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Provisional Peer-Reviewed Toxicity Values for

2-Ethylhexanol
(CASRN 104-76-7)

U.S. EPA Office of Research and Development
National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (Cincinnati, OH)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
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	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 2-ETHYLHEXANOL (CASRN 104-76-7)

BACKGROUND

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

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

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

DISCLAIMERS

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

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

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

QUESTIONS REGARDING PPRTVS

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development's (ORD's) NCEA, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

2-Ethylhexanol (2-EH; also called 2-ethyl-1-hexanol), CASRN 104-76-7, belongs to the class of compounds known as aliphatic alcohols. 2-EH is a volatile organic compound (VOC) that has been identified as a metabolite and degradation product of diethylhexyl phthalate (DEHP) (ChemIDplus, 2018). It is mainly used in the manufacture of ester plasticizers for soft poly(vinyl chloride) (PVC), and the second largest application is in the production of 2-ethylhexyl acrylate (Bahrmann et al., 2013). It can also be used as a penetrant in mercerizing textiles; as a solvent for dyes, resins, oils, paints, lacquers, baking finishes, and nitrocellulose; as a wetting agent; as a defoaming agent; and in textile finishing compounds, inks, rubber, paper, lubricants, photography, and dry cleaning (HSDB, 2014). 2-EH is listed on the U.S. EPA's Toxic Substances Control Act (TSCA) public inventory (U.S. EPA, 2018b); it is registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2018) and is also listed as a high production volume (HPV) chemical in the U.S. and Europe under the U.S. EPA's HPV Challenge Program and Organisation for Economic Co-operation and Development (OECD) (U.S. EPA, 2016; OECD, 1995). 2-EH is subject to the Section 4 Test Rule under TSCA Flag T (U.S. EPA, 2015).

Commercial production of 2-EH occurs via a four-step process: (1) aldolization of butyraldehyde and subsequent dehydration, (2) separation of the aldolization solution, (3) hydrogenation of unsaturated 2-ethyl-2-hexenal as an intermediate product, and (4) fractionation of 2-EH (Bahrmann et al., 2013). As an HPV chemical, 2-EH has an annual production volume of over 2 million pounds in Europe and 1 million pounds in the United States (U.S. EPA, 2016; OECD, 1995). 2-EH is also a naturally occurring plant volatile, specifically identified in a variety of fruits (ChemIDplus, 2018).

The empirical formula for 2-EH is $C_8H_{18}O$. Its chemical structure is shown in Figure 1, and Table 1 summarizes its physicochemical properties. 2-EH is a combustible, colorless liquid at room temperature (ChemIDplus, 2018). Its moderate vapor pressure indicates that it will exist almost entirely as a vapor in the atmosphere. The estimated half-life of vapor-phase 2-EH in air by reaction with photochemically produced hydroxyl radicals is 9.7 hours. 2-EH's moderate Henry's law constant indicates that it may volatilize from moist surfaces, but its vapor pressure suggests that it is not expected to volatilize from dry soils. The water solubility and low soil adsorption coefficient for 2-EH indicate that it may leach to groundwater or undergo runoff after a rain event. 2-EH may also undergo ready biodegradation in the environment, based on screening tests (ECHA, 2018).

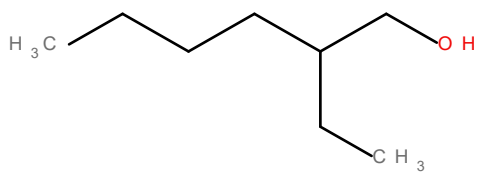

Figure 1. 2-Ethylhexanol (CASRN 104-76-7) Structure

Table 1. Physicochemical Properties of 2-Ethylhexanol (CASRN 104-76-7)

Property (unit)	Value
Physical state	Liquid
Boiling point (°C)	184[a]
Melting point (°C)	−74[a]
Density (g/cm^3 at 20°C)	0.833[c]
Vapor pressure (mm Hg at 25°C)	0.136[a]
pH (unitless)	NA
pKa (unitless)	15.75 (estimated)[c]
Solubility in water (mol/L at 25°C)	6.02×10^{-3}[a]
Octanol-water partition coefficient (log K_{ow})	2.9[c]
Henry's law constant (atm-m^3/mol at 25°C)	3.01×10^{-5} (estimated)[a]
Soil adsorption coefficient log K_{oc} (L/kg)	83.7 (estimated)[a]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	1.84×10^{-11} (estimated)[a]
Atmospheric half-life (hours)	9.7 (estimated)[b]
Relative vapor density (air = 1)	4.49[d]
Molecular weight (g/mol)	130[a]
Flash point (closed cup in °C)	75[c]

[a]Data were extracted from the U.S. EPA CompTox Chemicals Dashboard (2-Ethyl-1-hexanol, CASRN 104-76-7. https://comptox.epa.gov/dashboard/DTXSID5020605. Accessed 24 April 2019).
[b]U.S. EPA (2012c).
[c]ECHA (2018).
[d]Lewis (2012).

NA = not applicable.

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

Table 2. Summary of Available Toxicity Values for 2-Ethylhexanol (CASRN 104-76-7)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2018a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2018)
IPCS	NV	NA	IPCS (2018)
CalEPA	NV	NA	CalEPA (2016); CalEPA (2018a); CalEPA (2018b)
OSHA	NV	NA	OSHA (2017a); OSHA (2017b)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2018)
AIHA (ERPG)	ERPG-3: 227 ppm (1,209 mg/m^3) ERPG-2: 120 ppm (639 mg/m^3) ERPG-1: 0.1 ppm (0.53 mg/m^3)	ERPG-3: Based on the absence of life-threatening health effects in mice, rats, and guinea pigs exposed at 227 ppm for 6 hr. ERPG-2: Based on a NOAEL of 120 ppm in rats exposed 6 hr/d, 5 d/wk for 90 d. ERPG-1: Based on perception of an objectionable odor at 0.1 ppm.	AIHA (2007)
Cancer			
IRIS	NV	NA	U.S. EPA (2018a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2016)
IARC	NV	NA	IARC (2018)
CalEPA	NV	NA	CalEPA (2011); CalEPA (2018a); CalEPA (2018b)
ACGIH	NV	NA	ACGIH (2018)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; AIHA = American Industrial Hygiene Association; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.
[b]Parameters: ERPG = emergency response planning guideline.

NA = not applicable; NOAEL = no-observed-adverse-effect level; NV = not available.

Literature searches were conducted in October 2015 and updated in August 2018 for studies relevant to the derivation of provisional toxicity values for 2-EH, CASRN 104-76-7. Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), American Industrial Hygiene Association (AIHA), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), International Agency for Research on Cancer (IARC), Japan Existing Chemical Data Base (JECDB), National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), OECD HPV, OECD International Uniform Chemical Information Database (IUCLID), OECD Screening Information Data Sets (SIDS), Occupational Safety and Health Administration (OSHA), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA HPV, U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Office of Water (OW), U.S. EPA Toxic Substances Control Act Test Submissions (TSCATS), and World Health Organization (WHO).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

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

Table 3A. Summary of Potentially Relevant Noncancer Data for 2-Ethylhexanol (CASRN 104-76-7)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
Numerous studies in humans have examined the relationship between indoor air quality and the adverse health effects of 2-EH and VOCs (Kishi et al., 2018; Wieslander et al., 2010; Putus et al., 2004; Tuomainen et al., 2004; Walinder et al., 2001; Norback et al., 2000; Wieslander et al., 1999; Norbäck et al., 1990). These studies generally observed eye, nose, and throat irritation. In an experimental study of short-term exposure to 2-EH in humans, the subjective ratings of eye and smell discomfort were significantly increased compared to clean air exposure and nasal and throat irritation ratings were also increased, albeit not significantly ($p \geq 0.08$) (Ernstgård et al., 2010). van Thriel et al. (2003) reported that the highest average subjective ratings were observed for annoyance and olfactory symptoms in male volunteers exposed to 2-EH for 4 hours as well as significantly decreased nasal flow and increased concentrations of the neuropeptide substance P in nasal fluid (an indicator of nasal chemosensory irritation) (van Thriel et al., 2003). In two follow-up studies by the same authors, significant increases in the perception and intensity of acute symptoms (olfactory symptoms, nasal irritation, eye irritation, odor, and/or annoyance) were observed with increasing exposure to 2-EH in male volunteers exposed for 4 hr (van Thriel et al., 2007; van Thriel et al., 2005). Another study conducted by the same group concluded that 2-EH was irritating to the eyes in participants exposed for 4 hr (Kiesswetter et al., 2005).							
Animal							
1. Oral (mg/kg-d)							
Subchronic	10 M/10 F, Dow Wistar albino rat, diet, 0, 0.01, 0.05, 0.25, or 1.25% for 89 d (M) or 90 d (F)	0, 7, 36, 170, 840 (M); 0, 7, 41, 190, 940 (F)	Increased liver weight; diffuse cloudy swelling in the liver and the kidneys (statistically significant in females only)	170 (M); 190 (F)	840 (M); 940 (F)	Mellon Institute of Industrial Research (1960) (mortality in control and some treated groups from lung infection or peritonitis, limited toxicological endpoints evaluated, and poor data reporting)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for 2-Ethylhexanol (CASRN 104-76-7)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Subchronic	10 M/10 F, F344 rat, gavage, 0, 25, 125, 250, or 500 mg/kg-d, 5 d/wk, 3 mo	0, 18, 89.3, 179, 357	Increased relative stomach, liver, and kidney (males only) weights; increased absolute liver (males only) and stomach (females only) weights; forestomach lesions (acanthosis)	89.3	179	Astill et al. (1996a); BASF (1991a)	PR
Subchronic	10 M/10 F, $B6C3F_1$ mouse, gavage, 0, 25, 125, 250, or 500 mg/kg, 5 d/wk, 3 mo	0, 18, 89.3, 179, 357	Increased relative stomach weight in males	89.3	179	Astill et al. (1996a); BASF (1991c); BASF (1991e)	PR
Chronic	50 M/50 F, F344 rat, gavage, 0 (water), 0 (vehicle), 50, 150, or 500 mg/kg-d, 5 d/wk, 24 mo	0, 36, 107, 357	Decreased body weight in M. Mortality, clinical signs, marked weight reductions and histological lesions in F at 357 mg/kg-d	36	107 (FEL = 357)	Astill et al. (1996b); BASF (1992a)	PR
Chronic	50 M/50 F, $B6C3F_1$ mouse, gavage, 0 (water), 0 (vehicle), 50, 200, or 750 mg/kg-d, 5 d/wk, 18 mo	0, 36, 143, 536	Increased early mortality, decreased body weight, increased histopathological lesions (fatty infiltration of the liver)	143	536 (FEL)	Astill et al. (1996b); BASF (1991b)	PR
Reproductive/ Developmental	**0 M/10 F, pregnant Wistar rat, gavage, 0 (water), 0 (vehicle), 1, 5, 10 mmol/kg on GDs 6−15**	**0, 130, 650, 1,300**	**Maternal: Severe toxicity (mortality, clinical signs, body-weight loss) at 1,300 mg/kg-d** **Fetal: Increased fetal incidences of skeletal variations, skeletal malformations, and skeletal retardations; decreased fetal body weight**	**Maternal: 650** **Fetal: 130**	**Maternal: 1,300 (FEL)** **Fetal: 650**	**Hellwig and Jäckh (1997); Confidential (1991)**	**PS, PR**

Table 3A. Summary of Potentially Relevant Noncancer Data for 2-Ethylhexanol (CASRN 104-76-7)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Reproductive/ Developmental	0 M/28 F, CD-1 mouse, microencapsulated in diet, 0, 0.009, 0.03, or 0.09% on GDs 0−17	0, 17, 59, 191	No significant effects	Maternal: 191 Fetal: 191	Maternal: NDr Fetal: NDr	NTP (1991)	NPR
Reproductive/ Developmental	0 M/50 F, pregnant CD-1 mouse, gavage, 0 or 1,525 mg/kg-d on GDs 6−13	0, 1,525	Maternal: Death, decreased body weight/body-weight gain Developmental: Decreased survival and growth of pups (PNDs 1−3)	Maternal: NDr Developmental: NDr	Maternal: 1,525 (FEL) Developmental: 1,525 (FEL)	Hardin et al. (1987); Hazleton Laboratories (1983)	PR
Reproductive/ Developmental	0 M/7 F, pregnant Wistar rat, gavage, 0, 6.25, or 12.5 mmol/kg on GD 12	0, 830, 1,700	Maternal: No effects reported Fetal: Decreased fetal body weight and increased number of surviving fetuses with malformations	Maternal: NDr Developmental: NDr	Maternal: NDr Developmental: NDr	Ritter et al. (1987) (limited toxicological endpoints evaluated, and poor data reporting)	PR
Reproductive/ Developmental	4−5 M/0 F, neonatal CD (S-D) rat pups, gavage, 167 mg/kg	0, 167	No significant effects	NDr	NDr	Li et al. (2000) (limited scope of study)	

Table 3A. Summary of Potentially Relevant Noncancer Data for 2-Ethylhexanol (CASRN 104-76-7)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
2. Inhalation (mg/m^3)							
Subchronic	10 M/10 F, Wistar rat, whole-body inhalation, 0, 15, 40, or 120 ppm, 6 hr/d, 5 d/wk, 90 d	HEC_{EXRESP}: 0, 14, 38, 114	No significant, treatment-related effects	114	NDr	Klimisch et al. (1998); BASF (1992b)	PR
Subchronic	**5−7 M, ICR mouse, whole-body inhalation, 0, 21.9, 65.8, or 153.2 ppm, 8 hr/d, 5−7 d/wk, up to 3 mo**	**HEC_{ET}: 0, 4.17, 12.5, 29.20**	**Morphological changes (e.g., inflammation) in the olfactory epithelium; leukocyte infiltration in the olfactory epithelium at 1 wk and 3 mo; altered expression of olfactory nerve-related markers in the olfactory epithelium and bulb at 1 wk and/or 3 mo; decreased glomerular diameter in the olfactory bulb at 3 mo**	**NDr**	**4.17**	**Miyake et al. (2016)**	**PS, PR**
Reproductive/ Developmental	15 F, S-D rat, 0 or 850 mg/m^3, 7 hr/d on GDs 1−19	HEC_{EXRESP}: 0, 248	No effects reported	248	NDr	Nelson et al. (1989)	PR

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Values are presented as ADDs (mg/kg-day) for oral effects and HECs (mg/m^3) for inhalation effects. HEC_{EXRESP} = (ppm × molecular weight ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × ratio of blood-gas partition coefficients (animal:human).
HEC_{ET} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × $RGDR_{ET}$ (animal:human) (U.S. EPA, 1994).
[c]Notes: PS = principal study; PR = peer reviewed; NPR = not peer reviewed.

ADD = adjusted daily dose; ET = extrathoracic; EXRESP = extrarespiratory effects; F = female(s); FEL = frank effect level; GD = gestation day; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); PND = postnatal day; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; RGDR = regional gas dose ratio; S-D = Sprague-Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for 2-Ethylhexanol (CASRN 104-76-7)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[a]**	**Critical Effects**	**Reference (comments)**	**Notes[b]**
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-d)					
Carcinogenicity	50 M/50 F, F344 rat, gavage, 0, 50, 150, or 500 mg/kg, 5 d/wk, 24 mo	0, 9.5, 27.9, 90.9 (M) 0, 8.4, 24.8, 81.2 (F)	No evidence of carcinogenicity	Astill et al. (1996b); BASF (1992a)	PR
Carcinogenicity	**50 M/50 F, B6C3F$_1$ mouse, gavage, 0, 50, 200, or 750 mg/kg, 5 d/wk, 18 mo**	**0, 5.5, 21.8, 79.9 (M) 0, 5.3, 21.1, 77.3 (F)**	**Hepatocellular carcinomas and adenomas**	**Astill et al. (1996b); BASF (1991b)**	**PS, PR**
2. Inhalation (mg/m^3)					
ND					

[a]Dosimetry: The units for oral exposures are expressed as HEDs (mg/kg-day); HED = adjusted daily animal dose (mg/kg-day) × $(BW_a \div BW_h)^{1/4}$ (U.S. EPA, 2005), using TWA body weights calculated from study reported body-weight data for rats and mice, and 70 kg for humans (U.S. EPA, 2011b).
[b]Notes: PR = peer reviewed; PS = principal study.

BW = body weight; F = female(s); HED = human equivalent dose; M = male(s); ND = no data; TWA = time-weighted average.

HUMAN STUDIES

Oral Exposures

No studies have been identified.

Inhalation Exposures

Although there were no human studies suitable for reference value derivation, there are several published human studies available that are briefly summarized in the text below.

Data for inhalation exposure in humans include experimental short-term exposures to 2-EH (Ernstgård et al., 2010; van Thriel et al., 2007; Kiesswetter et al., 2005; van Thriel et al., 2005; van Thriel et al., 2003), as well as several studies that evaluated adverse health effects (such as "sick building syndrome" [SBS]) from exposures to volatile organic compounds (VOCs; including 2-EH) and other substances (Kishi et al., 2018; Wieslander et al., 2010; Putus et al., 2004; Tuomainen et al., 2004; Walinder et al., 2001; Norback et al., 2000; Wieslander et al., 1999; Norbäck et al., 1990). Supporting data include case reports of 2-EH exposure (Kondo et al., 2007; Kamijima et al., 2002) and human health evaluations at sites of potential 2-EH exposure (Shell Oil, 1987; NIOSH, 1984, 1983).

Numerous studies have examined the relationship between indoor air quality and the adverse health effects of 2-EH and VOCs (Kishi et al., 2018; Wieslander et al., 2010; Putus et al., 2004; Tuomainen et al., 2004; Walinder et al., 2001; Norback et al., 2000; Wieslander et al., 1999; Norbäck et al., 1990). In the subset of studies that evaluated health effects in buildings where dampness is specifically a problem (e.g., those with concrete or masonry floors, etc.), 2-EH and 1-butanol (by-products of dampness-mediated degradation of diethylhexyl phthalate [DEHP] in PVC flooring) were the focus of the investigation, but the levels of respirable dust, molds, and/or bacteria were also considered. The levels of 2-EH in these settings typically ranged from about <1−100 µg/m^3 (although one study reported levels as high as 1,556 µg/m^3). The types of health effects assessed in these studies included subjective symptoms of SBS (characterized by irritation of the eyes, upper airways, and/or skin; headache; cough; and/or fatigue), symptoms of asthma, nasal lavage parameters, tear film stability, and respiratory function (measured using rhinometry and/or spirometry). Effects attributed to poor indoor air quality (and 2-EH exposure) were ocular and nasal irritation (in multiple studies), airway constriction, decreased tear film stability, changes in the levels of some biomarkers in the lavage fluid (indicative of inflammation), symptoms of asthma (but not doctor-diagnosed asthma), and/or an increased occurrence of viral (but not bacterial) respiratory infections. However, considering that the subjects were exposed to multiple contaminants, it is not possible to attribute these effects to 2-EH exposure alone.

Similar types of effects were reported in occupational case reports of 2-EH exposure (Kondo et al., 2007; Kamijima et al., 2002). A college professor with multiple chemical sensitivity (MCS) from exposure to the VOCs in campus buildings showed symptoms consistent with SBS, including eye and throat irritation, cough, headache, blurred vision, and a slight fever. These symptoms were most apparent in a faculty meeting room where 2-EH was the predominant VOC (469 µg/m^3, compared to ≤30 µg/m^3 for other VOCs). In contrast, symptoms subsided in her office, where 2-EH levels were substantially lower (85 µg/m^3; the concentrations of all other VOCs varied by <10 µg/m^3 among these areas). Subsequent blood analyses showed a high serum concentration of 2-EH in the affected individual (4.6 ng/mL vs. ≤0.1 ng/mL for other VOCs) compared to other patients with an onset of SBS (Kondo et al., 2007).

Symptoms associated with effects on the central nervous system (CNS) and irritation of the respiratory tract were also identified in NIOSH Human Health Evaluations at sites of potential 2-EH exposure. In a survey of office workers with complaints of SBS-like symptoms (including headache, nausea, dizziness, and numbness), numerous indoor air contaminants in addition to 2-EH were identified at detectable levels (e.g., metals, solvents, terpinene, and dimethyloctane), but the levels of 2-EH were nonquantifiable. Furthermore, the levels of these contaminants were <1% of their respective OSHA standards (if available), likely because corrective measures had been implemented. Therefore, the compound(s) responsible for these symptoms was not clear (NIOSH, 1984). In another case, some rescue workers responding to an explosion from the nitration of 2-EH, as well as subjects in the surrounding area, showed symptoms that included ocular and respiratory irritation, headache, and cough (NIOSH, 1983). Although these effects are consistent with those observed in other studies, the results are confounded by exposures to multiple contaminants, and no estimates of exposure were reported.

Another industrial survey evaluated pregnancy-related morbidity in Shell Oil Company employees assigned to jobs with potential 2-EH exposure based on their job descriptions (groups of female workers assigned to jobs with potential 2-EH exposure and those ever in a job with a description that listed 2-EH). No specific estimates of 2-EH exposure were reported. Pregnancy outcomes were evaluated based on a query of the company's health surveillance system. No significant effects on reproductive outcomes were observed in workers assigned to jobs with 2-EH exposure. The rate of spontaneous abortions were similar among women assigned to jobs with potential 2-EH exposure and in all female employees with potential exposure to 2-EH (past or present) (Shell Oil, 1987). However, various study limitations were apparent (including the small number of pregnancies evaluated, the lack of reliable estimates of 2-EH exposure, and the absence of a control group).

Experimental studies of short-term exposure to 2-EH evaluated a comprehensive set of subjective symptoms and compared the results with physiological measurements of eye, nose, and/or lung irritation (Ernstgård et al., 2010; van Thriel et al., 2007; Kiesswetter et al., 2005; van Thriel et al., 2005; van Thriel et al., 2003). One of the studies (van Thriel et al., 2007) also examined the neurotoxic potential of 2-EH.

Ernstgård et al. (2010)

Healthy volunteers (16 males and 14 females; aged 22−49 years with a mean age of 31 years) were exposed in random order to clean air or 2-EH as a vapor at 1 mg/m^3 for 2 hours while at rest. Twelve (40%) of the volunteers had laboratory-verified atopy (genetic predisposition to develop allergic diseases), representing a possible sensitive subpopulation. Exposure periods were at least 2 weeks apart. Symptom ratings were recorded at six time points (prior to exposure, after 3, 60, and 118 minutes of exposure, and 15 and 200 minutes postexposure); the questionnaire (encompassing the following 10 symptoms: smell, eye, nose, and throat irritation, dyspnea, headache, fatigue, dizziness, nausea, and intoxication) required subjects to grade responses on a 0−100 mm visual analog scale (VAS) with 0 mm corresponding to "not at all" and 100 mm corresponding to "almost unbearable." Blinking frequency (defined as blinks per minute for 2-minute intervals) was measured 2 minutes before exposure and throughout the entire exposure period. Precorneal film stability, measured as tear film break-up time (BUT) in each eye, was assessed using a biomicroscope just prior to and following exposure and 3 hours postexposure. To evaluate epithelial damage to the cornea and/or conjunctivae, lissamine green was instilled into the lower conjunctival sac of the eye 4 hours after exposure and the eye was examined using a

binocular microscope with a slit lamp. Nasal lavage was performed immediately before and after exposure, and at 3 hours postexposure. The lavage fluid was analyzed for the following biomarkers: eosinophilic cationic protein (ECP), myeloperoxidase (MPO), lysozyme, and albumin. At the same time points, acoustic rhinometry was performed to determine nasal volume (from the nostril to 7 cm into the nasal cavity) and minimal cross-section area (based on an average of 3 measurements/nostril). Irritation in the airways and lungs was evaluated by dynamic spirometry (pre- and postexposure, 3 hours after exposure); the endpoints evaluated were vital capacity, forced vital capacity (FVC), forced expiratory volume, peak expiratory flow, and forced expiratory flows in the middle half of FVC (FEF25, FEF50, and FEF75). Using a single-breath technique, a transfer test was conducted to assess the diffusion capacity of carbon dioxide (prior to exposure and 20 minutes after exposure).

Numerical data for symptoms ratings were provided only for the 60- and 118-minute time points in the study report, but data for some symptoms at additional time points were presented graphically (Ernstgård et al., 2010). The scores for two symptoms, eye discomfort and solvent smell, were significantly increased during 2-EH exposure relative to clean air exposure. After 118 minutes of 2-EH exposure, the median eye irritation score reached 7 mm compared to 3 mm for clean air. The perception of solvent smell reached a maximum within 1 hour of exposure; the median score was 26 mm (corresponding to a "somewhat" or "rather" strong smell) compared to 7 mm for clean air ($p < 0.0001$). The median score for solvent smell at 2 hours was about half the value observed at 1 hour, owing to adaptation; there was also evidence for a "chamber effect" (odor perception in clean air) throughout the exposure period. Nasal and throat irritation ratings following almost 2 hours of 2-EH exposure were increased, albeit not quite significantly ($p \geq 0.08$). In addition, ratings of irritation (of the nose, eyes, or throat) were not significantly associated with ratings of smell (based on Spearman correlation tests). Scores for all other symptoms were at or near 0 throughout the duration of the 2-EH exposure. There were no significant effects on any of the other endpoints evaluated. Differences were not observed based on gender or atopy status.

van Thriel et al. (2003)

Male volunteers ($n = 24$, with a mean age of 24 years) were exposed to 2-EH at mean concentrations of 1.53, 10.63, and 21.88 ppm for 4 hours (with 2 days between sessions, 3−4 sessions total). These concentrations are equivalent to 8.15, 56.62, and 116.5 mg/m^3, respectively. Minimum and maximum exposure levels for the low-, mid-, and high-exposure groups were 1.39−1.58 ppm (7.40−8.42 mg/m^3), 1.23−20.20 ppm (6.55−107.6 mg/m^3), and 1.76−42.07 ppm (9.37−224.1 mg/m^3), respectively. Oscillations in solvent concentration (c) during exposure were described by these functions: exposure duration (t), average solvent concentration (A_0), and the value of the difference from the average to intended maximum concentration (a), assuming a cycle duration of 60 minutes and phasing of 1.5 ($c = A_0 + a \sin [2\pi t \div 60 + 1.5]$). Ratings of well-being (tenseness, tiredness, and annoyance) and acute health symptoms ratings (29 symptoms, not individually specified) were recorded at nine time points during exposure (50 minutes prior to exposure [as baseline], 1, 26, 59, 85, 129, 145, 173, 199, and 232 minutes after the initiation of exposure, and 52 minutes postexposure); the former were assessed using a validated seven-point visual rating scale, the latter were assessed using an extended version of the "acute symptoms" test from the Swedish Performance Evaluation System (SPES). The initial SPES (for 12 symptoms associated with the olfactory system and nasal/eye irritation) was expanded to encompass 29 symptoms; severity was ranked on a scale of 0 ("not at all") to 5 ("very, very much"). Like-symptoms were grouped together for analyses (nonlinear regression fitting). Symptom groups were prenarcotic (four symptoms), olfactory (four symptoms), taste (three symptoms), respiratory

(three symptoms), nasal irritation (five symptoms), eye irritation (seven symptoms), and other irritation (three symptoms). For the purposes of this study (which focused on chemosensory exposure effects), analyses were limited to olfactory symptoms, annoyance, nasal irritation, eye irritation, and nasal and eye irritation combined ("sensory irritation"). Anterior active rhinomanometry (AAR) was performed immediately before and after exposure to evaluate measures of nasal airway resistance (airflow, transnasal pressure gradient between nostrils and nasopharynx, and anterior pressure). Nasal lavage was done 30 minutes prior to exposure and immediately after exposure to measure neuropeptide substance P levels (as an indicator of nasal chemosensory irritation). Additional analyses (using Spearman rank correlation) were performed to evaluate potential associations between subjective chemosensory ratings and objective physiological variables.

Chemosensory ratings for the low-exposure group were not shown (van Thriel et al., 2003). With respect to analyses at 56.62 and 116.5 mg/m^3, the highest average ratings were observed for annoyance and olfactory symptoms; ratings for sensory irritation were low (<1). However, the scores for all chemosensory endpoints evaluated (including sensory irritation) varied consistently with oscillations in exposure concentration (i.e., the goodness-of-fit [R^2] values were >0.50). Overall, ≥67% of the variance in these ratings at the mid- and high-exposure levels could be explained by nonlinear regression analyses indicating a positive dose-response relationship. When sensory irritation endpoints (i.e., nasal irritation and eye irritation) were analyzed separately, the symptoms associated with nasal irritation varied most consistently with exposure (R^2 = 0.92 and 0.91 at the moderate and high-exposure levels, respectively); eye irritation scores were more variable (R^2 = 0.17 and 0.54 at the same exposure concentrations). Changes in nasal and eye irritation scores as a function of time of exposure were presented graphically in the study report; overall ratings for these individual endpoints were not shown. AAR measurements showed decreased nasal flow (postexposure relative to pre-exposure) in subjects exposed to 2-EH at an average concentration of 116.5 mg/m^3 ($p < 0.01$); there were no significant effects at the low- or moderate-exposure concentrations, and the reduction in nasal flow at the highest exposure concentration was not significantly different than that at other exposure levels. Analyses of substance P levels in nasal lavage (presented graphically in the study report) showed increased substance P postexposure relative to pre-exposure at the high-exposure concentration (p = 0.01). The difference between post- and pre-exposure values was significantly increased at the high-exposure concentration relative to the low-exposure concentration (p = 0.03). Additional analyses conducted to evaluate correlations between chemosensory ratings and physiological variables did not reveal any clear, exposure-related associations.

van Thriel et al. (2007); van Thriel et al. (2005)

In two follow-up studies by the same authors, male volunteers were exposed to 2-EH as a vapor for 4 hours at variable (Experiment A) or constant (Experiment B) time-weighted average (TWA) exposure concentrations of 1.5, 10, and 20 ppm (in succession and at least 2 days apart). These concentrations are equivalent to 8.0, 53, and 110 mg/m^3, respectively. The maximum exposure concentration under variable conditions was 42 ppm (220 mg/m^3). Both experiments used healthy participants with self-reported multiple chemical sensitivity (sMCS); these individuals were identified using a standardized questionnaire on chemical and general environmental sensitivity (CGES) and age-matched controls. Subjects diagnosed with asthma, allergic rhinitis, or chronic diseases (diabetes, liver disease, etc.) were excluded. Experiment A comprised 12 sMCS subjects and 12 age-matched controls (mean age = 24 years); Experiment B used 7 sMCS subjects and 15 age-matched controls (mean age = 23 years). In both experiments, half of the subjects (a mix of

controls and sMCS subjects) were exposed in the morning, and half were exposed in the afternoon. Steady-state concentrations were used for the 8.0 mg/m^3 exposure level. As in the 2003 study, the 2005 study evaluated the severity of acute health symptoms (29 in total) as ranked on a scale of 0−5 at various time points: 50 minutes prior to exposure, during exposure (at 1, 26, 59, 85, 120, 145, 173, 199, and 232 minutes) and 52 minutes following exposure; time points were selected to correspond with minima and maxima exposure concentrations (for Experiment A). Given the focus of the study (chemosensory effects), subsequent analyses were confined to olfactory symptoms, nasal irritation, and eye irritation. The other focus of the 2007 study was on neurobehavioral tests: namely, "divided attention" (DA), working memory (WM), and vigilance tasks (VT). For the DA test, subjects were required to process and respond accurately to multiple stimuli (i.e., visual and auditory) simultaneously. The WM test asked subjects to memorize a series of two-digit numbers that appeared on the screen for 1.5 seconds and to compare these values to an earlier number (2-back; delayed comparison test). For the VT test, subjects viewed the movement of a yellow dot within a circular display of 24 red dots and were asked to document when the yellow dot crossed over two red dots (rather than one). Each neurobehavioral test (5−30 minutes in duration) was performed twice (following 5 and 175 minutes of exposure) in order (DA, WM, VT); the following variables were measured: reaction times (RTs), detection rates (HITs), and false alarms (FAs). Subjects were trained in the DA and WM tasks on the day of the medical examination to avoid learning effects across exposure sessions. In both studies, subjects also used the labeled magnitude scale (LMS) tool (Green et al., 1996) to estimate the intensity of odor (2005 study only) or annoyance (2007 study only), nasal irritation, and eye irritation. Using this tool, the subject indicated the intensity of each of the three symptoms using a slider positioned alongside six categorical ratings (ranging from barely detectable to strongest imaginable). Ratings were collected three times during each exposure period (at 65, 128, and 160 minutes; time points selected to approximate TWA concentrations).

Results from the 2005 study showed that, in both Experiment A and Experiment B, acute symptoms were significantly ($p < 0.05$ by analysis of variance [ANOVA]) affected by the following factors: the TWA concentration of 2-EH, the time course of exposure, and the interaction of these two factors [data presented graphically; van Thriel et al. (2005)]. With respect to Experiment A, variation in mean ratings for olfactory symptoms, nasal irritation, and eye irritation were typically high, because responses mimicked the time course of concentration. In Experiment B (using constant exposure concentrations), a significant exposure-response was also seen, but the variation in response over time was low. In general, ratings for olfactory symptoms decreased, nasal irritation remained unchanged, and eye irritation increased throughout exposure. There was a significant difference for Experiment B only among the responses of control and sMCS subjects, and the sMCS subjects showed heightened chemosensory responses (especially for olfactory symptoms). With respect to olfactory symptoms, control subjects exposed to 2-EH at a constant concentration of 53 or 110 mg/m^3 showed decreased ratings over time (the effect was less profound at 8.0 mg/m^3). In contrast, sMCS subjects initially showed the highest ratings at 53 mg/m^3, but those ratings tended to decrease over time, whereas ratings at 110 mg/m^3 increased and stabilized throughout exposure.

With the exception of the DA task, no significant exposure-related effects were reported in neurobehavioral tests (van Thriel et al., 2007). In the DA task, HITs significantly decreased ($p = 0.03$ based on ANOVA analysis) as the exposure concentration increased. Based on the data shown graphically in the study report for control and sMCS subjects exposed under variable or constant conditions in the morning or in the afternoon (eight exposure conditions in total),

decreased HITs could be explained mainly by concentration-related reductions in HITs in sMCS subjects (especially for the group exposed to variable concentrations in the morning, but also those exposed to constant concentrations in the afternoon). A significant increase in RTs at the end of exposure relative to the beginning of exposure (681 vs. 672 ms; $p = 0.05$) regardless of exposure condition was also noted (HITs and FAs were unaffected). There were no significant findings with respect to the WM task. While subjects' performance on the VT task was not affected by exposure-related factors, the study authors reported an "observable vigilance decrement" (significance not reported) during the VT task, as evidenced by increased RTs and decreased HITs from the first 6-minute interval (487 ms and 92%, respectively) of the task to the last 6-minute interval (521 ms and 85%); the number of FAs was too small for analyses. A significant interaction was also noted between exposure duration and the "time of task" ($p = 0.01$; no further details provided).

In both studies, the intensity of chemosensory effects (ranked using the LMS) was significantly affected by 2-EH exposure (van Thriel et al., 2007; van Thriel et al., 2005). In the earlier study, 2-EH exposure (in Experiments A and B) significantly increased the average intensity of odor, nasal irritation, and eye irritation ($p < 0.01$ based on ANOVA) in a concentration-related manner, from weak or barely detectable at 8.0 mg/m^3 to strong or very strong at 110 mg/m^3 (data presented graphically in the study report; average values with no evaluation of variation over time). In general, the intensity of these effects (especially for sensory irritation) was higher at 53 and 110 mg/m^3 under variable exposure conditions (Experiment A) compared to constant exposure conditions (Experiment B). Intensity ratings were not significantly different among control and sMCS subjects. Similarly, the second study reported that the intensity of annoyance, nasal irritation, and eye irritation significantly increased ($p < 0.01$ by multivariate analysis of variance [MANOVA]) in a concentration-related manner; however, there was also a significant interaction between exposure concentration, experiment (A vs. B), and sensitivity (control vs. sMCS subjects) (van Thriel et al., 2005). The ratings of sMCS subjects were higher than controls for Experiment B; however, control responses were higher for Experiment A. Ratings for subjects in Experiment A reflected the variable exposure concentrations, whereas ratings for Experiment B were relatively stable. There was evidence of adaptation (i.e., a reduction in ratings over time) in annoyance and nasal irritation ratings only in subjects exposed to a constant concentration of 53 mg/m^3 (but not 110 mg/m^3). In general (regardless of exposure condition), ratings for annoyance (on average very strong) were higher than those for eye and nasal irritation (on average strong).

Taken together, the data from these two studies showed significant increases in the perception and intensity of acute symptoms (olfactory symptoms, nasal irritation, eye irritation, odor, and/or annoyance) with increasing exposure to 2-EH. Other than a decrement in accuracy on the DA task in a subset of chemically sensitive individuals (sMCS subjects), no significant effects on neurobehavioral tests (including WM and VT tasks) were observed at concentrations up to 110 mg/m^3.

Kiesswetter et al. (2005)

Another study conducted by the same group specifically evaluated eye blinks as an indicator of sensory irritation in non-sMCS and sMCS participants exposed during constant (Experiment C) and variable (Experiment V) exposures under the same experimental conditions. As in the previous studies, the variable experiment used 12 non-sMCS subjects and 12 sMCS subjects, but 12 non-sMCS subjects and 8 sMCS subjects were used for constant exposure conditions. Demographical information for these subjects (and the degree of overlap with the subjects used in

the preceding experiments) was not provided. A half-hour vigilance test was performed to examine blink frequency. The test was carried out twice (once near the start and once near the end of exposure). Two 5-minute sections (i.e., Section A and Section B) within each test were selected for blink analysis; these sections corresponded to the highest and lowest exposure levels during variable test conditions. Based on ANOVA analyses, blink rates were significantly affected by exposure concentration under both constant and variable conditions ($p < 0.01$); the strongest effects were seen during variable exposure (i.e., the difference in blink rate in Section 1 [trough exposure] compared to Section 2 [peak exposure]). Blink rates also increased significantly over time (from the start of the experiment to the end; $p < 0.05$), suggesting that adaptation did not occur. There was little to no difference in blink rates among non-sMCS and sMCS subjects (one significant difference seen under constant conditions at the start only). The study authors concluded that 2-EH was irritating to the eyes in both groups of subjects under both constant and variable exposure conditions; the response was concentration-related with no evidence of adaptation.

ANIMAL STUDIES

Oral Exposures

The database for oral exposure in animals consists of two subchronic-duration studies [one gavage study in rats and mice (Astill et al., 1996a; BASF, 1991a, c, e) and one non-peer-reviewed dietary study in rats (Mellon Institute of Industrial Research, 1960)]. There is also one chronic-duration gavage study in rats and mice (Astill et al., 1996b; BASF, 1992a, 1991b). The available reproductive and developmental toxicity studies include one neonatal (Li et al., 2000) and several gestational studies in rats and mice (Hellwig and Jäckh, 1997; Confidential, 1991; NTP, 1991; Hardin et al., 1987; Ritter et al., 1987; Hazleton Laboratories, 1983).

Subchronic-Duration Studies

Mellon Institute of Industrial Research (1960) (non-peer-reviewed study)

In a non-peer-reviewed study, groups of Dow Wistar albino rats (10/sex) were administered diets containing 0, 0.01, 0.05, 0.25, or 1.25% 2-EH for 89 days (males) or 90 days (females). The study authors calculated equivalent doses based on food consumption and body weight to be 0, 7, 36, 170, and 840 mg/kg-day for males and 0, 7, 41, 190, and 940 mg/kg-day for females. Mortality was presumably monitored regularly (time points not specified). Body weights were measured three times in the first week and weekly thereafter. At study termination, all rats were subjected to necropsy, and liver and kidney weights were recorded. Urinary bladders were examined for concretions. Histopathological examinations (using hematoxylin-eosin staining) of the following tissues were performed on all surviving control and high-dose animals, as well as treated animals that died during the study: lung, kidney, liver, heart, spleen, pancreas, stomach, duodenum, descending colon, testes or ovary, esophagus, trachea, thyroid, adrenal, and urinary bladder. A subset of these tissues (i.e., lung, liver, kidney, and urinary bladder) were examined in animals exposed at 0.05 and 0.25%; tissues from the 0.01% group were not examined histologically.

Data for effects in rats treated with 2-EH, when available, are shown in Table B-1 (Mellon Institute of Industrial Research, 1960). Most of the data provided were presented as individual animal data; means and standard deviations (SDs) were calculated for this PPRTV assessment when necessary. However, for terminal body weight and body-weight gain, there is uncertainty associated with the data values at 7 mg/kg-day in males and at 41 mg/kg-day in females (see Table B-1) owing to the illegibility of individual data values in the study report. Mortality (0−3 animals/group, including controls) was attributed to lung infection or peritonitis (not to treatment). No statistically significant, adverse effects on food consumption were reported

(36 mg/kg-day [males] and 41 mg/kg-day [females] consistently ate more food than controls). With respect to body weights, in-life data (presented graphically in the study report), body-weight gains, and terminal body weights were provided. Although overall body-weight gains varied by >10% relative to controls in some dose groups, terminal body weights in all groups of treated rats were similar to controls (i.e., ≥90% of control values). At necropsy, there were no significant, treatment-related effects on kidney weights. However, absolute and relative (as percentage of body weight) liver weights were significantly increased by 10−14% in 840-mg/kg-day males and 940-mg/kg-day females (note a ≥10% increase in absolute and relative liver and kidney weight is considered biologically significant by the U.S. EPA for the purposes of this PPRTV assessment). The study authors reported significantly increased ($p < 0.05$) incidences of gross lesions in males (cortical degeneration of the kidney) at 840 mg/kg-day and females (congestion and/or swelling of the liver) at 940 mg/kg-day; although incidence data for these effects were provided in the study report, these values are completely illegible at all doses and thus are not shown in Table B-1. Histopathological examinations revealed significant increases in the incidence of diffuse cloudy swelling in the kidneys (more specifically, the proximal convoluted tubules) and livers of females exposed at 940 mg/kg-day. These lesions were also increased in males at 840 mg/kg-day, but the differences from controls were not significant. Although there are several study limitations (mortality in control and some treated groups, limited toxicological endpoints evaluated, and poor data reporting), these limitations do not preclude identification of no-observed-adverse-effect levels (NOAELs) of 170 mg/kg-day (males) and 190 mg/kg-day (females) and lowest-observed-adverse-effect levels (LOAELs) of 840 mg/kg-day (males) and 940 mg/kg-day (females) based on statistically and/or biologically significant increases in absolute and relative liver weights in both sexes and increased incidences of microscopic liver and kidney lesions (significant in females only).

Astill et al. (1996a) (published report); BASF (1991a), BASF (1991c), and BASF (1991e) (non-peer-reviewed studies)

Groups of F344 rats and B6C3F$_1$ mice (10/sex/group) were administered 2-EH (99.8% purity) in aqueous Cremophor EL (polyoxyl-35 castor oil) via gavage at 0 (vehicle-only control), 25, 125, 250, or 500 mg/kg-day 5 days/week for 3 months (about 93−94 days for male and female rats and 96−97 days for male and female mice, respectively) (Astill et al., 1996a; BASF, 1991a, c, e). Additional groups (three/sex) were exposed to 2-EH at the same dose levels for 3 months to specifically evaluate hepatic peroxisome proliferation. Doses of 0, 25, 125, 250, and 500 mg/kg-day were adjusted for continuous exposure to 0, 18, 89.3, 179, and 357 mg/kg-day by multiplying the administered gavage dose by (5/7) days per week. Animals were monitored once daily (on weekends and holidays) or twice daily (on weekdays) for mortality, and at least once daily for clinical signs of toxicity. Body weights were measured prior to study initiation, weekly thereafter, and at study termination. Average daily food consumption was determined weekly. Hematology (hematocrit [Hct]; hemoglobin [Hb]; red blood cells [RBCs], total and differential white blood cells [WBCs], reticulocyte, and platelet counts; mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]; and thromboplastin time) and clinical chemistry (blood urea nitrogen [BUN], creatinine [rats only], total protein, albumin, globulin, total bilirubin [rats only], glucose, cholesterol, triglycerides, sodium, potassium, chloride, inorganic phosphate, calcium [rats only], the activities of alanine aminotransferase [ALT], alkaline phosphatase [ALP], γ-glutamyl transferase [GGT], and aspartate aminotransferase [AST, rats only]) evaluations were performed on Days 29 and 84 (rats) or Days 96−97 (mice). Rats (but not mice) from the control and 357-mg/kg-day groups were subjected to ophthalmological evaluations at study initiation and at study termination. The animals

from all exposure groups were subjected to necropsy; weights of the adrenals, brain, stomach, kidneys, liver, testes, and ovaries were recorded. Complete histopathological examinations (of approximately 40 tissues and including all gross lesions; using hematoxylin-eosin staining) were conducted in rats and mice administered 0 or 357 mg/kg-day. The liver (including gall bladders in mice), lung, spleen, kidney, stomach, sternum, femur, and bone marrow (from the femur) were microscopically examined in all groups of rats and mice. The liver was also stained with oil red to evaluate lipid content. The livers of animals in peroxisome proliferation-only groups were weighed; cyanide-insensitive palmitoyl-Coenzyme A (pCoA) oxidation activity and protein concentration were determined.

Effects in rats related to 2-EH exposure are presented in Table B-2 (males) and Table B-3 (females) (Astill et al., 1996a; BASF, 1991a). All rats survived until study termination. No significant clinical signs of toxicity were reported. Although the body weights of rats treated at 357 mg/kg-day were statistically significantly less than controls (starting at Week 4 in males and Week 11 in females, 7−8% at study termination), body weights remained within 10% of their respective controls throughout the study. There were no significant effects on food consumption. Hematology and clinical chemistry findings included significant increases in Day 84 reticulocyte counts in rats of both sexes at 357 mg/kg-day (21−25% higher than controls) and in serum total protein (13%) and albumin (16%) in male (but not female) rats at 357 mg/kg-day. Other statistically significant changes in hematology and clinical chemistry endpoints were sporadic and of questionable toxicological significance (decreased activities of ALP and ALT, a transient reduction in glucose at Day 29, decreased serum cholesterol). There were no significant ophthalmological findings. At 357 mg/kg-day, relative (percentage of body weight) and absolute liver and relative kidney weights were statistically and biologically significantly increased in males. Absolute kidney weight was statistically but not biologically significantly increased in males at 357 mg/kg-day. Relative stomach and testes weights were also statistically significantly increased in males at 357 mg/kg-day. In females treated with 357 mg/kg-day, relative liver weight was statistically and biologically significantly increased. Absolute liver and relative kidney weights were statistically but not biologically significantly increased in females at 357 mg/kg-day. Relative and absolute (only at 357 mg/kg-day) stomach weights were also statistically significantly increased in females at ≥179 mg/kg-day. In both sexes, statistically but not biologically (<10%) significant increases in relative organ weights (liver and kidney) were also seen at 179 mg/kg-day. At gross necropsy, the presence of single or multiple elevated foci in the forestomach was noted in 2/10 males and 4/10 females at 357 mg/kg-day. Microscopic examinations of the forestomach revealed acanthosis in 2/10 males and 5/10 females at 357 mg/kg-day (compared to 0/10 in controls and in other dose groups); the difference from controls was statistically significant in females (see Tables B-2 and B-3). No statistically significant histopathological effects were reported in the glandular stomach, liver, kidney, or other organs. Rats in the 357 mg/kg-day peroxisome proliferation-only group showed increased pCoA activity (6.5- and 3.4-fold higher than control males and females, respectively); there were no significant effects at ≤179 mg/kg-day. Body-weight gains in the peroxisome proliferation group were decreased to a similar extent as in the main study (no further details were provided).

A NOAEL and LOAEL of 89.3 and 179 mg/kg-day, respectively, are identified in female rats based on statistically significantly increased relative stomach weight. Further, increased relative stomach weights, observed at 357 mg/kg-day (11 and 15% higher than controls in males and females, respectively), occurred in conjunction with an increase in the incidence of acanthosis in the forestomach of treated rats (reaching statistical significance in females only).

Effects in mice related to 2-EH exposure are presented in Table B-4 (Astill et al., 1996a; BASF, 1991e). One spontaneous death was reported in a female mouse treated at 179 mg/kg-day (after 90 days of exposure). The cause of death was determined to be liver damage (after hemorrhage into an ovarian pouch); death was not attributed to treatment. There were no consistent, dose-related effects on the incidence of clinical signs, food consumption, body weights, or hematology and clinical chemistry parameters. The only noteworthy change in organ weights was statistically significantly increased relative (percentage of body weight) stomach weight in male mice at 179 and 357 mg/kg-day; the increases were of similar magnitude (13−14% increase) in both dose groups. Absolute stomach weights were not statistically significantly increased in males, and there was no effect on absolute or relative stomach weight in females. Gross pathology findings were limited to the observation of dark red foci in the glandular stomach of 2/10 females treated at 357 mg/kg-day (not statistically significant). Histopathological examinations showed evidence for forestomach effects (namely slight focal or multifocal acanthosis) at 357 mg/kg-day in 2/10 males and 1/10 females (compared to 0/10 in controls and all other dose groups). Liver necrosis, noted in one 179-mg/kg-day female (as focal necrosis) and one 357-mg/kg-day female (as single cell necrosis), was considered incidental by the study authors. In the peroxisome proliferation-only group, no significant effects on clinical signs, food consumption, body weights, or pCoA activity were observed in male or female mice (BASF, 1991c).

A LOAEL of 179 mg/kg-day with a corresponding NOAEL of 89.3 mg/kg-day is identified for this study based on increased relative stomach weight in male mice.

Chronic-Duration/Carcinogenicity Studies

Astill et al. (1996b) (published report); BASF (1992a); BASF (1991b) (non-peer-reviewed studies)

Groups of F344 rats (50/sex/group) were administered 2-EH in 0.005% aqueous Cremophor EL via gavage at 0 (vehicle-only control), 0 (distilled water control), 50, 150, or 500 mg/kg-day, 5 days/week for 24 months. Doses of 0, 50, 150, and 500 mg/kg-day were adjusted for continuous exposure to 0, 36, 107, and 357 mg/kg-day by multiplying the administered gavage dose by (5/7) days per week. Groups of B6C3F$_1$ mice (50/sex/group) were similarly treated at 0 (vehicle-only control), 0 (distilled water control), 50, 200, or 750 mg/kg-day, 5 days/week for 18 months (until Weeks 79−81). Doses of 0, 50, 200, and 750 mg/kg-day were adjusted for continuous exposure to 0, 36, 143, and 536 mg/kg-day by multiplying the administered gavage dose by (5/7) days per week. The animals were monitored twice daily (on weekdays) or once daily (on weekends) for mortality and clinical signs of toxicity. Detailed clinical examinations were performed weekly. Weekly food consumption was determined every 4 weeks. Body weights were measured prior to study initiation, weekly for the first 13 weeks, and monthly thereafter. Hematology parameters (differential RBC and WBC counts, including morphology evaluations) were evaluated at 12, 18, and 24 months (rats only). All animals (whether sacrificed at study termination or sacrificed moribund) were subjected to necropsy. Organ weights (of the stomach, liver, kidneys, spleen, brain, and testes) were recorded for animals sacrificed on schedule. Complete histopathological examinations (of approximately 40 tissues and including all gross lesions; using hematoxylin-eosin staining) were performed.

Significant effects in rats related to 2-EH exposure are presented in Tables B-5 and B-6 (males and females, respectively) (Astill et al., 1996b; BASF, 1992a). Except for body weight and body-weight gain in males (slightly decreased [by 7%] in water controls relative to vehicle-only controls), there were no significant differences among the two control groups. The results discussed

herein focus on differences between the 2-EH-treated rats and the vehicle-only control group; however, for comparison purposes, data for both control groups are shown in Tables B-5 and B-6. Mortality was markedly increased in females at 357 mg/kg-day (52% at 357 mg/kg-day compared to 28% in controls). An increased incidence of some clinical signs of toxicity (specifically, poor general condition [characterized by lethargy and unkemptness] and/or labored breathing) were noted in both sexes at 357 mg/kg-day; however, these clinical signs were statistically significantly increased in female rats only (based on statistical analyses performed for this review; see Table B-6). No consistent, dose-related effects on food consumption were reported. Body weights and body-weight gain were statistically significantly decreased at doses as low as 36 mg/kg-day (in males), and were decreased ≥10% compared to their respective control groups in males at ≥107 mg/kg-day and females at ≥357 mg/kg-day. For the purposes of this assessment, a ≥10% decrease in body weight is considered biologically significant. There were no consistent, treatment-related effects on hematology parameters. At gross necropsy, a significantly increased incidence of focal lung lesions was observed in both high-dose males and females (see Tables B-5 and B-6).

In general, the absolute weights of most organs were decreased, whereas their relative (percentage of body weight) weights were significantly increased. Statistically significant reductions in absolute organ weights were seen for the stomach (males only at ≥36 mg/kg-day), liver (−16%, 357-mg/kg-day males only), kidney (−7%, 357-mg/kg-day females only), and brain (males at ≥107 mg/kg-day and females at 357 mg/kg-day). The relative weights of these organs were statistically significantly increased compared to controls as follows: relative stomach weights were increased in males at ≥107 mg/kg-day and in all groups of treated females (by 6−21%), relative liver weights were increased in females at ≥107 mg/kg-day (by 11−13%; no dose-related response was observed in males), and relative kidney and brain weights were increased in both sexes at ≥107 mg/kg-day (by 7−22 and 9−20%, respectively). Male rats also showed significantly increased relative (but not absolute) testes weights at 357 mg/kg-day. The toxicological significance of these organ-weight changes is unclear; the opposing direction of absolute and relative organ-weight changes suggests a confounding effect of body-weight changes at the same doses.

With respect to histopathological changes observed, the incidences of bronchopneumonia and liver and lung congestion were significantly increased at 357 mg/kg-day in both sexes. However, congestion was diagnosed in decedents only. Furthermore, the study authors indicated that the diagnosis of congestion was complicated by a high incidence of animals with malignant lymphomas in the liver and lungs, particularly in the vehicle control group (13 of 17 male decedents and 8 of 13 female decedents). Other lesions that were increased in 357 mg/kg-day females relative to vehicle controls were hemosiderin in the spleen, kidney congestion, and hyperplasia of the mesenteric and mandibular lymph nodes (see Tables B-5 and B-6). There was no evidence of treatment-related carcinogenicity in male or female rats at up to 357 mg/kg-day (i.e., the incidence of tumors was comparable among all treatment groups, including controls).

Based on decreased body weight in male rats (≥10% compared to water- and vehicle-controls), NOAEL and LOAEL values of 36 and 107 mg/kg-day (respectively) are identified. The 357-mg/kg-day dose level is considered a frank effect level (FEL) for female rats based on mortality, significantly increased incidences of clinical signs (including poor general condition), and marked reductions in body weight (21%).

Effects in mice related to 2-EH exposure are presented in Tables B-7 and B-8 (males and females, respectively) (Astill et al., 1996b; BASF, 1991b). Except for a few types of histopathological lesions (considered to be incidental), there were no significant differences between the water and vehicle-only control groups; comparisons discussed here are based on differences between 2-EH-treated mice and vehicle-only controls (data for both control groups are shown in Tables B-7 and B-8). Mortality was 4−8% in all dose groups (including both control groups); the 536-mg/kg-day group, however, showed a mortality rate of 30% ($p < 0.01$ in both sexes). The increase in mortality was evident within 8 weeks of study initiation in females and 28 weeks in males. No treatment-related clinical signs of toxicity were reported. Food consumption was significantly decreased at 536 mg/kg-day (by 9% in males and 13% in females relative to controls) over the course of the study. Statistically significant reductions in body weight and body-weight gain were seen at ≥143 mg/kg-day (in males), but this reduction was greater than ≥10% compared to controls only at 536 mg/kg-day in both sexes (a ≥10% decrease in body weight is considered to be biologically significant by the U.S. EPA for the purposes of this PPRTV assessment). Significant changes in hematology parameters (increased polymorphonuclear neutrophils and decreased lymphocyte counts at 12 and/or 18 months) were noted in 536-mg/kg-day males only (see Tables B-7 and B-8). No significant findings were reported at gross necropsy. Numerous organ weights were statistically significantly affected at 536 mg/kg-day. At this dose, relative (percentage of body weight) stomach and liver weights were increased 16−18% and 11−21% in both sexes, respectively; absolute liver and stomach weights were unaffected. Absolute brain weights were statistically significantly decreased in both sexes, whereas relative brain weights were statistically significantly increased. Similarly, absolute kidney weights were decreased (males, −18%; females, −6%), whereas relative kidney weights were decreased (males, −8%) or increased (females, 13%). Although relative testes weights were significantly increased (5−13%) in all groups of treated males, these changes were not dose related, and there was no effect on absolute testes weights. The observed organ-weight changes (predominantly unchanged or decreased absolute weights coupled to increased relative organ weights) are consistent with, and likely secondary to, the observed decreases in body weight. Histopathological examinations revealed significantly increased incidences of liver and lung congestion in mice treated at 536 mg/kg-day; however, these effects occurred mostly (with respect to the lung) or entirely (with respect to the liver) in decedents (i.e., likely post mortem effects). Peripheral fatty infiltration of the liver was significantly increased in rats of both sexes at 536 mg/kg-day, primarily in survivors. Other lesions reported in survivors by the study authors were basophilic foci and focal hyperplasia in the liver. Small (not statistically significant) increases in the incidence of focal hyperplasia of the epithelium of the forestomach were noted in both males and females at 536 mg/kg-day (see Tables B-7 and B-8).

A NOAEL of 143 mg/kg-day is identified for this study but a LOAEL cannot be identified because the next highest dose, 536 mg/kg-day, is considered a FEL in both sexes based on increased early onset mortality and markedly decreased body weight (30%).

Carcinogenicity data in mice are shown in Table B-9 (Astill et al., 1996b; BASF, 1991b). Both male and female mice showed statistically significant trends for increased hepatocellular carcinoma with dose when tested by the time-dependent Peto test performed by the study authors that considers the relatively high mortality in these groups (although the only pairwise increase was in high-dose females). The study authors did not report the results of combined statistical analysis of hepatocellular adenoma or carcinoma. An adenoma was detected in one 536-mg/kg-day male (and no females). Statistical analysis of the combined adenoma or carcinoma male data performed

by the U.S. EPA for this PPRTV assessment did not find a significant pairwise increase in males treated at 536 mg/kg-day compared to vehicle-only controls. The study authors noted that (1) no metastases were observed (indicative of a low grade of malignancy) and (2) the observed incidence of hepatocellular carcinomas was within the historical control range at the testing facility (0−22% in males, 0−14% in females). The study authors concluded that 2-EH is an equivocal hepatocellular carcinogen in male mice and is a weak or equivocal hepatocellular carcinogen in female mice.

Reproductive/Developmental Studies

Hellwig and Jäckh (1997) (published study); Confidential (1991) (non-peer-reviewed)

In a study designed to compare the developmental toxicity of various alcohols, pregnant Wistar rats (10/group) were administered 2-EH (≥99.5% purity) via gavage (in distilled water and 0.005% Cremophor EL as an emulsifier) at 1, 5, or 10 mmol/kg-day (the study authors calculated dose equivalents of 130, 650, or 1,300 mg/kg-day) on Gestation Days (GDs) 6−15 and sacrificed on GD 20. Distilled water and vehicle-only control groups were used. Mortality and clinical signs of toxicity were monitored at least once daily. Food consumption and body weights were recorded every 2−3 days (GDs 0, 1, 3, 6, 8, 10, 13, 15, 17, and 20) in pregnant dams only. At sacrifice on GD 20, maternal animals were subjected to gross pathology examinations, and uterine weights were recorded (pregnant dams at scheduled sacrifice). The uterus and ovaries were evaluated for numbers of corpora lutea and implantations (including live fetuses and dead implantations, defined as the sum of early resorptions, late resorptions, and dead fetuses). Placental weights were determined. Conception rate and pre- and postimplantation losses were calculated. All fetuses were sexed, weighed, and examined for external abnormalities. Half of the fetuses were fixed in Bouin's solution and examined for visceral variations or malformations; the remaining half were fixed in ethyl alcohol and examined for skeletal retardations, variations, or malformations. Statistics were performed using both the litter and the fetus as units of analysis. For the purposes of this PPRTV assessment, fetal incidence data are the preferred unit of analysis over litter incidence data because the sample numbers are larger for fetuses than litters.

Significant effects are shown in Table B-10 (Hellwig and Jäckh, 1997; Confidential, 1991). For the purposes of this review, the effects discussed here are based on comparisons between treated rats and the vehicle-only control group; however, data for both control groups are shown in Table B-10. Marked maternal toxicity, as evidenced by a 60% mortality rate by GD 13, severe clinical signs of toxicity (including abnormal position, unsteady gait, apathy, nasal discharge, piloerection, and others), a marked reduction in food consumption, a 15% reduction in body weight (by GD 15), body-weight loss during the treatment period, and decrease in maternal net weight change from GD 6 were observed at 1,300 mg/kg-day. Animals that died showed discoloration of the liver and/or lung edema at necropsy. Significant developmental effects reported at this dose included a decreased pregnancy rate at time of cesarean section (40% compared to 100% in controls; associated with maternal mortality), and in surviving animals, seven- to eightfold increases in percent postimplantation loss and resorptions (mainly early), a 50% reduction in the percentage of pregnant dams that produced viable fetuses, and decreased mean fetal body weights. Only two litters were produced in the 1,300-mg/kg-day group. The fetal incidences of visceral variations (dilated renal pelvis, hydroureter) and skeletal malformations (absent thoracic vertebrae, and sternebrae bipartite with ossification centers dislocated) were statistically significantly increased at 1,300 mg/kg-day (see Table B-10). The fetal incidences of skeletal variations (accessory lumbar vertebrae and 14th ribs, rudimentary cervical ribs, and 13th ribs absent or shortened) and retardations (thoracic vertebral body/bodies and sternebrae not ossified, sternebrae incompletely ossified or reduced in size) were significantly increased at ≥650 mg/kg-day (see Table B-10). Litter

incidences of all abnormalities in the 1,300-mg/kg-day group were 100%, but not statistically significant due to the small number available and high control incidences.

Other than one 650 mg/kg-day-animal that died from gavage error (on GD 10), no mortality was observed at ≤650 mg/kg-day. Piloerection was noted in two dams treated at 650 mg/kg-day. Maternal body weight measured on GD 15 or 20, maternal carcass weight (terminal body weight minus uterine weight), or maternal net weight change from GD 6 (carcass weight − GD 6 body weight) were not statistically significantly changed at ≤650 mg/kg-day. The body-weight gains of rats treated at 130 and 650 mg/kg-day were 15−16% lower than controls during the dosing period (GDs 6−15); rats treated at 650 mg/kg-day also gained 8% less than controls throughout gestation (GDs 0−20). However, these body-weight measures do not represent only maternal body weight but also fetal body weight. In fetuses, decreased fetal body weights were observed at 650 mg/kg-day (10% lower than controls based on the combined sexes; 11% for males and 9% for females when considered separately). For the purposes of this PPRTV assessment, a ≥5% decrease in fetal body weight is considered biologically significant by the U.S. EPA. No effects on conception rate, numbers of corpora lutea, rates of pre- and postimplantation loss, resorptions, or numbers of live/dead fetuses were seen at ≤650 mg/kg-day.

A FEL of 1,300 mg/kg-day is identified for this study based on severe toxicity (mortality, clinical signs, and body-weight loss) in maternal animals. The next highest dose (650 mg/kg-day) is a NOAEL for maternal toxicity. Based on the statistically significant increases in fetal incidences of skeletal variations and retardations and statistically and biologically significantly decreased fetal body weight, a developmental LOAEL of 650 mg/kg-day is identified for this study with a corresponding NOAEL of 130 mg/kg-day.

NTP (1991)

Time-mated CD-1 Swiss mice (28/group) were treated with microencapsulated 2-EH (>99% purity) at 0, 0.009, 0.03, or 0.09% in the diet on GDs 0−17. The study authors calculated equivalent doses that correspond to average intakes of 0, 17, 59, and 191 mg/kg-day. Maternal animals were monitored daily for mortality and clinical signs of toxicity. Food consumption and body weights were measured on GDs 0, 3, 6, 9, 12, 15, and 17. At sacrifice on GD 17, body, liver, and uterine weights were recorded; uterine contents were examined for numbers of implantation sites, resorptions, and live and dead fetuses. Corpora lutea (ovaries) were counted. Endpoints evaluated in all fetuses included body weight and sex (determined by a fresh tissue dissection technique) and presence/absence of external morphological abnormalities and visceral and skeletal variations and malformations. The heads of half of the fetuses were fixed in Bouin's solution and examined using a free-hand sectioning technique. The litter was the unit for statistical analyses.

No mortality occurred in maternal animals (NTP, 1991). The only clinical sign of toxicity reported was hyperactivity, observed in one dam treated at 59 mg/kg-day (GD 6) and one dam treated at 191 mg/kg-day (GDs 6, 9, and 12). There were no significant effects on food consumption. Maternal body weight and body-weight gain (including weight gain corrected for gravid uterine weight) of treated mice were ≥90% of control values throughout the study; gravid uterine weights were also comparable among treated mice and controls. No significant effects on absolute or relative liver weights were observed. The pregnancy rate at sacrifice was 93−96% across all treatment groups (including controls). Numbers of corpora lutea (per dam) and resorptions and implantations (per litter) were unaffected by treatment. Furthermore, there were no significant effects on the numbers of live/dead fetuses, litter size, fetal body weights, sex of fetuses,

or the incidences of variations or malformations (total, visceral, or skeletal). The highest dose of 191 mg/kg-day is identified as a NOAEL for maternal and developmental toxicity. No LOAEL was identified.

Hardin et al. (1987) (published report); Hazleton Laboratories (1983) (non-peer-reviewed report)

In a study employing a short-term in vivo testing methodology to screen various chemicals, pregnant CD-1 mice (50/group) were administered 2-EH at 1,525 mg/kg-day (the approximate lethal dose of 10% of the population [LD_{10}] based on a preliminary dose range-finding experiment) via gavage in corn oil on GDs 6−13 and were permitted to deliver their litters. The mice were monitored at least once daily for mortality and clinical signs of toxicity. Maternal body weights were recorded (for pregnant females only) on GDs 6 and 17, and Postnatal Day (PND) 3 [according to Hardin et al. (1987)] or on GDs 7, 14, and 18, and PND 3 (Hazleton Laboratories, 1983). Developmental endpoints evaluated included mean numbers of live and dead pups and pup body weights (on PNDs 1 and 3), and pup viability and pup body-weight gain (from PNDs 1−3). Pups (whether alive or dead) were not examined for external malformations. Females that failed to deliver a litter by GD 22 were sacrificed and their uteri examined for gross evidence of failed pregnancy. If no evidence was found, uteri were stained with sodium sulfide to identify implantation sites.

Significant effects in mice treated with 2-EH are shown in Table B-11 (Hardin et al., 1987; Hazleton Laboratories, 1983). In some cases, data in the two reports were similar in magnitude but different in value (owing, at least in part, to variations in the times at which specific endpoints were measured); in these cases, data from the more complete report (Hazleton Laboratories, 1983) are discussed here. Mortality was observed in 35% of treated mice compared to 0% controls (Hardin et al., 1987; Hazleton Laboratories, 1983). One treated animal that died (on GD 8) due to a dosing error was omitted from analyses. All other deaths (one on GD 17; all others on GDs 8−13) were attributed to treatment (no cause of death was specified). Clinical signs of toxicity (languidness, ataxia, coldness to touch, wet stains, oily coat, and/or dark red discharge) were noted in treated mice, predominantly during GDs 7−14 (with some signs being observed in fewer animals on GDs 15−18). The body weights of 2-EH-treated dams were significantly decreased by 9−15% relative to controls at all time points except GD 7 (see Table B-11). Similarly, maternal body-weight gains encompassing treatment (GDs 7−14) and pregnancy (GDs 7−18) were markedly reduced in treated mice (33 and 37% lower than controls, respectively). No data were provided with respect to gravid uterine weights. However, pregnancy was likewise affected: the number of pregnant females was lower in treated mice (20 compared to 34 for controls). No data for nonpregnant females (with respect to implantation sites) were provided. In addition, a smaller percentage of pregnant mice in the 2-EH group produced a viable litter (defined as a litter with at least one live pup on PND 1); the rate was 97% in controls compared to 55% in 2-EH-treated mice.

With respect to pups, the number of live pups per litter was significantly decreased (by 35−50%) and (consequently) the number of dead pups per litter was significantly increased (by about 15-fold) in 2-EH-treated mice on PNDs 1 and 3 [Hardin et al. (1987); Hazleton Laboratories (1983) and Table B-11]. Pup weights (expressed as mean pup weight/litter) were also significantly lower for treated mice than controls at these time points (by 13% on PND 1 and 23% on PND 3). Pup survival and growth from PNDs 1−3 were also affected; viability per litter was reduced from 98% in controls to 73% in the 2-EH group, and surviving animals gained substantially less weight than their untreated counterparts (33% less than controls). These data identify a FEL of

1,525 mg/kg-day (the only dose tested) based on severe maternal toxicity (mortality and decreased body-weight gain) and developmental toxicity (decreased survival and growth from PNDs 1−3). Because 1,525 mg/kg-day is the only dose tested, identification of a NOAEL is precluded.

Ritter et al. (1987)

In a study designed to evaluate the teratogenicity of DEHP and its metabolites, pregnant Wistar rats (7 litters/group) were administered 2-EH (unknown purity) via gavage, undiluted, at 0, 6.25, or 12.5 mmol/kg (0, 1.0, or 2.0 mL/kg) on GD 12. Based on a density of 0.833 g/mL for 2-EH, these doses are equivalent to about 0, 830, and 1,700 mg/kg as calculated by the U.S. EPA for the purposes of this PPRTV assessment. The rats were sacrificed on GD 20 and cesarean sections performed. Numbers of implantation sites and resorbed or dead fetuses were counted. Live fetuses were weighed and examined for external malformations. Half of the fetuses were evaluated for skeletal anomalies (by staining with alcian blue and alizarin red S); the remaining half were evaluated for soft tissue anomalies (by staining with Bouin's fluid preparatory). Statistical analyses were not performed.

Effects in 2-EH treated rats are shown in Table B-12 (Ritter et al., 1987). The number of implantations (91−113 per dose group, including controls) and the percentage of resorbed/dead fetuses (about 8.5−10% for each dose group) were not affected by treatment. However, mean fetal body weights were decreased in treated rats by 5% relative to controls at 830 mg/kg and by 15% at 1,700 mg/kg (no measure of variance for these data was provided). Furthermore, there was a significant, dose-related increase in the percentage of surviving fetuses with malformations (0% in controls compared to 2% at 830 mg/kg and 22% at 1,700 mg/kg). The malformations reported in rats treated with 2-EH at 1,700 mg/kg were hydronephrosis (8%), tail and limb defects (5 and 10%, respectively), and other (1%). No further information was provided. Owing to study limitations (limited number of evaluated endpoints and inadequate data reporting), no NOAEL or LOAEL values are identified.

Li et al. (2000)

Neonatal male CD Sprague-Dawley (S-D) rat pups (3 days old; 4−5/group) were administered 2-EH as a single dose via gavage at 167 mg/kg and sacrificed 24 hours after dosing. The right testis of each pup was fixed in 2% glutaraldehyde (in phosphate-buffered saline), embedded in glycol methacrylate, sectioned, and stained with hematoxylin for morphological examinations (using bright-field microscopy). The left testis was fixed in 10% buffered formalin, sectioned, and visualized for 5-bromo-2′-deoxyuridine (BrdU) immunostaining to evaluate the rate of Sertoli cell proliferation. No morphological changes were detected in the 2-EH-treated rats compared to controls. The rate of Sertoli cell proliferation was not significantly affected by treatment. Owing to the limited scope of this study, no NOAEL or LOAEL values can be identified.

Inhalation Exposures

The database for inhalation exposure in animals is limited to two subchronic-duration studies, one in rats (Klimisch et al., 1998; BASF, 1992b) and one in mice (Miyake et al., 2016), and one developmental toxicity study in rats (Nelson et al., 1989). Study deficiencies (limited study details and poor reporting) were apparent in the Nelson et al. (1989) study.

Subchronic-Duration Studies

Klimisch et al. (1998) (published study); BASF (1992b) (non-peer-reviewed study)

Wistar rats (10/sex/group) were exposed to 2-EH as a vapor by whole-body exposure at mean measured concentrations of 0, 15, 40, or 120 ppm (with the highest concentration corresponding to vapor saturation), 6 hours/day, 5 days/week for 90 days (65 exposures). These concentrations are equivalent to 0, 80, 213, and 638 mg/m^3. Mortality and clinical signs of toxicity were monitored daily. Body weights were recorded 1 day prior to study initiation and weekly thereafter. Hematology (WBC, RBC, platelet, and differential blood cell counts; Hb; Hct; MCV, MCH, and MCHC; thromboplastin time) and clinical chemistry (activities of ALT, AST, and ALP; urea, creatinine, total bilirubin, total protein, albumins, and globulins; glucose, cholesterol, and triglycerides; levels of sodium, potassium, chloride, inorganic phosphate, and calcium) endpoints were evaluated on study Day 94. Ophthalmological examinations were performed at study initiation and at study termination. All animals were subjected to necropsy; select organ weights (lungs, liver, kidneys, adrenal glands, and testes) were recorded. Complete histopathological examinations (>30 tissues and including gross lesions) were performed in all control and 640-mg/m^3 animals using hematoxylin-eosin staining. A subset of these tissues (including all gross lesions, the nasal cavity [three levels], trachea with larynx and bifurcation, lungs, liver, and mediastinal lymph node) were evaluated histologically in the 80- and 213-mg/m^3 groups. Liver homogenates were evaluated for cyanide-insensitive pCoA oxidation (as a marker for peroxisome proliferation).

No significant treatment-related effects were observed on any of the parameters evaluated. The highest dose of 638 mg/m^3 (HEC = 114 mg/m^3) is identified as a NOAEL. No LOAEL is identified. In accordance with U.S. EPA (1994) methodology, the concentrations of 0, 80, 213, and 638 mg/m^3 were converted to human equivalent concentrations (HECs) of 0, 14, 38, and 114 mg/m^3 for extrarespiratory effects from a Category 3 gas.[2]

Miyake et al. (2016)

Male ICR mice (5–7/group) were exposed to 2-EH by whole-body exposure at target concentrations of 0, 20, 60, or 150 ppm, 8 hours/day, 5 days/week for 1 or 3 months, or for 8 hours/day, 7 days/week for 1 week. Mean analytical concentrations for 3 months were measured at 0, 21.9, 65.8, and 153.2 ppm. The study authors reported that the mean concentration of the 20-ppm group differed by less than 5 ppm between the different time periods. These concentrations are equivalent to 0, 27.7, 83.3, and 193.9 mg/m^3. Body weights were recorded weekly throughout the exposure period. Organ weights including liver were also measured but it is unclear from the study which other organ weights were examined. For the 1-week exposure groups, mice were decapitated one day after the last exposure. For the 1- and 3-month exposure groups, mice were anesthetized the day after the last exposure and transcardially perfused with 4% (w/v) paraformaldehyde phosphate buffer to facilitate the histopathological examination of the olfactory bulb. After sacrifice, brain and nasal cavities were removed and examined histologically. The olfactory epithelium of the nasal cavity from all exposure groups were analyzed via immunohistochemical staining for the following parameters: CD45, CD3, neutrophil elastase (NE), olfactory marker protein (OMP), and proliferating cell nuclear antigen (PCNA). The olfactory bulb in the brain from only the 3-month exposure groups were analyzed via immunohistochemical

[2]CONC (HEC) = CONC (mg/m^3) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood-air partition coefficient ratio U.S. EPA (1994). The value for the rat blood-air partition coefficient for 2-EH is unknown, so the default ratio of 1 was applied.

staining for the following parameters: OMP, tyrosine hydroxylase (TH), ionized calcium-binding adapter molecule 1 (Iba1), and doublecortin (Dcx). The glomerular diameter of the olfactory bulb was also measured.

One mouse from the control group died at the start of Week 5 from unknown causes. No other mortalities were reported. The study authors stated that body weights were significantly altered in mice exposed to 83.3 and 193.9 mg/m^3 as follows: increased at the end of Weeks 1, 4, and 5 (both concentrations), decreased at the end of Week 3 (83.3 mg/m^3 only), decreased at the end of Week 6 (193.9 mg/m^3 only), and increased at the end of Week 2 (27.7 mg/m^3 only). However, the biological significance of these weight changes could not be ascertained because the study authors did not include sufficient quantitative data (i.e., magnitude of change). No effects on body weight were reported after Week 7 of the exposure period at any concentration tested. The study authors reported increased relative liver weight at 193.9 mg/m^3 after 3 months of exposure; the biological significance of this change is also unknown due to the lack of quantitative data reported. No other changes in other organ weights were observed. The study authors suggested that decreased body weight and increased relative liver weight could be due to increased lipid metabolism via the 2-EH-induced activation of peroxisome proliferator-activated receptors. After 1 week of exposure, the study authors qualitatively reported the following morphological changes in the olfactory epithelium of the nasal cavity: inflammation, degeneration, deciliation, decreased thickness, reduced number of olfactory cells, infiltration of inflammatory cells in the epithelium and lamina propria, and indistinct basement membrane. The study authors reported these morphological alterations to be concentration dependent and statistically significant at 83.3. and 193.9 mg/m^3. Also at 1 week of exposure, the high iron diamine-alcian blue staining of the Bowman's gland was qualitatively reported to decrease with increased exposure concentrations. This change could have been due to a decreased number of Bowman's glands or reduced secretion of sulfomucin. No morphological changes were observed in the 1-month exposure groups; the effects observed at 1 week of exposure had been repaired by regeneration of cell components in the olfactory epithelium. After 3 months of exposure, morphological changes in the olfactory epithelium were again statistically significant based on pathology scoring at the two highest concentrations and consisted of inflammatory cell infiltration and expansion of the Bowman's glands (see Table B-13). No 2-EH-induced lesions were reported in the respiratory epithelium.

The study authors also evaluated the infiltration of leukocytes in the olfactory epithelium via immunostaining for CD45, CD3, and NE. The number of CD45-positive cells was qualitatively reported to be increased at 1 week and 3 months at the two highest concentrations, but the study authors did not report the statistical significance of this effect. The NE-positive cell count was qualitatively stated to be significantly increased at ≥83.3 mg/m^3 at 1 week of exposure but not at 3 months. The number of CD3-positive cells was not increased at 1 week but was significantly increased at 3 months at the two highest concentrations (see Table B-13). The study authors qualitatively stated that no change in these markers of leukocyte infiltration occurred in the 1-month exposure groups. The effect of 2-EH exposure on olfactory nerve-related markers (i.e., OMP and PCNA) via immunostaining was also examined. The expression of OMP was significantly decreased at all concentrations after 1 week and 3 months (see Table B-13) of exposure; no change was observed at 1 month. The expression of PCNA was significantly decreased at all concentrations at 1 week and only at 193.9 mg/m^3 at 3 months (see Table B-13). The decreased expression of OMP and PCNA are indicative of a loss of olfactory neurons. At 1 month of exposure, PCNA expression was qualitatively reported to be significantly increased at ≥83.3 mg/m^3.

In the olfactory bulb, the glomerular diameter and the expression of TH, an inhibitory synapse marker, were both significantly decreased after 3 months of exposure to 2-EH at 193.9 mg/m^3 (see Table B-13). The decreased expression of TH is indicative of a reduction in the number of inhibitory interneurons and altered olfactory function. The expression of OMP was significantly decreased in the olfactory bulb at ≥83.3 mg/m^3 (see Table B-13). 2-EH exposure at 193.9 mg/m^3 significantly increased the expression of Iba1 and Dcx, which are both markers of migrating cells during neuronal regeneration, indicating that inflammation occurred. Based on these observed changes, the study authors concluded that 3 months of exposure to 2-EH caused damage to the olfactory bulb, including inflammation and reduction in the number of olfactory neurons.

A LOAEL of 27.7 mg/m^3 (HEC = 4.17 mg/m^3) is identified for this study based on the decreased number of OMP-positive cells in the olfactory epithelium of the nasal cavity. Because 27.7 mg/m^3 is the lowest concentration tested, identification of a NOAEL is precluded. In accordance with U.S. EPA (1994) methodology, the concentrations of 0, 27.7, 83.3, and 193.9 mg/m^3 were converted to human equivalent concentrations (HECs) of 0, 4.17, 12.5, and 29.20 mg/m^3 for male mice for extrathoracic respiratory effects.[3]

Chronic-Duration/Carcinogenicity Studies

No studies have been identified.

Reproductive/Developmental Studies

Nelson et al. (1989)

In a study designed to compare the inhalation developmental toxicity of various alcohols, pregnant female S-D rats (approximately 15/group) were exposed to 2-EH as a vapor at mean measured concentrations of 0 or 850 mg/m^3 (saturation) 7 hours/day on GDs 1−19. Maternal animals were weighed daily during the first week and weekly thereafter; total food and water consumption was measured weekly (i.e., GDs 7, 14, and 20). At sacrifice on GD 20, uteri (with ovaries) were removed; numbers of corpora lutea, implantations, resorption sites, and live fetuses were recorded. All fetuses were weighed, sexed, and examined for external malformations; half were evaluated for skeletal malformations (using alizarin red S staining) and the remaining half were evaluated for visceral abnormalities (using Bouin's solution).

Effects in dams exposed to 2-EH are shown in Table B-14 (Nelson et al., 1989). Mortality and clinical signs of toxicity (if they occurred) were not reported. Dams exposed to 2-EH showed statistically significantly decreased food consumption (9% lower than controls). Although there were no statistically significant effects on maternal body weights, rats allocated to the 2-EH group weighed on average 16% more than controls at study initiation; by Day 20, the weights of 2-EH dams were only 5% higher than controls (the study report does not indicate the methods by which the animals were allocated to specific exposure groups). During the study (i.e., from GDs 0−20), 2-EH-exposed dams gained 21% less weight than controls. No exposure-related effects on the numbers of corpora lutea, implantations, resorptions, or live fetuses or sex of fetuses were reported

[3]HEC calculated by treating 2-ethylhexanol as a Category 1 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ET} = exposure level (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × $RGDR_{ET}$, where $RGDR_{ET}$ for all exposure groups was calculated to be 0.1505 using Equation 4-28 in U.S. EPA (1994) and minute volume (V_E) values of 0.03116 L/minute based on the mean reference body weight of 0.02695 kg for male BAF_1 and $B6C3F_1$ mice in a subchronic-duration study U.S. EPA (1994) and the following default values from U.S. EPA (1994): V_E of 13.8 L/minute for humans and SA_{ET} of 33 cm^2 for mice and 200 cm^2 for humans.

(data for implantations and total numbers of live fetuses per litter were not shown; no measure of variance was provided for resorption data). The fetal body weights of males and females were 97 and 95% of controls, respectively (see Table B-14). No malformations were observed. Small (not statistically significant) numbers of fetuses from 2-EH-exposed dams showed skeletal abnormalities characterized by reversible delays in ossification of the caudal vertebrae, sternum, metacarpals, and/or hind paw phalanges (data not presented by the study authors). Although the study report contained deficiencies (unclear number of animals/group, limited study details, and poor data reporting), they did not preclude identifying the tested exposure concentration of 850 mg/m^3 (HEC = 248 mg/m^3) as a NOAEL for developmental effects.[4]

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Tests Evaluating Genotoxicity and/or Mutagenicity

A number of genotoxicity tests have been conducted (see Table 4A); data for several of these tests were available only from non-peer-reviewed sources. Genotoxicity tests in vitro (mutation, clastogenicity, deoxyribonucleic acid [DNA] repair, cell transformation, and unscheduled DNA synthesis) produced predominantly negative results. Reverse mutations were not induced in *Salmonella typhimurium* or *Escherichia coli* strains at concentrations up to 5,000 µg/plate in multiple studies (Agarwal et al., 1985; Shimizu et al., 1985; Zeiger et al., 1985; Kirby et al., 1983; Litton Bionetics, 1983b; Zeiger et al., 1982; Tenneco, 1980). Although Seed (1982) reported positive results in strain TA100 (under unspecified activation conditions), weak mutagenicity was observed only at concentrations associated with high levels of cytotoxicity (about 1 mM and above). Results were considered equivocal in a DNA repair assay in *E. coli* since positive and negative results were obtained depending on the vehicle used (ethanol or dimethylsulfoxide [DMSO]); the study authors suggested that there was a synergistic effect between ethanol and 2-EH (Tenneco, 1980). In mammalian cells, studies of mutation (in mouse lymphoma and Chinese hamster ovary [CHO] cells), chromosomal aberrations (CAs) (in CHO cells), cell transformation (in mouse BALB/3T3 cells), and unscheduled DNA synthesis (in rat hepatocytes) all yielded negative results, typically up to concentrations that elicited cytotoxicity (Litton Bionetics, 1987, 1985a, b; Kirby et al., 1983; Litton Bionetics, 1983a; Phillips et al., 1982; Tenneco, 1980).

A limited number of genotoxicity tests in vivo were available; results were mostly negative. There was no evidence for dominant lethal mutations in mice treated with 2-EH via gavage at up to 1,000 mg/kg-day (SRI International, 1981). CAs were not observed in rats following short-term oral exposure (Putman et al., 1983; Tenneco, 1980). However, there was a statistically significant increase in the incidence of micronuclei (MN) in the bone marrow of male mice dosed twice with 2-EH via intraperitoneal (i.p.) injection (Litton Bionetics, 1982). No increased induction of MN was observed in similarly treated female mice or in male or female mice treated via a single i.p. injection. The study authors attributed the significant increase in males to an unusually low spontaneous incidence of MN in the corresponding control group. Taken together, studies evaluating genotoxicity/mutagenicity for 2-EH produced mostly negative results.

[4]In accordance with U.S. EPA (1994) methodology, the NOAEL of 850 mg/m^3 was converted to a NOAEL (HEC) of 248 mg/m^3 for extrarespiratory effects from a Category 3 gas, based on the following equation for gestational exposure: CONC (HEC) = CONC (mg/m^3) × (hours exposed ÷ 24 hours) × blood-air partition coefficient ratio (default = 1) (U.S. EPA, 1994).

Supporting Animal Studies

A number of studies have evaluated the acute inhalation and oral toxicity of 2-EH (see Table 4B):

- No mortality was observed in rats or guinea pigs exposed to a saturated vapor of 2-EH for 8 hours (Bio/dynamics, 1989; Mellon Institute of Industrial Research, 1951, 1940);
- The 4-hour median lethal concentration (LC_{50}) in S-D CD rats exposed to 2-EH as a vapor/aerosol is <5,000 mg/m^3 (Bio/dynamics, 1989);
- Oral median lethal dose (LD_{50}) values in male rats range from 2,830−7,000 mg/kg (Mellon Institute of Industrial Research, 1962, 1956, 1940); and
- The oral LD_{50} values in male rabbits and in mixed guinea pigs are ~1,470 and 600 mg/kg, respectively (Mellon Institute of Industrial Research, 1962, 1940).

Numerous short-term-duration (generally 9−12 days in duration) oral toxicity studies have been conducted using different vehicles (propylene glycol, corn oil, Cremophor EL, and microencapsulated 2-EH) in F344 rats and B6C3F$_1$ mice (Astill et al., 1996a; BASF, 1991d, f, g, h, i, k, l, m). These studies consistently identified the stomach and liver (also spleen and kidney, especially in animals that died) as the targets of 2-EH-induced toxicity (see Table 4B). In a developmental study in F344 rats conducted via the dermal route, there was no evidence of fetotoxicity or teratogenicity at doses that caused maternal toxicity (i.e., decreased body weight) (Tyl et al., 1992; BushyRun, 1989).

Metabolism/Toxicokinetic Studies

Evidence from oral studies conducted in rodents indicates that 2-EH is readily absorbed from the gastrointestinal (GI) tract (Deisinger et al., 1994; Eastman Kodak, 1992; Albro, 1975). Based on the observation that 2-EH was not detected in the blood of dosed male rats, metabolism (leading to the formation of 2-ethylhexanoic acid) is considered rapid (Deisinger et al., 1994; Eastman Kodak, 1992). Gavage studies in male and female rats (at doses ranging from 50−500 mg/kg; single and/or repeated exposures) showed that, regardless of single or repeated exposures, about 70−80% of the oxidative and conjugated metabolites of 2-EH were eliminated in the urine; lesser amounts of oxidative and conjugated metabolites of 2-EH were detected in expired air (6−14%) and the feces (8−15%). Elimination was rapid, occurring within about 24−28 hours of dosing (Deisinger et al., 1994; Eastman Kodak, 1992; Albro, 1975). The urinary metabolites identified in these studies (and in an additional rabbit study) were predominantly glucuronides of oxidized metabolites of 2-EH, including 2-ethyladipic acid, 2-ethylhexanoic acid, 5-hydroxy-2-ethylhexanoic acid, 6-hydroxy-2-ethylhexanoic acid, 2-ethyl-5-ketohexanoic acid, and/or 2-ethyl-1,6-hexanedioic acid; only small amounts of unchanged 2-EH were detected (Deisinger et al., 1994; Eastman Kodak, 1992; Albro, 1975; Kamil et al., 1953). Based on differences in the profiles of metabolites detected in urine at 50 and 500 mg/kg, there was some evidence of metabolic saturation at the high dose (Deisinger et al., 1994; Eastman Kodak, 1992). However, there was no evidence of metabolic induction after repeated low-dose exposure [compared to single low-dose exposures; Deisinger et al. (1994); Eastman Kodak (1992)].

Dermal studies showed that neat 2-EH (applied at 1,000 mg/kg for 6 hours) is not readily absorbed through the skin of male rats. Less than 5% of 2-EH was absorbed; the rest was recovered from the skin surface. As in the oral studies, absorbed 2-EH was mainly excreted via the urine as glucuronide conjugates of 2-EH metabolites, with lesser amounts being detected in expired air and the feces (Deisinger et al., 1994; Eastman Kodak, 1992). Based on data from in vitro percutaneous

absorption studies, the rate of absorption of 2-EH through rat skin is approximately six times higher than that of the human stratum corneum (Barber et al., 1992; Eastman Kodak, 1990).

Several studies that evaluated the metabolites of DEHP have shown that 2-EH alters liver metabolism, as seen by data showing that 2-EH inhibits mouse alcohol dehydrogenase and rat ketone body production in vitro (Badr et al., 1990; Agarwal et al., 1982) and induces mouse cytosolic epoxide hydrolase in vivo (Hammock and Ota, 1983).

Mode-of-Action/Mechanistic Studies

A number of studies have evaluated the major metabolites of DEHP, namely mono(2-ethylhexyl) phthalate (MEHP) and 2-EH, to elucidate their roles (if any) in the mode of action (MOA) for DEHP-induced toxicity (particularly in the liver and the testes). In various studies, 2-EH was investigated for its ability to alter fatty acid metabolism (Bojes and Thurman, 1996, 1994; Cornu et al., 1992; Moody and Reddy, 1982), intracellular Ca^{2+} levels (Hijioka et al., 1991), cellular respiration (Keller et al., 1992b; Keller et al., 1992a; Keller et al., 1991; Keller et al., 1990), peroxisome proliferation (Dirven et al., 1992; Keith et al., 1992; Pollack et al., 1989; Keith et al., 1988; Hodgson, 1987; Mitchell et al., 1985; Gray et al., 1983; Gray et al., 1982; Moody and Reddy, 1978), and cell proliferation in the liver, which precedes tumor formation. Similarly, 2-EH was tested for its effects on Sertoli cell function to determine whether it is involved in DEHP-induced testicular toxicity (Piché et al., 2012; Williams and Foster, 1988; Gray and Beamand, 1984). In general, these studies found that 2-EH was a weak inducer of liver and testicular toxicity.

Table 4A. Summary of 2-Ethylhexanol (CASRN 104-76-7) Genotoxicity

Endpoint	Test System	Dose/ Concentration[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537	3.3−220 µg/plate	−	−	Positive and negative controls responded appropriately. Slight clearing of the background lawn was noted at 220 µg/plate.	Zeiger et al. (1985); Zeiger et al. (1982)
Mutation	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; *Escherichia coli* WP2uvrA	1−1,000 µg/plate	−	−	Positive and negative controls responded appropriately.	Shimizu et al. (1985)
Mutation	*S. typhimurium* strains TA98, TA100, TA1535, TA1538	100−2,000 µg/plate	−	−	These strains (and strains TA1537 and TA2637) were not mutagenic in spot tests. Cytotoxicity was noted in all strains and was enhanced in the presence of activation.	Agarwal et al. (1985)
Mutation	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538	10−5,000 µg/plate	−	−	Cytotoxicity and/or a precipitate was noted at 1,000 µg/plate (TA1535 strain only without activation) and 5,000 µg/plate.	Tenneco (1980)
Mutation	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538	0.01−1.0 µL/plate	−	−	Positive and negative controls responded appropriately.	Kirby et al. (1983)
Mutation	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538	0.002−1.8 µL/plate	−	−	Study report provided data tables only. Results interpreted as negative in the absence of a twofold increase in the number of revertants.	Litton Bionetics (1983b)
Mutation	*S. typhimurium* strain TA100	0, 0.5, 1.0, 1.5 mM	(+)	NR	Significant cytotoxicity was associated with a weak mutagenic response. The report indicated that activation inhibited the mutagenic response but does not explicitly state whether the results were considered weak positive or negative in the presence of activation.	Seed (1982)

Table 4A. Summary of 2-Ethylhexanol (CASRN 104-76-7) Genotoxicity						
Endpoint	**Test System**	**Dose/ Concentration[a]**	**Results without Activation[b]**	**Results with Activation[b]**	**Comments**	**References**
DNA repair	*E. coli* strains W3110 (pol A+) and p3478 (pol A−)	0, 10, 50, 100, 250, 500 µg/mL (in EtOH or DMSO)	±	±	Overall results were considered equivocal; the results were positive using EtOH as the test vehicle, and negative using DMSO.	Tenneco (1980)
Genotoxicity studies in mammalian cells—in vitro						
Mutation	L5178Y TK ± mouse lymphoma cells	0.013−1.0 µL/mL	−	−	Cytotoxicity was noted at ≥0.24 µL/mL; complete toxicity occurred at 1.0 µL/mL.	Kirby et al. (1983); Tenneco (1980)
Mutation (HGPRT locus)	CHO cells	0, 20, 50, 100, 200, 250, 300 nL/mL (−S9); 0, 100, 200, 250, 300, 350, 400 nL/mL (+S9)	−	−	Increases in mutant frequency at 200 nL/mL (−S9) and 250 and 400 nL/mL (+S9) were not considered indicative of mutagenicity because responses were small, without dose-response, and not confirmed in duplicate cultures.	Litton Bionetics (1985b); Litton Bionetics (1985a)
CAs	CHO cells	0, 1.5, 1.9, 2.2, 2.4, 2.8 mM	−	NA	A slight (not statistically significant) response was noted at 2.4 mM. No mitoses occurred at 2.8 mM.	Phillips et al. (1982)
Cell transformation	Mouse BALB/3T3 cells	0, 96, 144, 180 nL/mL	NA	−	Positive and negative controls responded appropriately.	Litton Bionetics (1983a)
Cell transformation	Mouse BALB/3T3 cells	0.188, 0.375, 0.75, 1.125, 1.5 µL/mL (Trial 1); 0.011, 0.043, 0.086, 0.129, 0.162 µL/mL (Trial 2)	−	NA	No evidence of transforming activity was observed under open-vessel (Trial 1) or closed-vessel conditions (Trial 2).	Litton Bionetics (1987)
Cell transformation	Mouse BALB/3T3 cells	0, 0.03, 0.1, 0.3 µL/mL	−	−	Positive and negative controls responded appropriately.	Tenneco (1980)
Unscheduled DNA synthesis	Rat hepatocytes	2.5−1,000 nL/mL	−	NA	Complete toxicity was observed at ≥500 nL/mL.	Tenneco (1980)

Table 4A. Summary of 2-Ethylhexanol (CASRN 104-76-7) Genotoxicity

Endpoint	Test System	Dose/ Concentration[a]	Results without Activation[b]	Results with Activation[b]	Comments	References
Genotoxicity studies in mammals—in vivo						
Dominant lethal assay	ICR/SIM mouse (20 M/group); dosed via gavage for 5 d; mated with 2 F/wk for 8 wk	0, 250, 500, 1,000 mg/kg-d	−	−	No significant effects on fertility indices or the average number of dead and total implants per pregnancy were observed.	SRI International (1981)
CAs (oral)	F344 rat (5 M/group); dosed via gavage for 5 d; sacrifice 6 hr after the last dose	0, 0.02, 0.07, 0.21 mL/kg-d	−	−	Positive and negative controls responded appropriately.	Putman et al. (1983); Tenneco (1980)
MN assay (i.p.)	$B6C3F_1$ mouse (4/sex/group); dosed via i.p. injection once or multiple times (two doses 24 hr apart); sacrifice 24−30 hr after the last dose	0, 456 mg/kg-d	(+)	(+)	An increased incidence of MN was observed in male mice dosed multiple times only; the positive response was considered an artifact of an unusually low incidence in the corresponding control group. Clinical signs (shallow breathing, hunched backs, eye irritation) were noted following dosing; all animals recovered within 24 hr.	Litton Bionetics (1982)

[a]Highest dose tested for negative results.
[b](+) = weak positive; + = positive; − = negative; ± = equivocal; NA = not applicable; NR = not reported.

CA = chromosomal aberration; CHO = Chinese hamster ovary; DMSO = dimethylsulfoxide; DNA = deoxyribonucleic acid; EtOH = ethyl alcohol; F = female(s); i.p. = intraperitoneal; M = male(s); MN = micronuclei; NA = not applicable; NR = not reported.

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Supporting evidence—noncancer effects in animals				
Acute toxicity (oral)	M albino rat (4−12/group, strain not specified) were administered 5,000, 6,000, 8,000, 10,000, 12,000, 15,000, or 18,000 mg/kg via gavage and observed for 14 d.	Mortality was 0, 45, 70, 70, 83, 75, and 100%, respectively. Death was preceded by narcosis and hypothermia. Congestion of the liver and spleen and pale kidneys were noted at necropsy.	LD_{50} = 7,000 mg/kg	Mellon Institute of Industrial Research (1940)
Acute toxicity (oral)	M rat (strain, number, doses administered not reported) dosed via gavage.	No supporting study information.	LD_{50} = 2,830 mg/kg	Mellon Institute of Industrial Research (1956)
Acute toxicity (oral)	M rat (strain, number, doses administered not reported) dosed via gavage.	No supporting study information.	LD_{50} = 4.46 mL/kg (~3,720 mg/kg)	Mellon Institute of Industrial Research (1962)
Acute toxicity (oral)	M rabbit (strain, number, doses administered not reported) dosed via gavage.	No supporting study information.	LD_{50} = 1.77 mL/kg (~1,470 mg/kg)	Mellon Institute of Industrial Research (1962)
Acute toxicity (oral)	Mixed guinea pig (5−10/group, sex not specified) were administered 500, 630, 795, or 1,260 mg/kg via gavage observed for 14 d.	Mortality was 40, 25, 30, and 100%, respectively. Death was preceded by narcosis and hypothermia. Congestion of the liver and spleen and pale kidneys were noted at necropsy.	LD_{50} = 600 mg/kg	Mellon Institute of Industrial Research (1940)
Short-term toxicity (oral)	F344 rat (5/sex/group) were administered 0, 100, 320, or 950 mg/kg-d via gavage (in corn oil) for 21 d. Endpoints evaluated included food consumption and body weights, serum cholesterol and triglycerides, and selected organ weights (liver, kidneys, and testes). Samples of the liver were viewed using electron microscopy to evaluate peroxisomes, for histological examinations of neutral fat, and for biochemical evaluations (determinations of cyanide-insensitive pCoA oxidation, microsomal lauric acid 11- and 12-hydroxylation, and total microsomal protein levels).	Decreased body-weight gain was noted in 950-mg/kg-d females. Triglycerides were significantly increased at 950 mg/kg-d (M only). At necropsy, absolute and relative liver weights were increased at 950 mg/kg-d (M) and ≥320 mg/kg-d (F). Relative kidney weights were significantly increased at 950 mg/kg-d (both sexes). Also at 950 mg/kg-d, increased lauric 11- and 12-hydroxylase activities (both sexes) and cyanide-insensitive pCoA oxidation (F only) were observed. Cyanide-insensitive pCoA oxidation was increased at ≥320 mg/kg-d (M). A dose-related increase in neutral lipids was noted in all treated animals. Hepatic peroxisomes were increased at 950 mg/kg-d (both sexes).	A NOAEL of 320 mg/kg-d and a LOAEL of 950 mg/kg-d are identified based on statistically and biologically significantly increased absolute and relative liver weights in male and female rats and biologically significantly increased relative kidney weight in female rats.	BIBRA (1987)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term toxicity (oral)	F344 rat (10/sex/group) were administered 0, 0.1, 0.33, 1.0, or 1.5 mL/kg-d (0, 83, 275, 834, or 1,250 mg/kg-d) via gavage (in water) for 5 d followed by 2 d without treatment, and 4 additional days of treatment (a total of 9 d of treatment in 12 d). Endpoints evaluated included mortality and clinical signs of toxicity, food and water consumption, body weights, hematology and clinical chemistry parameters, organ weights (brain, liver, kidneys, lungs, stomach, spleen, adrenals, and testes), and gross and microscopic pathology.	One high-dose male died. Clinical signs (hypoactivity, ataxia, prostration, delayed righting reflex, muscle twitch, lacrimation and/or urine stains) were noted at ≥834 mg/kg-d; signs (unkempt appearance and urine-stained fur) were irreversible at 1,250 mg/kg-d. Food consumption was significantly decreased at ≥275 mg/kg-d (M) (not strictly dose related) and at ≥834 mg/kg-d (F). Although body weights were decreased at the same doses, they remained within 10% of controls except in the 1,250-mg/kg-d male (decreased by 17% on study D 11). Males treated at 1,250 mg/kg-d and females treated at ≥834 mg/kg-d showed significantly decreased numbers of total leukocytes and lymphocytes (20−45% lower than their respective control groups). At necropsy, increased absolute and relative liver and stomach weights (in both sexes at ≥834 mg/kg-d) and decreased absolute and/or relative spleen weights (at 1,250 mg/kg-d [M] and at ≥834 mg/kg-d [F]) were observed. Statistically significant and/or dose-related increases in the incidence or severity of microscopic effects were observed at ≥275 mg/kg-d (both sexes), including lesions of the forestomach (hyperkeratosis, mucosal hyperplasia, edema, gastritis, and exocytosis), thymus (lymphoid cell degeneration), and spleen (lymphoid cell degeneration and decreased amount of extramedullary hematopoiesis).	A NOAEL of 83 mg/kg-d and a LOAEL of 275 mg/kg-d are identified for this study based on a significantly increased incidence of stomach lesions in male and female rats.	BushyRun (1988)

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Short-term toxicity (oral)	In the study described above, F344 rat (10/sex/group) were administered nominal concentrations of 0, 350, and 700 ppm (maximum attainable concentration) in drinking water for 9 d. The same endpoints were evaluated. Calculated doses on D 4 and 9 were 68.0 and 54.2 mg/kg-d for 350-ppm M (mean = 61.1 mg/kg-d), 159.1 and 143.3 mg/kg-d for 700-ppm M (mean = 151.2 mg/kg-d), 80.8 and 65.9 mg/kg-d (mean = 73.4 mg/kg-d) for 350-ppm F, and 181.3 and 166.0 mg/kg-d (mean = 173.7 mg/kg-d) for 700-ppm F.	No significant, treatment-related effects were observed.	A NOAEL of 750 ppm (~174 mg/kg-d) is identified for this study based on the lack of significant, treatment-related effects.	BushyRun (1988)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term toxicity (oral)	F344 rat (10/sex/group) were administered 0, 100, 330, 1,000, or 1,500 mg/kg-d via gavage (in propylene glycol) 9 times in 11 d. Endpoints evaluated included mortality and clinical signs of toxicity, food and water consumption, body weights, hematology and clinical chemistry parameters, organ weights (brain, liver, kidneys, lungs, stomach, spleen, adrenals, and testes), and gross (but not microscopic) pathology.	Mortality occurred at 1,500 mg/kg-d only (all F and 6/10 M). Clinical signs (lethargy, ataxia, piloerection, uncoordinated movements of the fore- and hindlimbs, abdominal or lateral position, loss of consciousness, urine-stained fur, hypothermia, and/or salivation) were noted at ≥330 mg/kg-d. Food consumption and body weights were decreased significantly at ≥1,000 mg/kg-d. Females exhibited decreased ALT at ≥100 mg/kg-d; hematological changes (decreased Hb, Hct, mean cell volume, and numbers of neutrophilic polymorphonuclear granulocytes) were observed at 330 mg/kg-d. Changes in clinical pathology (those mentioned above and including decreased numbers of leukocytes, lymphocytes, and monocytes) were also observed in both sexes at 1,000 mg/kg-d and in surviving males at 1,500 mg/kg-d. At necropsy, low-dose M showed decreased relative (but not absolute) liver weights. At all other doses (≥330 mg/kg-d), absolute and relative stomach weights were increased. Absolute and relative spleen weights were decreased at ≥1,000 mg/kg-d. Relative kidney weight was increased and relative testes weight was decreased in surviving 1,500 mg/kg-d M. Foci were observed in the forestomach (but not glandular stomach) of rats treated at ≥330 mg/kg-d (both sexes).	A FEL of 1,500 mg/kg-d is identified based on high mortality at this dose. A NOAEL of 100 mg/kg-d and a LOAEL of 330 mg/kg-d are identified based on changes in clinical pathology and increased absolute/relative stomach weights accompanied by evidence of gross pathology (i.e., foci) in both sexes.	BASF (1991l)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term toxicity (oral)	F344 rat (10/sex/group) were administered 0, 100, 330, 1,000, or 1,500 mg/kg-d via gavage (in corn oil) 9 times in 11 d. Endpoints evaluated were the same as the gavage study described above.	One 1,500-mg/kg-d female and one 1,000-mg/kg-d male died. Clinical signs (piloerection, ataxia, urine stains, lethargy, and/or salivation) were seen in a few rats of each sex at 330 mg/kg-d, and in most/all animals at ≥1,000 mg/kg-d. Food consumption and body weights were significantly decreased at ≥1,000 mg/kg-d; the body weights of treated rats were <90% of controls at 1,500 mg/kg-d. Changes in hematology (decreased MCV and/or MCH, lymphocytes, leukocytes, monocytes, and reticulocytes) and/or clinical chemistry (decreased ALT activity, cholesterol, and glucose; increased total protein) were observed only at 1,000 and 1,500 mg/kg-d. At necropsy, only relative testes weight was affected (increased) at 330 mg/kg-d. At 1,000 and 1,500 mg/kg-d, increased absolute and/or relative stomach and liver weights and decreased absolute and/or relative spleen weights were observed. Forestomach changes were noted at doses as low as 330 mg/kg-d (thickening of the wall in 3 M and foci in 1 M); the incidence of these effects increased in a dose-related manner (in both sexes) at 1,000 and 1,500 mg/kg-d.	A NOAEL of 330 mg/kg-d and a LOAEL of 1,000 mg/kg-d are identified based on clinical signs of toxicity, decreased body weight, changes in clinical pathology, organ-weight changes (increased liver and stomach weights and decreased spleen weights), and an increased incidence of forestomach effects in both sexes.	BASF (1991k)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term toxicity (oral)	F344 rat (10/sex/group) were administered 0, 100, 330, 1,000, or 1,500 mg/kg-d via aqueous gavage (in Cremophor EL) 9 times in 11 d. Endpoints evaluated were the same as the gavage studies described above, except that microscopic pathology was performed.	No mortality was reported. Clinical signs (including ataxia, lethargy, abdominal or lateral position, piloerection, apathy, and/or urine stains) were seen in several animals treated at 1,000 mg/kg-d and all animals treated at 1,500 mg/kg-d. Food consumption was significantly decreased in both sexes at 1,000 mg/kg-d. Although body weights were significantly reduced at 1,000 mg/kg-d (F), the body weights of treated animals remained within 10% of controls except at 1,500 mg/kg-d (decreased 17% in M and 13% in F by D 10). Changes in hematology (decreased reticulocytes) and/or clinical chemistry (decreased cholesterol and glucose, increased ALT activity) were observed only at 1,000 and 1,500 mg/kg-d. At necropsy, only relative kidney weight in females was affected (increased) at 330 mg/kg-d. At 1,000 and 1,500 mg/kg-d, increased absolute and/or relative stomach and liver weights and decreased absolute and/or relative spleen weights were observed. Some additional relative (but not absolute) organ-weight changes were also noted (increased relative kidney weight in both sexes, increased relative adrenal, lung, or brain weights in one sex). Gross pathology examinations revealed the presence of foci in the forestomach of a few rats treated at 1,000 mg/kg-d and in many rats (4 M and 7 F) treated at 1,000 mg/kg-d. Increased incidences of histopathological lesions occurred at 1,000 and 1,500 mg/kg-d, and included effects on the forestomach (hyperkeratosis, focal or multifocal acanthosis, and/or inflammatory edema), spleen (parenchymal involution of lymphoreticular tissue), thymus (decreased size and/or lymphocyte depletion), and/or liver (hypertrophy of hepatocytes). Inflammatory edema of the forestomach (1 F) and decreased thymus size (2 M and 1 F) were observed at 330 mg/kg-d.	A NOAEL of 330 mg/kg-d and a LOAEL of 1,000 mg/kg-d are identified based on clinical signs of toxicity, decreased food consumption, changes in clinical pathology parameters, organ-weight effects (increased stomach and liver weights and decreased spleen weights), and histopathological findings (specifically of the forestomach) in both sexes.	Astill et al. (1996a); BASF (1991i)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term toxicity (oral)	F344 rat (10/sex/group) were administered microencapsulated 2-EH in the diet at 0, 0.46, 0.92, 1.38, or 2.57% (w/w) (about 0, 500, 980, 1,430, or 2,590 mg/kg-d for M and 0, 540, 1,060, 1,580, or 2,820 mg/kg-d for F) for 11 d. Endpoints evaluated were the same as the gavage studies described above, except that microscopic pathology was performed.	No mortality occurred, and no clinical signs of toxicity were reported. Food consumption was significantly decreased on D 4 and/or D 10 at ≥500 mg/kg-d (M) and ≥1,060 mg/kg-d (F). Although body weights were significantly decreased at doses as low as 1,430 mg/kg-d (M), they remained within 10% of controls except at 2,590-mg/kg-d (M) and 2,820-mg/kg-d (F) (decreased by 23 and 18%, respectively, on D 10). Changes in clinical pathology seen at ≥500 mg/kg-d (M) included decreased cholesterol and triglyceride levels and decreased ALT activity; females treated at ≥540 mg/kg-d also showed decreased cholesterol levels. Additional effects at higher doses included increased total protein (at ≥980 mg/kg-d [M] and at 2,820 mg/kg-d [F]), decreased platelets (at 2,590 mg/kg-d [M] and at ≥1,580 mg/kg-d [F]), and decreased glucose, reticulocytes, MCV, and/or MCH and increased RBCs (at 2,590 mg/kg-d [M] and/or at 2,820 mg/kg-d [F]). At necropsy, relative (but not absolute) stomach weights were increased in 540-mg/kg-d females only. Increased absolute and/or relative stomach and liver weights were consistently seen at ≥980 mg/kg-d (M) and 1,060 mg/kg-d (F). Histopathological examinations revealed liver effects (hypertrophy of hepatocytes) and forestomach effects (focal or multifocal acanthosis); these lesions were observed in "most" animals at 1,430/1,580 and 2,590/2,820 mg/kg-d, respectively.	NOAEL values of 500 mg/kg-d (M) and 540 mg/kg-d (F) and LOAEL values of 980 mg/kg-d (M) and 1,060 mg/kg-d (F) are identified based on increased stomach and liver weights in both sexes.	BASF (1991m)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term toxicity (oral)	$B6C3F_1$ mouse (10/sex/group) were administered 0, 100, 330, 1,000, or 1,500 mg/kg-d via gavage (in propylene glycol) 9 times in 11 d. Endpoints evaluated included mortality and clinical signs of toxicity, food and water consumption, body weights, hematology and clinical chemistry parameters, organ weights (brain, liver, kidneys, lungs, stomach, spleen, adrenals, and testes), and gross (but not microscopic) pathology.	Mortality occurred at 1,000 mg/kg-d (1 M and 1 F) and 1,500 mg/kg-d (4 M and 6 F). Clinical signs (including ataxia, lethargy, piloerection, dyspnea, hypothermia, abdominal or lateral position, and/or loss of consciousness) were noted at ≥1,000 mg/kg-d. Food consumption was significantly decreased in 1,500-mg/kg-d male only (on D 4). At necropsy, increased absolute and/or relative stomach and liver weights were observed in both sexes at ≥330 mg/kg-d. Changes in absolute or relative spleen weight occurred at ≥1,000 mg/kg-d, but only in one sex. Decreased absolute/relative testes weights were seen at 1,500 mg/kg-d. Foci were observed in the forestomach of mice treated at ≥330 mg/kg-d.	A FEL of 1,000 mg/kg-d is identified owing to mortality. A NOAEL of 100 mg/kg-d and a LOAEL of 330 mg/kg-d are identified based on organ-weight changes and macroscopic forestomach effects, which were significant (M) at 330 mg/kg-d (with a dose-related trend [F]).	BASF (1991d)
Short-term toxicity (oral)	$B6C3F_1$ mouse (10/sex/group) were administered 0, 100, 330, 1,000, or 1,500 mg/kg-d via gavage (in corn oil) 9 times in 11 d. Endpoints evaluated were the same as the gavage study described above.	One male treated at 1,500 mg/kg-d died. Clinical signs of toxicity (including ataxia, lethargy, piloerection, abdominal position, and/or unconsciousness) were noted at 1,500 mg/kg-d only. At necropsy, absolute and relative testes weights were decreased at ≥1,000 mg/kg-d. At 1,500 mg/kg-d, additional organ-weight changes were observed (increased absolute and relative stomach weights in both sexes; increased relative liver and kidney weights [F only]). Gross pathology examinations showed the presence of foci in the forestomach of 7 M and 2 F mice treated at 1,500 mg/kg-d.	A NOAEL of 330 mg/kg-d and a LOAEL of 1,000 mg/kg-d are identified based on decreased testes weight in male mice.	BASF (1991g)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term toxicity (oral)	$B6C3F_1$ mouse (10/sex/group) were administered 0, 100, 330, 1,000, or 1,500 mg/kg-d via aqueous gavage (in Cremophor EL) 9 times in 11 d. Endpoints evaluated were the same as the gavage studies described above, except that microscopic pathology was performed.	Mortality occurred at 1,000 mg/kg-d (1 F) and 1,500 mg/kg-d (1 M and 4 F). Clinical signs (including ataxia, piloerection, abdominal or lateral position, loss of consciousness, and/or lethargy) were observed at 330 and 1,000 mg/kg-d (in 1 M and 1 F, respectively); effects were pronounced at 1,500 mg/kg-d. At necropsy, increased absolute and/or relative stomach weights were observed at ≥1,000 mg/kg-d. Gross pathology examinations revealed forestomach foci in mice treated at 1,000 mg/kg-d (3 M and 2 F) and 1,500 mg/kg-d (7 M and 5 F). Microscopic forestomach effects (acanthosis, hyperkeratosis, ulceration, and/or inflammatory edema) were noted at ≥330 mg/kg-d. At 1,000 and/or 1,500 mg/kg-d, changes in liver (hypertrophy of hepatocytes) and testes (tubular giant cells) pathology were reported. Mice that died showed histopathological changed in the kidney (tubular dilation and nephrosis of renal cortex) and liver (centrilobular fatty infiltration).	A FEL of 1,000 mg/kg-d is identified based on mortality (F). NOAEL and LOAEL values of 330 and 1,000 mg/kg-d are identified based on increased absolute and/or relative stomach weights accompanied by histopathological changes.	Astill et al. (1996a); BASF (1991f)
Short-term toxicity (oral)	$B6C3F_1$ mouse (10/sex/group) were administered microencapsulated 2-EH in the diet at 0, 0.22, 0.44, 0.66, or 1.32% (w/w) (about 0, 550, 1,150, 1,800, or 4,450 mg/kg-d [M] and 0, 750, 1,750, 2,650, or 5,750 mg/kg-d [F]) for 11 d. Endpoints evaluated were the same as the gavage studies described above, except that microscopic pathology was performed.	The significant, treatment-related effect reported was decreased body weight in males treated at ≥1,800 mg/kg-d and in females treated at 5,750 mg/kg-d. The body weights of treated mice stayed within 90% of controls throughout the study.	Since body weights remained within 90% of controls throughout the study, a NOAEL of 5,750 mg/kg-d (F) is identified.	BASF (1991h)

Table 4B. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Acute toxicity (inhalation)	Rat and guinea pig (6/group, strain and sex not specified) were exposed to a saturated mist for 8 hr and observed for 14 d. Gross and microscopic examinations were performed.	No mortality occurred. Irritation of the eyes and nose was noted. No abnormalities were seen in rats. Guinea pigs showed slight lung congestion and light, cloudy swelling of the kidney (one animal).	No mortality was observed in rats and guinea pigs exposed to a saturated vapor.	Mellon Institute of Industrial Research (1940)
Acute toxicity (inhalation)	Rat (6/group, strain and sex not specified) were exposed to saturated vapor exposure for 8 hr.	No supporting study information.	No mortality observed in rats exposed to a saturated vapor.	Mellon Institute of Industrial Research (1951)
Acute toxicity (inhalation)	S-D CD rat (3/sex/group) were exposed whole-body as a vapor/aerosol at 5,000 mg/m^3 or as a saturated vapor (890 mg/m^3) for 4 hr and observed for 7 d. Necropsies were not performed.	Mortality was 0/6 and 6/6 in the 890- and 5,000-mg/m^3 groups, respectively. Clinical signs (including labored breathing, nasal discharge, prostration, closed eyes, chromodacryorrhea) were noted in the 5,000-mg/m^3 group.	LC_{50} = >890 mg/m^3 (vapor); <5,000 mg/m^3 (vapor/aerosol)	Bio/dynamics (1989)

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Other routes-developmental toxicity	F344 rat (8 or 25/group) were administered 0, 0.5, 1.0, 2.0, or 3.0 mL/kg-d (equivalent to 0, 420, 840, 1,680, or 2,520 mg/kg-d) in a range-finding study or 0, 0.3, 1.0, or 3.0 mL/kg-d (equivalent to 0, 252, 840, or 2,520 mg/kg-d) in a main study via the dermal route under occluded conditions for 6 hr/d on GDs 6−15 and sacrificed on GD 21. Maternal animals were monitored daily for clinical signs and skin irritation. Maternal body weights were recorded on GDs 0, 6, 9, 12, 15, and 21; food consumption was measured for 3-d intervals through GD 21. Maternal uterine and liver weights were recorded; spleen, adrenals, kidneys, and thymus weights were weighed in the main study only. Numbers of corpora lutea were counted; the ovaries, cervices, vaginas, and abdominal and thoracic cavities were examined grossly. The uteri were examined for numbers of live and dead fetuses; nonpregnant F were examined for resorption sites. Fetuses were weighed, sexed, and examined for external malformations and variations. In the main study, about half of the fetuses from each litter were examined for visceral and craniofacial abnormalities; the other half were examined for skeletal malformations and variations.	No mortality occurred. Clinical signs included nasal and ocular effects, as well as a high incidence of exfoliation and encrustation (all treatment levels). Skin irritation (erythema, with no edema) was observed at ≥840 mg/kg-d. Statistically significant effects on maternal body-weight gains were occasionally seen; body-weight gain during the treatment period (GDs 6−15) was decreased at 1,680 and 2,520 mg/kg-d in the range-finding study only (decreased 47 and 43% relative to sham controls, respectively). There was no effect on body-weight gain on GDs 0−21 in either study. At necropsy, the only finding was residual exfoliation and crusting at the application site at the mid- and high-treatment levels (doses not further specified). No significant, treatment-related effects on gestational endpoints (total and nonviable implants, early or late resorptions, live or dead fetuses, fetal sex ratio, or fetal body weights) were observed. There were no significantly increased incidences of external, visceral, or skeletal malformations or variations in treated rats compared to controls.	A NOAEL of 252 mg/kg-d and a LOAEL of 840 mg/kg-d is identified for skin irritation (erythema). The NOAEL for developmental toxicity is 2,520 mg/kg-d. 2-EH did not induce developmental toxicity at doses that caused maternal toxicity.	Tyl et al. (1992); BushyRun (1989)

ALT = alanine aminotransferase; 2-EH = 2-ethylhexanol; F = female(s); FEL = frank effect level; GD = gestation day; Hb = hemoglobin; Hct = hematocrit; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; LOEL = lowest-observed-effect level; M = male(s); MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; pCoA = palmitoyl-Coenzyme A; RBC = red blood cell; S-D = Sprague-Dawley.

DERIVATION OF PROVISIONAL VALUES

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

Table 5. Summary of Noncancer Reference Values for 2-Ethylhexanol (CASRN 104-76-7)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/ M and F	Increased fetal skeletal variations	7×10^{-2}	BMDL	7.37	100	Hellwig and Jäckh (1997); Confidential (1991)
Chronic p-RfD (mg/kg-d)	Rat/ M and F	Increased fetal skeletal variations	7×10^{-2}	BMDL	7.37	100	Hellwig and Jäckh (1997); Confidential (1991)
Subchronic p-RfC (mg/m^3)	Mouse/ M	Increased diameter of Bowman's glands in the olfactory epithelium of the nasal cavity	4×10^{-3}	BMCL	1.11	300	Miyake et al. (2016)
Chronic p-RfC (mg/m^3)	Mouse/ M	Increased diameter of Bowman's glands in the olfactory epithelium of the nasal cavity	4×10^{-4}	BMCL	1.11	3,000	Miyake et al. (2016)

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

Table 6. Summary of Cancer Reference Values for 2-Ethylhexanol (CASRN 104-76-7)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$ (adjusted)	Mouse/M	Hepatocellular (carcinoma or adenoma)	9.5×10^{-3}	Astill et al. (1996b); BASF (1991b).
p-IUR $(mg/m^3)^{-1}$	NDr			

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

DERIVATION OF ORAL REFERENCE DOSES

Studies that are potentially relevant to the derivation of provisional reference dose (p-RfD) values include two subchronic-duration studies [one gavage study in rats and mice (Astill et al., 1996a; BASF, 1991a, c, e) and one non-peer-reviewed dietary study in rats (Mellon Institute of Industrial Research, 1960)]. There is also one chronic-duration gavage study in rats and mice (Astill et al., 1996b; BASF, 1992a, 1991b), one limited neonatal exposure study in rats (Li et al., 2000), and several developmental studies of gestational exposure in rats and mice (Hellwig and Jäckh, 1997; Confidential, 1991; NTP, 1991; Hardin et al., 1987; Ritter et al., 1987; Hazleton Laboratories, 1983). Subchronic and chronic p-RfDs are derived based on the available studies.

Derivation of a Subchronic Provisional Reference Dose

The laboratory animal oral toxicity database as a whole identifies the liver, kidney, stomach, and fetus as sensitive noncancer toxicity targets of repeated exposure to 2-EH. The developmental study in rats administered 2-EH via gavage on GDs 6−15 is selected as the principal study for deriving the subchronic p-RfD (Hellwig and Jäckh, 1997; Confidential, 1991), with rationale provided below. Increased fetal incidence of skeletal variations is identified as the critical effect. The study was reported in both a peer-reviewed publication and technical report and was conducted according to Good Laboratory Practice (GLP) standards with an adequate number of dose groups, sufficient group sizes and litters, and quantitation of results to describe dose-response relationships for the critical effects. Details of the study are provided in the "Review of Potentially Relevant Data" section.

With respect to 2-EH-induced liver toxicity, increased relative liver weight (as much as 29% higher than controls) was observed in male and female rats treated at an adjusted daily dose (ADD) of 357 mg/kg-day in a subchronic-duration study in rats (Astill et al., 1996a; BASF, 1991a). In rats administered 2-EH in the diet at 840 mg/kg-day (males) or 940 mg/kg-day (females) for up to 90 days, relative liver weight was also increased and was accompanied by cloudy swelling (diffuse) of hepatocytes (statistically significant in females only) (Mellon Institute of Industrial Research, 1960). Numerous short-term-duration oral toxicity studies in rats and mice administered 2-EH in the diet or via gavage for 9−21 days also identified the liver as a target of 2-EH-induced toxicity. In these studies, increased liver weights were observed. Histopathological examinations (when performed) frequently showed liver changes, including hypertrophy of hepatocytes and/or evidence of peroxisome proliferation (Astill et al., 1996a; BASF, 1991d, f, g, h, i, k, l, m; BIBRA, 1987).

Increased relative kidney weights were observed in male rats treated at an ADD of 357 mg/kg-day in the Astill et al. (1996a) and BASF (1991b) study. Female rats treated with 2-EH in the diet for 90 days at 940 mg/kg-day showed tubular cloudy swelling (diffuse) of the kidneys. Kidney effects (increased weight; histopathological effects in animals that died only) were also frequently identified in short-term-duration toxicity studies (Astill et al., 1996a; BASF, 1991d, f, g, h, i, k, l, m).

Increased relative stomach weights (≥179 mg/kg-day) and histopathological changes in the forestomach (acanthosis) were noted in rats at 357 mg/kg-day (Astill et al., 1996a; BASF, 1991a). Increased relative stomach weight was also observed in male mice at ≥179 mg/kg-day (Astill et al., 1996a; BASF, 1991e, l). Several of the short-term-duration gavage studies identified increased stomach weights, gross observations of foci in the forestomach, and/or

histopathological forestomach effects (hyperkeratosis, acanthosis, and/or inflammatory edema) (BASF, 1991d, f, g, h, i, k, l, m).

Identification of developmental toxicity as a health hazard from repeated oral exposure to 2-EH comes from several reports. Hardin et al. (1987) reported maternal (i.e., mortality, decreased body weight and body-weight gain) and developmental (i.e., decreased survival and growth of pups) toxicity at the only dose tested (1,525 mg/kg-day) in mice, which is identified as a FEL in mice. Ritter et al. (1987) reported decreased fetal-body weight and increased fetal malformations following maternal exposure to 2-EH on GD 12; however, inadequate reporting did not allow for the identification of a NOAEL or LOAEL for this study. In a development study in rats (Hellwig and Jackh, 1997; Confidential, 1991), decreased fetal body weight and increased fetal incidences of skeletal effects (e.g., malformations) were observed at ≥650 mg/kg-day. The fetal incidences of visceral variations (dilated renal pelvis, and hydroureter), and skeletal malformations (absent thoracic vertebrae and sternebrae bipartite with ossification centers dislocated) were statistically significantly increased at 1,300 mg/kg-day (see Table B-10). The fetal incidences of skeletal variations (accessory lumbar vertebrae and 14th ribs, rudimentary cervical ribs, and 13th ribs absent or shortened) and retardations (thoracic vertebral body/bodies and sternebrae not ossified, sternebrae incompletely ossified or reduced in size) were significantly increased at ≥650 mg/kg-day (see Table B-10).

To provide a common basis for comparing potential points of departure (PODs) and critical effects for deriving a subchronic p-RfD for 2-EH, data sets representing the most sensitive endpoints (e.g., liver, kidney, stomach, and developmental effects) were selected for benchmark dose (BMD) analysis. Based on a comparison of the PODs, the most sensitive treatment-related changes from the oral toxicity database for 2-EH, were reported in the developmental study conducted by Hellwig and Jäckh (1997) and Confidential (1991) and the subchronic-duration gavage study in rats and mice (Astill et al., 1996a; BASF, 1991a). All available continuous or dichotomous-variable models in the Benchmark Dose Software (BMDS, Version 2.7) were fit to the data sets for the most sensitive endpoints presented in Table C-1. Appendix C contains details of the modeling results for these data sets. The HED, in mg/kg-day, was used as the dose metric except for relative stomach weight (see below). Because increased fetal incidence of skeletal malformations in rats (Hellwig and Jäckh, 1997; Confidential, 1991) was statistically significant only at 325 mg/kg-day (HED) where severe maternal toxicity was also observed, the effect was not considered as a potential POD because the interpretation of this effect is confounded by the overt maternal toxicity. For this same reason, the data for decreased fetal body weight and increased fetal incidence of skeletal variations and retardations in rats were BMD modeled without the highest dose tested (325 mg/kg-day [HED]). The benchmark response (BMR) for changes in liver or kidney weight used was a 10% relative deviation (RD) change from control means, which is considered a biologically significant response. The BMR for changes in stomach weight used was 1 standard deviation (SD) change from control means, because no information is available regarding the change in this response that would be considered biologically significant. The BMR for decreased fetal body weight used was 5% RD change from control means, which is considered a biologically significant response and 5% extra risk for dichotomous developmental data. One or more of the models provided adequate fit for each data set except increased absolute liver weight in male rats (Astill et al., 1996a; BASF, 1991a) and decreased fetal body weight and increased fetal incidence of skeletal retardations in rats (Hellwig and Jäckh, 1997; Confidential, 1991). Candidate PODs, including the benchmark dose lower confidence limits (BMDLs) from the selected models, are presented in Table 7.

In U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, U.S. EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for deriving an oral reference dose (RfD) under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite, but not for portal-of-entry effects. A validated human physiologically based toxicokinetic model for 2-EH is not available for use in extrapolating doses from animals to humans. Furthermore, the most sensitive endpoints being considered are not portal-of-entry effects, except changes in stomach weight in rats. The $BW^{3/4}$ scaling factor was not applied to the stomach-weight changes because allometric scaling has not been extensively evaluated with portal-of-entry effects. However, scaling by $BW^{3/4}$ is relevant for deriving HEDs for effects other than stomach changes.

Following U.S. EPA (2011b) guidance, the doses administered resulting in the most sensitive endpoints are converted to an HED through application of a dosimetric adjustment factor (DAF) derived as follows:

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

where

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

Study-specific body weight is used to calculate the DAF for each dose group (U.S. EPA, 2011b). Calculated HEDs are presented in Table C-1 for male and female rats and mice exposed subchronically to 2-EH (Astill et al., 1996a; BASF, 1991a) and female rats exposed to 2-EH during pregnancy (Hellwig and Jäckh, 1997; Confidential, 1991).

Table 7. Candidate PODs in Rodents Administered 2-Ethylhexanol (CASRN 104-76-7) for the Derivation of the Subchronic p-RfD

Endpoint	NOAEL (HED) (mg/kg-d)	LOAEL (HED) (mg/kg-d)	BMDL (HED)[a] (mg/kg-d)	POD (HED) (mg/kg-d)
Rats Astill et al. (1996a); BASF (1991a)				
Absolute liver weight in males	43.0	85.7[b]	NDr	43.0 (NOAEL)
Relative liver weight in males	43.0	85.7[b]	45	45 ($BMDL_{10}$)
Relative kidney weight in males	43.0	85.7[b]	48	48 ($BMDL_{10}$)
Relative stomach weight in males[c]	179	357[d]	130	130 ($BMDL_{1SD}$)
Relative liver weight in females	39.4	75.0[b]	45	45 ($BMDL_{10}$)
Relative stomach weight in females[c]	89.3	179[d]	87	87 ($BMDL_{1SD}$)
Mice Astill et al. (1996a); BASF (1991e); BASF (1991c)				
Relative stomach weight in males[c]	89.3	179[d]	62	62 ($BMDL_{1SD}$)
Rats Hellwig and Jäckh (1997); Confidential (1991)				
Fetal body weight	32.5	163[e]	NDr	32.5 (NOAEL)
Fetal skeletal variations[f]	32.5	163[d]	7.37	7.37 ($BMDL_{05}$)
Fetal skeletal retardations	32.5	163[d]	NDr	32.5 (NOAEL)

[a]Modeling results are described in more detail in Appendix C.
[b]Increase was ≥10% compared to control values.
[c]As discussed above, doses for stomach-weight changes were not converted to HEDs.
[d]Change was statistically significantly increased compared to control values.
[e]Change was ≥5% compared to control values.
[f]Chosen as the critical effect for deriving the subchronic p-RfD.

BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose.

Among all the sensitive endpoints evaluated, the lowest POD (HED) following oral exposure to 2-EH is for increased fetal incidence of skeletal variations (i.e., accessory lumbar vertebrae and 14th ribs, rudimentary cervical ribs, and 13th ribs, absent or shortened). The $BMDL_{05}$ (HED) for fetal skeletal variations is expected to be protective of all developmental effects during a susceptible life stage, as well as any potential liver, kidney, and stomach systemic effects observed following subchronic 2-EH exposure. Thus, the $BMDL_{05}$ (HED) for fetal skeletal variations (7.37 mg/kg-day) is selected as the POD for derivation of the subchronic p-RfD.

$$\textbf{Subchronic p-RfD} = BMDL_{05}\text{ (HED)} \div UF_C$$
$$= 7.37\text{ mg/kg-day} \div 100$$
$$\mathbf{= 7 \times 10^{-2}\text{ mg/kg-day}}$$

Table 8 summarizes the uncertainty factors for the subchronic p-RfD for 2-EH.

Table 8. Uncertainty Factors for the Subchronic p-RfD for 2-Ethylhexanol (CASRN 104-76-7)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following 2-EH exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 1988).
UF_D	3	A UF_D of 3 ($10^{0.5}$) is applied to account for deficiencies and uncertainties in the database. Well-conducted oral subchronic- and chronic-duration animal toxicity studies of 2-EH are available in rats and mice (Astill et al., 1996a; BASF, 1991a, c, e). Developmental toxicity studies are available in rats and mice. Severe maternal effects were noted at high doses. There are no two-generation reproductive toxicity studies of 2-EH.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 2-EH 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 developmental toxicity resulting from a narrow period of exposure was used as the critical effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	100	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; DAF = dosimetric adjustment factor; 2-EH = 2-ethylhexanol; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Confidence in the subchronic p-RfD for 2-EH is medium as explained in Table 9.

Table 9. Confidence Descriptors for the Subchronic p-RfD for 2-Ethylhexanol (CASRN 104-76-7)

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the study is medium. Although the study by Hellwig and Jäckh (1997) and Confidential (1991) is a peer-reviewed and GLP-conducted study, it tested a limited number of animals (8−10 maternal animals per dose group). Furthermore, there was a large degree of maternal toxicity at the high dose, resulting in that dose being excluded from the dose-response assessment.
Confidence in database	M	Confidence in the database is medium. The database includes two subchronic-duration studies (one gavage study in rats and mice and one dietary study in rats), a chronic-duration study in rats and mice, one limited neonatal exposure study in rats, and several developmental studies of gestational exposure in rats and mice. There are no two-generation reproductive toxicity studies of 2-EH. Furthermore, there are no oral toxicity studies that assessed CNS effects, which were observed in humans exposed to 2-EH via inhalation.
Confidence in subchronic p-RfD[a]	M	Overall confidence in the subchronic p-RfD is medium.

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

CNS = central nervous system; 2-EH = 2-ethylhexanol; GLP = Good Laboratory Practice; H = high; M = medium; p-RfD = provisional reference dose.

Derivation of a Chronic Provisional Reference Dose

The developmental study in rats administered 2-EH via gavage on GDs 6−15 is also selected as the principal study for deriving the chronic p-RfD (Hellwig and Jäckh, 1997; Confidential, 1991). Increased fetal incidence of skeletal variations is identified as the critical effect.

In addition to the subchronic-duration and developmental studies considered for the derivation of the subchronic p-RfD described above, there was one chronic-duration gavage study in rats and mice (Astill et al., 1996b; BASF, 1992a). The chronic-duration study in rats (Astill et al., 1996b; BASF, 1992a) is well designed and provides data that adequately describe a dose-response relationship for body-weight following exposure to 2-EH for 5 days/week for 24 months (see Tables B-5, B-6, and C-2). The most sensitive endpoint reported in the chronic-duration study by Astill et al. (1996b) and BASF (1992a) was decreased body weight in male (at ≥107 mg/kg-day) and female rats (at ≥357 mg/kg-day) (see Table C-2). The companion chronic-duration toxicity/carcinogenicity study in mice noted increased mortality, decreased body weight, and changes in relative organ weights and liver histopathology, but these effects occurred at higher doses (Astill et al., 1996b; BASF, 1991b). Developmental toxicity studies in rats also reported decreased body weights in maternal animals at ≥650 mg/kg-day (Hellwig and Jäckh, 1997; Confidential, 1991; Hardin et al., 1987; Hazleton Laboratories, 1983).

Following U.S. EPA (2011b) guidance, the doses administered resulting in the most sensitive endpoints are converted to an HED through application of a DAF derived as follows:

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

where

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

Study-specific body weight is used to calculate the DAF for each dose group (U.S. EPA, 2011b). Calculated HEDs are presented in Tables C-1 and C-2 for female rats exposed to 2-EH during pregnancy (Hellwig and Jäckh, 1997; Confidential, 1991) and for male and female rats exposed chronically to 2-EH (Astill et al., 1996b; BASF, 1992a), respectively.

To determine potential PODs for the chronic p-RfD, data sets for the most sensitive treatment-related endpoints following chronic exposure to 2-EH were modeled using BMD analysis and compared to the most sensitive treatment-related change reported in the developmental study conducted by Hellwig and Jäckh (1997) and Confidential (1991) (see Table C-1). All available continuous-variable models in the BMDS (Version 2.7) were fit to the data sets for decreased body weights in males and females (Astill et al., 1996b; BASF, 1992a). In Appendix C, modeling results for these data sets are summarized in Tables C-13 and C-14. The HED in mg/kg-day was used as the dose metric. The BMR for decreased body weight used was 10% RD change from control means, which is considered a biologically significant response. As stated above, the BMR for decreased fetal body weight used was 5% RD change from control means for continuous data and 5% extra risk for dichotomous developmental data. For the developmental effects, the data were modeled without the highest dose of 325 mg/kg-day (HED) because there was severe maternal toxicity (i.e., 60% mortality and a 20% decrease in body weight) at that dose that confounds the interpretation of fetal changes. One or more of the models provided adequate fit for each data set except decreased body weight in females (see Table C-14); models with the lowest AIC were selected in each case. Candidate PODs, including the BMDLs from the selected models, are presented in Table 10.

Table 10. Candidate PODs in Rats Administered 2-Ethylhexanol (CASRN 104-76-7) for the Derivation of the Chronic p-RfD

Endpoint	NOAEL (HED) (mg/kg-d)	LOAEL (HED) (mg/kg-d)	BMDL (HED)[a] (mg/kg-d)	POD (HED) (mg/kg-d)
Astill et al. (1996b); BASF (1992a)				
Terminal body weight in males	9.5	27.9[b]	19	19 ($BMDL_{10}$)
Terminal body weight in females	24.8	81.2[b]	NDr	24.8 (NOAEL)
Hellwig and Jäckh (1997); Confidential (1991)				
Fetal skeletal variations[c]	**32.5**	**163[d]**	**7.37**	**7.37 ($BMDL_{05}$)**

[a]Modeling results are described in more detail in Appendix C.
[b]Change was ≥10% compared to control values.
[c]Chosen as the critical effect for deriving the chronic p-RfD.
[d]Change was statistically significantly increased compared to control values.

BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose.

When the BMD results in Table 10 are compared, the lowest POD (HED) is for increased fetal incidence of skeletal variations. The $BMDL_{05}$ (HED) for fetal skeletal variations is expected to be protective of all developmental effects during a susceptible life stage, as well as any potential systemic effects observed following chronic 2-EH exposure. Thus, the $BMDL_{05}$ (HED) for fetal skeletal variations (7.37 mg/kg-day) is again selected as the POD for deriving the chronic p-RfD which is derived as follows:

$$\textbf{Chronic p-RfD} = BMDL_{05}\text{ (HED)} \div UF_C$$
$$= 7.37\text{ mg/kg-day} \div 100$$
$$\mathbf{= 7 \times 10^{-2}\ mg/kg\text{-}day}$$

Table 11 summarizes the uncertainty factors for the chronic p-RfD for 2-EH.

Table 11. Uncertainty Factors for the Chronic p-RfD for 2-Ethylhexanol (CASRN 104-76-7)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following 2-EH exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 1988).
UF_D	3	A UF_D of 3 ($10^{0.5}$) is applied to account for deficiencies and uncertainties in the database. Well-conducted oral subchronic- and chronic-duration animal toxicity studies of 2-EH are available in rats and mice (Astill et al., 1996a; BASF, 1991a, c, e). Developmental toxicity studies are available in rats and mice. Severe maternal effects were noted at high doses. There are no two-generation reproductive toxicity studies of 2-EH.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 2-EH 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 developmental toxicity resulting from a narrow period of exposure was used as the critical effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	100	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; DAF = dosimetric adjustment factor; 2-EH = 2-ethylhexanol; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Confidence in the chronic p-RfD for 2-EH is medium as explained in Table 12.

Table 12. Confidence Descriptors for the Chronic p-RfD for 2-Ethylhexanol (CASRN 104-76-7)

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the study is medium. Although the study by Hellwig and Jäckh (1997) and Confidential (1991) is a peer-reviewed and GLP-conducted study, it tested a limited number of animals (8−10 maternal animals per dose group). Furthermore, there was a large degree of maternal toxicity at the high dose, resulting in that dose being excluded from the dose-response assessment.
Confidence in database	M	Confidence in the database is medium. The database includes two subchronic-duration studies, a chronic-duration study in mice and rats, one limited neonatal exposure study in rats, and several developmental studies of gestational exposure in rats and mice. There are no two-generation reproductive toxicity studies of 2-EH. Furthermore, there are no oral toxicity studies that assessed CNS effects, which were observed in humans exposed to 2-EH via inhalation.
Confidence in chronic p-RfD[a]	M	Overall confidence in the chronic p-RfD is medium.

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

CNS = central nervous system; 2-EH = 2-ethylhexanol; GLP = Good Laboratory Practice; H = high; M = medium; p-RfD = provisional reference dose.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of a Subchronic Provisional Reference Concentration

The database of potentially relevant studies for deriving a subchronic inhalation reference value for 2-EH includes a subchronic-duration study in Wistar rats (Klimisch et al., 1998; BASF, 1992b), a subchronic-duration study in male ICR mice (Miyake et al., 2016), and a developmental study in S-D rats (Nelson et al., 1989). The subchronic-duration inhalation study in male ICR mice (Miyake et al., 2016) is selected as the principal study, and increased diameter of Bowman's glands in the olfactory epithelium of the nasal cavity is identified as the critical effect. The Bowman's glands play a major role in the ability to smell by releasing nasal fluid that trap odorants and binds them to receptors located on olfactory sensory neurons. The nasal secretions from the Bowman's gland also protect the olfactory mucosa from infection and dehydration (Hellier, 2016). Morphological changes in the Bowman's glands could affect its function and impact the sense of smell. As discussed above, exposure to 2-EH has been shown to cause "sick building syndrome" in humans with one of the symptoms being an increased sense of smell. Therefore, it is possible that 2-EH-induced effects on the Bowman's glands could be related to effects observed in humans.

The Miyake et al. (2016) study was published in a peer-reviewed journal. The study is adequate regarding design (e.g., inclusion of controls and several exposure levels) and performance pertaining to examination of potential toxicity endpoints, and presentation of materials, methods, and results. Regarding the histopathology performed in the study, additional caudal nasal cross sections beyond the more anterior (rostral) region of the nose were not taken, but the study did perform a very complete morphological assessment of the changes in the

olfactory bulb size. Details of the study are provided in the "Review of Potentially Relevant Data" section.

No significant treatment-related effects were reported in either the subchronic-duration study (Klimisch et al., 1998; BASF, 1992b) or developmental study (Nelson et al., 1989) in rats. Potential PODs for these studies are a NOAEL (HEC) of 114 mg/m^3 for the subchronic-duration study and a NOAEL (HEC) of 248 mg/m^3 for the developmental study. In the subchronic-duration study by Miyake et al. (2016), the effects of 2-EH on the olfactory system (i.e., the olfactory epithelium of the nasal cavity and the olfactory bulb of the brain) were examined in mice exposed to 2-EH via inhalation for up to 3 months. Severity scores for morphological alterations in the olfactory epithelium were significantly increased at ≥12.5 mg/m^3 (HEC) in mice exposed to 2-EH for 1 week and 3 months. The study authors also reported changes in the expression of nerve-related markers (e.g., OMP, TH, etc.) in the olfactory epithelium and bulb at ≥4.17 mg/m^3 (HEC). In accordance with U.S. EPA (1994) methodology, the following dosimetric adjustments are made for male mice with a NOAEL for respiratory effects in the extrathoracic (ET) region:

Exposure concentration adjustment for continuous exposure:

$$\begin{aligned} CONC_{ADJ} &= \text{Exposure CONC} \times (\text{MW} \div 24.45) \times \\ &\quad (\text{hours exposed} \div 24) \times (\text{days exposed} \div 7 \text{ days per week})\ ^{5} \\ &= 21.9 \text{ ppm} \times (130 \div 24.45) \times (8 \text{ hours} \div 24 \text{ hours}) \times \\ &\quad (5 \text{ days} \div 7 \text{ days}) \\ &= 27.7 \text{ mg/m}^3 \end{aligned}$$

HEC conversion for respiratory effects:

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

where

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

where

$V_{E[mouse]}$ = Mouse minute volume [mouse = 0.03116 L/min, based on the mean reference body weight of 0.02695 kg for male BAF_1 and $B6C3F_1$ mice in a subchronic-duration study (U.S. EPA, 1994)]

$V_{E[human]}$ = 13.8 L/min

$SA_{ET[mouse]}$ = Mouse default surface area of the ET region (3 cm^2)

$SA_{ET[human]}$ = Human default surface area of the ET region (200 cm^2)

$$\begin{aligned} \text{Male mouse } RGDR_{ET} &= (0.03116 \text{ L/min} \div 3 \text{ cm}^2) \div (13.8 \text{ L/min} \div 200 \text{ cm}^2) \\ &= 0.1505 \end{aligned}$$

$$\begin{aligned} CONC_{RESP}\ (HEC) &= CONC_{ADJ} \times RGDR_{ET} \\ &= 27.7 \text{ mg/m}^3 \times 0.1505 \\ &= 4.17 \text{ mg/m}^3 \end{aligned}$$

[5]CONC = concentration from the Miyake et al. (2016) study.

All available continuous models in the BMDS (Version 2.7) were fit to the data sets (see Table B-13) from the inhalation study in mice by Miyake et al. (2016), which was the only inhalation study that reported significant treatment-related effects. Appendix C contains details of the modeling results for these data sets. The HEC, in mg/m^3, was used as the dose metric. The BMR for all changes observed in the Miyake et al. (2016) study was 1 SD change from control means, because no information is available regarding the change in response that would be considered biologically significant. One or more of the models provided adequate fit for each data set except increased number of CD3-, Iba1-, and Dcx-positive cells. Candidate PODs, including the benchmark concentration lower confidence limits (BMCLs) from the selected models, are presented in Table 13.

Table 13. Candidate PODs in Rodents Administered 2-Ethylhexanol (CASRN 104-76-7) for the Derivation of the Subchronic p-RfC[a]

Endpoint	NOAEL (HEC) (mg/m^3)	LOAEL (HEC) (mg/m^3)	BMCL (HEC)[b] (mg/m^3)	POD (HEC) (mg/m^3)
Morphological alterations in the OE	4.17	12.5[c]	NDr	4.17 (NOAEL)
Diameter of Bowman's glands in the OE[d]	**4.17**	**12.5[c]**	**1.11**	**1.11 ($BMCL_{1SD}$)**
CD3-positive cells in the OE	4.17	12.5[c]	NDr	4.17 (NOAEL)
OMP-positive cells (ratio of OMP[+] cells to olfactory epithelium cells) in the OE	NDr	4.17[c]	3.14	3.14 ($BMCL_{1SD}$)
PCNA-positive cells in the OE	12.5	29.20[c]	11.5	11.5 ($BMCL_{1SD}$)
Glomerular diameter in the OB	12.5	29.20[c]	8.67	8.67 ($BMCL_{1SD}$)
OMP-positive cells in the OB	4.17	12.5[c]	5.72	5.72 ($BMCL_{1SD}$)
TH-positive cells in the OB	12.5	29.20[c]	3.59	3.59 ($BMCL_{1SD}$)
Iba1-positive cells in the OB	12.5	29.20[c]	NDr	12.5 (NOAEL)
Dcx-positive cells in the OB	12.5	29.20[c]	NDr	12.5 (NOAEL)

[a]Miyake et al. (2016).
[b]Modeling results are described in more detail in Appendix C.
[c]Change was statistically significantly increased compared to control values.
[d]Chosen as the critical effect for deriving the subchronic p-RfC.

BMCL = benchmark concentration lower confidence limit; Dcx = doublecortin; HEC = human equivalent concentration; Iba1 = ionized calcium-binding adapter molecule 1; LOAEL = lowest-observed-adverse-effect level; NDr = not determined; NOAEL = no-observed-adverse-effect level; OE = olfactory epithelium; OB = olfactory bulb; OMP = olfactory marker protein; PCNA = proliferating cell nuclear antigen; POD = point of departure; p-RfC = provisional reference concentration; PCNA = proliferating cell nuclear antigen; SD = standard deviation; TH = tyrosine hydroxylase.

The potential PODs for deriving the subchronic p-RfC for 2-EH include a NOAEL (HEC) of 114 mg/m^3 and NOAEL (HEC) of 248 mg/m^3, both for the lack of significant, treatment-related effects in rats from the subchronic-duration (Klimisch et al., 1998; BASF, 1992b) and developmental (Nelson et al., 1989) studies, respectively. The most sensitive POD from the Miyake et al. (2016) study is a $BMCL_{1SD}$ of 1.11 mg/m^3 (HEC) for increased diameter

of the Bowman's glands in the olfactory epithelium of the nasal cavity in male mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016). Among the candidate endpoints for potential critical effect, the lowest POD is the $BMCL_{1SD}$ of 1.11 mg/m^3 (HEC) for increased diameter of the Bowman's glands in the olfactory epithelium of the nasal cavity in male mice. Effects on the olfactory system were also reported in humans that were acutely exposed to 2-EH via inhalation, providing further support that the olfactory system is indeed a target for inhalation exposure to 2-EH (Ernstgård et al., 2010; van Thriel et al., 2007; Kiesswetter et al., 2005; van Thriel et al., 2005; van Thriel et al., 2003).

The subchronic-duration inhalation study by Miyake et al. (2016) with a LOAEL (HEC) of 4.17 mg/m^3 and no corresponding NOAEL is selected as the principal study for deriving the subchronic p-RfC. The critical effect is increased diameter of the Bowman's glands in the olfactory epithelium of the nasal cavity in male ICR mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016) with a $BMCL_{1SD}$ of 1.11 mg/m^3 (HEC); this $BMCL_{1SD}$ is selected as the POD for deriving the subchronic p-RfC. The subchronic p-RfC for 2-EH is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfC} &= BMCL_{1SD}\text{ (HEC)} \div UF_C \\ &= 1.11\text{ mg/m}^3 \div 300 \\ &= \mathbf{4 \times 10^{-3}\text{ mg/m}^3} \end{aligned}$$

Table 14 summarizes the uncertainty factors for the subchronic p-RfC for 2-EH.

Table 14. Uncertainty Factors for the Subchronic p-RfC for 2-Ethylhexanol (CASRN 104-76-7)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans using toxicokinetic cross-species dosimetric adjustment for respiratory effects from a Category 1 gas, as specified in U.S. EPA (1994) guidelines for deriving RfCs.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. Repeated-exposure inhalation toxicity data for 2-EH are limited to two subchronic-duration studies, one in mice and one in rats, and a developmental study in rats (Miyake et al., 2016; Klimisch et al., 1998; BASF, 1992b; Nelson et al., 1989). The limited developmental toxicity study in rats by inhalation exposure found no effects at concentrations up to saturation (Nelson et al., 1989). However, developmental effects were found to be the most sensitive endpoint for subchronic or chronic oral 2-EH exposure and thus more comprehensive studies would be warranted. There are no two-generation reproductive toxicity studies of 2-EH.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of 2-EH in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMCL.
UF_S	1	A UF_S of 1 is applied because the POD comes from a subchronic-duration study of mice.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMCL = benchmark concentration lower confidence limit; 2-EH = 2-ethylhexanol; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; RfC = inhalation reference concentration; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

The confidence descriptors for the subchronic p-RfC are described in Table 15.

Table 15. Confidence Descriptors for the Subchronic p-RfC for 2-Ethylhexanol (CASRN 104-76-7)

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the principal study is medium. The study was peer reviewed, tested multiple exposure levels in groups of adequate size in male mice, and measured exposure concentrations in all groups. However, the study is not comprehensive, focusing primarily on the olfactory system, and only tested one sex of mice (males).
Confidence in database	L	Confidence in the database is low. Repeated-exposure inhalation toxicity data for 2-EH are limited to two subchronic-duration studies, one in mice and one in rats, and a developmental study in rats (Miyake et al., 2016; Klimisch et al., 1998; BASF, 1992b; Nelson et al., 1989). The limited developmental toxicity study in rats by inhalation exposure found no effects at concentrations up to saturation (Nelson et al., 1989). However, developmental effects were found to be the most sensitive endpoint for oral 2-EH exposure and thus more comprehensive studies would be warranted. There are no two-generation reproductive toxicity studies of 2-EH.
Confidence in subchronic p-RfC[a]	L	Overall confidence in the subchronic p-RfC is low.

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

2-EH = 2-ethylhexanol; L = low; M = medium; p-RfC = provisional reference concentration.

Derivation of a Chronic Provisional Reference Concentration

In the absence of toxicity studies in humans or animals chronically exposed to 2-EH by inhalation, a chronic p-RfC for 2-EH is derived using the subchronic POD (HEC). Justification for selecting the critical effect and principal study are described in the previous section of this document.

The chronic p-RfC for 2-EH, based on a $BMCL_{1SD}$ (HEC) of 1.11 mg/m^3 in male mice exposed to 2-EH for 3 months, is derived as follows:

$$\textbf{Chronic p-RfC} = BMCL_{1SD}\ (HEC) \div UF_C$$
$$= 1.11\ mg/m^3 \div 3{,}000$$
$$= \mathbf{4 \times 10^{-4}\ mg/m^3}$$

Table 16 summarizes the uncertainty factors for the chronic p-RfC for 2-EH.

Table 16. Uncertainty Factors for the Chronic p-RfC for 2-Ethylhexanol (CASRN 104-76-7)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans, using toxicokinetic cross-species dosimetric adjustment for respiratory effects from a Category 1 gas, as specified in U.S. EPA (1994) guidelines for deriving RfCs.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. Repeated-exposure inhalation toxicity data for 2-EH are limited to two subchronic-duration studies, one in mice and one in rats, and a developmental study in rats (Miyake et al., 2016; Klimisch et al., 1998; BASF, 1992b; Nelson et al., 1989). The limited developmental toxicity study in rats by inhalation exposure found no effects at concentrations up to saturation (Nelson et al., 1989). However, developmental effects were found to be the most sensitive endpoint for subchronic or chronic oral 2-EH exposure and thus more comprehensive studies would be warranted. There are no two-generation reproductive toxicity studies of 2-EH.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of 2-EH in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMCL.
UF_S	10	A UF_S of 10 is applied because the POD comes from a subchronic-duration study of mice.
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMCL = benchmark concentration lower confidence limit; 2-EH = 2-ethylhexanol; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; RfC = inhalation reference concentration; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

The confidence descriptors for the chronic p-RfC are described in Table 17.

Table 17. Confidence Descriptors for the Chronic p-RfC for 2-Ethylhexanol (CASRN 104-76-7)

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the principal study is medium. The study was peer reviewed, tested multiple exposure levels in groups of adequate size in male mice, and measured exposure concentrations in all groups. However, the study is not comprehensive, focusing primarily on the olfactory system, and only tested one sex of mice (males).
Confidence in database	L	Confidence in the database is low. Repeated-exposure inhalation toxicity data for 2-EH are limited to two subchronic-duration studies, one in mice and one in rats, and a developmental study in rats (Miyake et al., 2016; Klimisch et al., 1998; BASF, 1992b; Nelson et al., 1989). The limited developmental toxicity study in rats by inhalation exposure found no effects at concentrations up to saturation (Nelson et al., 1989). However, developmental effects were found to be the most sensitive endpoint for oral 2-EH exposure and thus more comprehensive studies would be warranted. There are no two-generation reproductive toxicity studies of 2-EH.
Confidence in chronic p-RfC[a]	L	Overall confidence in the chronic p-RfC is low.

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

2-EH = 2-ethylhexanol; L = low; M = medium; p-RfC = provisional reference concentration.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Following U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, the cancer weight of evidence (WOE) for 2-EH is *"Suggestive Evidence of Carcinogenic Potential"* for oral exposure (see Table 18). In the chronic-duration cancer bioassays in rats and mice following oral exposure to 2-EH (Astill et al., 1996b; BASF, 1992a, 1991b), there were significant dose-related trends for hepatocellular carcinoma in male and female mice. A single adenoma was detected in one 536-mg/kg-day male (and no females), but the study authors did not report the results of combined statistical analysis of hepatocellular adenoma or carcinoma in male mice. The incidence of hepatocellular carcinoma was significantly increased in female mice at the highest dose tested based on pairwise comparison to vehicle controls. There was no evidence of treatment-related carcinogenicity in male or female rats. Although these data are consistent with one of the examples provided in the U.S. EPA's Cancer Guidelines (U.S. EPA, 2005) for the descriptor *"Likely to Be Carcinogenic to Humans"* (which states that supporting data for this descriptor include "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans"), the incidence of hepatocellular tumors was statistically significantly increased only in female mice at the highest dose tested, and there was no evidence of cancer in male or female rats treated with 2-EH for 2 years. Furthermore, the data for hepatocellular tumors in male mice only showed a significant dose-related trend and were not significant based on a pairwise comparison test. As stated in the Cancer Guidelines (U.S. EPA, 2005), one of the examples for a chemical to be considered to have *"Suggestive Evidence of Carcinogenic Potential"* is "a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor *"Likely to Be Carcinogenic to Humans."* The Cancer Guidelines (U.S. EPA, 2005) further state that the

descriptor *"Suggestive Evidence of Carcinogenic Potential"* is appropriate when "the weight of evidence is suggestive of carcinogenicity, a concern for potential carcinogenic effects is raised, but the data are not judged sufficient for a stronger conclusion." Thus, based on these guidelines and the carcinogenicity data from available animal studies, the WOE descriptor of *"Suggestive Evidence of Carcinogenic Potential"* is appropriate for 2-EH for the oral route of exposure.

For the inhalation route of exposure, the cancer WOE for 2-EH is *"Inadequate Information to Assess Carcinogenic Potential"* based on the lack of information on carcinogenicity for this route, as described in Table 18.

Table 18. Cancer WOE Descriptor for 2-Ethylhexanol (CASRN 104-76-7) by Oral Exposure

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	No human data are available.
"Likely to Be Carcinogenic to Humans"	NS	NA	The available animal bioassays do not support this.
"Suggestive Evidence of Carcinogenic Potential"	**Selected**	**Oral**	**In the chronic-duration oral cancer bioassays of 2-EH in rats and mice (Astill et al., 1996b; BASF, 1992a, 1991b), there were significant dose-related trends for hepatocellular carcinoma in male and female mice. The incidence of hepatocellular carcinoma was significantly increased in female mice at the highest dose tested based on pairwise comparison to vehicle controls. There was no evidence of treatment-related carcinogenicity in male or female rats.**
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Inhalation**	**This descriptor is selected due to the lack of any information on the carcinogenicity of 2-EH by inhalation exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	The available animal bioassays do not support this.

2-EH = 2-ethylhexanol; F = female(s); M = male(s); NA = not applicable; NS = not selected; WOE = weight of evidence.

MODE-OF-ACTION DISCUSSION

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

"mutagenicity, mitogenesis, programmed cell death, cytotoxicity with reparative cell proliferation, and immune suppression" (pp. 1−10).

Genotoxicity tests of 2-EH in vitro (mutation, clastogenicity, DNA repair, cell transformation, and unscheduled DNA synthesis) have produced predominantly negative results in both bacterial systems and in mammalian cells (see Table 4A). Results were also mostly negative in a limited number of genotoxicity tests in vivo. No additional data regarding potential mechanisms of carcinogenicity are available. Thus, a detailed MOA discussion for 2-EH is precluded.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of a Provisional Oral Slope Factor

The 18-month carcinogenicity study in mice conducted by Astill et al. (1996b) and BASF (1991b) was selected as the principal study for the development of a provisional oral slope factor (p-OSF). This study was conducted in accordance with GLP principles, the results are peer reviewed, and the study meets the standards of study design and performance with respect to the number of animals used, the examination of potential toxicity endpoints, and the presentation of information.

Male and female mice (but not rats) exposed to 2-EH for 18 months (5 days/week) showed evidence for a carcinogenic response via the oral route of exposure (Astill et al., 1996b; BASF, 1991b). Evidence for carcinogenicity in mice includes:

- Significant dose-related trends for hepatocellular carcinoma in female mice based on time-independent tests (simple Peto and Cochran-Armitage tests performed by the study authors; $p < 0.01$ and 0.05, respectively) and in male and female mice based on time-dependent analyses that consider the relatively high mortality in these groups (Peto test performed by the study authors; $p < 0.05$ in males and $p < 0.01$ in females).
- A significantly increased incidence of hepatocellular carcinomas in female mice at 536 mg/kg-day relative to vehicle controls based on Fisher's exact test performed by the study authors. The incidence of carcinoma and carcinoma or adenoma (combined) was not statistically significantly increased in male mice at any dose by pairwise comparison to vehicle controls.

Because significant trends were observed in both sexes (see Table B-9), the incidences of hepatocellular carcinomas in both male and female mice were modeled using BMD analysis to determine the potential POD for the p-OSF. An adenoma was detected in one 536-mg/kg-day male (and no females). The study authors did not report the results of combined statistical analysis of hepatocellular adenoma or carcinoma, but the combined incidence in males was modeled using BMD analysis.

Multistage Cancer models in the U.S. EPA BMDS (Version 2.7) were fit to the male and female incidence data of the tumor types shown in Table B-9, and modeling results are summarized in Appendix D. The BMR used was 10% extra risk. The HED in mg/kg-day was used as the dose metric. To account for group differences in survival, data for tumor incidence in male and female mice were also modeled using a Poly-3 survival-adjusted number at risk. The Poly-k approach (Piegorsch and Bailer, 1997; Portier and Bailer, 1989; Bailer and Portier, 1988) is a survival-adjusted quantal-response method to assess neoplastic and non-neoplastic

lesion prevalence when differences in survival are apparent across dose-groups. This method scales the denominator (i.e., number of animals per dose group) according to the amount of time on a study the animals survived. Animals that develop the lesion of interest or survive to the end of the exposure period are assigned a weight of 1. Animals that do not develop the lesion and die before the end of the study period are given a weight equal to the fraction of the study period for which they survived raised to the third power. For each dose group, all the individual animal weights are summed, and this new value is the survival-adjusted incidence for that dose group. The Multistage Cancer model (1-degree) provided an adequate fit to the data sets. From the Multistage Cancer models, predicted BMDs associated with 10% extra risk (BMD_{10}) and their 95% lower confidence limits ($BMDL_{10}$) are shown in Table 19 (also see Appendix D).

Table 19. BMD_{10} and $BMDL_{10}$ Values from Best Fitting Models for Tumor Data in Mice Treated Chronically with 2-Ethylhexanol (CASRN 104-76-7) via Gavage[a, b]

Endpoint	Best Fitting Model	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)	Potential p-OSF $(mg/kg\text{-}d)^{-1}$
Hepatocellular carcinoma or adenoma; M	Multistage Cancer (1-degree); unadjusted	66	31	3.2×10^{-3}
	Multistage Cancer (1-degree); Poly-3-adjusted[c]	**49**	**25**	$\mathbf{4.0 \times 10^{-3}}$
Hepatocellular carcinoma; F	Multistage Cancer (1-degree); unadjusted	63	35	2.9×10^{-3}
	Multistage Cancer (1-degree); Poly-3-adjusted[c]	44	27	3.7×10^{-3}

[a]Astill et al. (1996b); BASF (1991b).
[b]Modeling results are described in more detail in Appendix D.
[c]Due to group differences in survival, data for tumor incidence in M and F mice were also modeled using a Poly-3 survival-adjusted number at risk.

BMD_{10} = benchmark dose 10% extra risk; $BMDL_{10}$ = 95% benchmark dose lower confidence limit; F = female(s); M = male(s); p-OSF = provisional oral slope factor.

Among the modeled tumor types, the lowest POD ($BMDL_{10}$ [HED] = 25 mg/kg-day) was obtained in modeling of the observed incidence of hepatocellular carcinoma or adenoma and Poly-3 weighted number at risk in male mice. The MOA by which 2-EH induces tumors is not known. In the absence of definitive information, a linear approach is used to obtain the slope from the POD. The p-OSF of 4.0×10^{-3} $(mg/kg\text{-}day)^{-1}$ was derived as follows:

$$\textbf{p-OSF (unadjusted)} = 0.1 \div BMDL_{10}\text{ (HED)} = 0.1 \div 25\text{ mg/kg-day} = \mathbf{4.0 \times 10^{-3}\ (mg/kg\text{-}day)^{-1}}$$

An adjustment was applied to account for the less-than-lifetime observation period (U.S. EPA, 1980). The Astill et al. (1996b)/BASF (1991b) bioassay was terminated after 18 months (compared to the reference mouse lifespan of 2 years) due to early mortality. Thus, due to the short duration of the study, it cannot be known how an increased duration (i.e., the full 2-year

lifetime exposure) might have influenced the tumor incidence in the low-dose treated rats. Therefore, an adjustment factor of $(L \div L_e)^3$ was applied to the unadjusted screening p-OSF, where L = the lifetime of the animal and L_e = the duration of experimental dosing (U.S. EPA, 1980). Using this adjustment, an adjusted screening p-OSF is derived as follows:

$$\begin{aligned} \textbf{p-OSF (adjusted)} &= \text{p-OSF (unadjusted)} \times (L \div L_e)^3 \\ &= 4.0 \times 10^{-3}\ (\text{mg/kg-day})^{-1} \times (24\ \text{months} \div 18\ \text{months})^3 \\ &= \mathbf{9.5 \times 10^{-3}\ (mg/kg\text{-}day)^{-1}} \end{aligned}$$

The adjusted p-OSF for 2-EH should not be used with exposure exceeding the POD ($BMDL_{10}$ [HED] = 25 mg/kg-day) because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of 2-EH.

Derivation of a Provisional Inhalation Unit Risk

There are no data available regarding the carcinogenicity of 2-EH by inhalation exposure, precluding derivation of a provisional inhalation unit risk (p-IUR) for 2-EH.

APPENDIX A. PROVISIONAL SCREENING VALUES

No provisional screening values are derived for 2-ethylhexanol.

APPENDIX B. DATA TABLES

Table B-1. Effects in Dow Wistar Albino Rats Treated with 2-Ethylhexanol (CASRN 104-76-7) in the Diet for 89 or 90 Days[a]

Male					
	Dose (mg/kg-d)				
Parameter	**0**	**7**	**36**	**170**	**840**
Number of animals	10	10	10	10	10
Mortality	2/10[b]	1/10	0/10	1/10	1/10
Body-weight gain[c] (g)	127.8 ± 25.30[d]	143.0 ± 34.14[e] (+12%)	141.0 ± 26.41 (+10%)	113.1 ± 42.76 (−12%)	114.6 ± 23.15 (−10%)
Terminal body weight[c] (g)	289.4 ± 40.65	314.3 ± 48.39[e] (+9%)	309.1 ± 29.81 (+7%)	279.1 ± 39.37 (−4%)	284.2 ± 23.42 (−2%)
Absolute organ weight[c] (g)					
Liver	9.95 ± 1.11	10.65 ± 1.42 (+7%)	10.43 ± 1.62 (+5%)	9.57 ± 1.86 (−4%)	10.96 ± 1.20 (+10%)
Kidney	2.06 ± 0.25	2.09 ± 0.34 (+1%)	2.15 ± 0.35 (+4%)	2.06 ± 0.20 (0%)	2.08 ± 0.17 (+1%)
Relative organ weight[c] (% BW)					
Liver	3.39 ± 0.18	3.41 ± 0.15 (+1%)	3.36 ± 0.30 (−1%)	3.41 ± 0.24 (+1%)	3.85 ± 0.24** (+14%)
Kidney	0.70 ± 0.04	0.67 ± 0.03 (−5%)	0.69 ± 0.06 (−1%)	0.74 ± 0.06 (+6%)	0.73 ± 0.05 (+5%)
Histopathology					
Kidney; tubular cloudy swelling (diffuse)	0/8 (0%)	NE	1/10 (10%)	2/9 (22%)	4/9 (44%)
Liver; cloudy swelling (diffuse)	0/8 (0%)	NE	1/10 (10%)	2/9 (22%)	3/9 (33%)
Liver; cloudy swelling (total[f])	5/8 (63%)	NE	5/10 (50%)	6/9 (68%)	6/9 (68%)
Female					
	Dose (mg/kg-d)				
Parameter	**0**	**7**	**41**	**190**	**940**
Number of animals	10	10	10	10	10
Mortality	3/10	0/10	2/10	0/10	1/10
Body-weight gain[c] (g)	61.1 ± 12.06	63.8 ± 16.86 (+4%)	69.5 ± 19.91[e] (+14%)	60.1 ± 14.75 (−2%)	59.0 ± 18.87 (−3%)
Terminal body weight[c] (g)	196.1 ± 13.75	196.4 ± 17.60 (0%)	202.4 ± 17.48[e] (+3%)	194.9 ± 14.70 (−1%)	193.8 ± 18.03 (−1%)

Table B-1. Effects in Dow Wistar Albino Rats Treated with 2-Ethylhexanol (CASRN 104-76-7) in the Diet for 89 or 90 Days[a]

Absolute organ weight[c] (g)					
Liver	7.24 ± 0.48	7.11 ± 0.55 (−2%)	7.40 ± 1.07 (+2%)	7.24 ± 0.75 (0%)	7.93 ± 0.63* (+10%)
Kidney	1.51 ± 0.13	1.42 ± 0.10 (−6%)	1.42 ± 0.39 (−6%)	1.52 ± 0.15 (+1%)	1.60 ± 0.13[g] (+6%)
Relative organ weight[c] (% BW)					
Liver	3.69 ± 0.13	3.62 ± 0.15 (−2%)	3.65 ± 0.40 (−1%)	3.71 ± 0.22 (+1%)	4.11 ± 0.27** (+11%)
Kidney	0.77 ± 0.04	0.72 ± 0.05 (−6%)	0.76 ± 0.07 (−1%)	0.78 ± 0.05 (+1%)	0.84 ± 0.12[g] (+9%)
Histopathology					
Kidney; tubular cloudy swelling (diffuse)	0/7 (0%)	NE	1/8 (13%)	4/10 (40%)	6/9* (68%)
Liver; cloudy swelling (diffuse)	0/7 (0%)	NE	0/8 (0%)	0/10 (0%)	6/9* (68%)
Liver; cloudy swelling (total[f])	1/7 (14%)	NE	3/8 (38%)	3/10 (30%)	9/9* (100%)

[a]Mellon Institute of Industrial Research (1960).
[b]Number affected/number examined.
[c]Means (for absolute weights and body-weight gain) and SDs (body-weight gain and all organ weights) were calculated by the U.S. EPA for the purposes of this PPRTV assessment based on individual animal data provided in the study report.
[d]Values represent means ± SD (surviving animals).
[e]Uncertainty is associated with this value owing to illegibility of individual data value(s) in the study report.
[f]Total = sum of diffuse + focal.
[g]n = 8; 1 value beyond 2 SDs from the mean was excluded from analyses.
*$p < 0.05$ based on statistics performed by study authors.
**$p < 0.01$.

BW = body weight; NE = not examined; SD = standard deviation.

Table B-2. Effects in Male F344 Rats Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a]

Parameter	Dose (mg/kg-d)				
	0	18	89.3	179	357
Number of animals	10	10	10	10	10
Terminal body weight (g)	279.4 ± 10.85[b]	281.0 ± 17.61 (+1%)	277.2 ± 16.32 (−1%)	270.9 ± 6.32 (−3%)	256.4 ± 11.21** (−8%)
Reticulocytes (% 10^{-3} RBCs); 84 d	20 ± 2	21 ± 3 (+5%)	20 ± 3 (0%)	19 ± 4 (−5%)	25 ± 3** (+25%)
Clinical chemistry; 84 d					
Total protein (g/L)	71.90 ± 5.23	74.21 ± 4.58 (+3%)	73.40 ± 6.32 (+2%)	73.28 ± 4.70 (+2%)	81.34 ± 6.52** (+13%)
Albumin (g/L)	40.13 ± 2.12	41.61 ± 2.42 (+4%)	41.32 ± 2.16 (+3%)	41.73 ± 2.03 (+4%)	46.69 ± 3.02** (+16%)
Absolute organ weight (g)					
Stomach	1.59 ± 0.10	1.57 ± 0.10 (−1%)	1.54 ± 0.06 (−3%)	1.58 ± 0.07 (−1%)	1.62 ± 0.07 (+2%)
Liver	7.74 ± 0.57	7.94 ± 0.77 (+3%)	7.95 ± 0.66 (+3%)	8.07 ± 0.27 (+4%)	9.17 ± 0.85** (+18%)
Kidney	1.94 ± 0.08	1.99 ± 0.13 (+3%)	1.98 ± 0.10 (+2%)	2.04 ± 0.07 (+5%)	2.07 ± 0.13* (+7%)
Testes	3.10 ± 0.10	3.07 ± 0.16 (−1%)	3.11 ± 0.11 (0%)	3.13 ± 0.07 (+1%)	3.00 ± 0.17 (−3%)
Relative organ weight (% BW)					
Stomach	0.57 ± 0.04	0.56 ± 0.03 (−2%)	0.56 ± 0.04 (−2%)	0.59 ± 0.03 (+4%)	0.63 ± 0.02** (+11%)
Liver	2.77 ± 0.11	2.82 ± 0.12 (+2%)	2.86 ± 0.10 (+3%)	2.98 ± 0.08** (+8%)	3.57 ± 0.22** (+29%)
Kidney	0.70 ± 0.02	0.71 ± 0.02 (+1%)	0.71 ± 0.03 (+1%)	0.75 ± 0.03* (+7%)	0.81 ± 0.04** (+16%)
Testes	1.11 ± 0.05	1.09 ± 0.04 (−2%)	1.13 ± 0.07 (+2%)	1.16 ± 0.03 (+5%)	1.17 ± 0.06* (+5%)
Histopathology					
Forestomach; acanthosis[c]	0/10[d] (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)
Mean pCoA activity (nmol/min-mg protein)[e]	3.38 ± 1.11	4.49 ± 0.78 (+33%)	5.21 ± 0.70 (+54%)	6.24 ± 1.83 (+85%)	22.0 ± 0.56* (+551%)

[a]Astill et al. (1996a); BASF (1991a).
[b]Values represent means ± SD.
[c]Sum acanthosis (focal or multifocal) and acanthosis (diffuse).
[d]Number affected/number examined.
[e]Peroxisome proliferation-only group; $n = 3$.
*$p < 0.05$ based on statistics performed by the study authors.
**$p < 0.01$.

BW = body weight; pCoA = palmitoyl-Coenzyme A; RBC = red blood cell; SD = standard deviation.

Table B-3. Effects in Female F344 Rats Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a]

Parameter	Dose (mg/kg-d)				
	0	18	89.3	179	357
Number of animals	10	10	10	10	10
Terminal body weight (g)	167.0 ± 4.96[b]	165.8 ± 8.73[c] (−1%)	162.2 ± 9.91 (−3%)	158.7 ± 8.41 (−5%)	155.1 ± 6.61** (−7%)
Reticulocytes (% 10^{-3} RBCs); 84 d	14 ± 2	14 ± 3 (0%)	14 ± 3 (0%)	14 ± 2 (0%)	17 ± 5* (+21%)
Clinical chemistry; 84 d					
Total protein (g/L)	69.37 ± 4.03	73.10 ± 6.03 (+5%)	68.59 ± 3.40 (−1%)	69.77 ± 4.52 (+1%)	71.33 ± 2.73 (+3%)
Albumin (g/L)	41.17 ± 2.22	43.11 ± 3.12 (+5%)	41.05 ± 1.44 (0%)	41.78 ± 2.06 (+1%)	43.14 ± 1.44 (+5%)
Absolute organ weight (g)					
Stomach	1.19 ± 0.07	1.17 ± 0.05 (−2%)	1.18 ± 0.07 (−1%)	1.19 ± 0.06 (0%)	1.27 ± 0.04** (+7%)
Liver	4.47 ± 0.28	4.49 ± 0.34 (0)	4.40 ± 0.27 (−2%)	4.57 ± 0.22 (+2%)	4.76 ± 0.16* (+6%)
Kidney	1.29 ± 0.06	1.28 ± 0.04 (−1%)	1.26 ± 0.07 (−2%)	1.28 ± 0.05 (−1%)	1.26 ± 0.05 (−2%)
Relative organ weight (% BW)					
Stomach	0.71 ± 0.03	0.71 ± 0.02 (0%)	0.73 ± 0.04 (+3%)	0.75 ± 0.03* (+6%)	0.82 ± 0.04** (+15%)
Liver	2.67 ± 0.11	2.71 ± 0.09 (+1%)	2.72 ± 0.10 (+2%)	2.88 ± 0.08** (+8%)	3.07 ± 0.07** (+15%)
Kidney	0.77 ± 0.02	0.77 ± 0.03 (0%)	0.78 ± 0.03 (+1%)	0.81 ± 0.03* (+5%)	0.82 ± 0.03** (+6%)
Histopathology					
Forestomach; acanthosis, focal or multifocal	0/10[d] (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	5/10† (50%)
Mean pCoA activity (nmol/min-mg protein)[e]	2.95 ± 2.36	4.54 ± 0.69 (+54%)	5.01 ± 0.74 (+70%)	6.6 ± 1.43 (+124%)	9.92 ± 2.26** (+236%)

[a]Astill et al. (1996a); BASF (1991a).
[b]Values represent means ± SD.
[c]SD not clearly legible in the study report.
[d]Number affected/number examined.
[e]Peroxisome proliferation-only group; $n = 3$.
*$p < 0.05$ based on statistics performed by the study authors.
**$p < 0.01$.
†$p < 0.05$ based on Fisher's exact test performed by the U.S. EPA for the purposes of this PPRTV assessment.

BW = body weight; pCoA = palmitoyl-Coenzyme A; RBC = red blood cell; SD = standard deviation.

Table B-4. Effects in B6C3F$_1$ Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a]

Parameter	Dose (mg/kg-d)				
	0	18	89.3	179	357
Male					
Number of surviving animals	10	10	10	10	10
Terminal body weight (g)	26.95 ± 2.02	26.26 ± 1.43 (−3%)	26.22 ± 1.58 (−3%)	25.80 ± 2.31 (−4%)	26.13 ± 1.76 (−3%)
Absolute organ weight (g)					
Liver	1.09 ± 0.06[b]	1.09 ± 0.08 (0%)	1.14 ± 0.08 (+5%)	1.12 ± 0.10 (+3%)	1.13 ± 0.08 (+4%)
Kidney	0.48 ± 0.05	0.50 ± 0.03 (+4%)	0.51 ± 0.03 (+6%)	0.49 ± 0.04 (+2%)	0.46 ± 0.03 (−4%)
Stomach	0.21 ± 0.01	0.20 ± 0.02 (−5%)	0.21 ± 0.02 (0%)	0.23 ± 0.05 (+10%)	0.24 ± 0.03 (+14%)
Relative organ weight (% BW)					
Liver	4.07 ± 0.16	4.15 ± 0.14 (+2%)	4.36 ± 0.33* (+7%)	4.36 ± 0.24* (+7%)	4.31 ± 0.24 (+6%)
Kidney	1.78 ± 0.10	1.91 ± 0.10* (+7%)	1.93 ± 0.11* (+8%)	1.90 ± 0.15 (+7%)	1.75 ± 0.10 (−2%)
Stomach	0.79 ± 0.07	0.77 ± 0.07 (−3%)	0.81 ± 0.09 (+3%)	0.90 ± 0.13* (+14%)	0.89 ± 0.10* (+13%)
Histopathology					
Forestomach; acanthosis, focal or multifocal	0/10[c] (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	2/10 (20%)
Female					
Number of surviving animals	10	10	10	9[d]	10
Terminal body weight (g)	21.11 ± 1.50	21.92 ± 1.16 (+4%)	20.80 ± 1.26 (−1%)	21.42 ± 1.16 (+1%)	20.77 ± 1.72 (−2%)
Absolute organ weight (g)					
Liver	1.03 ± 0.06	1.08 ± 0.09 (+5%)	1.06 ± 0.06 (+3%)	1.05 ± 0.05 (+2%)	1.03 ± 0.12 (0%)
Kidney	0.35 ± 0.03	0.37 ± 0.02 (+6%)	0.35 ± 0.02 (0%)	0.35 ± 0.02 (0%)	0.35 ± 0.02 (0%)
Stomach	0.24 ± 0.03	0.24 ± 0.03 (0%)	0.23 ± 0.03 (−4%)	0.23 ± 0.02 (−4%)	0.23 ± 0.02 (−4%)
Relative organ weight (% BW)					
Liver	4.89 ± 0.22	4.91 ± 0.26 (0%)	5.09 ± 0.24 (+4%)	4.90 ± 0.21 (0%)	4.97 ± 0.33 (+2%)
Kidney	1.67 ± 0.09	1.66 ± 0.10[e] (−1%)	1.69 ± 0.07 (+1%)	1.66 ± 0.05 (−1%)	1.71 ± 0.08 (+2%)
Stomach	1.13 ± 0.13	1.07 ± 0.12 (−5%)	1.13 ± 0.18 (0%)	1.11 ± 0.13 (−2%)	1.13 ± 0.10 (0%)

Table B-4. Effects in B6C3F$_1$ Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a]

Parameter	Dose (mg/kg-d)				
	0	18	89.3	179	357
Histopathology					
Forestomach; acanthosis, focal or multifocal	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)

[a]Astill et al. (1996a); BASF (1991e).
[b]Values represent means ± SD based on data for surviving animals.
[c]Number affected/number examined.
[d]One female mouse died after 90 days of exposure from liver damage after hemorrhage into one ovarian pouch.
[e]$n = 9$. No explanation was given but based on data for individual animals provided in the study report, 1 value was likely regarded as an outlier (more than 2 SDs lower than the mean).
*$p < 0.05$ based on statistics performed by the study authors.
**$p < 0.01$.

BW = body weight; SD = standard deviation.

Table B-5. Select Non-neoplastic Effects in Male F344 Rats Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 24 Months[a]

Parameter	Dose (mg/kg-d)				
	0 (water)	0 (vehicle)	36	107	357
Number of animals	50	50	50	50	50
Mortality	16/50[b] (32%)	17/50 (34%)	23/50 (46%)	16/50 (32%)	19/50 (38%)
Clinical signs					
Poor general condition	7/50 (14%)	12/50 (24%)	14/50 (28%)	15/50 (30%)	14/50 (28%)
Labored breathing	2/50 (4%)	1/50 (2%)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Terminal body weight (g)	349.7 ± 27.5[c]	368.1 ± 30.4	349.5 ± 28.2* (−5%)	328.8 ± 26.9** (−11%)	282.9 ± 24.0** (−23%)
Body-weight gain (g)	247.6 ± 27.5	266.5 ± 30.7	245.2 ± 28.0** (−8%)	223.7 ± 26.2** (−16%)	178.7 ± 23.4** (−33%)
Gross lesions					
Lung; foci	5/50 (10%)	4/50 (8%)	7/50 (14%)	6/50 (12%)	13/50† (26%)
Absolute organ weight (g)					
Stomach	2.03 ± 0.14	2.06 ± 0.13	1.96 ± 0.16* (−5%)	1.96 ± 0.13* (−5%)	1.91 ± 0.13** (−7%)
Liver	12.43 ± 2.44	12.54 ± 2.05	11.67 ± 2.09 (−7%)	12.53 ± 3.03 (0%)	10.56 ± 1.57** (−16%)
Kidney	2.98 ± 2.48	2.67 ± 0.25	2.66 ± 0.23 (0%)	2.66 ± 0.25 (0%)	2.54 ± 0.24 (−5%)
Brain	2.08 ± 0.04	2.10 ± 0.04	2.07 ± 0.06 (−1%)	2.06 ± 0.07* (−2%)	1.97 ± 0.06** (−6%)
Testes	5.01 ± 1.90	4.85 ± 1.73	4.10 ± 1.41	4.40 ± 1.53	4.58 ± 1.35

Table B-5. Select Non-neoplastic Effects in Male F344 Rats Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 24 Months[a]

Parameter	Dose (mg/kg-d)				
	0 (water)	0 (vehicle)	36	107	357
			(−15%)	(−9%)	(−6%)
Relative organ weight (to BW)					
Stomach	0.60 ± 0.04	0.58 ± 0.04	0.59 ± 0.05 (+2%)	0.62 ± 0.04** (+7%)	0.70 ± 0.07** (+21%)
Liver	3.69 ± 0.83	3.53 ± 0.42	3.47 ± 0.50 (−2%)	3.96 ± 0.95* (+12%)	3.85 ± 0.47 (+9%)
Kidney	0.89 ± 0.78	0.76 ± 0.05	0.80 ± 0.09 (+5%)	0.85 ± 0.10** (+12%)	0.93 ± 0.09** (+22%)
Brain	0.62 ± 0.06	0.60 ± 0.05	0.62 ± 0.06 (+3%)	0.66 ± 0.06** (+10%)	0.72 ± 0.06** (+20%)
Testes	1.47 ± 0.53	1.38 ± 0.48	1.22 ± 0.42 (−12%)	1.39 ± 0.45 (+1%)	1.66 ± 0.42* (+20%)
Histopathology					
Liver; congestion	6/50 (12%)	5/50 (10%)	7/50 (14%)	4/50 (8%)	14/50* (28%)
Lung; congestion	7/50 (14%)	5/50 (10%)	4/50 (8%)	4/50 (8%)	11/50* (22%)
Lung; bronchopneumonia	4/50 (8%)	5/50 (10%)	2/50 (4%)	2/50 (4%)	14/50* (28%)
Spleen; hemosiderin	30/50 (60%)	32/50 (64%)	12/50 (24%)	5/50 (10%)	36/50 (72%)
Mesenteric lymph nodes; hyperplasia	37/50 (74%)	35/50 (70%)	9/50 (18%)	6/50 (12%)	39/50 (78%)
Mandibular lymph nodes; hyperplasia	39/50 (78%)	38/50 (76%)	9/50 (18%)	8/50 (16%)	42/50 (84%)
Kidney; congestion	4/50 (8%)	5/50 (10%)	7/50 (14%)	4/50 (8%)	6/50 (12%)
Prostate; atrophy	35/50 (70%)	28/50 (52%)	34/50 (68%)	40/50 (80%)	36/50* (72%)

[a]Astill et al. (1996b); BASF (1992a).
[b]Number affected/number examined.
[c]Values represent means ± SD.
*$p < 0.05$ compared to the vehicle-only control group based on statistics performed by the study authors.
**$p < 0.01$.
†$p < 0.05$ compared to vehicle-only control based on Fisher's exact test performed by the U.S. EPA for the purposes of this PPRTV assessment.

BW = body weight; SD = standard deviation.

Table B-6. Select Non-neoplastic Effects in Female F344 Rats Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 24 Months[a]

Parameter	Dose (mg/kg-d)				
	0 (water)	**0 (vehicle)**	**36**	**107**	**357**
Number of animals	50	50	50	50	50
Mortality	8/50 (16%)	14/50 (28%)	14/50 (28%)	13/50 (26%)	26/50† (52%)
Clinical signs					
Poor general condition	3/50 (6%)	8/50 (16%)	7/50 (14%)	11/50 (22%)	21/50†† (42%)
Labored breathing	0/50 (0%)	3/50 (6%)	3/50 (6%)	5/50 (10%)	12/50† (24%)
Terminal body weight (g)	261.3 ± 19.8[b]	259.7 ± 27.1	252.1 ± 15.1 (−3%)	236.2 ± 24.7** (−9%)	205.6 ± 21.4** (−21%)
Body-weight gain (g)	181.0 ± 18.7	177.5 ± 27.0	170.5 ± 14.8 (−4%)	155.9 ± 23.6** (−12%)	123.3 ± 22.2** (−31%)
Gross lesions					
Lung; foci	3/50 (6%)	7/50 (14%)	4/50 (8%)	9/50 (18%)	15/50† (30%)
Absolute organ weight (g)					
Stomach	1.66 ± 0.10	1.64 ± 0.13	1.71 ± 0.11 (+4%)	1.64 ± 0.16 (0%)	1.59 ± 0.09 (−3%)
Liver	9.27 ± 1.32	8.74 ± 1.46	9.00 ± 0.99 (+3%)	8.93 ± 1.56 (+2%)	7.97 ± 1.07 (−9%)
Kidney	2.04 ± 0.16	2.03 ± 0.21	2.03 ± 0.12 (0%)	2.01 ± 0.18 (−1%)	1.89 ± 0.11** (−7%)
Brain	1.92 ± 0.05	1.90 ± 0.05	1.91 ± 0.04 (+1%)	1.89 ± 0.05 (−1%)	1.82 ± 0.05** (−4%)
Relative organ weight (to BW)					
Stomach	0.66 ± 0.05	0.66 ± 0.06	0.70 ± 0.05* (+6%)	0.72 ± 0.08** (+9%)	0.79 ± 0.08** (+20%)
Liver	3.69 ± 0.52	3.49 ± 0.53	3.68 ± 0.35 (+5%)	3.89 ± 0.60** (+11%)	3.94 ± 0.28** (+13%)
Kidney	0.81 ± 0.07	0.82 ± 0.13	0.83 ± 0.05 (+1%)	0.88 ± 0.08** (+7%)	0.94 ± 0.08** (+15%)
Brain	0.77 ± 0.07	0.77 ± 0.09	0.78 ± 0.05 (+1%)	0.84 ± 0.11** (+9%)	0.91 ± 0.09** (+18%)
Histopathology					
Liver; congestion	2/50 (4%)	4/50 (8%)	7/50 (14%)	6/50 (12%)	23/50* (46%)
Lung; congestion	1/50 (2%)	2/50 (4%)	4/50 (8%)	6/50 (12%)	18/50** (36%)
Lung; bronchopneumonia	0/50 (0%)	3/50 (6%)	2/50 (4%)	4/50 (8%)	15/50** (30%)
Spleen; hemosiderin	35/50(70%)	36/50 (72%)	7/50 (14%)	8/50 (16%)	44/50* (88%)
Mesenteric lymph nodes; hyperplasia	38/50 (76%)	40/50 (80%)	11/50 (22%)	7/50 (14%)	46/50* (92%)

Table B-6. Select Non-neoplastic Effects in Female F344 Rats Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 24 Months[a]

Parameter	Dose (mg/kg-d)				
	0 (water)	0 (vehicle)	36	107	357
Mandibular lymph nodes; hyperplasia	40/50[c] (80%)	42/50 (84%)	10/50 (20%)	10/50 (20%)	47/50* (94%)
Kidney; congestion	1/50 (2%)	4/50 (8%)	6/50 (12%)	4/50 (8%)	16/50** (32%)

[a]Astill et al. (1996b); BASF (1992a).
[b]Values represent means ± SD.
[c]Number affected/number examined.
*$p < 0.05$ compared to the vehicle-only control group based on statistics performed by the study authors.
**$p < 0.01$.
†$p < 0.05$ compared to vehicle-only control based on Fisher's exact test performed by the U.S. EPA for the purposes of this PPRTV assessment.
††$p < 0.01$.

BW = body weight; SD = standard deviation.

Table B-7. Select Non-neoplastic Effects in Male B6C3F$_1$ Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 18 Months[a]

Parameter	Dose (mg/kg-d)				
	0 (water)	0 (vehicle)	36	143	536
Number of animals	50	50	50	50	50
Mortality	2/50[b] (4%)	2/50 (4%)	2/50 (4%)	2/50 (4%)	15/50†† (30%)
Food consumption (g/animal-d)[c]	5.6 ± 0.7[d]	5.6 ± 0.7	5.4 ± 0.6 (−4%)	5.5 ± 0.6 (−2%)	5.1 ± 0.6† (−9%)
Terminal body weight (g)	42.6 ± 4.1	42.7 ± 3.5	40.9 ± 4.0 (−4%)	40.7 ± 4.5* (−5%)	37.4 ± 3.0** (−12%)
Body-weight gain (g)	18.9 ± 4.0	19.4 ± 3.4	17.8 ± 4.0 (−8%)	17.6 ± 4.0* (−9%)	14.3 ± 2.8** (−26%)
Neutrophils (%); 18 mo	18.00 ± 5.94	20.54 ± 7.57	19.19 ± 6.32 (−7%)	22.29 ± 9.12 (+9%)	26.86 ± 13.50†† (+31%)
Lymphocytes (%); 18 mo	78.88 ± 6.96	76.60 ± 7.58	77.79 ± 6.24 (+2%)	74.19 ± 8.14[e] (−3%)	70.57 ± 13.19†† (−8%)
Absolute organ weight (g)					
Stomach	0.32 ± 0.04	0.33 ± 0.03	0.31 ± 0.04 (−6%)	0.33 ± 0.05 (0%)	0.34 ± 0.04 (+3%)
Liver	1.59 ± 0.60	1.61 ± 0.60	1.47 ± 0.40 (−9%)	1.61 ± 0.46 (0%)	1.61 ± 0.38 (0%)
Kidney	0.76 ± 0.09	0.76 ± 0.06	0.75 ± 0.09 (−1%)	0.71 ± 0.10** (−7%)	0.62 ± 0.06** (−18%)

Table B-7. Select Non-neoplastic Effects in Male B6C3F1 Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 18 Months[a]

Parameter	Dose (mg/kg-d)				
	0 (water)	0 (vehicle)	36	143	536
Brain	0.50 ± 0.02	0.50 ± 0.02	0.50 ± 0.02 (0%)	0.49 ± 0.02* (−2%)	0.48 ± 0.02** (−4%)
Testes	0.24 ± 0.02	0.23 ± 0.02	0.24 ± 0.02 (+4%)	0.23 ± 0.02 (0%)	0.23 ± 0.02 (0%)
Relative organ weight (to BW)					
Stomach	0.85 ± 0.08	0.86 ± 0.09	0.84 ± 0.09 (−2%)	0.89 ± 0.13 (+3%)	1.0 ± 0.13** (+16%)
Liver	4.30 ± 2.01	4.30 ± 1.87	4.01 ± 1.21 (−7%)	4.42 ± 1.29 (+3%)	4.77 ± 1.25 (+11%)
Kidney	2.04 ± 0.17	2.01 ± 0.21	2.04 ± 0.20 (+1%)	1.93 ± 0.18 (−4%)	1.84 ± 0.15** (−8%)
Brain	1.35 ± 0.13	1.33 ± 0.12	1.38 ± 0.14 (+4%)	1.36 ± 0.13 (+2%)	1.43 ± 0.11** (+8%)
Testes	0.63 ± 0.06	0.61 ± 0.06	0.65 ± 0.05** (+7%)	0.64 ± 0.06* (+5%)	0.69 ± 0.04** (+13%)
Histopathology					
Lung; congestion	1/50 (2%)	1/50 (2%)	1/50 (2%)	2/50 (4%)	9/50** (18%)
Liver; congestion	1/50 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	7/50** (14%)
Liver; peripheral fatty infiltration	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	31/50** (62%)
Liver; basophilic foci	4/50 (8%)	4/50 (8%)	5/50 (10%)	12/50* (24%)	6/50 (12%)
Liver; focal hyperplasia	2/50 (4%)	7/50 (14%)	4/50 (8%)	9/50 (18%)	10/50 (20%)
Forestomach; focal hyperplasia	0/50 (0%)	1/50 (2%)	1/50 (2%)	1/50 (2%)	5/50 (10%)

[a]Astill et al. (1996b); BASF (1991b).
[b]Number affected/number examined.
[c]For this endpoint, means and SDs for the entire study period were calculated by the U.S. EPA for the purposes of this PPRTV assessment based on data for individual time points provided in the study report.
[d]Values represent means ± SD.
[e]Value not clearly legible in the study report (BASF, 1991b).
*$p < 0.05$ compared to the vehicle-only control group based on statistics performed by the study authors.
**$p < 0.01$.
†$p < 0.05$ compared to vehicle-only control based on Fisher's exact test (for categorical data) or Student's *t*-test (for continuous data) performed by the U.S. EPA for the purposes of this PPRTV assessment.
††$p < 0.01$.

BW = body weight; SD = standard deviation.

Table B-8. Select Non-neoplastic Effects in Female B6C3F$_1$ Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 18 Months[a]

Parameter	Dose (mg/kg-d)				
	0 (water)	**0 (vehicle)**	**36**	**143**	**536**
Number of animals	50	50	50	50	50
Mortality	2/50[b] (4%)	4/50 (8%)	2/50 (4%)	4/50 (8%)	15/50†† (30%)
Food consumption (g/animal-d)[c]	6.6 ± 0.8[d]	6.3 ± 0.7	6.6 ± 0.7 (+5%)	6.2 ± 0.8 (−2%)	5.5 ± 0.5†† (−13%)
Terminal body weight (g)	42.0 ± 6.9	41.1 ± 5.6	40.6 ± 5.8 (−1%)	39.9 ± 5.4 (−3%)	35.5 ± 4.2** (−14%)
Body-weight gain (g)	22.6 ± 6.8	21.8 ± 5.3	21.1 ± 5.4 (−3%)	20.4 ± 5.4 (−6%)	16.5 ± 4.0** (−24%)
Neutrophils (%); 18 mo	20.40 ± 7.09	22.64 ± 10.74	22.65 ± 8.40 (0%)	21.85 ± 7.60 (−3%)	25.11 ± 8.96 (+11%)
Lymphocytes (%); 18 mo	77.10 ± 7.48	74.87 ± 11.62	74.92 ± 8.64 (0%)	75.77 ± 8.39 (+1%)	72.09 ± 9.68 (−4%)
Absolute organ weight (g)					
Stomach	0.34 ± 0.04	0.34 ± 0.04	0.34 ± 0.04 (0%)	0.34 ± 0.04 (0%)	0.34 ± 0.04 (0%)
Liver	1.38 ± 0.15	1.37 ± 0.15	1.37 ± 0.21 (0%)	1.42 ± 0.32 (+4%)	1.40 ± 0.15 (+2%)
Kidney	0.48 ± 0.04	0.47 ± 0.04	0.46 ± 0.03 (−2%)	0.45 ± 0.04 (−4%)	0.44 ± 0.04** (−6%)
Brain	0.51 ± 0.02	0.51 ± 0.02	0.51 ± 0.01 (0%)	0.50 ± 0.02** (−2%)	0.48 ± 0.02** (−6%)
Relative organ weight (to BW)					
Stomach	0.91 ± 0.18	0.94 ± 0.15	0.94 ± 0.15 (0%)	0.97 ± 0.15 (+3%)	1.11 ± 0.11** (+18%)
Liver	3.67 ± 0.49	3.75 ± 0.54	3.79 ± 0.53 (+1%)	4.08 ± 1.48 (+9%)	4.54 ± 0.28** (+21%)
Kidney	1.27 ± 0.20	1.28 ± 0.20	1.28 ± 0.18 (0%)	1.28 ± 0.17 (0%)	1.44 ± 0.16** (+13%)
Brain	1.37 ± 0.25	1.41 ± 0.22	1.43 ± 0.23 (+1%)	1.42 ± 0.19 (+1%)	1.57 ± 0.21** (+11%)
Histopathology					
Lung; congestion	1/50 (2%)	2/50 (4%)	0/50 (0%)	1/50 (2%)	10/50* (20%)
Liver; congestion	1/50 (2%)	0/50 (0%)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Liver; peripheral fatty infiltration	0/50 (0%)	1/50 (2%)	0/50 (0%)	3/50 (6%)	22/50** (44%)
Liver; basophilic foci	2/50 (4%)	1/50 (2%)	2/50 (4%)	4/50 (8%)	6/50*,[e] (12%)

Table B-8. Select Non-neoplastic Effects in Female B6C3F$_1$ Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 18 Months[a]

Parameter	Dose (mg/kg-d)				
	0 (water)	0 (vehicle)	36	143	536
Liver; focal hyperplasia	1/50 (2%)	0/50 (0%)	3/50 (6%)	4/50*, [e] (8%)	1/50 (2%)
Forestomach; focal hyperplasia	1/50 (2%)	1/50 (2%)	0/50 (0%)	1/50 (2%)	4/50 (8%)

[a]Astill et al. (1996b); BASF (1991b).
[b]Number affected/number examined.
[c]For this endpoint, means and SDs for the entire study period were calculated by the U.S. EPA for the purposes of this PPRTV assessment based on data for individual time points provided in the study report.
[d]Values represent means ± SD.
[e]Statistical significance reported by the study authors not confirmed by Fisher's exact test performed by the U.S. EPA for the purposes of this PPRTV assessment (one-tailed, $p > 0.05$).
*$p < 0.05$ compared to the vehicle-only control group based on statistics performed by the study authors.
**$p < 0.01$.
†$p < 0.05$ compared to vehicle-only control based on Fisher's exact test (for categorical data) or Student's *t*-test (for continuous data) performed by the U.S. EPA for the purposes of this PPRTV assessment.
††$p < 0.01$.

BW = body weight; PPRTV = provisional peer-reviewed toxicity value; SD = standard deviation.

Table B-9. Cancer Effects in Male and Female B6C3F$_1$ Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 18 Months[a]

Male					
ADD (HED), mg/kg-d	**0 (water)**	**0 (vehicle)**	**36 (5.5)**	**143 (21.8)**	**536 (79.9)**
Number of animals	50	50	50	50	50
Hepatocellular adenoma	0/50[b] (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Hepatocellular carcinoma	4/50 (8%)	6/50[c] (12%)	3/50 (6%)	7/50 (14%)	9/50 (18%)
Hepatocellular adenoma or carcinoma	4/50 (8%)	6/50 (12%)	3/50 (6%)	7/50 (14%)	10/50[d] (20%)
Female					
ADD (HED), mg/kg-d	**0 (water)**	**0 (vehicle)**	**36 (5.3)**	**143 (21.1)**	**536 (77.3)**
Number of animals	50	50	50	50	50
Hepatocellular adenoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Hepatocellular carcinoma	1/50 (2%)	0/50[c, e] (0%)	1/50 (2%)	3/50 (6%)	5/50* (10%)
Hepatocellular adenoma or carcinoma	1/50 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)	5/50* (10%)

[a]Astill et al. (1996b); BASF (1991b).
[b]Number affected/number examined.
[c]Significant ($p < 0.05$) trend based on time-dependent test (Peto test) performed by the study authors.
[d]Based on statistical analyses (Fisher's exact test) performed by the U.S. EPA for the purposes of this PPRTV assessment, the combined incidence of carcinoma or adenoma was not significantly increased in males treated at 536 mg/kg-day compared to vehicle-only controls.
[e]Significant ($p < 0.05$) trend based on time-independent tests (Cochran-Armitage and Peto tests) performed by the study authors.
*$p < 0.05$ compared to the vehicle-only control group based on Fisher's exact test performed by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose.

Table B-10. Effects in Wistar Rats Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Gavage on GDs 6−15[a]

Parameter	Dose (mg/kg-d)				
	0 (water)	0 (vehicle)	130	650	1,300
Maternal Effects					
Number of dams	10	10	10	10	10
Mortality	0/10[b] (0%)	0/10 (0%)	0/10 (0%)	1/10 (10%)	6/10 (60%)†
Food consumption; GDs 6−15 (g/animal-d)	23.6 ± 1.51[c]	23.9 ± 1.98	23.2 ± 1.14 (−3%)	21.7 ± 1.91 (−9%)	13.3 ± 4.42** (−44%)
Maternal body weight; GD 15 (g)	303.0 ± 16.34	309.0 ± 15.96	303.8 ± 17.32 (−2%)	296.3 ± 7.11 (−4%)	261.3 ± 48.29* (−15%)
Maternal body weight; GD 20 (g)	375.0 ± 19.90	384.2 ± 25.99	377.4 ± 23.81 (−2%)	367.1 ± 12.84 (−4%)	308.9 ± 63.25** (−20%)
Maternal body-weight gain; GDs 6−15 (g)	48.6 ± 3.33	51.6 ± 3.40	44.1 ± 18.20 (−15%)	43.6 ± 5.25†† (−16%)	−3.1 ± 50.26** (−106%)
Maternal body-weight gain; GDs 0−20 (g)	143.5 ± 7.90	153.4 ± 13.70	147.8 ± 24.14 (−4%)	140.5 ± 15.11[d] (−8%)	73.6 ± 61.60** (−52%)
Maternal net weight change from GD 6[e]	42.9 ± 3.8	44.7 ± 6.19	45.4 ± 16.03	38.4 ± 5.84	11.6 ± 27.52*
Gravid uterine weight (g)	77.7 ± 9.15	82.2 ± 10.87	72.2 ± 17.14 (−12%)	75.9 ± 9.80 (−8%)	32.9 ± 37.64** (−60%)
Dams with viable fetuses	10/10 (100%)	10/10 (100%)	10/10 (100%)	9/9 (100%)	2/4 (50%)
% Postimplantation loss	8.2 ± 6.07	7.0 ± 7.59	5.0 ± 7.12 (−28%)	4.5 ± 4.56 (−36%)	54.7 ± 52.88** (+680%)
Resorptions	1.2 ± 0.97	1.1 ± 1.20	0.6 ± 0.94 (−45%)	0.7 ± 0.71 (−36%)	7.8 ± 7.50** (+609%)
Fetal Effects					
Number of litters	9	10	10	9	2
Fetal body weight on GD 20 (g)	3.80 ± 0.324	3.82 ± 0.177	3.80 ± 0.249 (−1%)	3.44 ± 0.227* (−10%)	2.86 ± 0.333** (−25%)
Fetal body weights; M (g)	3.88 ± 0.350[f]	3.92 ± 0.211	3.90 ± 0.273 (−1%)	3.50 ± 0.222* (−11%)	2.87 ± 0.314** (−27%)
Fetal body weights; F (g)	3.70 ± 0.297	3.70 ± 0.137	3.70 ± 0.228 (0%)	3.36 ± 0.267 (−9%)	2.85 ± 0.363** (−23%)
Visceral variations					
Fetal incidence	23/59 (39%)	29/71 (41%)	18/62 (29%)	22/62 (36%)	10/13 (77%)*
Litter incidence	6/9 (67%)	9/10 (90%)	8/10 (80%)	8/9 (89%)	2/2 (100%)
Skeletal malformations					
Fetal incidence	1/65 (2%)	2/75 (3%)	2/68 (3%)	6/65 (9%)	4/15 (27%)**
Litter incidence	1/9 (11%)	2/10 (20%)	2/10 (20%)	3/9 (33%)	2/2 (100%)

Table B-10. Effects in Wistar Rats Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Gavage on GDs 6−15[a]

Parameter	Dose (mg/kg-d)				
	0 (water)	0 (vehicle)	130	650	1,300
Skeletal variations					
Fetal incidence	23/65 (35%)	17/75 (23%)	23/68 (34%)	27/65* (42%)	10/15** (67%)
Litter incidence	7/9 (78%)	6/10 (60%)	8/10 (80%)	7/9 (78%)	2/2 (100%)
Skeletal retardations					
Fetal incidence	28/65 (43%)	38/75 (51%)	31/68 (46%)	51/65** (79%)	15/15** (100%)
Litter incidence	8/9 (89%)	10/10 (100%)	8/10 (80%)	9/9 (100%)	2/2 (100%)

[a]Hellwig and Jäckh (1997); Confidential (1991).
[b]Number affected/number examined.
[c]Values represent (litter) means ± SD.
[d]Marginally significant; p = 0.08 based on statistical analysis (t-test) performed by the U.S. EPA for the purposes of this PPRTV assessment.
[e]Net weight change from GD 6 = (terminal body weight – gravid uterine weight) – GD 6 BW.
[f]Value(s) not clearly legible in the study report.
†$p < 0.05$ compared to the vehicle-only control group based on statistics performed by the U.S. EPA for the purposes of this PPRTV assessment.
††$p < 0.01$.
*$p < 0.05$ compared to the vehicle-only control group based on statistics performed by study authors.
**$p < 0.01$.

BW = body weight; F = female(s); GD = gestation day; M = male(s); SD = standard deviation.

Table B-11. Significant Effects in CD-1 Mice Administered 2-Ethylhexanol (CASRN 104-76-7) via Gavage on GDs 6−13[a]

Parameter	Dose (mg/kg-d)	
	0	1,525
Maternal Effects		
Number of dams	50	50
Mortality	0/50[b] (0%)	17/49[c,] † (35%)
Maternal body weight; GD 7 (g)	29.9 ± 2.35[d]	29.0 ± 2.07 (−3%)
Maternal body weight; GD 14 (g)	37.1 ± 2.89	33.8 ± 1.58* (−9%)
Maternal body weight; GD 18 (g)	47.9 ± 5.01	40.5 ± 6.38* (−15%)
Maternal body weight; PND 3 (g)	36.8 ± 2.68	33.6 ± 3.81* (−9)
Maternal body-weight gain; GDs 7−14 (g)	7.2 ± 2.72	4.8 ± 2.73* (−33%)
Maternal body-weight gain; GDs 7−18 (g)	18.0 ± 5.18	11.4 ± 5.86* (−37%)
Number of viable litters/number of pregnant F[e]	33/34	11/20*
Reproductive index (%)[f]	97	55*
Pup Effects		
Number of litters	33	11
Number of live pups/litter		
PND 1	9.9 ± 2.36	6.4 ± 3.23*[, g] (−35%)
PND 3	9.8 ± 2.46	4.9 ± 3.70* (−50%)
Number of dead pups/litter		
PND 1	0.1 ± 0.29	1.5 ± 1.63*[, h] (+1,400%)
PND 3	0.1 ± 0.24	1.5 ± 2.02 (+1,400%)
Pup weights (g)		
PND 1	1.6 ± 0.13[h]	1.4 ± 0.17* (−13%)
PND 3	2.2 ± 0.19	1.7 ± 0.31* (−23%)
Pup viability/litter (%); PNDs 1−3	98.2 ± 8.80	73.4 ± 32.20* (−25%)
Pup-weight change (%); PNDs 1−3	35.3 ± 6.28	23.7 ± 13.15* (−12%)

[a]Hardin et al. (1987); Hazleton Laboratories (1983).
[b]Number affected/number examined.
[c]The denominator is not 50 because the death of 1 F (owing to a dosing error) was omitted from analysis.
[d]Values represent means ± SD.
[e]A viable litter was defined as a litter that had at least one live pup on Day 1.
[f]Reproductive index = (number of females that produced viable litters ÷ number of proven pregnant females) × 100.
[g]Value is not identical to that shown in the Hardin et al. (1987) publication (6.8 ± 3.4*).
[h]Value(s) not clearly legible in the study report.
*$p < 0.05$ based on statistics performed by the study authors.
†$p < 0.01$ compared to the control group based on statistics (*t*-test) performed by the U.S. EPA for the purposes of this PPRTV assessment.

F = female(s); GD = gestation day; PND = postnatal day; SD = standard deviation.

Table B-12. Effects in Wistar Rats Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Gavage on GD 12[a]

Parameter	Dose (mg/kg-d)		
	0	**830**	**1,700**
Number of dams	7	7	7
Number of implantations	91	104 (+14%)	113 (+24%)
Resorbed/dead fetuses (%)	9.6 ± 4.1[b]	10.1 ± 9.1 (+0.5%)	8.5 ± 1.7 (−1%)
Mean fetal body weight (g)	4.1[c]	3.9 (−5%)	3.5 (−15%)
Survivors malformed (%)	0.0 ± 0.0	2.0 ± 1.3 (+2%)	22.2 ± 14.7[d], † (+22%)

[a]Ritter et al. (1987).
[b]Values represent means ± SEM.
[c]Mean (no measure of variance was provided).
[d]Malformations reported included hydronephrosis (8%), tail and limb defects (5 and 10%), and other (1%).
†$p < 0.01$ compared to the control group based on statistics (*t*-test) performed by the U.S. EPA for the purposes of this PPRTV assessment.

GD gestation day; SEM = standard error of the mean.

Table B-13. Effects in ICR Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7) as a Vapor 8 Hours/Day for 3 Months[a]

Parameter	Exposure Concentration (ppm) (HEC_{ET}, mg/m^3)[b, c]			
	0 (0)	**21.9 (4.17)**	**65.8 (12.5)**	**153.2 (29.20)**
Olfactory Epithelium Effects				
Morphological alterations (severity scores)[f]	1[d]	1.6	2.9**	3.8**
Diameter of Bowman's glands (µm)	6.80 ± 1.3[e]	9.80 ± 2.0	15.0 ± 3.9**	16.3 ± 1.6**
CD3-positive cells (/mm^2)	0 ± 0	1.03 ± 1.4	10.3 ± 9.9*	18.5 ± 12**
OMP-positive cells (ratio of OMP[+] cells to olfactory epithelium cells)	0.791 ± 0.16	0.473 ± 0.20**	0.411 ± 0.086**	0.143 ± 0.079**
PCNA-positive cells (/mm^2)	12.5 ± 3.6	11.3 ± 4.5	9.55 ± 4.8	5.67 ± 4.8*
Olfactory Bulb Effects				
Glomerular diameter (µm)	80 ± 2.1	77.9 ± 2.1	77.9 ± 2.8	62.1 ± 2.8**
OMP-positive cells (pixel)	28.7 ± 4.0	29.0 ± 2.4	24.4 ± 3.8*	19.1 ± 0.81**
TH-positive cells (pixel)	27.0 ± 7.2	23.2 ± 3.6	21.2 ± 3.3	17.9 ± 2.8**
Iba1-positive cells (/mm^3)	28,237 ± 3,548	24,075 ± 4,838	25,723 ± 2,903	37,688 ± 2,580*
Dcx-positive cells (/mm^3)	8,588 ± 1,342	9,876 ± 3,580	6,355 ± 1,006	12,007 ± 1,454*

[a]Miyake et al. (2016).
[b]Analytical exposure concentrations were converted to HECs for extrathoracic respiratory effects using the following equation: HEC_{ET} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. $RGDR_{ET}$ is the extrathoracic regional gas-dose ratio (animal:human) (U.S. EPA, 1994).
[c]Data were digitally extracted using GrabIt! software.
[d]Mean; no measure of variance was reported.
[e]Values represent means ± SD.
[f]Severity scores: 1 (normal), 2 (slight), 3 (moderate), and 4 (severe).
*$p < 0.05$ based on statistics performed by the study authors.
**$p < 0.01$ based on statistics performed by the study authors.

Dcx = doublecortin; ET = extrathoracic respiratory effects; HEC = human equivalent concentration; Iba1 = ionized calcium-binding adapter molecule 1; MW = molecular weight; OMP = olfactory marker protein; PCNA = proliferating cell nuclear antigen; RGDR = regional gas dose ratio; SD = standard deviation; TH = tyrosine hydroxylase.

Table B-14. Effects in S-D Rats Exposed to 2-Ethylhexanol (CASRN 104-76-7) as a Vapor 7 Hours/Day on GDs 1−19[a]

Parameter	Exposure Concentration (mg/m^3)	
	0	850
Maternal Effects		
Number of dams (approximate)	15	15
Maternal body weight; GD 0 (g)	243 ± 25[b]	283 ± 18 (+16%)
Maternal body weight; GD 20 (g)	354 ± 32	371 ± 20 (+5%)
Maternal body-weight gain; GDs 0−20 (g)	111[c]	88 (−21%)
Feed consumption (g)	117 ± 13	106 ± 15* (−9%)
Resorptions per litter	0.4	0.3 (−25%)
Fetal Effects		
Fetal body weight; males (g)	3.28 ± 0.27	3.18 ± 0.30 (−3%)
Fetal body weight; females (g)	3.19 ± 0.20	3.02 ± 0.20 (−5%)

[a]Nelson et al. (1989).
[b]Values represent (litter) means ± SD.
[c]Mean; no measure of variance was reported.
*$p < 0.05$ based on statistics performed by the study authors.

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

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING OF NONCANCER ENDPOINTS

As discussed in the body of the report under "Derivation of Subchronic Provisional Oral Reference Dose," the most sensitive treatment-related changes were reported in the developmental study conducted by Hellwig and Jäckh (1997) and Confidential (1991) and in the subchronic-duration gavage study in rats and mice (Astill et al., 1996a; BASF, 1991a); these changes are presented in Table C-1. Endpoints selected to determine potential points of departure (PODs) for the subchronic provisional reference dose (p-RfD) using benchmark dose (BMD) analysis were as follows: (1) absolute liver weight in male rats; (2) relative liver, kidney, and stomach weight in male rats; (3) relative liver and stomach weight in female rats (Astill et al., 1996a; BASF, 1991a); (4) relative stomach weight in male mice (Astill et al., 1996a; BASF, 1991e, l); (5) fetal body weight; and (6) fetal skeletal malformations, variations, and retardations (Hellwig and Jäckh, 1997; Confidential, 1991). Summaries of modeling approaches and results (see Tables C-3 through C-12) for each data set follow.

The most sensitive endpoints showing treatment-related changes in the study of rats administered 2-ethylhexanol (2-EH) via gavage 5 days/week for 24 months (Astill et al., 1996b; BASF, 1992a) were decreased body weight in males and females (see Tables B-5, B-6, and C-2). Data sets for these endpoints were selected to determine potential PODs for the chronic p-RfD, using BMD analysis. Summaries of modeling approaches and results (see Tables C-13 and C-14) for each data set follow.

As discussed in the body of the report under "Derivation of Subchronic Provisional Inhalation Reference Concentration," the most sensitive treatment-related changes due to inhalation exposure of 2-EH were reported in male mice from the Miyake et al. (2016) study and are presented in Table B-13. Endpoints selected to determine potential PODs for the subchronic provisional reference concentration (p-RfC) using BMD analysis were as follows: (1) diameter of Bowman's glands in the olfactory epithelium, (2) CD3-positive cells in the olfactory epithelium, (3) olfactory marker protein (OMP)-positive cells in the olfactory epithelium, (4) proliferating cell nuclear antigen (PNCA)-positive cells in the olfactory epithelium, (5) glomerular diameter in the olfactory bulb, (6) protein (OMP)-positive cells in the olfactory bulb (7) tyrosine hydroxylase (TH)-positive cells in the olfactory bulb, (8) ionized calcium-binding adapter molecule 1 (Iba1)-positive cells in the olfactory bulb, and (9) doublecortin (Dcx)-positive cells in the in the olfactory bulb. Summaries of modeling approaches and results (see Tables C-15 through C-23) for each data set follow.

MODELING PROCEDURE FOR DICHOTOMOUS NONCANCER DATA

BMD modeling of dichotomous noncancer data was conducted with the U.S. EPA's Benchmark Dose Software (BMDS, Version 2.7). For these data, the Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, and Weibull dichotomous models available within the software were fit using a benchmark response (BMR) of 10% extra risk. The Multistage model is run for all polynomial degrees up to $n - 1$, where n is the number of dose groups including control. Adequacy of model fit was judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), scaled residuals at the data point (except the control) closest to the predefined benchmark response (absolute value <2.0), and visual inspection of the model fit. In the cases where no best model was found to fit to the data, a reduced data set without the high-dose group

was further attempted for modeling and the result was present along with that of the full data set. Among the models providing adequate fit, the benchmark dose lower confidence limit (BMDL) from the model with the lowest Akaike's information criterion (AIC) was selected as a potential POD when BMDL values were sufficiently close. Otherwise, the lowest BMDL was selected as a potential POD.

MODELING PROCEDURE FOR CONTINUOUS NONCANCER DATA

BMD modeling of continuous data is conducted with U.S. EPA's BMDS (Version 2.7). All continuous models available within the software are fit using a BMR of 1 standard deviation (SD) relative risk or 10% extra risk when a biologically determined BMR is available (e.g., BMR 10% relative deviation [RD] for body weight based on a biologically significant weight loss of 10%), as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b). An adequate fit is judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals near the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination is made as to whether the variance across dose groups is homogeneous. If a homogeneous variance model is deemed appropriate based on the statistical test provided by BMDS (i.e., Test 2), the final BMD results are estimated from a homogeneous variance model. If the test for homogeneity of variance is rejected ($p < 0.1$), the model is run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model does not adequately fit the data (i.e., Test 3; $p < 0.1$), the data set is considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL/benchmark concentration lower confidence limit (BMCL) is selected if the BMDL/BMCL estimates from different models vary >threefold; otherwise, the BMDL/BMCL from the model with the lowest AIC is selected as a potential POD from which to derive the oral reference dose/inhalation reference concentration (RfD/RfC).

MODELING PROCEDURE FOR NESTED DICHOTOMOUS NONCANCER DATA

BMD modeling of nested dichotomous noncancer developmental effects was conducted with the U.S. EPA's BMDS (Version 2.7). A BMR of 5% extra risk was used for developmental effects, as an excess risk of 5% approximates the no-observed-adverse-effect level (NOAEL) for most developmental studies. In addition, developmental studies provide increased statistical power compared to regular toxicity studies (i.e., use of pups as the observational subject) and developmental effects are often considered to be severe. The Nested Logistic model includes a litter-specific covariate and intralitter correlation to address intralitter similarity. The litter-specific covariate considers the condition of the exposed dam before the onset of exposure, and the intralitter correlation statistically describes the similarity of responses among pups in the same litter. For each data set, the Nested Logistic model was fit with and without each of the selected model parameters (i.e., litter-specific covariate, intralitter covariate). Adequacy of the model fit was judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), scaled residuals at the data point (except the control) closest to the predefined benchmark response (absolute value <2.0), and visual inspection of the model fit. Among the models providing adequate fit, the BMDL from the model with the lowest AIC was selected as a potential POD when BMDL values were sufficiently close.

Table C-1. Selected Non-neoplastic Endpoints in Rats or Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7)					
Astill et al. (1996a); BASF (1991a)					
Male Rats					
Adjusted daily dose (mg/kg-d) (HED)[a]	**0**	**18 (4.3)**	**89.3 (21.4)**	**179 (43.0)**	**357 (85.7)**
Number of animals	10	10	10	10	10
Absolute liver weight	7.74 ± 0.57[b]	7.94 ± 0.77 (+3%)	7.95 ± 0.66 (+3%)	8.07 ± 0.27 (+4%)	9.17 ± 0.85** (+18%)
Relative liver weight	2.77 ± 0.11	2.82 ± 0.12 (+2%)	2.86 ± 0.10 (+3%)	2.98 ± 0.08** (+8%)	3.57 ± 0.22** (+29%)
Relative kidney weight	0.70 ± 0.02	0.71 ± 0.02 (+1%)	0.71 ± 0.03 (+1%)	0.75 ± 0.03* (+7%)	0.81 ± 0.04** (+16%)
Relative stomach weight[c]	0.57 ± 0.04	0.56 ± 0.03 (−2%)	0.56 ± 0.04 (−2%)	0.59 ± 0.03 (+4%)	0.63 ± 0.02** (+11%)
Female Rats					
Adjusted daily dose (mg/kg-d) (HED)[a]	**0**	**18 (4.0)**	**89.3 (19.6)**	**179 (39.4)**	**357 (75.0)**
Number of animals	10	10	10	10	10
Relative liver weight	2.67 ± 0.11	2.71 ± 0.09 (+1%)	2.72 ± 0.10 (+2%)	2.88 ± 0.08** (+8%)	3.07 ± 0.07** (+15%)
Relative stomach weight[c]	0.71 ± 0.03	0.71 ± 0.02 (0%)	0.73 ± 0.04 (+3%)	0.75 ± 0.03* (+6%)	0.82 ± 0.04** (+15%)

Table C-1. Selected Non-neoplastic Endpoints in Rats or Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7)					
Astill et al. (1996a); BASF (1991e); BASF (1991c)					
Male Mice					
Adjusted daily dose (mg/kg-d)	**0**	**18**	**89.3**	**179**	**357**
Number of animals	10	10	10	10	10
Relative stomach weight[c]	0.79 ± 0.07	0.77 ± 0.07 (−3%)	0.81 ± 0.09 (+3%)	0.90 ± 0.13* (+14%)	0.89 ± 0.10* (+13%)
Hellwig and Jäckh (1997); Confidential (1991)					
Adjusted daily dose (mg/kg-d) (HED)[a]	**0**	**130 (32.5)**	**650 (163)**	**1,300 (325)**	
Fetal body weight on GD 20 (g)	3.82 ± 0.177	3.80 ± 0.249 (−1%)	3.44 ± 0.227* (−10%)	2.86 ± 0.333** (−25%)	
Skeletal malformations—fetal incidence	2/75 (3%)	2/68 (3%)	6/65 (9%)	4/15** (27%)	
Skeletal variations—fetal incidence	17/75 (23%)	23/68 (34%)	27/65* (42%)	10/15** (67%)	
Skeletal retardations—fetal incidence	38/75 (51%)	31/68 (46%)	51/65** (79%)	15/15** (100%)	

[a]HED = adjusted daily animal dose (mg/kg-day) × $(BW_a \div BW_h)^{1/4}$ (U.S. EPA, 2005), using TWA body weights calculated from study reported body-weight data for rats and using 70 kg for humans (U.S. EPA, 2011b).
[b]Values expressed as mean ± SD (% change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[c]As discussed above, doses for stomach-weight changes were not converted to HEDs.

*$p < 0.05$ based on statistics performed by the study authors.
**$p < 0.01$.

BW = body weight; GD = gestation day; HED = human equivalent dose; SD = standard deviation; TWA = time-weighted average.

Table C-2. Data for the Decreased Body Weight of Rats Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Gavage 5 Days/Week for 24 Months[a]

Male				
Parameter	ADD (HED)[b], mg/kg-d			
	0	36 (9.5)	107 (27.9)	357 (90.9)
Number of animals	33	27	34	31
Body weight at study termination (g)	368.1 ± 30.4[c]	349.5 ± 28.2 (−5%)	328.8 ± 26.9 (−11%)	282.9 ± 24.0 (−23%)
Female				
Parameter	ADD (HED), mg/kg-d			
	0	36 (8.4)	107 (24.8)	357 (81.2)
Number of animals	36	37	37	24
Body weight at study termination (g)	259.7 ± 27.1	252.1 ± 15.1 (−3%)	236.2 ± 24.7 (−9%)	205.6 ± 21.4 (−21%)

[a]Astill et al. (1996b); BASF (1992a).
[b]HED = adjusted daily animal dose (mg/kg-day) × $(BW_a \div BW_h)^{1/4}$ (U.S. EPA, 2005), using TWA body weights calculated from study reported body-weight data for rats and using 70 kg for humans (U.S. EPA, 2011b).
[c]Mean ± SD.

ADD = adjusted daily dose; BW = body weight; HED = human equivalent dose; SD = standard deviation; TWA = time-weighted average.

Model Predictions for Increased Absolute Liver Weight in Male Rats (Astill et al., 1996a; BASF, 1991a)

The procedure outlined above for continuous data was applied to the data for increased absolute liver weight in male F344 rats treated with 2-EH via gavage for 3 months (Astill et al., 1996a; BASF, 1991a) (see Table C-1). Table C-3 summarizes the BMD modeling results. Neither the constant nor the nonconstant variance models provided adequate fit to the variance data; thus, these data were not suitable for BMD modeling.

Table C-3. Modeling Results for Increased Absolute Liver Weights in Male F344 Rats Administered 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a, b]

Model	Test for Significant Difference *p*-Value[c]	Variance *p*-Value[d]	Means *p*-Value[d]	Scaled Residuals for Dose Group[e]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Constant variance							
Exponential (Model 2)[f]	<0.0001	0.01742	0.3539	−1.357	11.76113	51.2915	39.2714
Exponential (Model 3)[f]	<0.0001	0.01742	0.7407	0.008858	11.10582	70.1208	47.6063
Exponential (Model 4)[f]	<0.0001	0.01742	0.162	−1.42	14.14542	50.277	37.3994
Exponential (Model 5)[f]	<0.0001	0.01742	0.436	0.009035	13.11232	69.8765	47.7935
Hill[f]	<0.0001	0.01742	0.4359	0.00905	13.112554	69.8668	47.7978
Linear[g]	<0.0001	0.01742	0.3031	−1.42	12.145307	50.2772	37.3999
Polynomial (2-degree)[g]	<0.0001	0.01742	0.8583	0.0979	9.268477	65.8413	46.5696
Polynomial (3-degree)[g]	<0.0001	0.01742	0.7779	0.0181	11.007912	69.505	47.7577
Power[f]	<0.0001	0.01742	0.7383	0.00903	11.112275	69.8781	47.793
Nonconstant variance							
Linear[g]	<0.0001	0.01888	0.1627	−1.35	13.605381	52.181	37.9956

[a]Astill et al. (1996a); BASF (1991b).
[b]No model was selected. Neither the constant nor nonconstant variance models provide adequate fit to the variance data.
[c]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[d]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[e]Scaled residuals at dose closest to BMD.
[f]Power restricted to ≥1.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose.

Model Predictions for Increased Relative Liver Weight in Male Rats (Astill et al., 1996a; BASF, 1991a)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in male F344 rats treated with 2-EH via gavage for 3 months (Astill et al., 1996a; BASF, 1991a) (see Table C-1). The BMD modeling results are summarized in Table C-4 and Figure C-1. The constant variance model did not provide adequate fit to the variance data. The nonconstant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by several of the included models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Polynomial 3-degree) is selected. For relative liver weight, the $BMDL_{10}$ of 45 mg/kg-day from this model is selected for this endpoint.

Table C-4. Modeling Results for Increased Relative Liver Weights in Male F344 Rats Administered 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Nonconstant variance							
Exponential (Model 2)[e]	<0.0001	0.3089	0.001957	−2.101	−142.2335	36.2632	31.0952
Exponential (Model 3)[e]	<0.0001	0.3089	0.4633	−0.06315	−153.536	53.0526	44.8859
Exponential (Model 4)[e]	<0.0001	0.3089	0.0001697	−2.079	−137.7124	35.6373	29.5695
Exponential (Model 5)[e]	<0.0001	0.3089	0.2	−0.07957	−151.4325	52.8248	44.8682
Hill[e,]	<0.0001	0.3089	0.1998	−0.0797	−151.4313	52.8221	44.8677
Linear[e]	<0.0001	0.3089	0.0005952	−2.08	−139.7124	35.6373	29.5695
Polynomial (2-degree)[g]	<0.0001	0.3089	0.4251	−0.309	−153.3640	51.5971	43.9782
Polynomial (3-degree)[f,g]	**<0.0001**	**0.3089**	**0.6541**	**0.0741**	**−154.2259**	**53.4491**	**45.0018**
Power[e]	<0.0001	0.3089	0.4399	−0.0796	−153.4326	52.8249	44.8682

[a]Astill et al. (1996a); BASF (1991j).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at dose closest to BMD.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among models that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = benchmark dose 10% extra risk; $BMDL_{10}$ = 95% benchmark dose lower confidence limit.

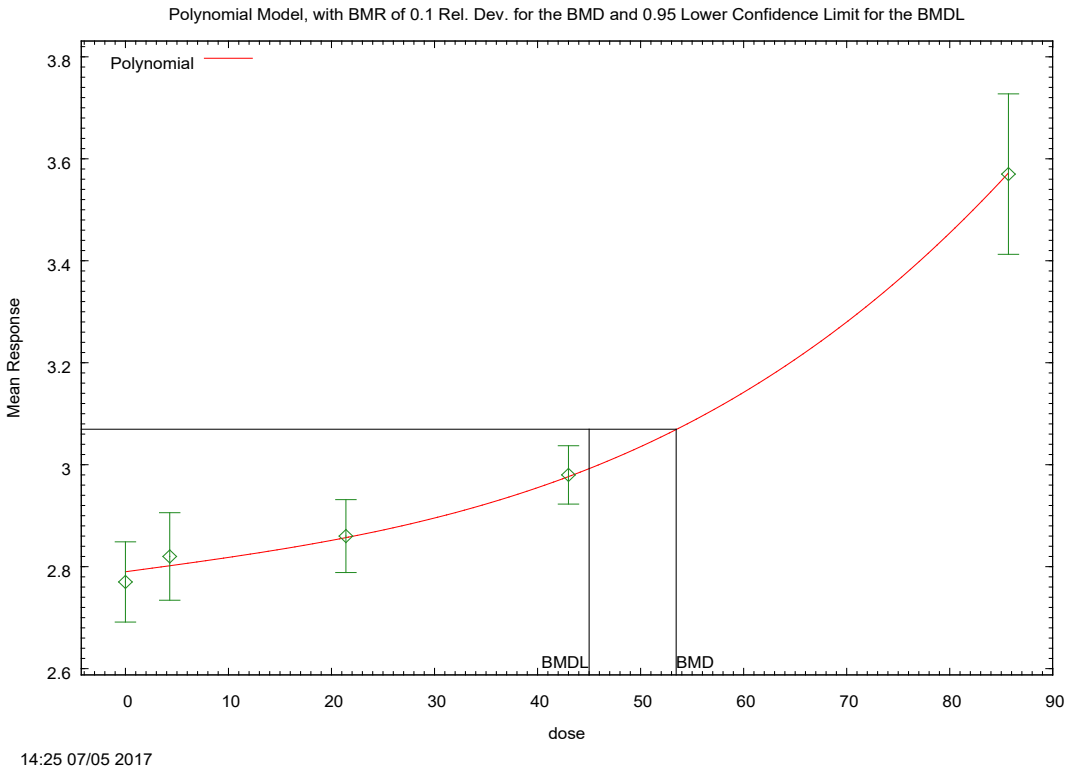

Figure C-1. Polynomial 3-Degree Model for Increased Relative Liver Weight in Male F344 Rats Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

Model Predictions for Increased Relative Kidney Weight in Male F344 Rats Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

The procedure outlined above for continuous data was applied to the data for increased relative kidney weight in male F344 rats treated with 2-EH via gavage for 3 months (Astill et al., 1996a; BASF, 1991a) (see Table C-1). The BMD modeling results are summarized in Table C-5 and Figure C-2. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all included models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Exponential 2) is selected. For relative kidney weight, the $BMDL_{10}$ of 48 mg/kg-day from this model is selected.

Table C-5. Modeling Results for Increased Relative Kidney Weights in Male F344 Rats Administered 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Constant variance							
Exponential (Model 2)[e, f]	**<0.0001**	**0.1351**	**0.365**	**−0.03743**	**−300.1957**	**55.6598**	**47.8532**
Exponential (Model 3)[e]	<0.0001	0.1351	0.3819	0.6324	−299.4481	62.3457	49.7456
Exponential (Model 4)[e]	<0.0001	0.1351	0.1614	−0.1682	−297.7261	54.4022	46.1082
Exponential (Model 5)[e]	<0.0001	0.1351	0.4185	0.0007963	−298.719	52.4009	43.6538
Hill[e]	<0.0001	0.1351	0.4182	0.0007	−298.7180	54.3476	44.01
Linear[g]	<0.0001	0.1351	0.3022	−0.168	−299.7265	54.4033	46.1302
Polynomial (2-degree)[g]	<0.0001	0.1351	0.3578	0.676	−299.3178	62.3791	48.8468
Polynomial (3-degree)[g]	<0.0001	0.1351	0.3578	0.676	−299.3178	62.3791	48.8468
Power[e]	<0.0001	0.1351	0.3936	0.614	−299.5089	62.1489	49.3059

[a]Astill et al. (1996a); BASF (1991b).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at dose closest to BMD.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among models that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = benchmark dose 10% extra risk; $BMDL_{10}$ = 95% benchmark dose lower confidence limit.

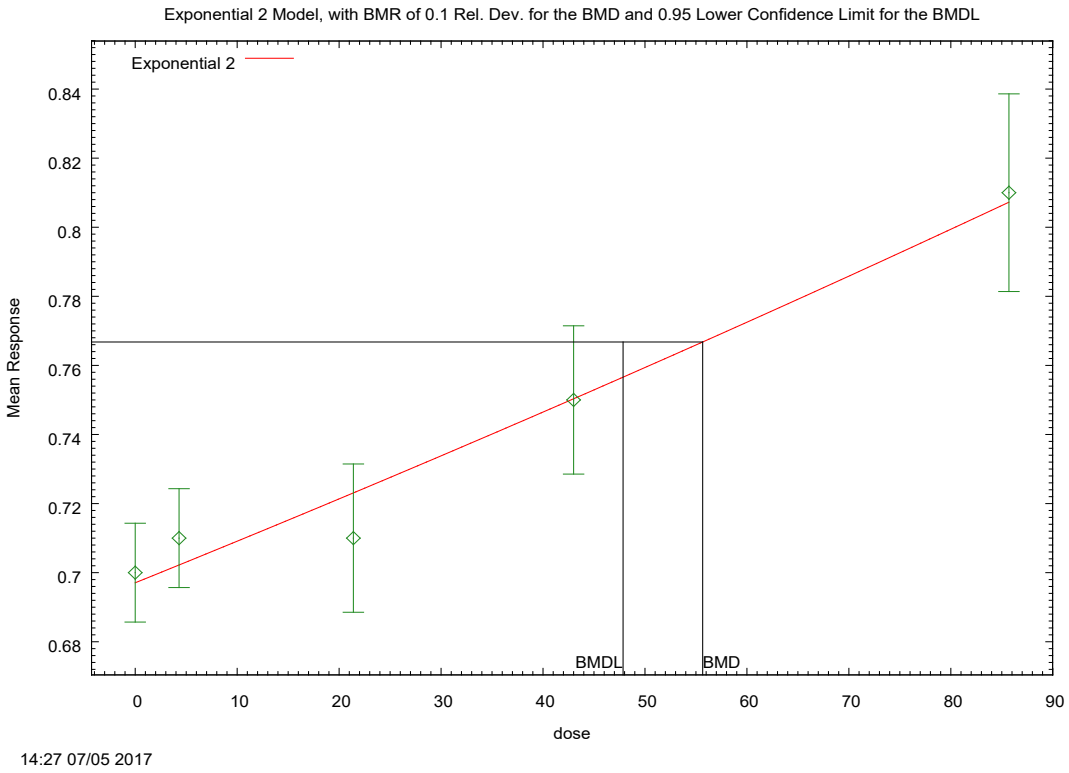

Figure C-2. Exponential 2 Model for Increased Relative Kidney Weight in Male F344 Rats Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

Model Predictions for Increased Relative Stomach Weight in Male F344 Rats Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

The procedure outlined above for continuous data was applied to the data for increased relative stomach weight in male F344 rats treated with 2-EH via gavage for 3 months (Astill et al., 1996a; BASF, 1991a) (see Table C-1). The BMD modeling results are summarized in Table C-6 and Figure C-3. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all included models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Exponential 2) is selected. For relative stomach weight, the $BMDL_{1SD}$ of 130 mg/kg-day from this model is selected.

Table C-6. Modeling Results for Increased Relative Stomach Weight in Male F344 Rats Administered 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Constant variance							
Exponential (Model 2)[e, f]	**<0.0001**	**0.2212**	**0.3036**	**−0.103**	**−287.1724**	**173.525**	**131.152**
Exponential (Model 3)[e]	<0.0001	0.2212	0.3833	0.6132	−286.8899	228.179	145.102
Exponential (Model 4)[e]	<0.0001	0.2212	0.1449	−0.1558	−284.9439	169.989	126.289
Exponential (Model 5)[e]	<0.0001	0.2212	0.4092	1.54×10^{-6}	−286.1265	181.2	148.611
Hill[e]	<0.0001	0.2212	0.7113	3.32×10^{-6}	−288.1265	181.894	146.441
Linear[g]	<0.0001	0.2212	0.2766	−0.156	−286.9442	169.992	126.294
Polynomial (2-degree)[g]	<0.0001	0.2212	0.3626	0.751	−286.7788	237.018	142.126
Polynomial (3-degree)[g]	<0.0001	0.2212	0.3626	0.751	−286.7788	237.018	142.126
Power[e]	<0.0001	0.2212	0.3903	0.6	−286.9260	226.878	144.22

[a]Astill et al. (1996a); BASF (1991b).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at dose closest to BMD.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among models that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; SD = standard deviation.

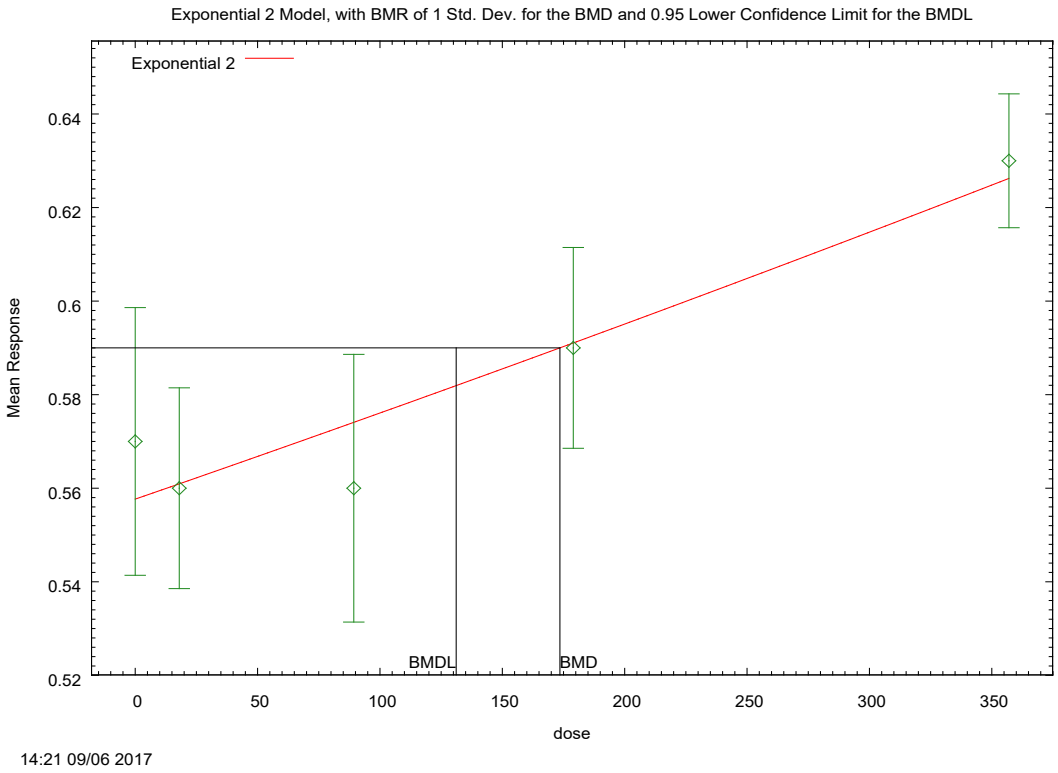

Figure C-3. Exponential 2 Model for Increased Relative Stomach Weight in Male F344 Rats Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

Model Predictions for Increased Relative Liver Weight in Female F344 Rats Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in female F344 rats treated with 2-EH via gavage for 3 months (Astill et al., 1996a; BASF, 1991a) (see Table C-1). The BMD modeling results are summarized in Table C-7 and Figure C-4. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all included models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Exponential 2) is selected. For relative liver weight, the $BMDL_{10}$ of 45 mg/kg-day from this model is selected.

Table C-7. Modeling Results for Increased Relative Liver Weight in Female F344 Rats Administered 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Constant variance							
Exponential (Model 2)[e, f]	**<0.0001**	**0.6481**	**0.311**	**0.3949**	**−185.2671**	**51.0066**	**44.6836**
Exponential (Model 3)[e]	<0.0001	0.6481	0.2303	0.8464	−183.9059	54.5788	45.4073
Exponential (Model 4)[e]	<0.0001	0.6481	0.1393	0.249	−182.9014	49.9416	43.2639
Exponential (Model 5)[e]	<0.0001	0.6481	0.3064	0.003548	−183.797	47.5836	41.2759
Hill[e]	<0.0001	0.6481	0.3052	0.00321	−183.7918	49.0486	41.8255
Linear[g]	<0.0001	0.6481	0.2679	0.249	−184.9019	49.9428	43.2655
Polynomial (2-degree)[g]	<0.0001	0.6481	0.2143	0.857	−183.7627	54.3407	44.3267
Polynomial (3-degree)[g]	<0.0001	0.6481	0.2143	0.857	−183.7627	54.3407	44.3267
Power[e]	<0.0001	0.6481	0.2398	0.825	−183.9874	54.472	44.6499

[a]Astill et al. (1996a); BASF (1991b).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMD.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among models that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = benchmark dose 10% extra risk; $BMDL_{10}$ = 95% benchmark dose lower confidence limit.

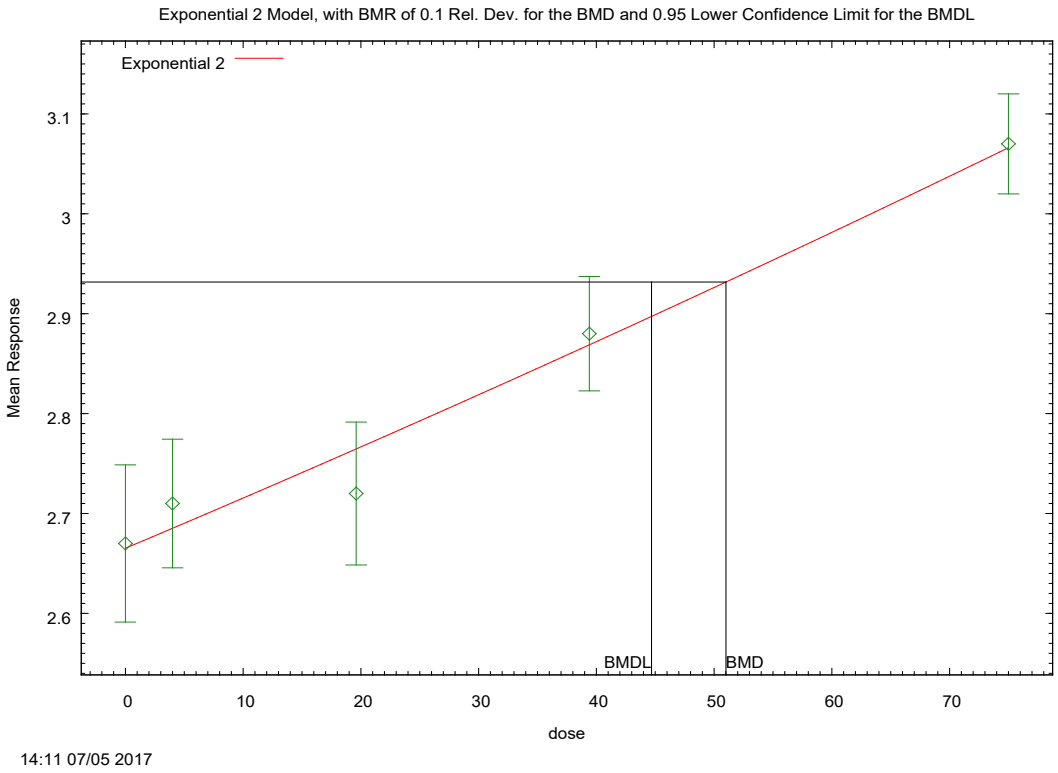

Figure C-4. Exponential 2 Model for Increased Relative Liver Weight in Female F344 Rats Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

Model Predictions for Increased Relative Stomach Weight in Female F344 Rats Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

The procedure outlined above for continuous data was applied to the data for increased relative stomach weight in female F344 rats treated with 2-EH via gavage for 3 months (Astill et al., 1996a; BASF, 1991a) (see Table C-1). The BMD modeling results are summarized in Table C-8 and Figure C-5. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all included models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Exponential 2) is selected. For relative stomach weight, the $BMDL_{1SD}$ of 87 mg/kg-day from this model is selected.

Table C-8. Modeling Results for Increased Relative Stomach Weight in Female F344 Rats Administered 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Constant variance							
Exponential (Model 2)[e, f]	**<0.0001**	**0.2212**	**0.756**	**−0.1024**	**−289.6202**	**106.785**	**86.5786**
Exponential (Model 3)[e]	<0.0001	0.2212	0.8998	−0.2348	−288.5965	142.132	90.0041
Exponential (Model 4)[e]	<0.0001	0.2212	0.4506	−0.1802	−287.2136	102.232	81.9437
Exponential (Model 5)[e]	<0.0001	0.2212	0.6279	−0.2545	−286.5728	142.657	85.271
Hill[e]	<0.0001	0.2212	0.6262	−0.256	−286.5705	142.715	85.1918
Linear[g]	<0.0001	0.2212	0.6608	−0.18	−289.2140	102.236	81.9476
Polynomial (2-degree)[g]	<0.0001	0.2212	0.9165	−0.173	−288.6334	140.534	87.3605
Polynomial (3-degree)[g]	<0.0001	0.2212	0.9377	−0.0908	−288.6790	138.367	87.5901
Power[e]	<0.0001	0.2212	0.8892	−0.254	−288.5728	142.655	87.0642

[a]Astill et al. (1996a); BASF (1991b).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMD.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among models that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; SD = standard deviation.

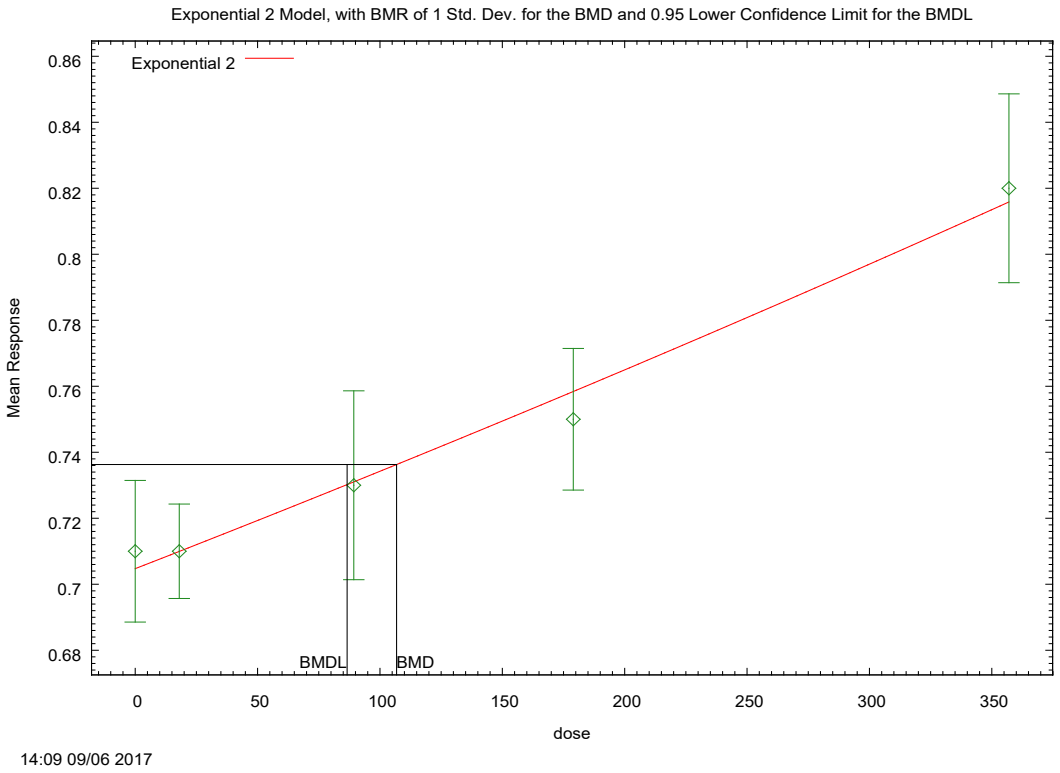

Figure C-5. Exponential 2 Model for Increased Relative Stomach Weight in Female F344 Rats Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

Model Predictions for Increased Relative Stomach Weight in Male B6C3F$_1$ Mice Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

The procedure outlined above for continuous data was applied to the data for increased relative stomach weight in male B6C3F$_1$ mice treated with 2-EH via gavage for 3 months (Astill et al., 1996a; BASF, 1991a) (see Table C-1). The BMD modeling results are summarized in Table C-9 and Figure C-6. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all included models. The BMDLs for the models providing adequate fit are not sufficiently close (i.e., differ by >threefold), so the model with the lowest BMDL (Exponential 4) is selected. For relative stomach weight, the BMDL$_{1SD}$ of 62 mg/kg-day from this model is selected.

Table C-9. Modeling Results for Increased Relative Stomach Weight in Male B6C3F$_1$ Mice Administered 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Constant variance							
Exponential (Model 2)[e]	0.008253	0.228	0.2098	−0.7226	−180.4891	277.528	189.93
Exponential (Model 3)[e]	0.008253	0.228	0.2098	−0.7226	−180.4891	277.528	189.93
Exponential (Model 4)[e, f]	**0.008253**	**0.228**	**0.2568**	**1.078**	**−180.2984**	**163.1**	**62.1258**
Exponential (Model 5)[e]	0.008253	0.228	0.5783	1.19×10^{-7}	−180.7082	105.713	89.5467
Hill[e]	0.008253	0.228	0.8568	-8.53×10^{-6}	−182.708201	101.62	89.7842
Linear[g]	0.008253	0.228	0.2291	1.7	−180.699138	267.534	177.731
Polynomial (2-degree)[g]	0.008253	0.228	0.2291	1.7	−180.699138	267.534	177.731
Polynomial (3-degree)[g]	0.008253	0.228	0.2291	1.7	−180.699138	267.534	177.731
Power[e]	0.008253	0.228	0.2291	1.7	−180.699138	267.534	177.731

[a]Astill et al. (1996a); BASF (1991b).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMD.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among models that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; SD = standard deviation.

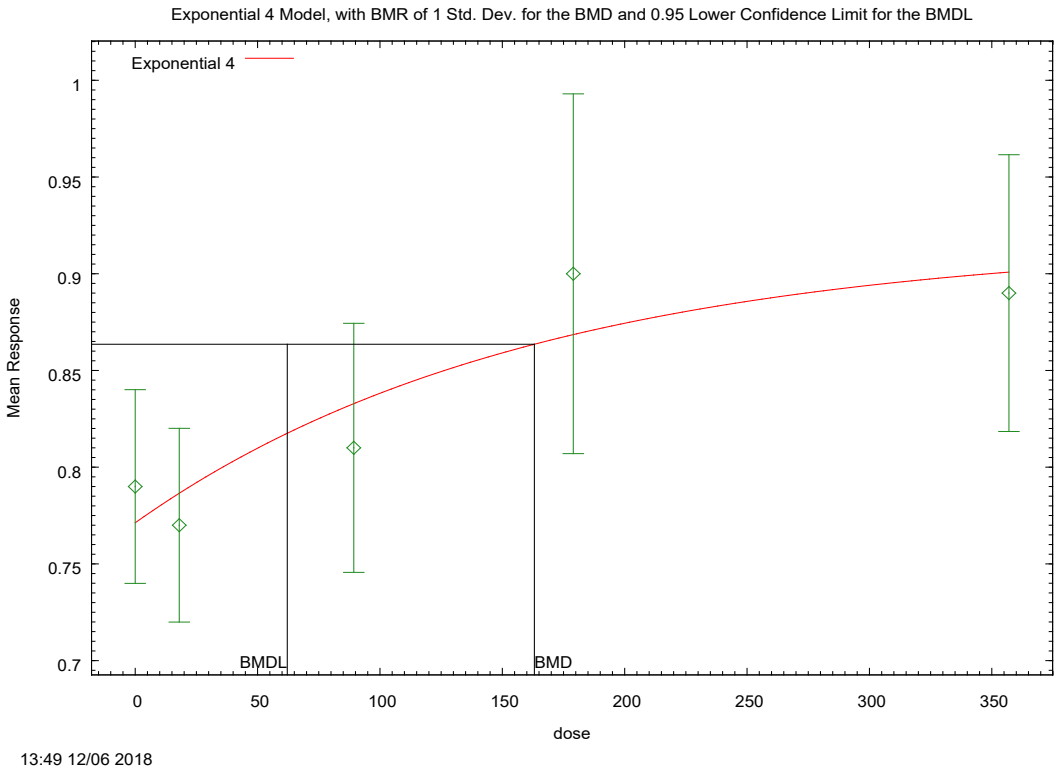

Figure C-6. Exponential 2 Model for Increased Relative Stomach Weight in Male B6C3F1 Treated with 2-Ethylhexanol via Gavage for 3 Months (Astill et al., 1996a; BASF, 1991a)

Model Predictions for Decreased Fetal Body Weight Following 2-Ethylhexanol Exposure via Gavage on Gestation Days 6−15 in Female Wistar Rats (Hellwig and Jäckh, 1997; Confidential, 1991)

The procedure outlined above for continuous data was applied to the data for decreased fetal body weight in pups of Wistar rats treated with 2-EH via gavage on Gestation Days (GDs) 6−15 (Hellwig and Jäckh, 1997; Confidential, 1991) (see Table C-1). Table C-10 summarizes the BMD modeling results. For decreased fetal body weight, the data were modeled without the highest dose of 325 mg/kg-day (HED) because there was severe maternal toxicity (i.e., 60% mortality and a 20% decrease in body weight) at that dose that confounds the interpretation of fetal body-weight changes. Therefore, only the BMD modeling results based on data without the highest dose group are summarized in Table C-10. Neither the constant nor nonconstant variance models provided adequate fit to the variance data using the full or reduced data set. This data set was not amenable to BMD modeling.

Table C-10. Modeling Results for Decreased Fetal Body Weight Following 2-Ethylhexanol (CASRN 104-76-7) Exposure via Gavage on Gestation Days 6−15 in Female Wistar Rats[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMD_{05} (mg/kg-d)	$BMDL_{05}$ (mg/kg-d)
Nonconstant variance							
Exponential (Model 2)[e]	<0.0001	0.0002566	0.02605	1.998	–834.9316	77.0138	69.4236
Exponential (Model 3)[e]	<0.0001	0.0002566	NDr	–0.01302	–837.8841	106.7	82.0473
Exponential (Model 4)[e]	<0.0001	0.0002566	0.02605	1.998	–834.9316	77.0138	67.0081
Hill[e]	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Linear[f]	<0.0001	0.0002566	0.03736	1.87	–835.550055	79.1485	71.7972
Polynomial (2-degree)[f]	<0.0001	0.0002566	NDr	–0.013	–837.884091	110.747	85.0661
Polynomial (3-degree)[f]	<0.0001	0.0002566	NDr	–0.013	–835.884091	119.479	85.0661
Power[e]	<0.0001	0.0002566	NDr	–0.013	–837.884091	107.59	82.8021

[a]Hellwig and Jäckh (1997); Confidential (1991).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMD.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{05} = benchmark dose 5% extra risk; $BMDL_{05}$ = 95% benchmark dose lower confidence limit; NDr = not determined.

Model Predictions for Increased Fetal Variations Following 2-Ethylhexanol Exposure via Gavage on Gestation Days 6−15 in Female Wistar Rats (Hellwig and Jäckh, 1997; Confidential, 1991)

The procedure outlined above for nested dichotomous data was applied to the data for increased fetal variations in Wistar rats treated with 2-EH via gavage on GDs 6−15 (Hellwig and Jäckh, 1997; Confidential, 1991) (see Table C-1). Table C-11 summarizes the BMD modeling results. For increased fetal incidence of skeletal variations, the data were modeled without the highest dose of 325 mg/kg-day (HED) because there was severe maternal toxicity (i.e., 60% mortality and a 20% decrease in body weight) at that dose that confounds the interpretation of fetal skeletal changes. Therefore, only the BMD modeling results based on data without the highest dose group are summarized in Table C-11. Including implantation sites as a covariate and using intralitter correlations had significant effects on the χ^2 goodness-of-fit statistics, AIC scores, and visual inspections. As assessed by the χ^2 goodness-of-fit statistic, AIC score, and visual inspection, only the NLogistic model with estimating intralitter correlations and not including implantation sites as a covariate provided an optimal fit (see Table C-11 and Figure C-7). For increased fetal variations, the $BMDL_{05}$ of 7.37 mg/kg-day from this model is selected.

Table C-11. Modeling Results for Increased Fetal Variations Following 2-Ethylhexanol (CASRN 104-76-7) Exposure via Gavage on GDs 6−15 in Female Wistar Rats[a]

Parameter	Litter-Specific Covariate; Intralitter Correlation[d]	No Litter-Specific Covariate; Intralitter Correlation[b]	Litter-Specific Covariate; No Intralitter Correlation	No Litter-Specific Covariate; No Intralitter Correlation
$BMDL_{05}$	173.095	**7.37139**	234.062	13.0394
BMD_{05}	346.19	**21.9447**	349.659	27.0881
p-Value[c]	0.6717	**0.501**	0.0007	0.0007
AIC	242.535	**249.404**	252.69	260.431

[a]Hellwig and Jäckh (1997); Confidential (1991).
[b]Selected model parameters. Lowest AIC among models that provided an adequate fit.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Model failed visual inspection.

AIC = Akaike's information criterion; BMD_{05} = benchmark dose 5% extra risk; $BMDL_{05}$ = 95% benchmark dose lower confidence limit; GD = gestation day.

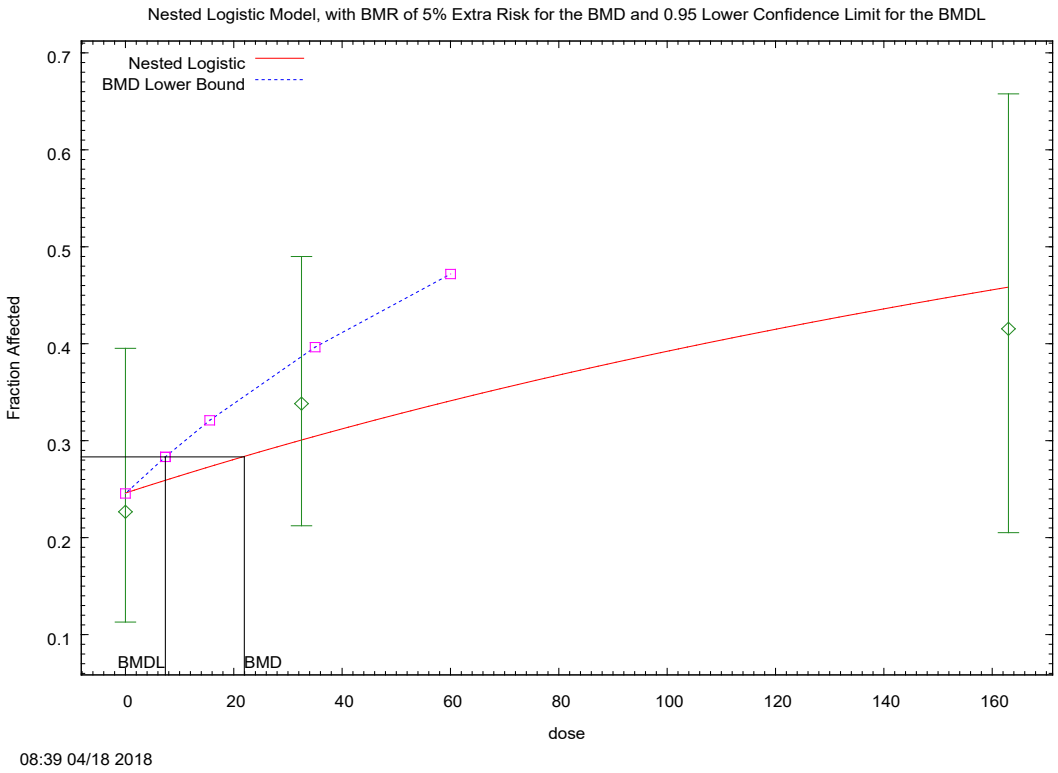

Figure C-7. Nested Logistic Model for Increased Fetal Variations Following 2-Ethylhexanol Exposure via Gavage on Gestation Days 6−15 in Female Wistar Rats (Hellwig and Jäckh, 1997; Confidential, 1991)

Text Output for Figure C-7:

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 BMDS Model Run
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 The probability function is:


 Prob. = alpha + theta1*Rij + [1 - alpha - theta1*Rij]/

                        [1+exp(-beta-theta2*Rij-rho*log(Dose))],

          where Rij is the litter specific covariate.

 Restrict Power rho >= 1.



 Total number of observations = 29
 Total number of records with missing values = 0
```

Total number of parameters in model = 8
Total number of specified parameters = 2

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
Number of Bootstrap Iterations per run: 1000
Bootstrap Seed: 1524055194

User specifies the following parameters:
theta1 = 0
theta2 = 0

Default Initial Parameter Values

alpha =	0.245569	
beta =	-6.03296	
theta1 =	0	Specified
theta2 =	0	Specified
rho =	1	
phi1 =	0.183845	
phi2 =	0.0680539	
phi3 =	0.374869	

Parameter Estimates

Variable	Estimate	Std. Err.
alpha	0.245569	0.0631849
beta	-6.03296	0.867426
rho	1	Bounded
phi1	0.183845	0.246128
phi2	0.0680539	NA
phi3	0.374869	NA

Log-likelihood: -119.702 AIC: 249.404

Litter Data

Dose	Lit.-Spec. Cov.	Est._Prob.	Litter Size	Expected	Observed	Scaled Residual
0.0000	13.0000	0.246	6	1.473	0	-1.0088
0.0000	13.0000	0.246	7	1.719	0	-1.0409
0.0000	15.0000	0.246	8	1.965	2	0.0193
0.0000	15.0000	0.246	7	1.719	4	1.3812
0.0000	15.0000	0.246	7	1.719	3	0.7757
0.0000	16.0000	0.246	6	1.473	0	-1.0088
0.0000	16.0000	0.246	8	1.965	0	-1.0671
0.0000	16.0000	0.246	8	1.965	4	1.1056
0.0000	17.0000	0.246	8	1.965	1	-0.5239
0.0000	21.0000	0.246	10	2.456	3	0.2454
32.5000	7.0000	0.300	3	0.900	2	1.2996
32.5000	11.0000	0.300	6	1.801	0	-1.3855
32.5000	11.0000	0.300	5	1.501	0	-1.2982
32.5000	13.0000	0.300	7	2.101	1	-0.7650
32.5000	13.0000	0.300	7	2.101	2	-0.0701
32.5000	14.0000	0.300	7	2.101	4	1.3198

32.5000	16.0000	0.300	8	2.401	3	0.3803
32.5000	17.0000	0.300	8	2.401	5	1.6501
32.5000	17.0000	0.300	8	2.401	2	-0.2546
32.5000	17.0000	0.300	9	2.701	4	0.7602
163.0000	11.0000	0.458	5	2.288	5	1.5398
163.0000	13.0000	0.458	7	3.203	0	-1.3482
163.0000	14.0000	0.458	7	3.203	2	-0.5064
163.0000	15.0000	0.458	7	3.203	4	0.3353
163.0000	15.0000	0.458	8	3.661	7	1.2448
163.0000	15.0000	0.458	7	3.203	2	-0.5064
163.0000	16.0000	0.458	8	3.661	2	-0.6191
163.0000	17.0000	0.458	8	3.661	5	0.4992
163.0000	17.0000	0.458	8	3.661	0	-1.3647

Scaled Residual(s) for Dose Group Nearest the BMD

Minimum scaled residual for dose group nearest the BMD = 1.3198
Minimum ABS(scaled residual) for dose group nearest the BMD = 1.3198
Average scaled residual for dose group nearest the BMD = 1.3198
Average ABS(scaled residual) for dose group nearest the BMD = 1.3198
Maximum scaled residual for dose group nearest the BMD = 1.3198
Maximum ABS(scaled residual) for dose group nearest the BMD = 1.3198
Number of litters used for scaled residual for dose group nearest the BMD = 1

Observed Chi-square = 28.3186

Bootstrapping Results

Number of Bootstrap Iterations per run: 1000

Bootstrap Chi-square Percentiles

Bootstrap Run	P-value	50th	90th	95th	99th
1	0.5070	28.5329	37.7451	39.7631	44.7794
2	0.4920	28.1849	37.8921	41.3515	47.9404
3	0.5040	28.3576	37.8756	40.6406	47.3071
Combined	0.5010	28.3314	37.8319	40.6425	47.0264

The results for three separate runs are shown. If the estimated p-values are sufficiently
stable (do not vary considerably from run to run), then then number of iterations is considered adequate. The p-value that should be reported is the one that combines the results of the three runs. If sufficient stability is not evident (and especially if the p-values are close to the critical level for determining adequate fit, e.g., 0.05),
then the user should consider increasing the number of iterations per run.

To calculate the BMD and BMDL, the litter specific covariate is fixed
at the mean litter specific covariate of all the data: 14.689655

Benchmark Dose Computation

```
Specified effect =          0.05

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       21.9447

            BMDL =       7.37139
```

Model Predictions for Increased Fetal Retardations Following 2-Ethylhexanol Exposure via Gavage on Gestation Days 6−15 in Female Wistar Rats (Hellwig and Jäckh, 1997; Confidential, 1991)

The procedure outlined above for nested dichotomous data was applied to the data for increased fetal retardations in Wistar rats treated with 2-EH via gavage on GDs 6−15 (Hellwig and Jäckh, 1997; Confidential, 1991) (see Table C-1). Table C-12 summarizes the BMD modeling results. For increased fetal incidence of skeletal retardations, the data were modeled without the highest dose of 325 mg/kg-day (HED) because there was severe maternal toxicity (i.e., 60% mortality and a 20% decrease in body weight) at that dose that confounds the interpretation of fetal skeletal changes. Therefore, only the BMD modeling results based on data without the highest dose group are summarized in Table C-12. Including implantation sites as a covariate and using intralitter correlations had significant effects on the χ^2 goodness-of-fit statistics, AIC scores, and visual inspections. As assessed by the χ^2 goodness-of-fit statistic, AIC score, and visual inspection, none of the NLogistic models provided an optimal fit (see Table C-12). This data set was not amenable to BMD modeling.

Table C-12. Modeling Results for Increased Fetal Retardations Following 2-Ethylhexanol (CASRN 104-76-7) Exposure via Gavage on GDs 6−15 in Female Wistar Rats[a]

Parameter	Litter-Specific Covariate; Intralitter Correlation[b]	No Litter-Specific Covariate; Intralitter Correlation[b]	Litter-Specific Covariate; No Intralitter Correlation	No Litter-Specific Covariate; No Intralitter Correlation
$BMDL_{05}$	2.99784	4.52848	5.31025	10.6269
BMD_{05}	115.268	115.965	52.8472	115.888
p-Value[c]	0.517	0.397	0.0007	0
AIC	243.692	247.109	254.613	271.796

[a]Hellwig and Jäckh (1997); Confidential (1991).
[b]BMD:BMDL ratio is too high, signifying there is uncertainty in estimating the BMDL.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's information criterion; BMD_{05} = benchmark dose 5% extra risk; BMDL = benchmark dose lower confidence limit; $BMDL_{05}$ = 95% benchmark dose lower confidence limit; GD = gestation day.

Model Predictions for Decreased Body Weight at Study Termination in Male F344 Rats Treated with 2-Ethylhexanol via Gavage for 24 Months (Astill et al., 1996b; BASF, 1992a)

The procedure outlined above for continuous data was applied to the data for decreased body weight in male F344 rats treated with 2-EH via gavage for 24 months (Astill et al., 1996b; BASF, 1992a) (see Table C-2). Table C-13 summarizes the BMD modeling results. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by the Exponential 4 and 5 models and the Hill model. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Hill model) is selected (see Figure C-8). For decreased body weight, the biologically relevant BMR of 10% RD is selected, yielding a $BMDL_{10}$ of 19 mg/kg-day.

Table C-13. Modeling Results for Decreased Body Weight in Male F344 Rats Administered 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 24 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Constant variance							
Exponential (Model 2)[e]	<0.0001	0.4099	0.055	−1.492	1,533.038	37.5406	33.853
Exponential (Model 3)[e]	<0.0001	0.4099	0.055	−1.492	1,533.038	37.5406	33.853
Exponential (Model 4)[e]	<0.0001	0.4099	0.4925	0.2944	1,529.708	25.6039	19.5673
Exponential (Model 5)[e]	<0.0001	0.4099	0.4925	0.2944	1,529.708	25.6039	19.5673
Hill[e, f]	**<0.0001**	**0.4099**	**0.5517**	**0.288**	**1,529.5918**	**25.3591**	**18.9584**
Linear[g]	<0.0001	0.4099	0.01787	−1.84	1,535.28639	40.8555	37.3042
Polynomial (2-degree)[g]	<0.0001	0.4099	0.01787	−1.84	1,535.28639	40.8555	37.3042
Polynomial (3-degree)[g]	<0.0001	0.4099	0.01787	−1.84	1,535.28639	40.8555	37.3042
Power[e]	<0.0001	0.4099	0.01787	−1.84	1,535.28639	40.8555	37.3042

[a]Astill et al. (1996b); BASF (1992a).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMD.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among models that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = benchmark dose 10% extra risk; $BMDL_{10}$ = 95% benchmark dose lower confidence limit.

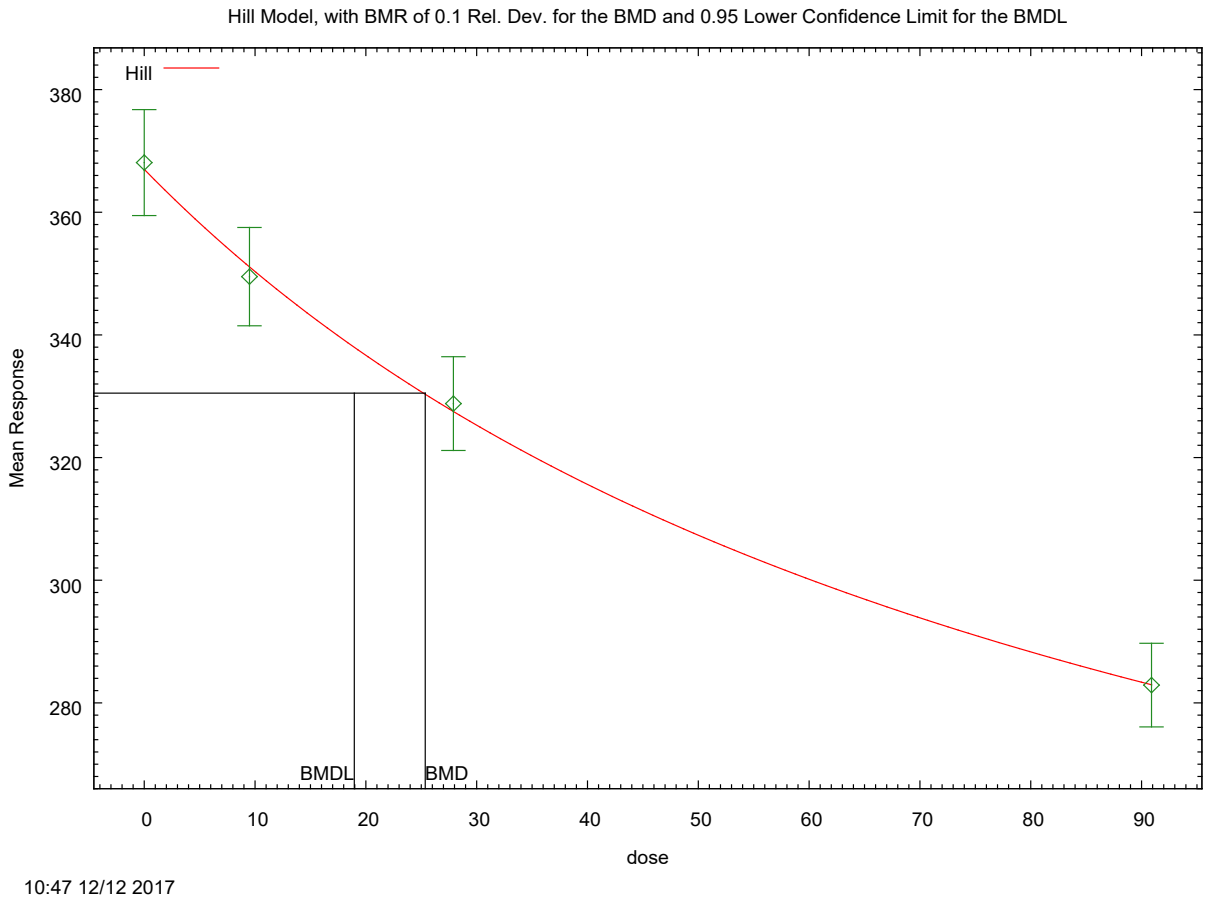

Figure C-8. Hill Model for Decreased Body Weight at Study Termination in Male F344 Rats Treated with 2-Ethylhexanol via Gavage for 24 Months (Astill et al., 1996b; BASF, 1992a)

Model Predictions for Decreased Body Weight at Study Termination in Female F344 Rats Treated with 2-Ethylhexanol via Gavage for 24 Months (Astill et al., 1996b; BASF, 1992a)

The procedure outlined above for continuous data was applied to the data for decreased body weight in female F344 rats treated with 2-EH via gavage for 24 months (Astill et al., 1996b; BASF, 1992a) (see Table C-2). Table C-14 summarizes the BMD modeling results. Neither the constant nor nonconstant variance models provided adequate fit to the variance data using the full or reduced data set. This data set was not amenable to BMD modeling.

Table C-14. Modeling Results for Decreased Body Weight in Female F344 Rats Administered 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 24 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Nonconstant variance							
Exponential (Model 2)[e]	<0.0001	<0.0001	0.9486	−0.04382	1,094.236	27.4323	20.8617
Exponential (Model 3)[e]	<0.0001	<0.0001	N/A	−0.02024	1,096.232	27.3874	20.8655
Exponential (Model 4)[e]	<0.0001	<0.0001	0.9486	−0.04382	1,094.236	27.4323	18.9954
Exponential (Model 5)[e]	<0.0001	0.001795	NDr	−0.04085	977.3824	27.6968	18.9199
Hill[e]	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Linear[f]	<0.0001	<0.0001	0.9894	−0.0249	1,094.232088	27.3368	21.0994
Polynomial (2-degree)[f]	<0.0001	<0.0001	NDr	−0.0202	1,096.231911	27.3145	21.0995
Polynomial (3-degree)[f]	<0.0001	<0.0001	NDr	−0.0202	1,098.231911	27.3093	21.0995
Power[e]	<0.0001	<0.0001	NDr	−0.0202	1,096.231911	27.3288	21.0995

[a]Astill et al. (1996b); BASF (1992a).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMD.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMD_{10} = benchmark dose 10% extra risk; $BMDL_{10}$ = 95% benchmark dose lower confidence limit; NDr = not determined.

Model Predictions for Increased Diameter of Bowman's Glands in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

The procedure outlined above for continuous data was applied to the data for increased diameter in ICR mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016) (see Table B-13). Table C-15 summarizes the BMC modeling results. The initial modeling of these data including all dose groups failed to provide an adequate fit to the data, as assessed by the χ^2 goodness-of-fit test. Therefore, only the BMC modeling results based on data without the high-dose group included are summarized in Table C-15 and Figure C-9. The nonconstant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all included models except Exponential 4 and 5 and Hill models. The BMCLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the models with the lowest AIC (Linear, Polynomial 2-degree, Polynomial 3-degree, and Power) are selected. For increased diameter of the Bowman's gland, the $BMCL_{1SD}$ of 1.11 mg/m^3 from these models is selected.

Table C-15. Modeling Results for Increased Diameter of Bowman's Glands in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Inhalation for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/kg-d)	$BMCL_{1SD}$ (mg/kg-d)
Nonconstant variance							
Exponential (Model 2)[e]	<0.0001	0.8476	0.2689	0.8578	57.9133	2.66935	1.74839
Exponential (Model 3)[e]	<0.0001	0.8476	0.2689	0.8578	57.9133	2.66936	1.74839
Exponential (Model 4)[e]	<0.0001	0.8476	NDr	−0.0284	58.69101	1.60493	0.769781
Exponential (Model 5)[e]	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Hill[e]	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Linear[f, g]	**<0.0001**	**0.8476**	**0.8106**	**−0.106**	**56.748452**	**1.75839**	**1.10808**
Polynomial (2-degree)[f, g]	**<0.0001**	**0.8476**	**0.8106**	**−0.106**	**56.748452**	**1.75839**	**1.10808**
Polynomial (3-degree)[f, g]	**<0.0001**	**0.8476**	**0.8106**	**−0.106**	**56.748452**	**1.75839**	**1.10808**
Power[e, f]	**<0.0001**	**0.8476**	**0.8106**	**−0.106**	**56.748452**	**1.75839**	**1.10808**

[a]Miyake et al. (2016).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMC.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among model that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; NDr = not determined; SD = standard deviation.

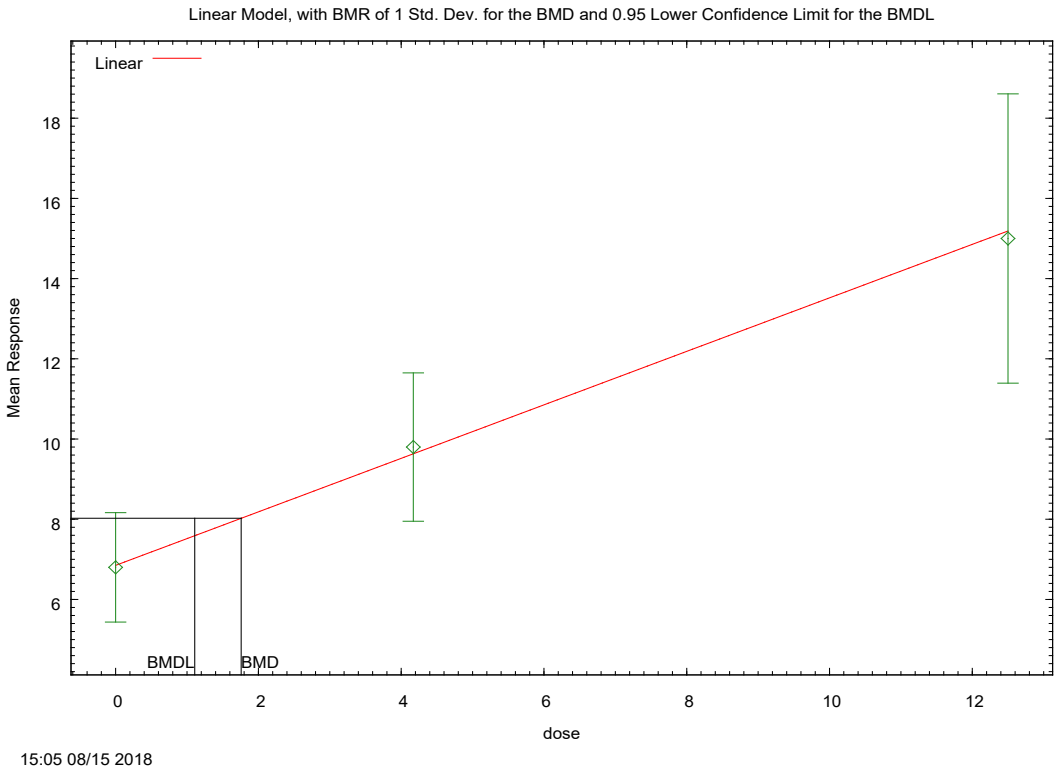

Figure C-9. Linear Model for Increased Diameter of Bowman's Glands in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

Model Predictions for Increased Number of CD3-Positive Cells in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

The procedure outlined above for continuous data was applied to the data for increased number of CD3-positive cells in the olfactory epithelium of the nasal cavity in ICR mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016) (see Table B-13). Table C-16 summarizes the BMC modeling results. Neither the constant nor nonconstant variance models provided adequate fit to the variance data using the full or reduced data set. This data set was not amenable to BMC modeling.

Table C-16. Modeling Results for Increased Number of CD3-Positive Cells in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Inhalation for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/kg-d)	$BMCL_{1SD}$ (mg/kg-d)
Nonconstant variance							
Exponential (Model 2)[e]	<0.0001	<0.0001	0.8936	–0.001534	94.03584	10.4885	8.74097
Exponential (Model 3)[e]	<0.0001	<0.0001	NDr	4.976	121.0273	79.0861	NDr
Exponential (Model 4)[e]	<0.0001	<0.0001	NDr	0	NDr	NDr	NDr
Exponential (Model 5)[e]	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Hill[e]	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Linear[f]	<0.0001	<0.0001	0.3674	–0.699	94.830496	6.37672	4.17971
Polynomial (2-degree)[f]	<0.0001	<0.0001	0.9678	0.00324	94.019578	9.0903	4.42983
Polynomial (3-degree)[f]	<0.0001	<0.0001	NDr	-1.87×10^{-6}	98.017947	9.68929	5.54314
Power[e]	<0.0001	<0.0001	NDr	-2.11×10^{-9}	96.017947	9.24935	5.54314

[a]Miyake et al. (2016).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMC.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; NDr = not determined; SD = standard deviation.

Model Predictions for Decreased Number of OMP-Positive Cells in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

The procedure outlined above for continuous data was applied to the data for decreased number of OMP-positive cells in the olfactory epithelium of the nasal cavity in ICR mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016) (see Table B-13). The BMC modeling results are summarized in Table C-17 and Figure C-10. The nonconstant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by the Exponential 2, 3, and 4 models. The BMCLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the models with the lowest AIC (Exponential 2, 3, and 4 models) are selected. For decreased number of OMP-positive cells in the olfactory epithelium of the nasal cavity, the $BMCL_{1SD}$ of 3.14 mg/m^3 from the Exponential 4 model is selected.

Table C-17. Modeling Results for Decreased Number of OMP-Positive Cells in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Inhalation for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/kg-d)	$BMCL_{1SD}$ (mg/kg-d)
Nonconstant variance							
Exponential (Model 2)[e]	<0.0001	0.1928	0.1891	–1.585	–75.57555	5.85444	3.68145
Exponential (Model 3)[e]	<0.0001	0.1928	0.1891	–1.585	–75.57555	5.85444	3.68145
Exponential (Model 4)[e, f]	**<0.0001**	**0.1928**	**0.1891**	**–1.585**	**–75.57555**	**5.85444**	**3.1366**
Exponential (Model 5)[e]	<0.0001	0.1928	0.068	–1.585	–73.57555	5.85444	3.68145
Hill[e]	<0.0001	0.1928	0.08033	–1.53	–73.847892	5.30912	2.38254
Linear[g]	<0.0001	0.1928	0.05275	–0.342	–73.021654	11.2189	8.0351
Polynomial (2-degree)[g]	<0.0001	0.1928	0.05275	–0.342	–73.021654	11.2189	8.0351
Polynomial (3-degree)[g]	<0.0001	0.1928	0.05275	–0.342	–73.021654	11.2189	8.0351
Power[e]	<0.0001	0.1928	0.05275	–0.342	–73.021654	11.2189	8.0351

[a]Miyake et al. (2016).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMC.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among model that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; OMP = olfactory marker protein; SD = standard deviation.

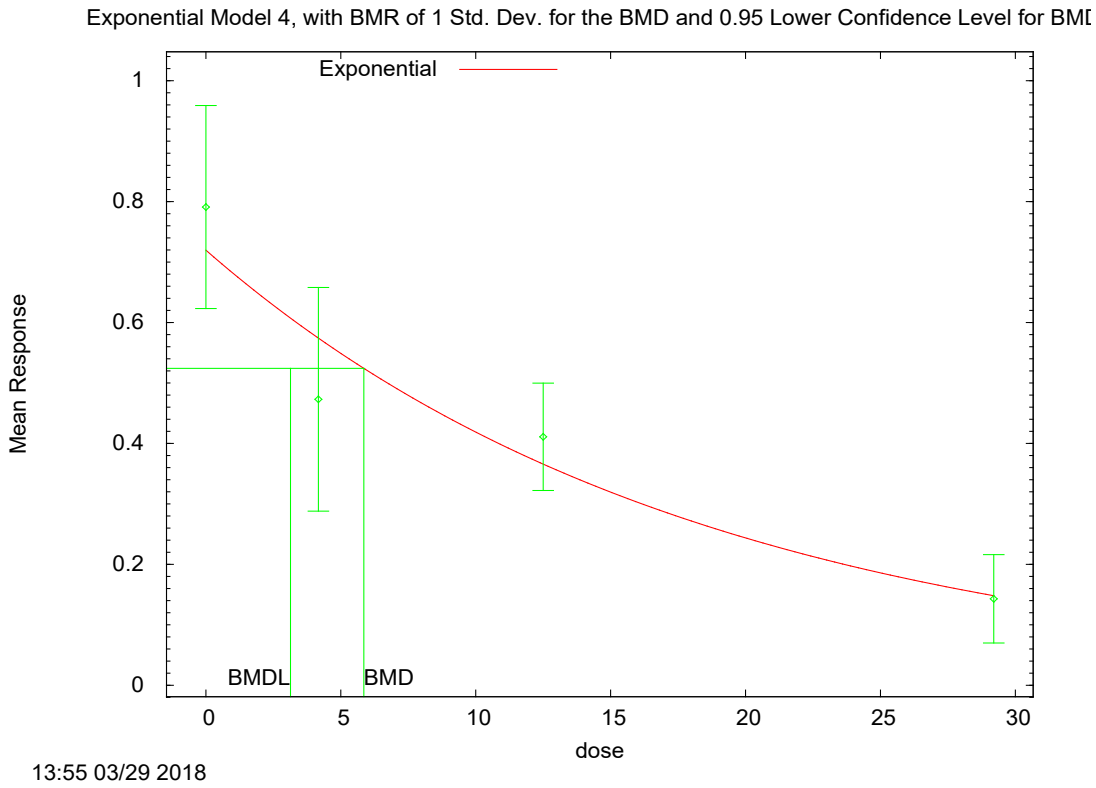

Figure C-10. Exponential 4 Model for Decreased Number of OMP-Positive Cells in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

Model Predictions for Decreased Number of PCNA-Positive Cells in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

The procedure outlined above for continuous data was applied to the data for decreased number of PCNA-positive cells in the olfactory epithelium of the nasal cavity in ICR mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016) (see Table B-13). The BMC modeling results are summarized in Table C-18 and Figure C-11. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all included models except the Exponential 5 model. The BMCLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the models with the lowest AIC (Polynomial 2-degree, Polynomial 3-degree, and Power) are selected. For decreased number of PCNA-positive cells in the olfactory epithelium of the nasal cavity, the $BMCL_{1SD}$ of 11.5 mg/m^3 from these models is selected.

Table C-18. Modeling Results for Decreased Number of PCNA-Positive Cells in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Inhalation for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/kg-d)	$BMCL_{1SD}$ (mg/kg-d)
Constant variance							
Exponential (Model 2)[e]	0.1465	0.8733	0.9498	0.2597	109.8212	15.2964	7.92323
Exponential (Model 3)[e]	0.1465	0.8733	0.854	0.09973	111.7521	17.2237	7.98115
Exponential (Model 4)[e]	0.1465	0.8733	0.9498	0.2597	109.8212	15.2964	5.31474
Exponential (Model 5)[e]	0.1465	0.8733	NDr	0.09973	113.7521	17.2237	7.98115
Hill[e]	0.1465	0.8733	0.9159	0.0419	111.729351	17.7558	4.77342
Linear[f]	0.1465	0.8733	0.03181	1.43	116.536305	–9,999	126.062
Polynomial (2-degree)[f, g]	**0.1465**	**0.8733**	**0.9942**	**0.0234**	**109.729916**	**17.9784**	**11.5389**
Polynomial (3-degree)[f, g]	**0.1465**	**0.8733**	**0.9942**	**0.0234**	**109.729916**	**17.9784**	**11.5389**
Power[e, g]	**0.1465**	**0.8733**	**0.9942**	**0.0234**	**109.729916**	**17.9784**	**11.5389**

[a]Miyake et al. (2016).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMC.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be negative.
[g]Selected models. Lowest AIC among models that provided an adequate fit.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; NDr = not determined; PCNA = proliferating cell nuclear antigen; SD = standard deviation.

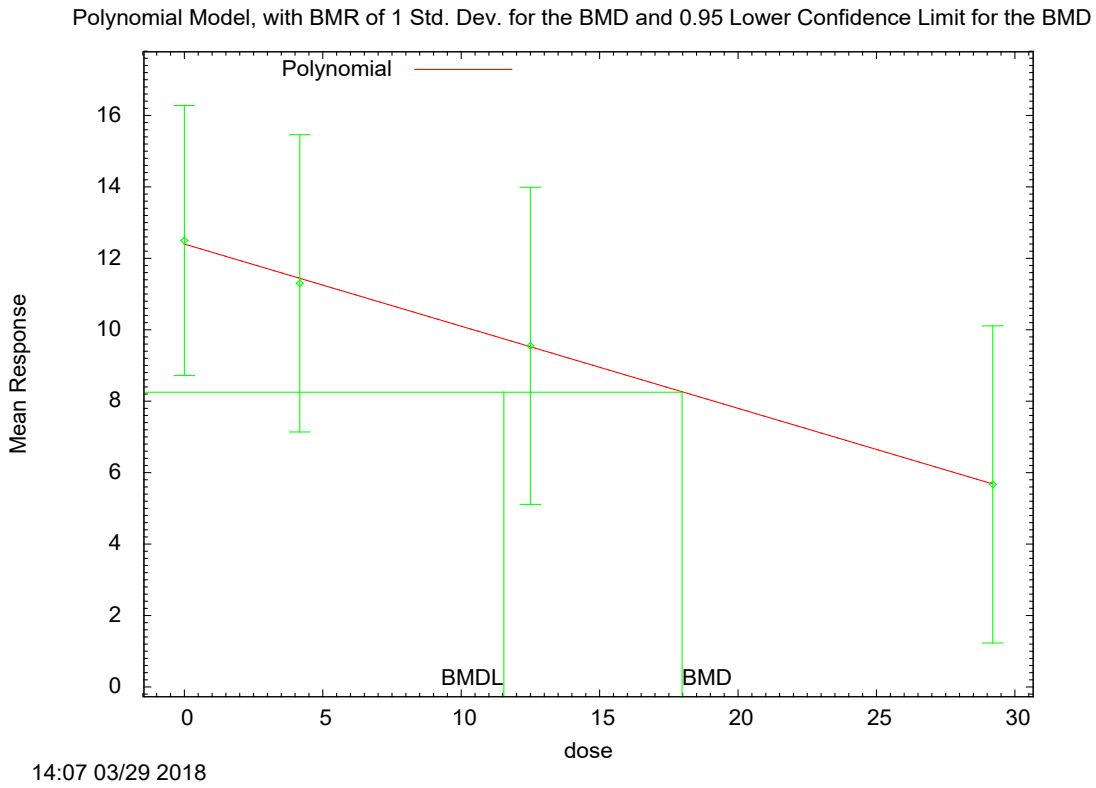

Figure C-11. Polynomial 2-Degree for Decreased Number of PCNA-Positive Cells in the Olfactory Epithelium of the Nasal Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

Model Predictions for Decreased Glomerular Diameter in the Olfactory Bulb of the Brain in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

The procedure outlined above for continuous data was applied to the data for decreased glomerular diameter in the olfactory bulb of the brain in ICR mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016) (see Table B-13). The BMC modeling results are summarized in Table C-19 and Figure C-12. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by the Exponential 3, Exponential 5, Polynomial 3-degree, and Power models. The BMCLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Polynomial 3-degree) is selected. For decreased glomerular diameter in the olfactory bulb of the brain, the $BMCL_{1SD}$ of 8.67 mg/m^3 from this model is selected.

Table C-19. Modeling Results for Decreased Glomerular Diameter in the Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Inhalation for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/kg-d)	$BMCL_{1SD}$ (mg/kg-d)
Constant variance							
Exponential (Model 2)[e]	<0.0001	0.7667	<0.0001	–0.7433	99.93473	5.197	4.00168
Exponential (Model 3)[e]	<0.0001	0.7667	0.1127	0.06175	82.44754	15.9383	10.9087
Exponential (Model 4)[e]	<0.0001	0.7667	<0.0001	–0.7433	99.93473	5.197	4.00168
Exponential (Model 5)[e]	<0.0001	0.7667	0.1127	0.06175	82.44754	15.9383	10.9087
Hill[e]	<0.0001	0.7667	NDr	0.0699	84.440034	15.9859	10.7732
Linear[f]	<0.0001	0.7667	<.0001	1.85	140.542612	–9,999	204.321
Polynomial (2-degree)[f]	<0.0001	0.7667	0.08259	1.46	82.919374	11.1254	9.92596
Polynomial (3-degree)[f, g]	**<0.0001**	**0.7667**	**0.1179**	**0.48**	**82.376899**	**14.245**	**8.66779**
Power[g, e]	<0.0001	0.7667	0.1134	0.0719	82.438191	15.9958	10.7427

[a]Miyake et al. (2016).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMC.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be negative.
[g]Selected models. Lowest AIC among models that provided an adequate fit.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; NDr = not determined; SD = standard deviation.

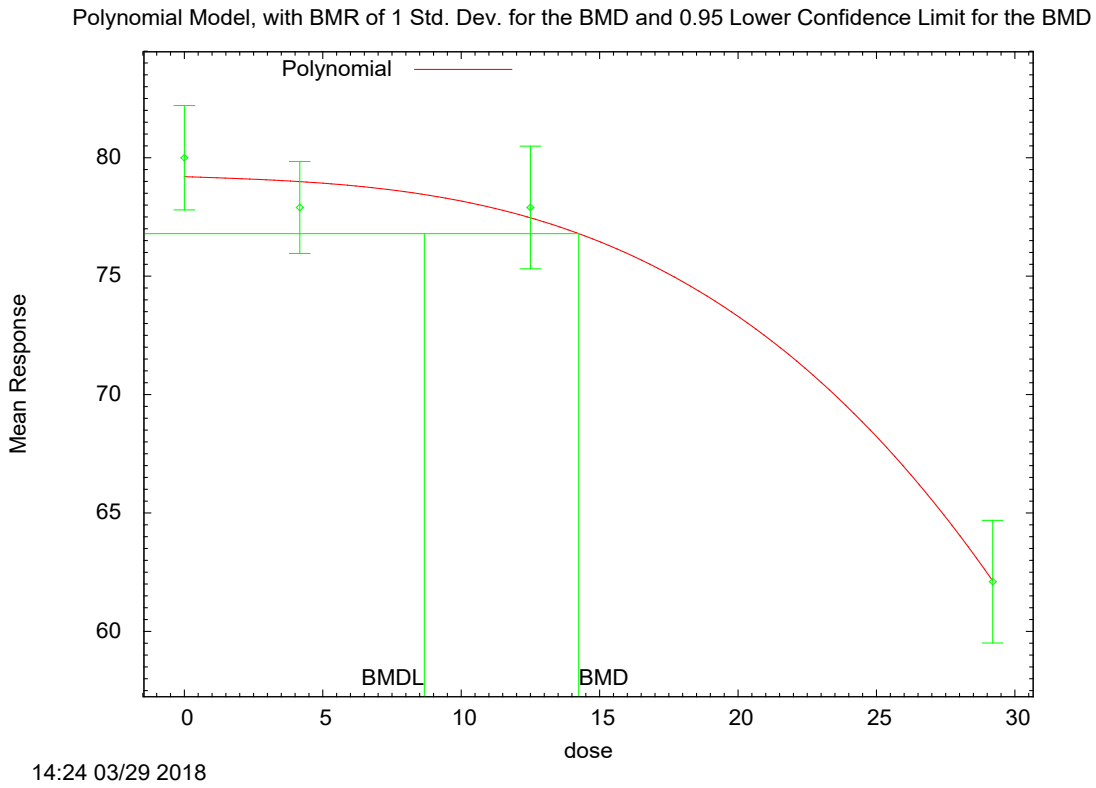

Figure C-12. Polynomial 3-Degree for Decreased Glomerular Diameter in the Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

Model Predictions for Decreased Number of OMP-Positive Cells in Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

The procedure outlined above for continuous data was applied to the data for decreased number of OMP-positive cells in the olfactory bulb of the brain in ICR mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016) (see Table B-13). Table C-20 summarizes the BMC modeling results. The initial modeling of these data including all dose groups failed to provide an adequate fit to the data, as assessed by the χ^2 goodness-of-fit test. Therefore, only the BMC modeling results based on data without the high-dose group included are summarized in Table C-20 and Figure C-13. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by the Exponential 2, Exponential 4, Polynomial 2-degree, and Polynomial 3-degree models. The BMCLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Polynomial 3-degree model) is selected. For decreased number of OMP-positive cells in the olfactory bulb of the brain, the $BMCL_{1SD}$ of 5.72 mg/m^3 from the Polynomial 3-degree model is selected.

Table C-20. Modeling Results for Decreased Number of OMP-Positive Cells in the Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Inhalation for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/kg-d)	$BMCL_{1SD}$ (mg/kg-d)
Constant variance							
Exponential (Model 2)[e]	0.05415	0.3983	0.2404	–0.3415	73.54965	8.4853	4.80775
Exponential (Model 3)[e]	0.05415	0.3983	NDr	-9.44×10^{-8}	74.20023	12.1444	5.52921
Exponential (Model 4)[e]	0.05415	0.3983	0.2404	–0.3415	73.54965	8.4853	4.00758
Exponential (Model 5)[e]	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Hill[e]	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Linear[f]	0.05415	0.3983	0.02407	0.897	77.62454	–9,999	43.4358
Polynomial (2-degree)[f]	0.05415	0.3983	0.6414	–0.0372	72.388258	10.3266	5.6273
Polynomial (3-degree)[f, g]	**0.05415**	**0.3983**	**0.7907**	**–0.00682**	**72.241793**	**11.0983**	**5.71511**
Power[e]	0.05415	0.3983	NDr	-3.04×10^{-9}	74.200226	12.2351	5.7413

[a]Miyake et al. (2016).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMC.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be negative.
[g]Selected models. Lowest AIC among models that provided an adequate fit.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; NDr = not determined; OMP = olfactory marker protein; SD = standard deviation.

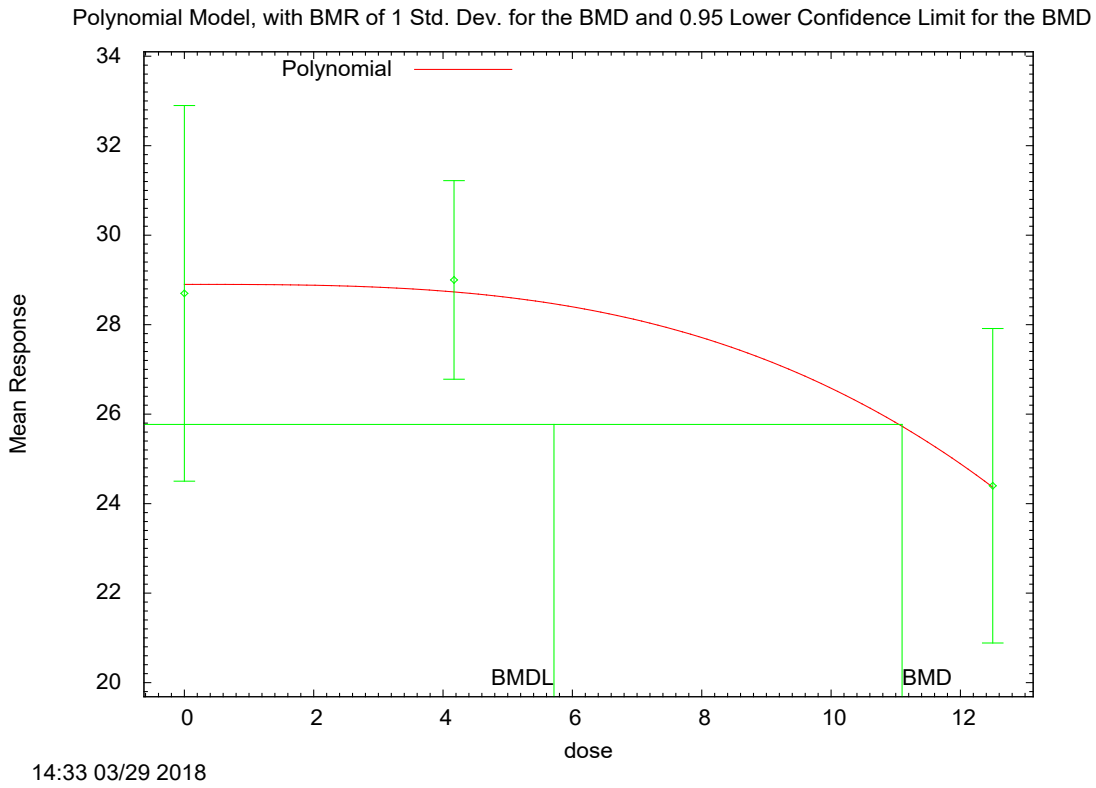

Figure C-13. Polynomial 3-Degree for Decreased Number of OMP-Positive Cells in the Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

Model Predictions for Decreased Number of TH-Positive Cells in Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

The procedure outlined above for continuous data was applied to the data for decreased number of TH-positive cells in the olfactory bulb of the brain in ICR mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016) (see Table B-13). The BMC modeling results are summarized in Table C-21 and Figure C-14. The nonconstant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all included models. The BMCLs for the models providing adequate fit are not sufficiently close (i.e., differ by >threefold), so the models with the lowest BMCL (Exponential 4 and 5 models) are selected. For decreased number of TH-positive cells in the olfactory bulb of the brain, the $BMCL_{1SD}$ of 3.59 mg/m^3 from the Exponential 4 and 5 models is selected.

Table C-21. Modeling Results for Decreased Number of TH-Positive Cells in the Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Inhalation for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/kg-d)	$BMCL_{1SD}$ (mg/kg-d)
Nonconstant variance							
Exponential (Model 2)[e]	0.00213	0.654	0.2442	–0.3891	107.0891	19.0429	11.1862
Exponential (Model 3)[e]	0.00213	0.654	0.2442	–0.3891	107.0891	19.0429	11.1862
Exponential (Model 4)[e, f]	**0.00213**	**0.654**	**0.311**	**0.548**	**107.2963**	**10.6561**	**3.58878**
Exponential (Model 5)[e, f]	**0.00213**	**0.654**	**0.311**	**0.548**	**107.2963**	**10.6561**	**3.58878**
Hill[e]	0.00213	0.654	0.3952	0.61	106.992906	9.29205	NDr
Linear[g]	0.00213	0.654	0.1865	0.148	107.629108	20.9134	13.2696
Polynomial (2-degree)[g]	0.00213	0.654	0.1865	0.148	107.629108	20.9134	13.2696
Polynomial (3-degree)[g]	0.00213	0.654	0.1865	0.148	107.629108	20.9134	13.2696
Power[f, e]	**0.00213**	**0.654**	**0.1865**	**0.148**	**107.629108**	**20.9134**	**13.2696**

[a]Miyake et al. (2016).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMC.
[e]Power restricted to ≥1.
[f]Selected models. Lowest BMCL among models that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; NDr = not determined; SD = standard deviation; TH = tyrosine hydroxylase.

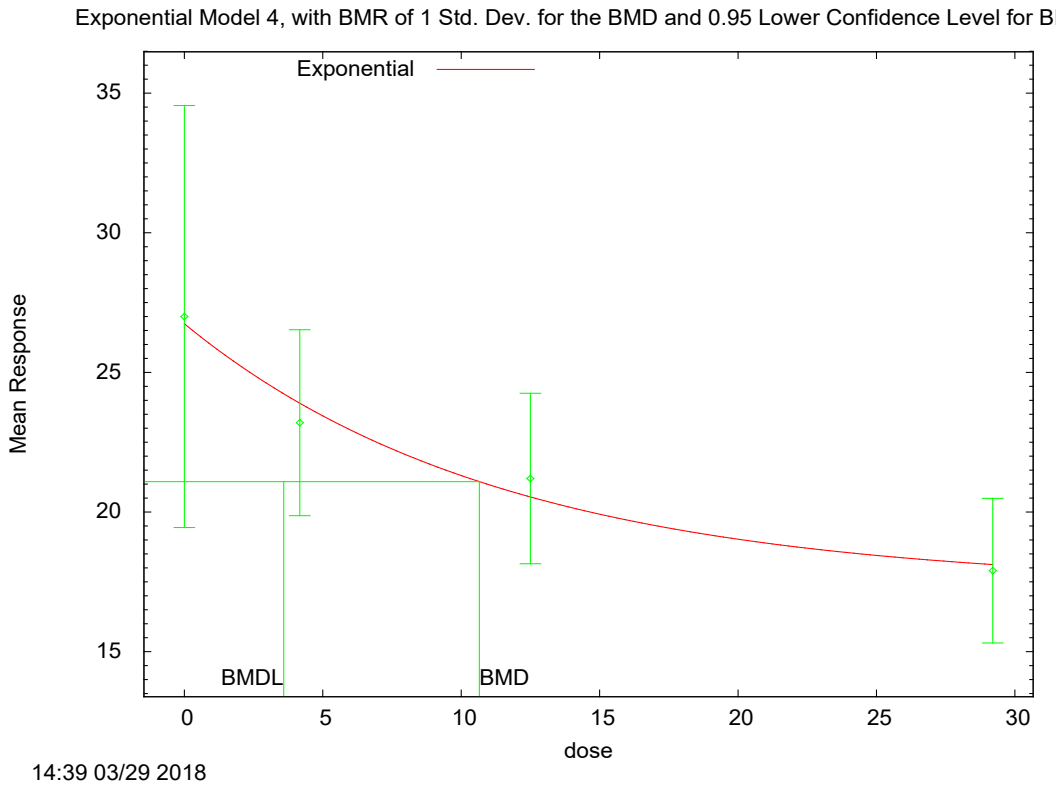

Figure C-14. Exponential 4 Model for Decreased Number of TH-Positive Cells in the Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

Model Predictions for Increased Number of Iba1-Positive Cells in Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

The procedure outlined above for continuous data was applied to the data for increased number of Iba1-positive cells in the olfactory bulb of the brain in ICR mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016) (see Table B-13). Table C-22 summarizes the BMC modeling results. Neither the constant nor nonconstant variance models provided adequate fit to the variance data using the full data set. This data set was not amenable to BMC modeling.

Table C-22. Modeling Results for Increased Number of Iba1-Positive Cells in the Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Inhalation for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/kg-d)	$BMCL_{1SD}$ (mg/kg-d)
Nonconstant variance							
Exponential (Model 2)[e]	<0.0001	0.5336	0.003127	−1.77	481.9362	13.1059	9.94605
Exponential (Model 3)[e]	<0.0001	0.5336	0.03183	0.003192	477.0084	23.0931	15.345
Exponential (Model 4)[e]	<0.0001	0.5336	0.0001987	−2.081	486.2443	12.1118	8.80593
Exponential (Model 5)[e]	<0.0001	0.5336	NDr	0.003325	479.0071	22.6623	15.1094
Hill[e]	<0.0001	0.5336	0.03197	−0.277	477.001284	14.5898	NDr
Linear[f]	<0.0001	0.5336	<0.0001	−0.28	505.383851	−9,999	52.6469
Polynomial (2-degree)[f]	<0.0001	0.5336	<0.0001	2.33	589.055535	−9,999	51.9659
Polynomial (3-degree)[f]	<0.0001	0.5336	<0.0001	2.33	589.075607	−9,999	14.97
Power[e]	<0.0001	0.5336	0.03186	0.00332	477.007142	22.6623	15.1094

[a]Miyake et al. (2016).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMC.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; Iba1 = ionized calcium-binding adapter molecule 1; NDr = not determined; SD = standard deviation.

Model Predictions for Increased Number of Dcx-Positive Cells in Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol via Inhalation for 3 Months (Miyake et al., 2016)

The procedure outlined above for continuous data was applied to the data for increased number of Dcx positive cells in the olfactory bulb of the brain in ICR mice exposed to 2-EH via inhalation for 3 months (Miyake et al., 2016) (see Table B-13). Table C-23 summarizes the BMC modeling results. Neither the constant nor nonconstant variance models provided adequate fit to the variance data using the full data set. This data set was not amenable to BMC modeling.

Table C-23. Modeling Results for Increased Number of Dcx-Positive Cells in the Olfactory Bulb of the Brain Cavity in Male ICR Mice Exposed to 2-Ethylhexanol (CASRN 104-76-7) via Inhalation for 3 Months[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/kg-d)	$BMCL_{1SD}$ (mg/kg-d)
Nonconstant variance							
Exponential (Model 2)[e]	<0.0001	0.0184	<0.0001	0.4599	457.4724	23.8777	17.3388
Exponential (Model 3)[e]	<0.0001	0.0184	0.0004841	1.62×10^{-7}	452.5633	28.7021	23.5487
Exponential (Model 4)[e]	<0.0001	0.0184	<0.0001	0.7851	461.039	24.9115	16.014
Exponential (Model 5)[e]	<0.0001	0.0184	NDr	1.84×10^{-6}	454.5633	28.3721	13.7625
Hill[e]	<0.0001	0.0184	NDr	6.63×10^{-6}	454.563332	28.4344	NDr
Linear[f]	<0.0001	0.0184	<.0001	–0.548	462.890803	–9,999	36.982
Polynomial (2-degree)[f]	<0.0001	0.0184	0.000597	0.219	453.234583	25.1026	20.8016
Polynomial (3-degree)[f]	<0.0001	0.0184	0.0014	0.082	451.530498	26.0806	23.0285
Power[e]	<0.0001	0.0184	0.00227	4.29×10^{-7}	450.563321	28.6184	23.1719

[a]Miyake et al. (2016).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at doses closest to BMC.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; Dcx = doublecortin; SD = standard deviation.

APPENDIX D. BENCHMARK DOSE CALCULATIONS FOR THE PROVISIONAL ORAL SLOPE FACTOR

BMD MODELING TO IDENTIFY POTENTIAL PODS FOR THE DERIVATION OF A PROVISIONAL ORAL SLOPE FACTOR

Significant dose-related trends were found for hepatocellular carcinomas in male and female mice (see Table B-9) in the principal study of mice administered 2-ethylhexanol (2-EH) via gavage 5 days/week for 18 months (Astill et al., 1996b; BASF, 1991b). Data for these endpoints were selected to determine the potential point of departure (POD) for the provisional oral slope factor (p-OSF), using benchmark dose (BMD) analysis. Summaries of modeling approaches and results (see Tables D-1 through D-4) for each data set follow.

MODEL-FITTING PROCEDURE FOR CANCER INCIDENCE DATA

The model-fitting procedure for dichotomous cancer incidence is as follows. The Multistage Cancer model in the U.S. EPA's Benchmark Dose Software (BMDS, Version 2.7) is fit to the incidence data using the extra risk option. The Multistage-Cancer model is run for all polynomial degrees up to $n - 1$ (where n is the number of dose groups including control). An adequate model fit is judged by three criteria: (1) goodness-of-fit p-value ($p < 0.1$), (2) visual inspection of the dose-response curve, and (3) scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among the models providing adequate fit to the data, the BMDL/BMCL (benchmark dose/concentration lower confidence limit) for the model with the lowest Akaike's information criterion (AIC) is selected as the POD. In accordance with U.S. EPA (2012b) *Benchmark Dose Technical Guidance* and the U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, BMD/BMC (benchmark dose/concentration) and BMDL/BMCL values associated with an extra risk of 10% are calculated.

Hepatocellular Carcinomas or Adenomas in Male B6C3F$_1$ Mice Treated with 2-Ethylhexanol via Gavage for 18 Months

The procedure outlined above for cancer incidence data was applied to the incidence data for hepatocellular carcinomas and adenomas in male B6C3F$_1$ mice treated with 2-EH via gavage for 18 months (Astill et al., 1996b; BASF, 1991b) (see Table B-9). To account for group differences in survival, data for tumor incidence in male mice were modeled using a Poly-3 survival-adjusted number at risk. Table D-1 summarizes the BMD modeling results for the unadjusted incidence of hepatocellular carcinomas or adenomas in males. Table D-2 summarizes the BMD modeling results for the Poly-3-weighted number at risk. BMDLs for models were sufficiently close (differed by less than two- to threefold), so the model with the lowest AIC was selected (Multistage 1-degree; see Figures D-1 and D-2). Modeling the observed incidence and Poly-3 weighted number at risk gives a more conservative BMDL than unadjusted number, thus the Poly-3-adjusted BMDL$_{10}$ for the 1-degree Multistage Cancer model of 25 mg/kg-day is selected.

Table D-1. BMD Model Predictions for Unadjusted Incidence of Hepatocellular Carcinomas or Adenomas in Male B6C3F$_1$ Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 18 Months[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual: Dose Nearest BMD[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Multistage Cancer (1-degree)[d, e]	**2**	**1.47**	**0.4795**	**−0.024**	**155.503**	**66.3299**	**30.9815**
Multistage Cancer (2-degree)[d]	1	1.47	0.2254	−0.028	157.503	66.6271	30.982
Multistage Cancer (3-degree)[d]	1	1.47	0.2254	−0.028	157.503	66.6271	30.982

[a]Astill et al. (1996b); BASF (1991b).
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group nearest the BMD.
[d]Power restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; DF = degree(s) of freedom.

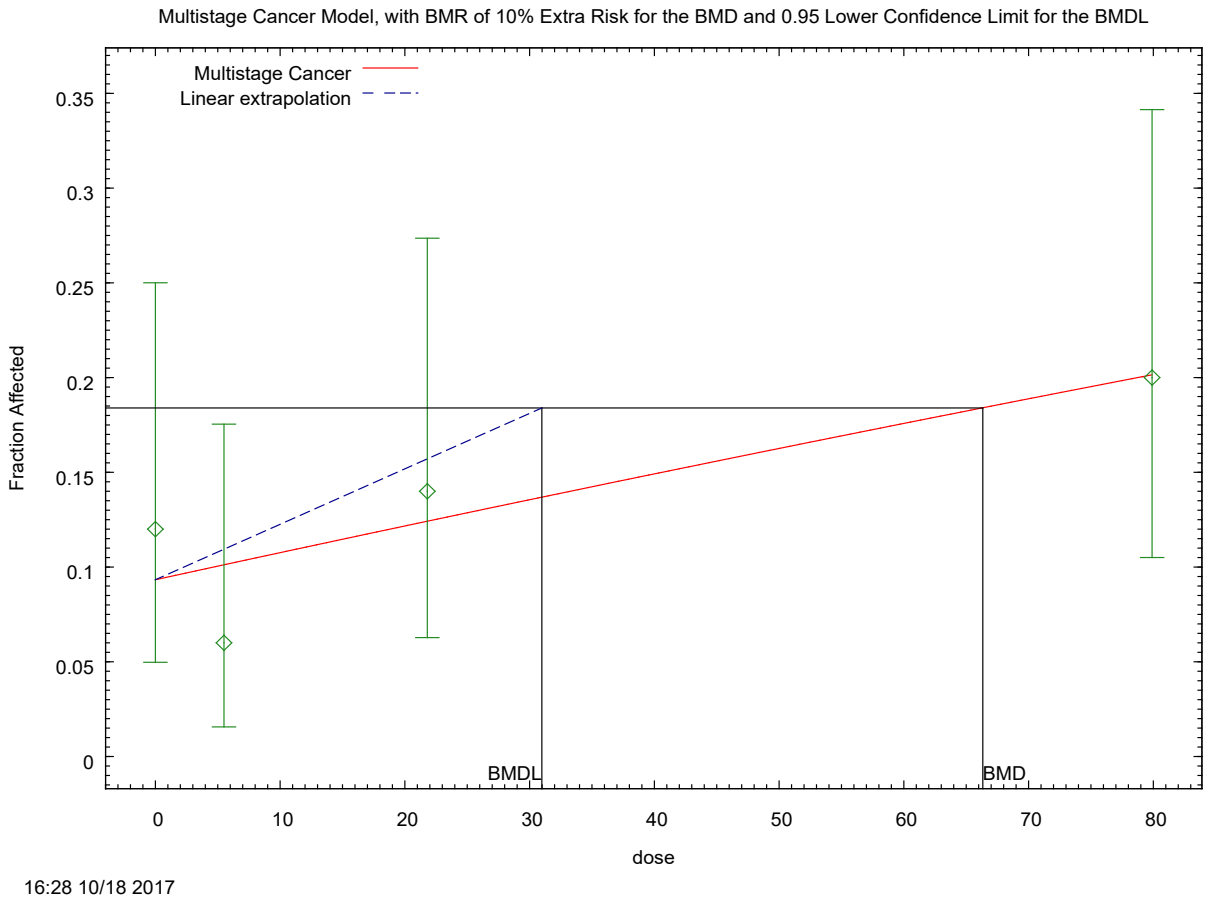

Figure D-1. Multistage Cancer 1-Degree BMD Model for Unadjusted Incidence of Hepatocellular Carcinomas or Adenomas in Male B6C3F$_1$ Mice Treated with 2-Ethylhexanol via Gavage for 18 Months (Astill et al., 1996b; BASF, 1991b)

Text Output for Figure D-1:

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MyDocuments/BMDS/BMDS2704/Data/msc_Dichotomous_Opt.(d)
        Gnuplot Plotting File:  //Aa.ad.epa.gov/ord/CIN/Users/main/A-E/bowens/Net
MyDocuments/BMDS/BMDS2704/Data/msc_Dichotomous_Opt.plt
                                                Wed Oct 18 16:28:03 2017
 ================================================================================

 BMDS_Model_Run
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive
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Dependent variable = Effect
Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1

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

Default Initial Parameter Values
Background = 0.0938431
Beta(1) = 0.00158119

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.56
Beta(1)	-0.56	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0932971	0.028343	0.0377459	0.148848
Beta(1)	0.00158843	0.000998223	-0.000368048	0.00354491

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-74.9629	4			
Fitted model	-75.7517	2	1.57766	2	0.4544
Reduced model	-77.2773	1	4.62884	3	0.2011

AIC: 155.503

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0933	4.665	6.000	50.000	0.649
5.5000	0.1012	5.059	3.000	50.000	-0.966
21.8000	0.1242	6.208	7.000	50.000	0.340
79.9000	0.2014	10.068	10.000	50.000	-0.024

Chi^2 = 1.47 d.f. = 2 P-value = 0.4795

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        66.3299

            BMDL =        30.9815

            BMDU =   3.80333e+007

Taken together, (30.9815, 3.80333e+007) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =    0.00322773
```

Table D-2. BMD Model Predictions for Poly-3-Adjusted Incidence of Hepatocellular Carcinomas or Adenomas in Male B6C3F1 Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 18 Months[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual: Dose Nearest BMD[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Multistage Cancer (1-degree)[d, e]	**2**	**1.47**	**0.4794**	**0.219**	**149.954**	**48.6288**	**24.5793**
Multistage Cancer (2-degree)[d]	1	1.44	0.2306	−0.033	151.928	53.5151	24.6449
Multistage Cancer (3-degree)[d]	1	1.44	0.2306	−0.033	151.928	53.5149	24.6449

[a]Astill et al. (1996b); BASF (1991b).
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group nearest the BMD.
[d]Power restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; DF = degree(s) of freedom.

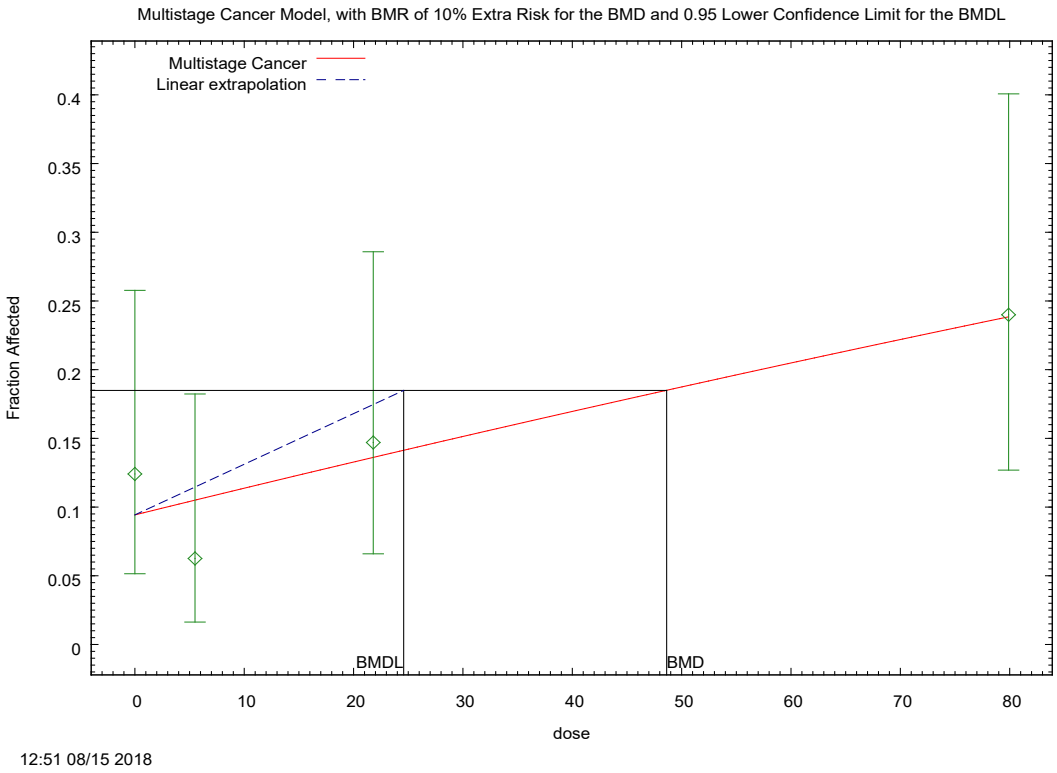

Figure D-2. Multistage Cancer 1-Degree BMD Model for Poly-3-Adjusted Incidence of Hepatocellular Carcinomas or Adenomas in Male B6C3F$_1$ Mice Treated with 2-Ethylhexanol via Gavage for 18 Months (Astill et al., 1996b; BASF, 1991b)

Text Output for Figure D-2:

```
=================================================================
         Multistage Model. (Version: 3.4;  Date: 05/02/2014)
         Input Data File: //Aa.ad.epa.gov/ord/CIN/Users/main/F-K/JKaiser/Net
MyDocuments/BMDS/BMDS2704/Data/msc_Dichotomouspol3adjmales_Msc1-BMR10.(d)
         Gnuplot Plotting File:  //Aa.ad.epa.gov/ord/CIN/Users/main/F-K/JKaiser/Net
MyDocuments/BMDS/BMDS2704/Data/msc_Dichotomouspol3adjmales_Msc1-BMR10.plt
                                                Wed Aug 15 12:51:17 2018
 =================================================================

 BMDS_Model_Run
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
```

Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1

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

Default Initial Parameter Values
Background = 0.0938868
Beta(1) = 0.00220263

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.52
Beta(1)	-0.52	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0943095	0.0293206	0.0368422	0.151777
Beta(1)	0.00216663	0.00116295	-0.000112708	0.00444597

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-72.1933	4			
Fitted model	-72.9771	2	1.5677	2	0.4566
Reduced model	-75.188	1	5.98943	3	0.1121

AIC: 149.954

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0943	4.560	6.000	48.349	0.709
5.5000	0.1050	5.036	3.000	47.940	-0.959
21.8000	0.1361	6.481	7.000	47.622	0.219
79.9000	0.2383	9.930	10.000	41.675	0.025

Chi^2 = 1.47 d.f. = 2 P-value = 0.4794

Benchmark Dose Computation

Specified effect = 0.1

```
Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        48.6288

            BMDL =        24.5793

            BMDU =        244.468

Taken together, (24.5793, 244.468) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =    0.00406847
```

Hepatocellular Carcinomas in Female B6C3F$_1$ Mice Treated with 2-Ethylhexanol via Gavage for 18 Months

The procedure outlined above for cancer incidence data was applied to the incidence data for hepatocellular carcinomas in female B6C3F$_1$ mice treated with 2-EH via gavage for 18 months (Astill et al., 1996b; BASF, 1991b) (see Table B-9). To account for group differences in survival, data for tumor incidence in female mice were also modeled using a Poly-3 survival-adjusted number at risk. Table D-3 summarizes the BMD modeling results for the unadjusted incidence of hepatocellular carcinomas in females. Table D-4 summarizes the BMD modeling results for the Poly-3-weighted number at risk. All models provided adequate fit to the data. The Multistage Cancer 2- and 3-degree models converged onto the Multistage Cancer 1-degree model for both data sets (see Figures D-3 and D-4). Modeling the observed incidence and Poly-3-weighted number at risk gives a more conservative BMDL than unadjusted number, thus the Poly-3-adjusted BMDL$_{10}$ for the 1-degree Multistage Cancer model of 27 mg/kg-day is selected.

Table D-3. BMD Model Predictions for Unadjusted Incidence of Hepatocellular Carcinomas in Female B6C3F$_1$ Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 18 Months[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual: Dose Nearest BMD[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Multistage Cancer (1-degree)[d, e]	**2**	**1.35**	**0.5092**	**−0.534**	**70.4171**	**62.6923**	**35.2874**
Multistage Cancer (2-degree)[d]	2	1.35	0.5092	−0.534	70.4171	62.6923	35.2874
Multistage Cancer (3-degree)[d]	2	1.35	0.5092	−0.534	70.4171	62.6923	35.2874

[a]Astill et al. (1996b); BASF (1991b).
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group nearest the BMD.
[d]Power restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. The Multistage Cancer 2- and 3-degree models converged onto the Multistage Cancer 1-degree model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; DF = degree(s) of freedom.

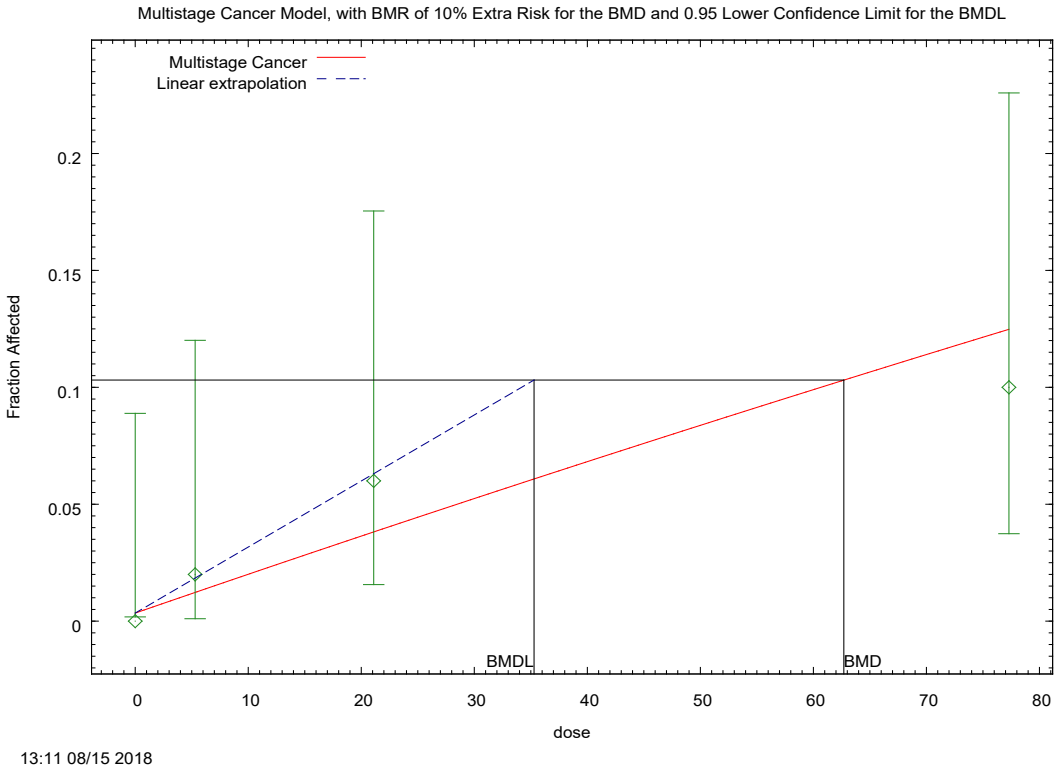

Figure D-3. Multistage Cancer 1-Degree BMD Model for Unadjusted Incidence of Hepatocellular Carcinomas in Female B6C3F$_1$ Mice Treated with 2-Ethylhexanol via Gavage for 18 Months (Astill et al., 1996b; BASF, 1991b)

Text Output for Figure D-3:

```
 ================================================================
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MyDocuments/BMDS/BMDS2704/Data/msc_Dichotomousnopol3adjfemales_Msc1-BMR10.(d)
        Gnuplot Plotting File:  //Aa.ad.epa.gov/ord/CIN/Users/main/F-K/JKaiser/Net
MyDocuments/BMDS/BMDS2704/Data/msc_Dichotomousnopol3adjfemales_Msc1-BMR10.plt
                                            Wed Aug 15 13:11:37 2018
 ================================================================

 BMDS_Model_Run
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


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



                  Default Initial Parameter Values
                     Background =    0.0143667
                        Beta(1) =   0.00124932


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.63

   Beta(1)        -0.63            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background       0.00345348        0.0137041          -0.0234061
0.0303131
        Beta(1)        0.0016806      0.000778964         0.000153855
0.00320734
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-32.5045	4			
Fitted model	-33.2085	2	1.40813	2	0.4946
Reduced model	-36.7042	1	8.39949	3	0.03844

AIC: 70.4171

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0035	0.173	0.000	50.000	-0.416
5.3000	0.0123	0.615	1.000	50.000	0.495
21.1000	0.0382	1.909	3.000	50.000	0.806
77.3000	0.1249	6.243	5.000	50.000	-0.532

Chi^2 = 1.35 d.f. = 2 P-value = 0.5092

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 62.6923

BMDL = 35.2874

BMDU = 188.051

Taken together, (35.2874, 188.051) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.00283387

Table D-4. BMD Model Predictions for Poly-3-Adjusted Incidence of Hepatocellular Carcinomas in Female B6C3F$_1$ Mice Treated with 2-Ethylhexanol (CASRN 104-76-7) via Gavage for 18 Months[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual: Dose Nearest BMD[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Multistage Cancer (1-degree)[d, e]	**3**	**0.70**	**0.8721**	**0.475**	**63.6119**	**44.2035**	**26.7312**
Multistage Cancer (2-degree)[d]	3	0.70	0.8721	0.475	63.6119	44.2035	26.7312
Multistage Cancer (3-degree)[d]	3	0.70	0.8721	0.475	63.6119	44.2035	26.7312

[a]Astill et al. (1996b); BASF (1991b).
[b]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group nearest the BMD.
[d]Power restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. The Multistage Cancer 2- and 3-degree models converged onto the Multistage Cancer 1-degree model.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; DF = degree(s) of freedom.

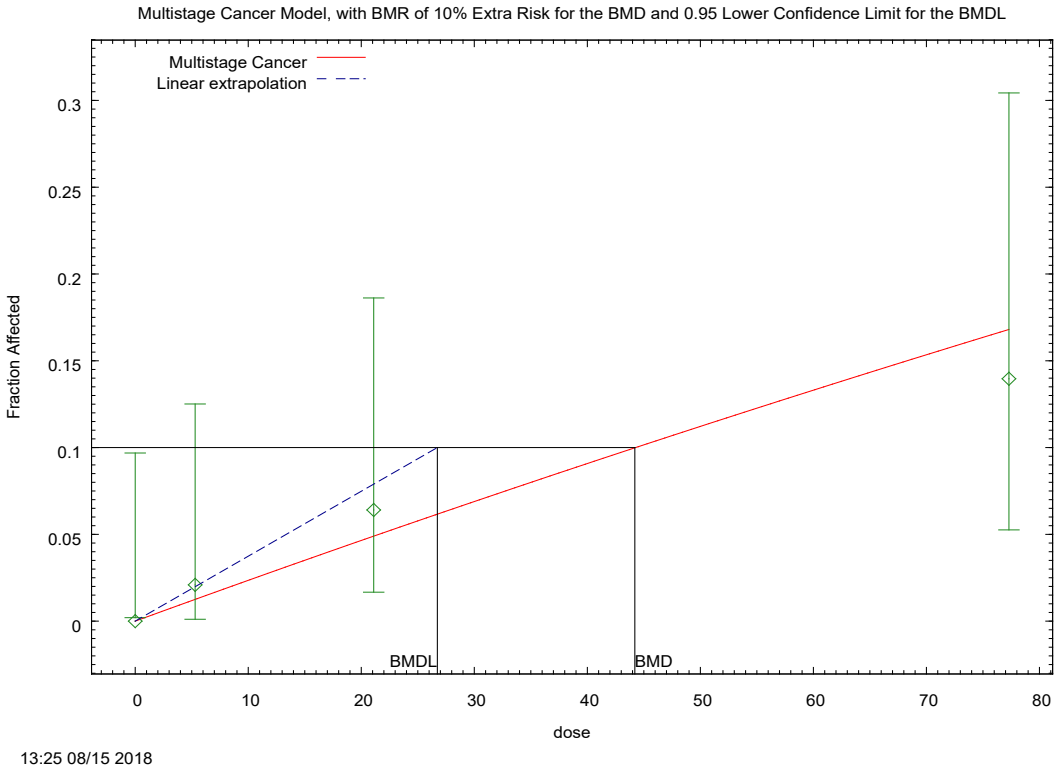

Figure D-4. Multistage Cancer 1-Degree BMD Model for Poly-3-adjusted Incidence of Hepatocellular Carcinomas in Female B6C3F$_1$ Mice Treated with 2-Ethylhexanol via Gavage for 18 Months (Astill et al., 1996b; BASF, 1991b)

Text Output for Figure D-4:

```
 ======================================================================
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MyDocuments/BMDS/BMDS2704/Data/msc_Dichotomouspol3adjfemales_Msc1-BMR10.(d)
        Gnuplot Plotting File:  //Aa.ad.epa.gov/ord/CIN/Users/main/F-K/JKaiser/Net
MyDocuments/BMDS/BMDS2704/Data/msc_Dichotomouspol3adjfemales_Msc1-BMR10.plt
                                            Wed Aug 15 13:25:00 2018
 ======================================================================

 BMDS_Model_Run
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


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



                  Default Initial Parameter Values
                     Background =    0.0112972
                        Beta(1) =   0.00185417


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                                  Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background               0              NA
```

```
       Beta(1)       0.00238353      0.000795164         0.000825041
0.00394203

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


                      Analysis of Deviance Table

      Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
    Full model        -30.4802         4
   Fitted model       -30.8059         1      0.651419      3          0.8846
  Reduced model       -35.5269         1       10.0934      3         0.01779

          AIC:         63.6119


                                Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size        Residual
  ---------------------------------------------------------------------------
   0.0000     0.0000         0.000     0.000      45.551        0.000
   5.3000     0.0126         0.601     1.000      47.837        0.519
  21.1000     0.0490         2.297     3.000      46.839        0.475
  77.3000     0.1683         6.025     5.000      35.806       -0.458

 Chi^2 = 0.70      d.f. = 3        P-value = 0.8721


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        44.2035

            BMDL =        26.7312

            BMDU =        108.057

Taken together, (26.7312, 108.057) is a 90     % two-sided confidence
```

APPENDIX E. REFERENCES

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