± 0.2517	2.166 ± 0.1785	2.361 ± 0.4068 (↑13%)	2.691 ± 0.4456** (↑28%)
Female	1.916 ± 0.1401	1.912 ± 0.1742	2.082 ± 0.2622	2.234 ± 0.4123* (↑17%)
Testes				
Male	0.225 ± 0.0404	0.214 ± 0.0621	0.226 ± 0.0309	0.198 ± 0.0322
Brain				
Male	0.502 ± 0.0254	0.505 ± 0.0467	0.513 ± 0.0268	0.517 ± 0.0131
Female	0.521 ± 0.0310	0.538 ± 0.0346	0.530 ± 0.0277	0.516 ± 0.0471
Lung				
Male	0.282 ± 0.0971	0.255 ± 0.0217	0.261 ± 0.0394	0.262 ± 0.0246
Female	0.240 ± 0.0130	0.236 ± 0.0220	0.254 ± 0.0233	0.254 ± 0.022
Terminal Euthanasia (Week 78)				
Body				
Male	37.2 ± 3.72	38.6 ± 4.03	40.1 ± 3.73**	41.0 ± 3.53** (↑10%)
Female	34.3 ± 3.46	35.2 ± 2.66	34.6 ± 3.50	35.4 ± 3.45
Kidney				
Male	0.797 ± 0.1631	0.868 ± 0.2045	0.858 ± 0.1139	0.844 ± 0.1166
Female	0.540 ± 0.0931	0.544 ± 0.0693	0.538 ± 0.0740	0.557 ± 0.0896
Liver				
Male	2.158 ± 0.4356	2.215 ± 0.4815	2.497 ± 0.6615* (↑14%)	2.540 ± 0.7349** (↑18%)
Female	1.997 ± 0.3508	2.080 ± 0.3335	2.136 ± 0.4264	2.359 ± 0.3776** (↑18%)
Testes				
Male	0.209 ± 0.0317	0.182 ± 0.0460**	0.198 ± 0.0403	0.202 ± 0.0388
Brain				
Male	0.512 ± 0.0284	0.521 ± 0.0458	0.527 ± 0.0445	0.506 ± 0.0283
Female	0.535 ± 0.0308	0.539 ± 0.0287	0.522 ± 0.0311	0.506 ± 0.0272**

Table B-22. Mean (±SD) Results of Selected Absolute Organ Weights in Mice Exposed to Isopropanol by Vapor Inhalation for up to 78 Weeks[a]

	Human Equivalent Concentration (HEC, mg/m^3)			
	0	**221**	**1,101**	**2,211**
Lung				
Male	0.289 ± 0.0816	0.285 ± 0.0601	0.301 ± 0.0783	0.311 ± 0.0709
Female	0.276 ± 0.0572	0.275 ± 0.0490	0.272 ± 0.0580	0.292 ± 0.0461
Recovery Euthanasia (Week 78—only exposed through Week 54)				
Body				
Male	41.9 ± 3.18	43.2 ± 3.52	43.3 ± 2.63	44.8 ± 1.61
Female	39.6 ± 3.67	37.0 ± 2.30	36.7 ± 5.09	40.1 ± 3.56
Kidney				
Male	0.865 ± 0.1282	0.829 ± 0.0851	0.892 ± 0.1317	0.908 ± 0.1317
Female	0.562 ± 0.0679	0.603 ± 0.025	0.596 ± 0.0828	0.599 ± 0.0965
Liver				
Male	2.028 ± 0.2806	2.305 ± 0.2732 (↑14%)	2.414 ± 0.3143* (↑19%)	2.822 ± 0.5201** (↑39%)
Female	2.367 ± 0.2323	2.388 ± 0.2338	3.201 ± 1.8984 (↑35%)	2.588 ± 0.8062
Testes				
Male	0.203 ± 0.0273	0.174 ± 0.0584	0.176 ± 0.0448	0.205 ± 0.0166
Brain				
Male	0.516 ± 0.0202	0.523 ± 0.0383	0.516 ± 0.0398	0.516 ± 0.0314
Female	0.546 ± 0.0257	0.529 ± 0.0375	0.512 ± 0.0147	0.524 ± 0.3487
Lung				
Male	0.277 ± 0.0321	0.292 ± 0.0253	0.323 ± 0.0722	0.306 ± 0.0415
Female	0.302 ± 0.0435	0.342 ± 0.0713	0.280 ± 0.0406	0.359 ± 0.0965

[a]Data were obtained from a technical report by the BushyRun (1994).

Significantly different from control.

*$p < 0.05$.
**$p < 0.01$.

Table B-23. Microscopic Findings in Selected Organs of Mice Exposed to Isopropanol by Vapor Inhalation[a]

		Number of Animals With Finding (%)							
		Animals Euthanized				Animals Found Dead/Euthanized Moribund			
Male									
Human Equivalent Concentration (HEC, mg/m^3)		**0**	**221**	**1,101**	**2,211**	**0**	**221**	**1,101**	**2,211**
Number of animals:		35	32	29	31	20	23	26	24
Seminal Vesicle	Ectasia	8 (23)	6 (19)	7 (24)	20 (65)**	7 (35)	5 (22)	11 (42)	15 (63)
Kidney	Tubular proteinosis	8 (23)	16 (50)*	14 (48)*	14 (45)	7 (35)	4 (17)	7 (27)	9 (38)
	Tubular dilation	0 (0)	5 (16)*	0 (0)	1 (3)	2 (10)	2 (9)	3 (12)	0 (0)
Female									
Human Equivalent Concentration (HEC, mg/m^3)		**0**	**221**	**1,101**	**2,211**	**0**	**221**	**1,101**	**2,211**
Number of animals:		42	35	43	37	13	20	12	18
Kidney	Tubular proteinosis	7 (17)	16 (46)**	15 (35)	16 (43)*	3 (23)	4 (20)	5 (42)	7 (39)
	Tubular dilation	1 (2)	0 (0)	3 (7)	6 (16)*	3 (23)	2 (10)	2 (17)	0 (0)
Adrenal Gland	Congestion	1 (2)	0 (0)	0 (0)	8 (22)*	1 (8)	0 (0)	0 (0)	4 (22)
Stomach	Mucosal cell hyperplasia	1 (2)	0 (0)	0 (0)	9 (24)**	0 (0)	1 (5)	0 (0)	0 (0)
Spleen	Extramedullary hematopoiesis	13 (31)	0 (0)	2 (5)	23 (62)**	7 (54)	8 (40)	3 (25)	9 (50)
	Hemosiderosis	7 (17)	0 (0)	1 (2)	14 (38)*	0 (0)	3 (15)	0 (0)	3 (17)

[a]Data were obtained from Table 4 on page 104 in Burleigh-Flayer et al. (1997).

Significantly different from control.

*$p < 0.05$.
**$p < 0.01$.

APPENDIX C. BMD OUTPUTS

MODELING PROCEDURE FOR CONTINUOUS DATA

The benchmark dose (BMD) modeling of continuous data was conducted with EPA's Benchmark Dose Software (BMDS version 2.1.2) (U.S. EPA, 2010). For these data, all continuous models available within the software were fit using a default BMR of 1 SD relative risk. For changes in liver, body, and kidney weights, a BMR of 10% change relative to the control mean was also used. For fetal and F1 pup effects, a BMR of 5% change relative to the control mean was used. An adequate fit was judged based on the goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was constant. If a constant variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model did not adequately fit the data (i.e., Test 3; *p*-value < 0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest benchmark dose lower confidence limit (BMDL) was selected if the BMDLs estimated from different models varied greater than 3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criteria (AIC) was selected as a potential POD from which to derive a p-RfD.

MODELING PROCEDURE FOR DICHOTOMOUS DATA

The BMD modeling of dichotomous data was conducted with EPA's BMDS (version 2.1.2). For these data, all of the dichotomous models (i.e., Gamma, Multistage, Logistic, Log-logistic, Probit, Log-Probit, and Weibull models) available within the software were fit using a default BMR of 10% extra risk based on the U.S. EPA's *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2012b). Adequacy of model fit was judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different models varied greater than 3-fold; otherwise, the BMDL from the model with the lowest AIC was selected as a potential POD from which to derive a p-RfD.

DECREASED FETAL BODY WEIGHT OF FEMALE RABBITS TREATED WITH ISOPROPANOL FROM GESTATION DAY 6 to 18 (Tyl et al., 1994)

All available continuous models in BMDS (version 2.1.2) (U.S. EPA, 2010) were fit to the decreased fetal body weight data from female rabbits treated with isopropanol from GD 6 to 18 (Tyl et al., 1994) (see Table B-4). For decreased fetal body weight, a BMR of a 5% change relative to the control mean was used. The homogeneity variance (Test 2) *p*-value of less than 0.1 indicates that nonconstant variance is the appropriate variance model. As assessed by the goodness-of-fit test and visual inspection, the Polynomial model provided the best fit model (see Table C-1 and Figure C-1). Estimated doses associated with 5% relative risk and the 95% lower confidence limit on these doses (BMD_{05} values and $BMDL_{05}$ values, respectively) were 284 and 120 mg/kg-day.

Table C-1. Model Predictions for Fetal Body Weight[a]							
Model	**BMD**	**BMDL**	***p*-value Test 2[b]**	***p*-value Test 3[b]**	***p*-value Test 4[b]**	**AIC**	**Conclusion**
Exponential (M2)	168	99.0	0.015	0.127	0.162	267	
Exponential (M3)	279	116	0.015	0.127	0.146	268	
Exponential (M4)	168	82.8	0.015	0.127	0.162	267	
Exponential (M5)	242	124	0.015	0.127	NDr	269	
Hill	242	124	0.015	0.172	0.135	267	
Power	281	120	0.015	0.127	0.144	268	
Polynomial	**284**	**120**	**0.015**	**0.172**	**0.255**	**266**	**Lowest AIC**
Linear	172	106	0.015	0.172	0.130	268	

[a]Tyl et al. (1994).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NDr = not determined.

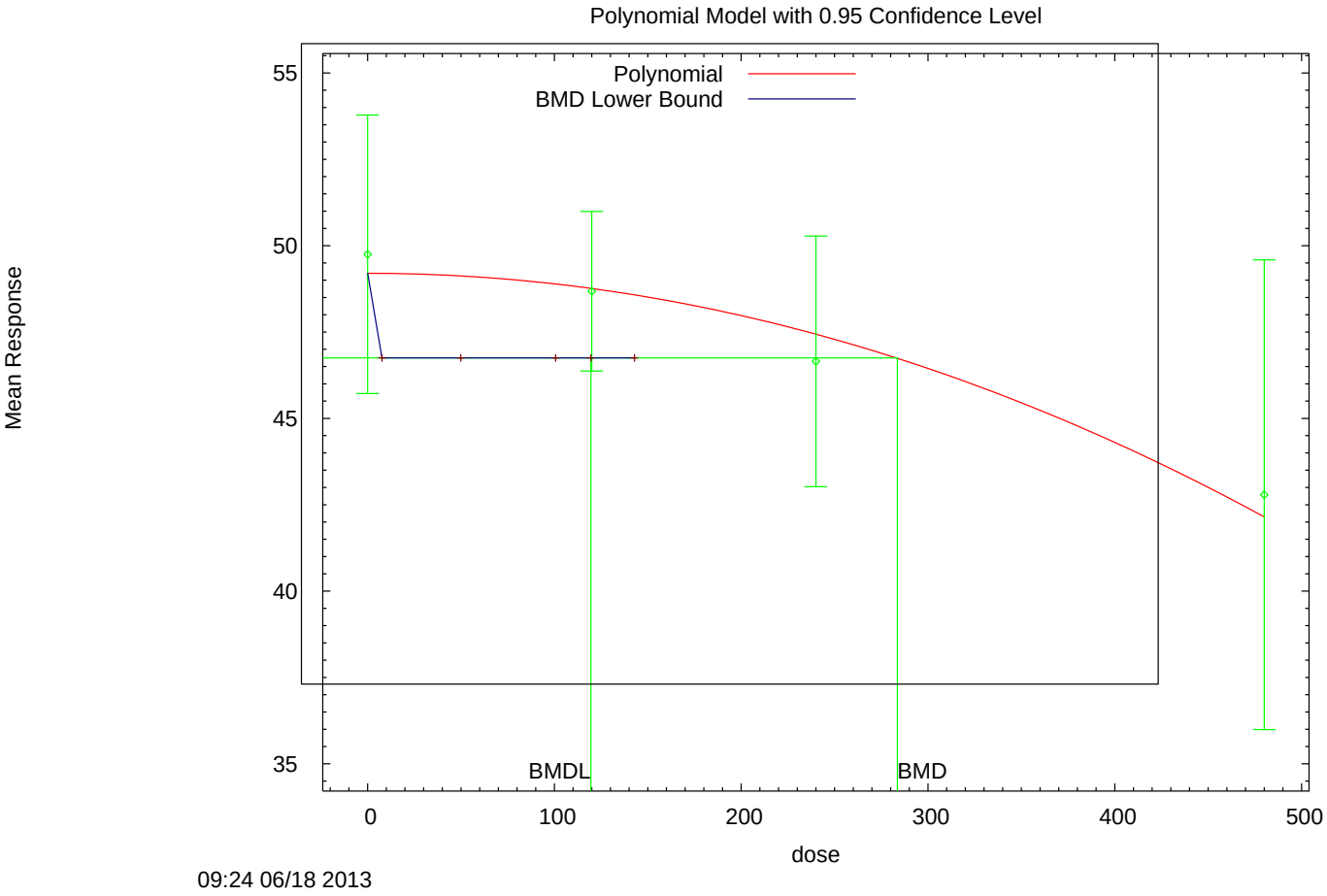

Figure C-1. Selected BMD Model (Polynomial) Output for Decreased Fetal Body Weight in Female Rabbits (Tyl et al., 1994)

Text Output for Polynomial BMD Model for Decreased Fetal Body Weight in Female Rabbits (Tyl et al., 1994)

```
================================================================================
        Polynomial Model. (Version: 2.16;  Date: 05/26/2010)
        Input Data File: C:\Documents and Settings\JKaiser\Desktop\modeling
results\ply_fetwet_isop_frabs_tyl_Ply-ModelVariance-BMR05-RestrictDown.(d)
        Gnuplot Plotting File: C:\Documents and Settings\JKaiser\Desktop\modeling
results\ply_fetwet_isop_frabs_tyl_Ply-ModelVariance-BMR05-RestrictDown.plt
                                        Thu Jul 25 09:27:59 2013
 ================================================================================

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

   The form of the response function is:

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


   Dependent variable = mean
   Independent variable = dose
```

```
   The polynomial coefficients are restricted to be negative
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                         lalpha =      3.92863
                            rho =            0
                         beta_0 =       49.834
                         beta_1 =      -0.0104
                         beta_2 = -9.02778e-006


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -beta_1
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                 lalpha          rho       beta_0       beta_2

    lalpha            1           -1        0.081        -0.15

       rho           -1            1       -0.081         0.15

    beta_0        0.081       -0.081            1        -0.55

    beta_2        -0.15         0.15        -0.55            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
         lalpha          28.6794           12.585             4.01327
53.3455
            rho         -6.46495          3.26642             -12.867          -
0.0628836
         beta_0          49.2116          1.04584             47.1618
51.2614
         beta_1                0               NA
         beta_2     -3.0586e-005     1.40009e-005       -5.80273e-005       -3.14463e-
006

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


     Table of Data and Estimated Values of Interest

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

0	15	49.8	49.2	7.28	5.73	0.364
120	13	48.7	48.8	3.82	5.9	-0.0557
240	15	46.6	47.4	6.55	6.45	-0.481
480	11	42.8	42.2	10.1	9.44	0.22

Model Descriptions for likelihoods calculated

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

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

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

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

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-130.995075	5	271.990150
A2	-125.772468	8	267.544936
A3	-127.533879	6	267.067758
fitted	-128.900848	4	265.801696
R	-134.426485	2	272.852970

Explanation of Tests

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

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	17.308	6	0.008215
Test 2	10.4452	3	0.01514
Test 3	3.52282	2	0.1718
Test 4	2.73394	2	0.2549

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

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

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

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


             Benchmark Dose Computation

Specified effect =          0.05

Risk Type        =     Relative risk

Confidence level =          0.95

             BMD =        283.633


            BMDL =         119.54
```

APPENDIX D. REFERENCES

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