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Provisional Peer-Reviewed Toxicity Values for

Endosulfan Sulfate
(CASRN 1031-07-8)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR ENDOSULFAN SULFATE (CASRN 1031-07-8)

BACKGROUND

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

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

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

DISCLAIMERS

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

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

QUESTIONS REGARDING PPRTVs

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

INTRODUCTION

Endosulfan sulfate, CASRN 1031-07-8, is a reaction product that forms due to oxidation, biotransformation, or photolysis of endosulfan (ATSDR, 2000). Endosulfan is an organochlorine insecticide that can be used on a wide variety of vegetables and fruits, cotton, and ornamental plants. It has no residential uses. Table 1 provides physiochemical properties of endosulfan sulfate and endosulfan. Chemical properties of endosulfan sulfate are similar to its parent compound, endosulfan (ATSDR, 2000). The empirical formula for endosulfan sulfate is $C_9H_6Cl_6O_4S$ (see Figure 1). The empirical formula for endosulfan is $C_9H_6C1_6O_3S$ (see Figure 2). Technical-grade endosulfan is a 7:3 mixture of conformational isomers α-endosulfan and β-endosulfan arising from the pyramidal stereochemistry of sulfur.

Table 1. Physicochemical Properties of Endosulfan Sulfate (CASRN 1031-07-8) and Endosulfan (CASRN 115-29-7)

Property (unit)	Value	
	Endosulfan Sulfate[a]	**Endosulfan[b]**
Boiling point (ºC)	ND	ND
Melting point (ºC)	181−182	106
Density (g/cm^3)	ND (a solid)	1.745
Vapor pressure (Pa at 25ºC)	1.0×10^{-11}	1.73×10^{-7} (approximate maximum of 0.2 ppm in air)
pH (unitless)	ND	7.2
Solubility in water (mg/L at 20ºC)	0.48	0.32 (α-form); 0.33 (β-form)
Relative vapor density (air = 1)	ND	ND
Molecular weight (g/mol)	422.95	406.93

[a]HSDB (2009).
[b]HSDB (2010).

ND = no data.

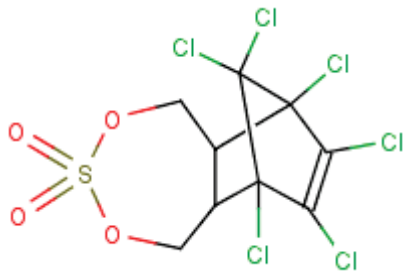

Figure 1. Endosulfan Sulfate Structure

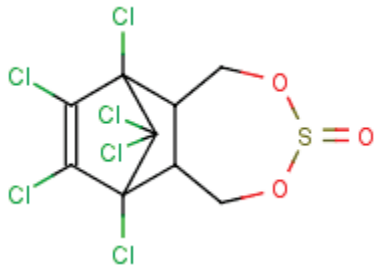

Figure 2. Endosulfan Structure

No potentially relevant data investigating the effects of repeat-dose oral or inhalation exposure in animals or humans have been identified for endosulfan sulfate. ATSDR (2000) has noted that very little difference in toxicity exists between endosulfan and endosulfan sulfate as indicated by acute and human case control studies. In addition, a structure similarity search using the ChemIDplus database indicates that the two compounds are 93.07% similar (NLM) with endosulfan being metabolized to endosulfan sulfate following absorption into the body (ATSDR, 2000). Finally, both endosulfan and endosulfan sulfate appear to exert neurotoxicity through a *gamma*-aminobutyric acid (GABA)-antagonistic mode of action (ATSDR, 2000; Cole and Casida, 1986). U.S. EPA (1994a) reports a reference dose (RfD) for chronic oral exposure of 6×10^{-3} mg/kg-day for endosulfan. Because endosulfan and endosulfan sulfate appear to share similar chemical, physical, and toxicological properties, endosulfan is considered a suitable surrogate to develop toxicological values for endosulfan sulfate. A more detailed discussion is provided in a following section.

A summary of available health-related values for endosulfan sulfate from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Endosulfan Sulfate (CASRN 1031-07-8) and Endosulfan (CASRN 115-29-7)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
Noncancer				
ACGIH	8-hr TLV-TWA: 1×10^{-1} mg/m^3 for endosulfan[c]	TLV-TWA based on lower respiratory tract irritation; liver and kidney damage	ACGIH (2013)	NA
	NV	NA	ACGIH (2013)	NA
ATSDR[d]	Oral Acute MRL: 7×10^{-3} mg/kg-d; Oral Int. MRL: 5×10^{-3} mg/kg-d; Oral Chr. MRL: 5×10^{-3} mg/kg-d for endosulfan	NA	ATSDR (2013)	NA
	NV for endosulfan sulfate	NA	ATSDR (2013)	NA
Cal/EPA	NV	NA	Cal/EPA (2008, 2012)[b]	8-6-2013[b]
NIOSH	REL-TWA: 1×10^{-1} mg/m^3 for endosulfan	NA	NIOSH (2010)	NA
	NV for endosulfan sulfate	NA	NIOSH (2010)	NA
OSHA	NV	NA	OSHA (2006)	NA
	8-hr PEL-TWA: 1×10^{-1} mg/m^3 for endosulfan	NA	OSHA (2011)	NA
	NV for endosulfan sulfate	NA	OSHA (2011)	NA
IRIS	RfD: 6×10^{-3} mg/kg-d for endosulfan	NA	U.S. EPA (1994a)	NA
	NV for endosulfan sulfate	NA	U.S. EPA	8-6-2013
Drinking water	NV	NA	U.S. EPA (2011)	NA
HEAST	Subchronic RfD: 6×10^{-3} mg/kg-d for endosulfan	NA	U.S. EPA (2011)	NA
	NV for endosulfan sulfate	NA	U.S. EPA (2011)	NA
CARA HEEP	NV	NA	U.S. EPA (1994b)	NA

Table 2. Summary of Available Toxicity Values for Endosulfan Sulfate (CASRN 1031-07-8) and Endosulfan (CASRN 115-29-7)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
WHO	Temporary acceptable daily intake for man of 0−0.008 mg/kg-BW for α-endosulfan, β-endosulfan, and endosulfan sulfate combined	NA	IPCS (1984)	NA
Cancer				
IRIS	NV	NA	U.S. EPA	8-6-2013
HEAST	NV	NA	U.S. EPA (2011)	NA
IARC	NV	NA	IARC (2013)	NA
NTP	NV	NA	NTP (2010)	NA
Cal/EPA	NV	NA	Cal/EPA (2009)[b]	8-6-2013[b]

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

[b]The Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) Toxicity Criteria Database (http://www.oehha.ca.gov/risk/ChemicalDB/index.asp) was also reviewed and found to contain no information on endosulfan sulfate and endosulfan.

[c]IFV = Inhalable Fraction and Vapor. ACGIH endnote used when material has sufficient vapor pressure to be present in both particle and vapor phases, with each contributing a significant portion of the dose at the TLV-TWA concentration. This endnote is typically used for substances with a Saturated Vapor concentration (SVC)/TLV ratio between 0.1 and 10.

[d]For duration, Acute = 1−14 d, Intermediate 15−364 d, and Chronic = ≥1 y.

BW = body weight; Chr. == chronic; IDLH = immediately dangerous to life or health; Int. Intermediate; MRL = minimal risk level; NA = not applicable; NSRL = no significant risk level; NV = not available; PEL = permissible exposure level; REL = recommended exposure level; TLV = threshold limit value; TWA = time weighted average.

Literature searches were conducted on sources published from 1900 through August 2013 for studies relevant to the derivation of provisional toxicity values for endosulfan sulfate (CASRN 1031-07-8) and endosulfan (CASRN 115-29-7). The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for toxicity values or exposure limits: ACGIH, ATSDR, Cal EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

BASIS FOR USE OF ENDOSULFAN TOXICITY DATA AS AN ESTIMATE OF TOXICITY FOR ENDOSULFAN SULFATE

Two major public health assessments (ATSDR, 2000; IPCS, 1984) provide support that the toxicity of endosulfan and endosulfan sulfate are similar. Metabolic data for humans cited in these documents show detection of endosulfan sulfate as the primary metabolite in several autopsy samples following acute ingestion of endosulfan, for example, in Boereboom et al. (1998).

This is also demonstrated in a number of kinetic studies in animals cited in ATSDR (2000) and IPCS (1984). Khanna et al. (1979) conducted an evaluation of the distribution of endosulfan and endosulfan sulfate in the brains of cats given a single intravenous (i.v.) injection of 3 mg/kg endosulfan. Peak concentrations of endosulfan in the brain were found at the earliest time point examined (15 minutes after administration) and subsequently decreased whereas endosulfan sulfate levels peaked in the brain at 1 hour postadministration and in the liver within 15 minutes postadministration. Based on the rapid appearance of endosulfan sulfate in the liver following i.v. administration of endosulfan (Khanna et al., 1979), it is concluded that endosulfan sulfate is a major metabolite of endosulfan and that the liver is a site of high metabolic activity.

Acute toxicity data in mice showed that the lethal dose for endosulfan sulfate was comparable to that of the α-isomer of endosulfan at 8 mg/kg (Dorough et al., 1978). IPCS (1984) described the study of NRCC (1975), in which endosulfan sulfate was noted as the only compound detected in tissues of rats exposed in the diet to endosulfan sulfate for 3 months at levels up to 500 mg/kg. No effects were detected other than increased liver or kidney weight. IPCS (1984) stated that endosulfan sulfate was administered to dogs for 3 months at levels of 0.75−2.5 mg/kg-day. The lowest dose did not have any effect, but the highest dose was not tolerated. The 1.5 mg/kg dose induced occasional signs of toxicity. Table 4 of this document provides summaries of additional subchronic-duration oral studies for endosulfan in rats and mice with effects noted in this exposure range. A chronic-duration study of endosulfan in beagle dogs showed neurological effects at the highest dose (approximately 2 mg/kg-day; Hoechst Celanese Corporation, 1989b). According to NRCC (1975), endosulfan sulfate appeared to have the same order of toxicity as endosulfan.

Endosulfan sulfate does not appear to be substantially more lipophilic than the parent compound. Of all the metabolites of endosulfan, endosulfan sulfate accumulates predominantly in the liver and kidneys (Hoechst Aktiengesellschaft, 1987).

Therefore, endosulfan could be considered acceptable as a surrogate for developing toxicity values for endosulfan sulfate.

BIODEGRADATION OF ENDOSULFAN

Appendix B provides information on the biodegradation of endosulfan.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 3 provides an overview of the relevant database for endosulfan and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. As previously mentioned, no potentially relevant data investigating the effects of repeat-dose oral or inhalation exposure were identified in animals or humans for endosulfan sulfate. The phrase "statistical significance," used throughout the document, indicates a p-value of <0.05.

Table 3. Summary of Potentially Relevant Data for Endosulfan (CASRN 115-29-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
			1. Oral (mg/kg-d)[a]					
Acute[c]	55-yr-old female, ingestion case study	NR	Mortality	NDr	NA	NDr	Bernardelli and Gennari (1987), as reported in ATSDR (2000)	PR
	Female (age unknown), accidental ingestion case study	NR	Renal failure; disseminated intravascular coagulation; thrombi in pulmonary arteries and aorta; cardiogenic shock; mortality 8 d after exposure; postmortem examination revealed bilateral pleural effusions, congested and edematous lungs, hyaline membranes, microatelectasia, polymorphonuclear lymphocytes and red cells in alveoli, and interstitial fibrosis	NDr	NA	NDr	Blanco-Coronado et al. (1992), as reported in ATSDR (2000)	PR
	Male (age unknown), accidental ingestion case study	NR	Muscle fasciculation; convulsions; tubular necrosis of the kidney; mortality 10 d following exposure due to cardio-respiratory arrest/heart failure and pulmonary edema	NDr	NA	NDr	Lo et al. (1995), as reported in ATSDR (2000)	PR
	20-yr-old male, ingestion case study	200 mL Thionax, 30% endosulfan (~1,500 mg/kg)	Hypoxia; pulmonary edema; tachycardia; hypertension; cardiogenic shock; convulsions; impaired psychomotor activity	NDr	NA	NDr	Shemesh et al. (1988), as reported in ATSDR (2000)	PR

Table 3. Summary of Potentially Relevant Data for Endosulfan (CASRN 115-29-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Acute[c]	Patient (sex and age unknown), ingestion case study	75 mL, 35% w/v (~375 mg/kg)	Nausea; vomiting; diarrhea; tonic-clonic seizures; myoclonic jerks; psychosis; cortical blindness; limb rigidity; reversible lesions of basal ganglia and occipital cortex	NDr	NA	NDr	Pradhan et al. (1997), as reported in ATSDR (2000)	PR
Short-term[d]	ND							
Long-term[e]	ND							
Chronic[f]	ND							
2. Inhalation (mg/m^3)[a]								
Acute[c]	18 agricultural workers (sex, age unknown), application of endosulfan to crops in absence of protective equipment	NR	Nausea; vomiting; dizziness; confusion; irritability; muscle twitching; tonic/clonic convulsions; conduction defects; increased dyspnea and respiratory rate; tachycardia; Bradycardia	NDr	NA	NDr	Chugh et al. (1998), as reported in ATSDR (2000)	PR
	22 agricultural workers (sex, age unknown), application of endosulfan to crops	NR	Nausea; vomiting; abdominal pain; diarrhea	NDr	NA	NDr	Singh et al. (1992), as reported in ATSDR (2000) (authors note results possibly due to dermal exposure because workers who suffered cuts on legs had more severe symptoms)	PR

Table 3. Summary of Potentially Relevant Data for Endosulfan (CASRN 115-29-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Acute[c]	Male (age unknown), industrial worker, single occupational exposure	NR	Repeated convulsions; impaired consciousness; disorientation; agitation; cognitive and emotional deterioration; impaired memory; impaired visual-motor coordination	NDr	NA	NDr	Aleksandrowicz (1979), as reported in ATSDR (2000)	PR
Short-term[d]	ND							
Long-term[e]	Children (number, sex, age not reported), homes near pesticide use	NR	No association with undescended testes	NDr	NA	NDr	García-Rodríguez et al. (1996), as reported in ATSDR (2000)	PR
	269,746 children in the Central Valley of California potentially exposed to endosulfan and other pesticides during gestation Wk 1−8, retrospective case-control study	NR	Increased incidence of autism spectrum disorder (ASD); exposure to multiple pesticides occurred simultaneously so was not possible to determine the relationship between ASD and endosulfan	NDr	NA	NDr	Roberts et al. (2007)	PR

Table 3. Summary of Potentially Relevant Data for Endosulfan (CASRN 115-29-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Long-term[e]	117/0 (117 cases, 90 controls), schoolchildren (10−19 yrs), retrospective cohort study analyzing male reproductive/developmental effects in exposed children	NR	The R^2 values corresponding to sexual maturity rating (SMR) of pubic hair, testes, and penis were 0.48, 0.43, and 0.43, respectively ($p < 0.001$), indicating that significant variance in SMR can be attributed to age and exposure; R^2 value of serum testosterone was 0.61 ($p < 0.001$), attributing 61% of variation to age, exposure, and serum luteinizing hormone (LH); increased ($p < 0.001$) endosulfan residues detected in 78% and 29% of the serum of exposed and control groups, respectively	NDr	NA	NDr	Saiyed et al. (2003); critiqued by Indulkar (2004)	PR
Chronic[f]	0/3 (3 cases, 7 controls), population-based occupational case-control study, cases had "probable" or "possible" exposure to endosulfan plus other xenoestrogens (no duration reported)	NR	Adjusted (core confounders and education) OR = 0.8 (CI, 0.2−3.2) Given small sample size, no significant conclusions drawn from this study	NDr	NA	NDr	Aschengrau et al. (1998)	PR
Animal								
1. Oral (mg/kg-d)[a]								
Subchronic[g]	10−12/0 per dose, Wistar rat, diet, 8, 12, 18, or 22 wk	0, 0.5, 0.9, 1.8 (Adjusted)	Decreased serum antibody titer, IgG concentrations, and LMI and MMI factors	0.5	NDr	0.9	Banerjee and Hussain (1986)	PR

Table 3. Summary of Potentially Relevant Data for Endosulfan (CASRN 115-29-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Chronic	50/50 per dose, S-D rat, diet, 2 yr	M: 0, 0.1, 0.3, 0.6, 2.9 F: 0, 0.1, 0.4, 0.7, 3.8 (Adjusted)	Decreased BW gain in males and females; increased incidence of marked progressive glomerulonephrosis and blood vessel aneurysms in males	0.6 (M) 0.7 (F)	NR	2.9 (M) 3.8 (F)	Hoechst Celanese Corporation (1989a), as summarized in U.S. EPA (1994a)	IRIS, PR
	6/6 per dose, beagle dog, diet, 1 yr	M: 0, 0.2, 0.65, 2.1 F: 0, 0.18, 0.57, 1.9 (Adjusted)	Decreased weight gain in males; neurological findings in males and females	0.65 (M) 0.57 (F)	NR	2.1 (M) 1.9 (F)	Hoechst Celanese Corporation (1989b), as summarized in U.S. EPA (1994a)	IRIS, PR
Developmental[h]	**0/30, Wistar rat, diet, GD 6−PND 21, pups sacrificed on PND 21 or PND 75**	**0, 3.74, 10.8, 29.8**	**Developmental LOAEL: decreased pup weight at PNDs 11 and 17** **BMDL: decreased pup weight in females at PND 11**	**NDr**	**0.29**	**3.74**	**Gilmore et al. (2006)**	**PS**
	0/24, Wistar rat, gavage, dams dosed on GD 15−PND 21, offspring sacrificed PND 65 or 140	0, 1.5, 3.0	Developmental LOAEL: increased absolute and relative testis weight; decreased sperm production and percentage of seminiferous tubules showing complete spermatogenesis at puberty BMDL: decreased daily sperm production rate in male offspring	NDr	0.68	1.5	Dalsenter et al. (1999)	PR

Table 3. Summary of Potentially Relevant Data for Endosulfan (CASRN 115-29-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Reproductive	2-generation reproductive study, 32/32 (F0), 28/28 (F1b), Crl:COBS CD(SD)BR rat, diet	M: 0, 0.2, 1.1, 5.4 F: 0, 0.25, 2.6, 6.6	Increased heart, liver, and kidney weights in F0 males	1.1	NDr	5.4	Hoechst Aktiengesell-schaft (1984a), as summarized in U.S. EPA (1994a)	PR
Carcinogenicity	Rat (number, strain, study and duration not reported)	NR	No treatment-related increases in tumors	NA	NA	NA	Hoechst Celanese Corporation (1989a), as summarized in U.S. EPA (2010)	PR
	Mouse (number, strain, study and duration not reported)	NR	No treatment-related increases in tumors	NA	NA	NA	Hoechst Celanese Corporation (1988), as summarized in U.S. EPA (2010)	PR
2. Inhalation (mg/m^3)[a]								
Short-term	Rat (number unknown), SPF Wistar rats, nose-only inhalation, 21 exposures over 29 d	0, 0.09, 0.18, 0.36	Decreased BW and leukocyte counts in males; increased creatinine in females	0.18	NDr	0.36	Hoechst Aktiengesell-schaft (1984b), as summarized in U.S. EPA (2010)	PR
Subchronic	ND							
Chronic	ND							

Table 3. Summary of Potentially Relevant Data for Endosulfan (CASRN 115-29-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

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

HEC_{ER} = (mg/m^3) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood gas partition coefficient.

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

[c]Acute = exposure for ≤24 hr (U.S. EPA, 2002).

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

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

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

[g]Table 4 summarizes additional subchronic-duration studies.

[h]Table 5 summarizes additional developmental studies.

BW = body weight; NA = not applicable; ND = no data; NDr = not determinable; NR = not reported; S-D = Sprague-Dawley.

HUMAN STUDIES

Oral Exposures

The effects of oral exposure of humans to endosulfan have been evaluated in five case-control studies, which are described in Appendix B (Bernardelli and Gennari, 1987, as reported in ATSDR, 2000; Blanco-Coronado et al., 1992, as reported in ATSDR, 2000; Lo et al., 1995, as reported in ATSDR, 2000; Shemesh et al., 1988, as reported in ATSDR, 2000; and Pradhan et al., 1997, as reported in ATSDR, 2000).

Short-term Studies

No studies were identified.

Long-term Studies

No studies were identified.

Chronic-duration Studies

No studies were identified.

Inhalation Exposures

The effects of inhalation exposure of humans to endosulfan have been evaluated in three case control studies, (Chugh et al., 1998, as reported in ATSDR, 2000; Singh et al., 1992, as reported in ATSDR, 2000; and Aleksandrowicz, 1979, as reported in ATSDR, 2000), three long-term studies (García-Rodríguez et al., 1996, as reported in ATSDR, 2000; Roberts et al., 2007; and Saiyed et al., 2003), and one chronic-duration study (Aschengrau et al., 1998). Appendix B summarizes these studies.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to endosulfan have been evaluated in 16 subchronic-duration studies (see Table 4), 2 chronic-duration studies (Hoechst Celanese Corporation, 1989a,b), 13 developmental studies (see Table 5), and 1 reproductive study (Hoechst Aktiengesellschaft, 1984a).

Subchronic-duration Studies

A total of 16 assays covering 2 species of animals (rats and mice) have been performed to evaluate the subchronic effects of endosulfan. Subchronic administration of endosulfan to rats and mice resulted in a number of effects with the most sensitive being immunological and neurological. Table 4 provides a summary of the available literature concerning the subchronic effects of endosulfan.

Banerjee and Hussain (1986)

Banerjee and Hussain (1986) conducted a peer-reviewed immunotoxicity study of endosulfan using male Wistar albino rats. The authors did not report compliance with Good Laboratory Practice (GLP) standards. Technical-grade endosulfan (70:30 α-endosulfan:β-endosulfan) was obtained from M/s Hindustan Insecticides Ltd. (India), and purity was not reported. The rats weighed 85−90 g upon receipt and were fed a standard laboratory diet containing 0, 5, 10, or 20 ppm endosulfan for 8−22 weeks. Interim sacrifices were conducted on 20−24 rats/dose group at 8, 12, 18, and 22 weeks. Corresponding average daily doses of 0, 0.5, 0.9, and 1.8 mg/kg-day are estimated based on standard food consumption

and body-weight values (U.S. EPA, 1988). In order to prepare the treatment diet, known quantities of endosulfan were first dissolved in groundnut oil, and then the mixture was manually blended into the standard laboratory diet for at least 30 minutes. Control subjects received standard laboratory diet mixed with the same quantity of groundnut oil. Water was provided ad libitum. All rats were housed 4 per cage with 12 hours of light and 12 hours of darkness. The temperature was maintained by air conditioning at 25°C. Body weights were recorded weekly. Food consumption and clinical observations were recorded daily. A total of 10−12 of the animals in each dose/control group from each exposure duration were immunized subcutaneously with tetanus toxoid in Freund's complete adjuvant 20 days prior to termination of treatment. An equal number from each group remained unimmunized. Blood samples were taken from each animal after termination of treatment by cardiac puncture. Upon sacrifice, peritoneal macrophages were collected from immunized rats only. The liver, spleen, and thymus of immunized rats were removed and weighed. The serum protein content, albumin:globulin ratio, and immunoglobulin (IgM and IgG) concentrations were determined for each rat. The serum antibody titer to tetanus toxoid was estimated for immunized rats using an indirect hemagglutination technique with microtiter plates. A solution of sheep red blood cells mixed with tetanus vaccine was used as antigen-coated cells for antibody titration. Leukocyte-rich plasma and peritoneal macrophages from immunized rats were used for the leukocyte migration inhibition (LMI) and macrophage migration inhibition (MMI) tests. Statistical significance between the treatment and control groups was determined using one-way analysis of variance (ANOVA) ($p < 0.05$ or 0.01).

This study is summarized to evaluate the subchronic effects of endosulfan, and for completeness, the study results that are considered of chronic duration (i.e., 18 and 22 weeks) are included. Banerjee and Hussain (1986) noted that no treatment-related effects were observed for clinical signs, mortality, growth rates, or food intake for any of the exposure durations (data not reported). Relative spleen weight was significantly reduced by 13% relative to controls at 1.8 mg/kg-day in immunized rats following 22 weeks of treatment. No significant effects to spleen weight were observed at any other dose level or exposure duration. Relative thymus weight was unaltered by treatment, and the study authors did not report any findings for liver weight. The serum globulin level was significantly decreased relative to controls (increased albumin:globulin ratio) at 1.8 mg/kg-day in immunized rats following 12, 18, or 22 weeks of treatment and at 0.9 mg/kg-day following 22 weeks of treatment (see Table C.4). No effects on serum globulin, IgG, or IgM levels were observed in unimmunized rats. However, treated immunized rats showed a significantly lower IgG level following immunization when compared with control immunized rats. As shown in Table C.5, this effect was seen at concentrations ≥0.9 mg/kg-day following 12, 18, or 22 weeks of treatment. The increase in IgM level following immunization was unaffected by treatment. The serum antibody titer to tetanus toxoid was significantly decreased in immunized rats compared with controls at concentrations ≥0.9 mg/kg-day following 8, 12, 18, or 22 weeks of treatment. As shown in Table C.6, mean values (expressed as $-\log_2$ antibody titer) at these dose levels (≥0.9 mg/kg-day) were affected in a dose- and time-dependent manner by treatment. Treatment at these dose levels (≥0.9 mg/kg-day) also significantly decreased LMI/MMI responses in immunized rats following 8, 12, 18, or 22 weeks of treatment, indicating a possible effect on cell-mediated immunity (see Tables C.7 and C.8). For the study considered subchronic in duration (8 and 12 weeks), a NOAEL of 0.5 mg/kg-day and a LOAEL of 0.9 mg/kg-day are determined based on statistical significance for decreased serum IgG concentration, decreased antibody titer to tetanus toxoid, and decreased LMI/MMI response in immunized rats. However, the cutoff for consideration of

toxicity for decreased serum IgG concentration is questionable and difficult to interpret. U.S. EPA does not provide specific guidance on developing toxicity assessments for immunologic endpoints, and there is no clear guidance on whether the statistically significant change in the serum IgG concentration should be considered biologically significant (IPCS/WHO, 1996, 2012), especially since other standard immunologic tests were not performed. Consultation with U.S. EPA scientists that have expertise in this area suggests that a 30% change could be considered biologically significant (personal communication), which was not attained in the Banerjee and Hussain (1986) study. Thus, decreased serum IgG concentration was not considered as a plausible POD for deriving a toxicity value.

Table 4. Summary of Oral Subchronic-Duration Studies for Endosulfan (CASRN 115-29-7)

Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry,[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	LOAEL[a,b]	Reference
Rat					
10−12/0, albino Wistar rat, diet, 8, 12, 18, or 22 wk; immunized with tetanus toxoid 20 d prior to termination of exposure or unimmunized; clinical signs and food consumption monitored daily (data not reported); BWs recorded weekly (data not reported); liver (data not reported), spleen, and thymus weighed; serum globulin level, IgM and IgG, and serum antibody titer against tetanus toxoid measured; LMI and MMI factors measured	0, 0.5, 0.9, or 1.8[d] (0, 5, 10, or 20 ppm in diet) (purity not reported, technical grade used)	Decreased serum antibody titer to tetanus toxoid and depressed LMI and MMI factors at ≥0.9 mg/kg-d after 8 or 12 wk; decreased serum IgG concentration in immunized rats at ≥0.9 mg/kg-d after 12 wk; decreased globulin level (increased albumin:globulin ratio) in immunized rats at 1.8 mg/kg-d after 12 wk (18- and 22-wk exposures considered chronic in duration therefore results are not reported here) LOAEL: decreased serum antibody titer and IgG concentration; decreased LMI and MMI factors	0.5	0.9	Banerjee and Hussain (1986)
25/25, CD S-D rat, diet, 13 wk; 5/5 kept in a 4-wk recovery group after treatment ended; ophthalmoscopic exams before treatment and at Wk 13 in control and high-dose rats; neurological examinations (locomotor reflexes) before treatment and at Wk 2, 6, and 13 in 10/10 from control and high-dose rats; all animals examined for grip reflex and ataxia at Wk 13; blood sampled from 10/10 at each dose level for hematological and clinical chemistry examinations at Wk 0, 6, and 12/13 (standard battery of tests, not specified); blood and plasma cholinesterase estimations at Wk 5 and 12 in 10/10 at each dose level; urine collected Wk 4 and 13 for standard urinalysis (specific tests not reported); organ weights and histopathological examination upon sacrifice (specific organs not reported)	M: 0, 0.64, 1.92, 3.85, or 23.41[g] F: 0, 0.75, 2.26, 4.59, or 27.17[g] (purity 97.2%)	Increased hair loss in females at ≥4.59 mg/kg-d (reversed during recovery); decreased water consumption (Wk 5) at ≥1.92 mg/kg-d in males and 27.17 mg/kg-d in females; decreased red blood cell count in males at ≥1.92 mg/kg-d after 6 wk and ≥3.85 mg/kg-d after 13 wk, and in females at ≥4.59 mg/kg-d after 6 wk and at 27.17 mg/kg-d after 13 wk; increased relative kidney weight in males at ≥3.85 mg/kg-d (reversed after recovery at 3.85 mg/kg-d but not at 23.41 mg/kg-d) and in females at 27.17 mg/kg-d; increased absolute liver weight (both sexes), decreased plasma and RBC cholinesterase activities and dark urine with increased ketones (females only), and increased epididymal weight at the high-dose level; increased brain cholinesterase activity in females at ≥4.59 mg/kg-d; granular/clumped pigmentation in kidney cells in males at ≥3.85 mg/kg-d and in females at 27.1 mg/kg-d (no cell death associated with these findings, decreases in pigmentation were seen during recovery); brown pigment in scattered hepatocytes (males only) and enlargement of hepatocytes (females only) at the high-dose level LOAEL: hematological effects after 6 wk (males)	0.64	1.92	Hoechst Aktiengesellschaft (1985a), as summarized in U.S. EPA (1994a), Cal/EPA (2008), IPCS (1989), and McGregor (1998)

Table 4. Summary of Oral Subchronic-Duration Studies for Endosulfan (CASRN 115-29-7)

Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry,[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	LOAEL[a,b]	Reference
11−16/16−26, albino rat, gavage, 30 d; terminal BWs and blood samples (biochemical analysis: GOT, GPT, alkaline phosphatase, protein, blood sugar; haematological analysis: RBC, WBC, Hb, DLC counts); weights and microscopic exam of liver, kidney, brain, spleen, testes, epididymis, ovary, uterus, vagina, and cervix	M: 0, 0.75, 2.5, or 5.0[c] F: 0, 0.25, 0.75, or 1.5[c] (purity 98%)	Clinical signs at highest dose levels in males and females included hyperexcitation, tremor, dyspnea, salivation during the first 3−4 d of dosing; increased relative liver, kidney, and testes weight in males at 5.0 mg/kg-d (data at lower doses not reported); decreased relative kidney weight in females at 1.5 mg/kg-d (data at lower doses not reported); increased liver and serum alkaline phosphatase, neutrophil, and RBC counts in males at 5.0 mg/kg-d (data at lower doses not reported); increased liver alkaline phosphatase and decreased serum alkaline phosphatase in females at 1.5 mg/kg-d; increased liver and serum protein in females at 1.5 mg/kg-d (data at lower doses not reported) LOAEL: biochemical changes and decreased relative kidney weight in females	0.75	1.5	Dikshith et al. (1984)
0/8, Wistar rat, gavage, 30 d; all animals were ovariectomized before treatment began; positive control group received 1 µg estradiol diproprionate intraperitoneally; treatment groups received either endosulfan alone or endosulfan plus 1 µg estradiol diproprionate daily; negative control group received vehicle alone; terminal BWs recorded; uterus, cervix, vagina, and pituitary weighed; microscopic examination of pieces of uterus and vagina and whole cervix; glycogen content of uterus, cervix, and vagina measured	0, 1.5 with or without 1 µg estradiol diproprionate[c] (purity not reported)	No effects following treatment with endosulfan alone; treatment with endosulfan and estradiol dipropionate caused increased relative uterus, cervix, vagina, and pituitary weights, and increased glycogen levels in the uterus, cervix, and vagina	1.5	NDr	Raizada et al. (1991)

Table 4. Summary of Oral Subchronic-Duration Studies for Endosulfan (CASRN 115-29-7)

Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry,[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	LOAEL[a,b]	Reference
16/0, albino Wistar rat, diet, 6 wk; each rat immunized with tetanus toxoid 25 d after beginning exposure; clinical signs and food consumption monitored daily; BWs recorded weekly (only final BWs reported); liver, spleen, and thymus weighed; serum globulin fractions, IgM and IgG concentrations, and serum antibody titer against tetanus toxoid measured; leukocyte and macrophage migration inhibition (LMI and MMI) factors measured	0, 1.8, 5.5, 9.3[d] (0, 10, 30, or 50 ppm in diet) (purity 98%)	Decreased serum antibody titer to tetanus toxoid and decreased LMI and MMI factors at ≥5.5 mg/kg-d; increased relative liver weight at 9.3 mg/kg-d; decreased serum IgM, IgG and γ-globulin levels at 9.3 mg/kg-d LOAEL: decreased serum antibody titer to tetanus toxoid and decreased LMI and MMI factors	1.8	5.5	Banerjee and Hussain (1987)
12/12, Wistar rat, diet, 13 wk; clinical observations and BWs recorded (interval not reported); neurotoxicity examined with functional observational battery (FOB), motor activity, locomotor activity, measured grip strength, foot splay, and neuropathology examination; plasma cholinesterase activity measured; histopathological examination of 6 animals/dose group (specific organs not reported)	M: 0, 2.11, 13.7, or 37.2[f] F: 0, 2.88, 16.6, or 45.5[f] (purity 98.1% and 96.5%)	Convulsions/death observed in one female and red nasal stain observed in 3 females at 45.5 mg/kg-d; decreased BWs on Day 7 in females at ≥16.6 mg/kg-d possibly due to palpability; decreased food consumption at Wk 1 in females at ≥16.6 mg/kg-d and males at 37.2 mg/kg-d; decreased plasma cholinesterase activity in females at ≥16.6 mg/kg-d; increased absolute and relative kidney and liver weights in females at ≥16.6 mg/kg-d and in males at ≥13.7 mg/kg-d LOAEL: increased absolute and relative kidney and liver weights in males	2.11	13.7	Sheets et al. (2004), as summarized in Cal/EPA (2008) and U.S. EPA (2010)

Table 4. Summary of Oral Subchronic-Duration Studies for Endosulfan (CASRN 115-29-7)

Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry,[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	LOAEL[a,b]	Reference
10−12/0, Wistar rat, gavage, 7 d/wk, 90 d; food consumption and BWs recorded every 15 d (n = 12); spontaneous motor activity and muscle coordination measured every 15 d (n = 10 for each); learning and memory tested using pole-climbing test 24 hr after last treatment (n = 24); 5-HT (5-hydroxytryptamine) concentration in the cerebrum and midbrain, brain protein concentration, and acetylcholinesterase activity measured (n = 10 each)	0 or 2[c] (purity 95%)	Increased spontaneous motor activity on Days 75 and 90; learning and memory deficits (manifested as decreased number responding and increased response time); increased 5-HT concentration in the cerebrum and midbrain LOAEL: increased motor activity; memory and learning deficits; and increased 5-HT levels in the cerebrum and midbrain	NDr	2	Paul et al. (1994)
10/10, Wistar rat, gavage, 90 d; BWs and behavior recorded (interval not reported); motor coordination measured every 15 d using rota-rod apparatus; unconditioned and conditioned avoidance test (pole-climbing) performed at the end of treatment	0 or 2[c] (purity 95%)	Decreased number of animals responding to simultaneous unconditioned and conditioned stimuli (impaired avoidance response to shock) in both sexes at 2 mg/kg-d LOAEL: impaired avoidance response to shock	NDr	2	Paul et al. (1992)
15−16/0, Long-Evans hooded rat, gavage, 3 d/wk for 7 wk, 5 mg/kg-d for 20 d or 10 mg/kg-d 3 d/wk to total 10 dosing days then challenged 14−16 d later with matching dose; detailed behavioral observations 30 min and 1 hr following the 1st, 10th, 21st, and challenge doses; electrical kindling performed 1−2 wk after challenge dose to measure threshold for inducing an after-discharge (AD), duration of development of an AD, and rate of kindling	0, 2.1, or 4.3[e] (purity not reported)	Enhanced seizure score (increased number of animals expressing myoclonic jerks) after challenge dose as compared with after 1st dose at both dose levels; decreased kindling rate (number of stimulation sessions required to produce the first stage 5 seizure) as compared with control at both dose levels LOAEL: increased incidence of myoclonic jerks observed following repeated doses; decreased kindling rate	NDr	2.1	Gilbert (1992)

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Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry,[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	LOAEL[a,b]	Reference
10/10, Wistar rat, diet, 30 d; mortality and initial and final BWs recorded; liver weighed; liver and serum concentrations of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, acetylcholinesterase, and alkaline phosphatase determined; spontaneous motor activity and motor coordination tested; additional group of 10/10 at low dose tested for learning and memory processes	0, 3, or 6[c] (purity 95%)	Increased relative liver weight in both sexes at ≥3 mg/kg-d (more markedly in females); increased motor activity in both sexes at ≥3 mg/kg-d (more markedly in males); increased liver and serum glutamic oxaloacetic transaminase and glutamic pyruvic transaminase in males at ≥3 mg/kg-d (these enzymes increased in females in liver samples at 6 mg/kg-d); increased liver and serum alkaline phosphatase in both sexes at ≥3 mg/kg-d; learning and memory deficits at ≥3 mg/kg-d in both sexes LOAEL: increased relative liver weight in both sexes; increased activities of liver enzymes indicative of liver injury; increased motor activity; memory and learning deficits	NDr	3	Paul et al. (1995)
6/0, Wistar rat, gavage, 7 d/wk, 30 d; additional 6/0 treated for 30 d followed by 7-d recovery period; BWs recorded (interval not reported); testes removed, weighed, and homogenized for analysis; measured testicular and plasma testosterone levels, plasma gonadotrophins (FSH and LH) levels, and activities of testicular enzymes: microsomal mixed function oxidases (MFO), steroidogenic enzymes, and glutathione-S-transferase	0, 7.5, 10, or 10 (30 d plus 7 d recovery)[c] (purity not reported, technical grade used)	Decreased plasma testosterone, FSH, LH, and testicular testosterone at ≥7.5 mg/kg-d; decreased activities of testicular steroidogenic enzymes, MFO system, and glutathione-S-transferase at ≥7.5 mg/kg-d; decreased testicular testosterone at 10 mg/kg following 7-d recovery period LOAEL: decreased plasma and testicular testosterone levels; decreased plasma FSH and LH levels; decreased activities of testicular enzymes	NDr	7.5	Singh and Pandey (1990)

Table 4. Summary of Oral Subchronic-Duration Studies for Endosulfan (CASRN 115-29-7)

Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry,[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	LOAEL[a,b]	Reference
20/0, SPF Wistar rat, diet, 30 d, with 4-wk recovery period in half of animals; rats monitored daily for behavior, appearance, and general health condition (including neurological signs, ophthalmologic changes, dental health); BWs and food consumption recorded weekly; gross examination at necropsy; liver, kidney, and brain weighed; histological examination of left kidney, liver, and brain using light or electron microscopy; residues of endosulfan measured in liver, kidney, and brain tissue	0, 34, or 67.8[f] (purity 97.9%)	Increased absolute and relative liver weight at ≥34 mg/kg-d (data not reported; effect not observed after recovery); increased absolute and relative kidney and brain weights at 67.8 mg/kg-d (data not reported; effect not observed after recovery); darkened kidneys, granular pigmentation and proliferation, and enlargement of lysosomes in renal proximal tubule cells at ≥34 mg/kg-d (data not reported; effect decreased after recovery) LOAEL: increased relative liver weight; histological changes in renal proximal tubule cells	NDr	34	Leist and Mayer (1987), as summarized in U.S. EPA (1994a), IPCS (1989) and McGregor (1998)
Unreported number (19 in high-dose group)/0, albino rat, gavage, 60 d; BWs recorded daily; liver, brain, spleen, kidney, lung, heart, testes, epididymis, ventral prostate, and seminal vesicles collected and weighed	0, 2.5, or 7.5[c] (purity not reported)	Mortality observed in all groups (2/unknown number in control group, 2/unknown number in mid-dose group, 8/19 in high-dose group); hyperactivity observed at 7.5 mg/kg-d; clonic tremors/convulsions observed in animals that died at 7.5 mg/kg-d; increased liver and lung weights were reported by the study authors; however, data not reported and it is unclear at what dose level the increased organ weights were seen LOAEL (frank-effect level [FEL]): mortality	NDr	2.5 (FEL)	Ansari et al. (1984)
Unreported number/0, albino rat, gavage, 30 d; BWs recorded (interval not reported); organs weighed (specific organs not reported); blood chemistry examined (specific tests not reported); histopathological examination (specific organs/tissues not reported)	0 or 11[f] (purity not reported)	Mortality observed at 11 mg/kg-d (3 animals, cause of death not reported) LOAEL (FEL): mortality	NDr	11 (FEL)	Nath et al. (1978), as summarized in McGregor (1998)

Table 4. Summary of Oral Subchronic-Duration Studies for Endosulfan (CASRN 115-29-7)

Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry,[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	LOAEL[a,b]	Reference
Mouse					
20/20, CD-1 mouse, diet, 13 wk; clinical signs, food consumption, and BWs recorded (interval not reported); hematology and clinical chemistry parameters examined (specific tests not reported); microscopic examination upon sacrifice (specific organs/tissues not reported)	M: 0, 0.24, 0.74, 2.13, or 7.3[f] F: 0, 0.27, 0.8, 2.39, or 7.52[f] (purity 97.2%)	Increased mortality in both sexes at the high dose (data not reported); decreased glucose levels in females at ≥0.8 mg/kg-d (data not reported); increased hemoglobin levels and decreased mean corpuscular hemoglobin concentration in females at all dose levels (data not reported); reduced neutrophil count and spleen weight in males at 7.3 mg/kg-d (data not reported); increased serum lipid concentration in females at 7.52 mg/kg-d (data not reported) LOAEL (FEL): mortality	2.13	7.3 (FEL)	Hoechst Aktiengesellschaft (1985b), as summarized in U.S. EPA (1994a), ATSDR (2000) and McGregor (1998)
10/10, Hoe:NMRKf (SPF 71) mouse, diet, 6 wk; clinical signs, food consumption, and BWs recorded (interval not reported); organs weighed and macroscopically examined (specific organs not reported); eyes microscopically examined upon sacrifice	M: 0 or 3.7[f] F: 0 or 4.6[f] (purity not reported)	Mortality observed in females at 4.6 mg/kg-d (2/10; cause of death unable to be determined); increased absolute and relative liver weights in females (data not reported) LOAEL (FEL): mortality in females	NDr	4.6 (FEL)	Donaubauer et al. (1985) Hoechst Aktiengesellschaft (1985b), as summarized in McGregor (1998) and ATSDR (2000)

[a]Dosimetry: NOAEL and LOAEL values are adjusted daily doses in mg/kg-d. No useful data were available to perform BMD modeling. Values are based on a 7:3 mixture of α-endosulfan and β-endosulfan unless otherwise noted.
[b]DU = data unsuitable; NA = not applicable; NV = not available; ND = no data; NDr = not determinable; NI = not identified; NP = not provided; NR = not reported; NR/Dr = not reported but determined from data; NS = not selected.
[c]Daily doses provided by the study author(s).
[d]Daily doses were calculated using the following equation: $Dose_{adj}$ = concentration in food (ppm or mg/kg) × Food Consumption per Day (kg/d) × (1 ÷ BW [kg]) × (Days Dosed ÷ Total Days).
[e]Doses provided by the study author(s) were adjusted for continuous exposure using the following equation: $Dose_{adj}$ = dose (mg/kg) × (Days Dosed ÷ Total Days)
[f]Daily doses as reported in the secondary source(s).
[g]Achieved daily doses as reported in Cal/EPA (2008).

BW = body weight; S-D = Sprague-Dawley.

Chronic-duration Studies

U.S. EPA (1994a) reviewed and provided study summaries for chronic-duration studies in rats and beagle dogs (Hoechst Celanese Corporation, 1989a,b). Table 3 provides the information for these studies. In addition, U.S. EPA (2010) evaluated the carcinogenic potential of endosulfan. No evidence of carcinogenicity was found in rats or mice exposed for 2 years to endosulfan via the oral route (Hoechst Celanese Corporation, 1988; 1989a, as reported by U.S. EPA, 2010). Details of the studies were not provided. U.S. EPA (2010) concluded that the doses were adequate in both studies and that endosulfan is classified as "*Not Likely to be Carcinogenic to Humans.*" Endosulfan sulfate is also classified as "*Not Likely to be Carcinogenic to Humans.*

Developmental and Reproductive Studies

A total of 14 studies have been performed to evaluate the developmental and reproductive effects of endosulfan in rats and rabbits. A number of effects on the male developmental system were reported including decreases in sperm production, spermatogenesis, and testis weight, and increases in morphological abnormalities in sperm. Table 5 provides a summary of the available literature concerning the developmental effects of endosulfan. In addition, the selected principal study for the screening subchronic p-RfD is summarized below. U.S. EPA (1994a) also reviewed and provided a summary for a two-generation reproductive study in rats (Hoechst Aktiengesellschaft, 1984a; see Table 3).

Gilmore et al. (2006) is selected as the principal study for deriving the subchronic p-RfD. In a developmental neurotoxicity study, Gilmore et al. (2006) administered doses of 0, 50, 150, or 400 ppm of endosulfan (purity of 99.1%; dissolved in acetone) via diet to groups of 30 female Wistar Cr:WI (Han) rats (Charles River Laboratories, Raleigh, NC) on Gestation Day (GD) 6 though Postnatal Day (PND) 21. Because this study contained confidential business information (CBI), the original report was not available for review. However, a U.S. EPA Office of Pesticide Program (OPP) Data Evaluation Record (DER) that provided the detailed results data was available. In addition, the study was evaluated by U.S. EPA. U.S. EPA (2010). However, there is no evidence of a formal external review which is a requirement for development of a provisional toxicity value. Therefore, as explained later in this document, a screening level toxicity value is developed.

The DER provided average daily doses of 0, 3.74, 10.8, or 29.8 mg/kg-day for the 0-, 50-, 150-, and 400-ppm groups, respectively; it is unclear if the study authors or DER reviewer converted the doses. Males were at least 15 weeks old at study initiation; it is unclear what the average male rat weighed. Females were at least 12 weeks old and weighed 159.2−218.9 g at study initiation. All animals were given 7 days to acclimate to test room conditions before treatment initiation. Dams were housed individually in plastic cages with bedding during gestation and lactation. The room was maintained at a temperature of 18−26ºC, with 30−70% humidity, and a 12-hour light/dark cycle. Animals were allowed food (Purina Mills Rodent Diet 5002) and water (Kansas City municipal water) ad libitum. Gilmore et al. (2006) is an acceptable reproductive/developmental study for development of toxicity values.

Parental animals were observed once daily in their cages for clinical signs of toxicity, mortality, morbidity, and behavioral changes. Dams were examined in more detail once daily from GD 6 through Lactational Day (LD) 21. Body weight and food consumption were recorded weekly during gestation and lactation. A functional observational battery (FOB) was completed

on GDs 13 and 20. Another set of 10 dams/dietary level was also examined using a FOB on LDs 11 and 21. Each dam was examined for delivery beginning on GD 20; the day of delivery was designated LD 0 for each dam and PND 0 for pups. Litters that contained fewer than three pups at delivery or less than seven pups by PND 4 were sacrificed and not necropsied. Litters were culled on PND 4 to yield four males and four females per litter (when possible).

After parturition, authors measured anogenital distance (AGD) and weight of individual pups. On Days 0, 4, 11, 17, and 21, authors recorded the number of live pups, sex, and individual weights. Pups were examined daily during lactation for signs of mortality and morbidity. Detailed observations for clinical signs of toxicity and body weights were recorded daily before weaning and once a week after weaning. On PND 21, authors examined all pups for pupil constriction. Beginning on PND 38 for males and PND 29 for females, authors examined animals daily and recorded the first observation of vaginal patency or balanopreputial separation. After PND 21, authors examined all animals twice daily for mortality and once daily for clinical signs. Weights were recorded once weekly. The authors did not record food consumption after weaning. The authors calculated the mating, live birth, and lactation indices.

When animals were approximately 50−60 days old, authors performed ophthalmic examinations (minimum of 10/sex/dose representing at least 20 litters/dose) of animals selected for perfusion at study termination. The pupillary reflex was tested, and the conjunctiva, cornea, lens, vitreous humor, retina, choroid, and optic disc were examined.

Males were sacrificed immediately after mating, and dams were sacrificed on LD 21 (after weaning). Routine necropsies were not performed on F0 generation males or females. Animals in the F1 generation were sacrificed on either PND 21 or 75 ± 5 days and given a gross necropsy that involved examination of all organs, body cavities, cut surfaces, external orifices and surfaces, and gross abnormalities. Lesions of the neural tissues or skeletal muscle were examined microscopically. All animals found dead also underwent necropsy. Animals selected for perfusion on PND 21 were anesthetized and then perfused via the left ventricle with a sodium nitrite flush followed by in situ fixation. The authors collected the brain with olfactory bulbs on PND 21 and collected the brain, spinal cord, both eyes (with optic nerves), selected peripheral nerves (sciatic, tibial, and sural), the gasserian ganglion, gastrocnemius muscle, and both forelimbs at study termination. Brain tissues from perfused animals and gross lesions from all animals were examined microscopically.

The authors evaluated continuous data for equality of variance using Bartlett's test. An ANOVA was completed for group means with equal variances. If the ANOVA was significant, the data were evaluated using a Dunnett's test. Nonparametric data were analyzed using the Kruskal-Wallis ANOVA followed by the Mann-Whitney U test. FOB tests were analyzed using ANOVA and Dunnett's test (continuous data) or General Linear Modeling and Categorical Modeling (CATMOD) procedures followed by Dunnett's test and an Analysis of Contrasts (categorical data). Pathology data were analyzed using a number of statistical tests, including Bartlett's test for homogeneity with ANOVA, the Kruskal-Wallis test (organ weight data and gross brain measurements), ANOVA, and/or *t*-tests (microscopic brain measurements).

The authors reported that statistically significant maternal clinical observations (hair loss, rearing) could not be definitively attributed to treatment with the test substance due to a lack of a dose-response relationship. Furthermore, the observations did not always occur in the same

dams. There were no treatment-related effects in FOB results. Table C.9 provides data on maternal body weight and food consumption. Dams experienced statistically significant, dose-dependent decreases in body weight throughout gestation. Gestational food consumption was also decreased in a statistically significant, dose-dependent manner. Food efficiency was nominally decreased in the mid- and high-dose groups on Days 6−13, but efficiency in these groups was comparable to or increased when compared with control values on GDs 13−20. Maternal body weight was significantly decreased on LDs 0, 4, and 7 in the mid- and high-dose groups. However, maternal food consumption was not significantly altered at any point during lactation.

Table C.10 provides pup body weights. Female pup weight was significantly decreased at the highest dose on PND 4 (before culling but not after). On PNDs 11, 17, and 21, statistically significant ($p < 0.01$), dose-dependent decreases occurred in both male and female pup weights in all litters from dams treated with endosulfan. Postweaning pup weight was significantly reduced in mid- and high-dose males from PNDs 28−70 and in high-dose females from PNDs 28−49. The authors also noted a significant decrease in days to sexual maturation (preputial separation) in male pups of the mid- and high-dose groups (see Table C.11). It is unclear whether the pup weight decrements at the low dose on PND 11 (9% relative to controls) and PND 17 (7% relative to controls) were due to unpalatable endosulfan in the dam's milk, a reduced milk supply, or a toxic effect of endosulfan in the milk. Either approach would yield an appropriate point of departure (POD) for derivation of a toxicity value (i.e., unpalatability of the dam's milk would be a biologically relevant response to dosing the dam, as would reduced milk supply or some toxicity to the pups associated with the milk itself). A significant decrease in vaginal opening in females was observed at 3.74 and 10.8 mg/kg-day but not at 29.8 mg/kg-day (see Table C.11). Rearing in high-dose males at PND 45 was increased in a dose-dependent manner (significant at the high dose only), but the authors did not consider this effect to be treatment related. Based on the dam and pup weight decreases, a developmental and maternal LOAEL of 3.74 mg/kg-day is identified. A NOAEL cannot be identified because the lowest dose was a LOAEL.

Table 5. Summary of Developmental Studies for Endosulfan (CASRN 115-29-7)

Study Type, Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry (mg/kg-d),[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	BMDL	LOAEL[a,b]	Reference
Rat						
Developmental, 0/30, Wistar Crl:WI (Han) rat, diet, dams and offspring provided treatment diet ad libitum on GD 6−PND 21 (weaning); dams and pups sacrificed on PND 21 or PND 75 ± 5; daily clinical observations and weekly recordings of maternal BW and food consumption during dosing; FOB of dams on GDs 13, 20 and LDs 11, 21; selected offspring from each group evaluated for BW, food consumption, onset of sexual maturation (balanopreputial separation/vaginal patency), FOB, motor activity, auditory startle habituation, learning and memory, ophthalmic examination, brain weight and neuropathology, and sperm analysis (testes and epididymal sperm)	0, 3.74, 10.8, or 29.8[c] (purity 99.1%)	Decreased maternal BW from GD 13−LD 7 at 10.8 mg/kg-d and decreased food consumption for GDs 6−13 at ≥3.74 mg/kg-d and for GDs 13−20 at ≥10.8 mg/kg-d Litter-based decreased pup weight at ≥3.74 mg/kg-d on PND 11 (both sexes) and PND 17 (males only); decreased pup weight on PNDs 35−70 in males at ≥10.8 mg/kg-d and in females on PNDs 28−49 at 29.8 mg/kg-d; delayed sexual development (day of preputial separation) in males at ≥10.8 mg/kg-d; increased rearing in females at 10.8 mg/kg-d on PND 21 and in males at 29.8 mg/kg-d on PND 45; decreased perfused fixed brain weight in PND-21 males at 29.8 mg/kg-d (relative fixed brain weight unaffected); decreased hippocampal gyrus (10% smaller than control) in females at 29.8 mg/kg-d Developmental LOAEL: decreased pup weight at PNDs 11 and 17 BMDL: Decreased pup BW in females at PND 11	Maternal: NDr Developmental: NDr	0.29	Maternal: 3.74 Developmental: 3.74	Gilmore et al. (2006)

Table 5. Summary of Developmental Studies for Endosulfan (CASRN 115-29-7)

Study Type, Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry (mg/kg-d),[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	BMDL	LOAEL[a,b]	Reference
Developmental, 0/24, Wistar rat, gavage, dams dosed GD 15−PND 21; maternal BWs during dosing and pup BWs during lactation recorded daily; litter size and number of viable offspring assessed; male offspring (1−2/litter; 15/group): investigated for age of testes descent and preputial separation, sacrificed on PND 65 (puberty) or PND 140 (adulthood) and investigated for changes in absolute and relative testes, epididymis, seminal vesicle, and ventral prostate weights; sperm and spermatid counts; daily sperm production rate; serum testosterone level; and histology of testes; different male offspring (15/group) mated with control virgin females on PND 120: maternal and fetal BW and pregnancy outcomes analyzed (mating/pregnancy/fertility rates)	0, 1.5, or 3.0[c] (purity 97%)	Reduced maternal BW on GDs 16, 17, and 18 at 3.0 mg/kg-d; increased absolute and relative testicular weights and decreased daily sperm production rate in male offspring at ≥1.5 mg/kg-d at puberty and 3.0 mg/kg-d at adulthood; decreased percentage of seminiferous tubules showing complete spermatogenesis at ≥1.5 mg/kg-d at puberty Maternal LOAEL: reduced maternal BW during gestation Developmental LOAEL: increased relative testis weight; decreased sperm production and percentage of seminiferous tubules showing complete spermatogenesis at puberty BMDL: Decreased daily sperm production rate in male offspring	Maternal: 1.5 Developmental: NDr	0.68	Maternal: 3.0 Developmental: 1.5	Dalsenter et al. (1999)

Table 5. Summary of Developmental Studies for Endosulfan (CASRN 115-29-7)

Study Type, Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry (mg/kg-d),[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	BMDL	LOAEL[a,b]	Reference
Developmental, 0/20−24, Wistar rat, gavage, dams dosed on GDs 7−16; clinical observations and BWs recorded (frequency not reported); sex ratio and reproductive parameters examined (specific parameters not reported); fetuses examined for skeletal and other abnormalities (further details not reported)	0, 0.66, 2, or 6[c] (purity 97.3%)	Maternal: mortality (4/20−24) and clinical signs of toxicity (convulsions, hypersalivation) observed at 6 mg/kg-d; Decreased maternal BW (data not reported) Developmental: increased incidence of fragmented thoracic vertebral centra at 6 mg/kg-d (data not reported) Maternal LOAEL (FEL): mortality Developmental LOAEL: not determinable due to effects seen only in the presence of mortality	Maternal: 2 Developmental: 2	NDr	Maternal: 6 (FEL) Developmental: NDr	Albrecht and Baeder (1993), as summarized in McGregor (1998)
Developmental, 0/10, Wistar rat, gavage, dams dosed throughout entire gestation period and through PND 28; maternal BWs recorded (frequency not reported); offspring examined for litter size, sex ratio, birth weight, and crown-to-rump length; offspring weights recorded during postnatal period (frequency not reported); male offspring examined for anogenital distance (PNDs 1, 28 and 90), cryptorchidism, hypospadia, incidence of apoptosis of testis germ cells, testis histology, daily sperm production, epididymal sperm count and morphology, and fertility	0, 0.5, 1.0, or 2.5[c] (purity not reported)	Maternal: mortality observed at 2.5 mg/kg-d (4/10) Developmental: no significant effects observed with any of the parameters examined Maternal LOAEL (FEL): mortality Developmental LOAEL: NDr	Maternal: 1.0 Developmental: 2.5	NDr	Maternal: 2.5 (FEL) Developmental: NDr	Zhu et al. (2000) (abstract only) and as summarized in Cal/EPA (2008)

Table 5. Summary of Developmental Studies for Endosulfan (CASRN 115-29-7)

Study Type, Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry (mg/kg-d),[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	BMDL	LOAEL[a,b]	Reference
Developmental, 0/number of females not reported, Druckrey rat, gavage, dams dosed GD 12 through parturition; offspring sexed and size and weight of litters were recorded; male offspring were fostered to untreated females that had given birth the prior day; male offspring monitored for dietary intake, BW, clinical signs and behavior (intervals not reported), and sacrificed at 100 d of age; epididymis, testes, seminal vesicles, prostate glands removed and weighed; sperm and spermatid counts and testicular marker enzyme levels (LDH, SDH, GGT, G6PDH) analyzed	0, 1.0, or 2.0[c] (purity 95.32%)	Decreased absolute and relative weights of testes, epididymis, and seminal vesicle at ≥1.0 mg/kg-d; decreased sperm count (epididymis) and spermatid count (testis) at ≥1.0 mg/kg-d; increased LDH activity and decreased SDH activity at ≥1.0 mg/kg-d Developmental LOAEL: decreased relative testes, epididymis, and seminal vesicle weights; decreased sperm and spermatid counts; increased testicular LDH activity; decreased testicular SDH activity	Developmental: NDr	NDr	Developmental: 1.0	Sinha et al. (2001)
Male developmental, 15/0, Druckrey rat, gavage, 5 d/wk, 70 d; BW recorded twice weekly; testes and epididymis weighed and analyzed; activities of testicular enzymes (marker enzymes of spermatogenesis: LDH, SDH, GGT, G6PDH) measured; cauda epididymis sperm count and morphology analyzed; intratesticular spermatid count analyzed	0, 1.8, 3.6, or 7.1[d] (purity 95.32%)	Increased testicular LDH, SDH, GGT, and G6PDH activities at ≥1.8 mg/kg-d; decreased cauda epididymis sperm counts at ≥1.8 mg/kg-d; decreased testis spermatid counts and sperm production rate at ≥3.6 mg/kg-d; increased altered sperm morphology (% sperm abnormality) at ≥3.6 mg/kg-d LOAEL: increased activities of testicular LDH, SDH, GGT, and G6PDH; decreased sperm counts in cauda epididymis	NDr	NDr	1.8	Sinha et al. (1995)

Table 5. Summary of Developmental Studies for Endosulfan (CASRN 115-29-7)

Study Type, Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry (mg/kg-d),[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	BMDL	LOAEL[a,b]	Reference
Developmental, 5/0, weaned (3-wk old) Druckrey rat, gavage, 5 d/wk, 69 d; BWs recorded twice weekly; upon sacrifice at 90 d of age, testes and epididymis removed and weighed; sperm and spermatid counts, sperm morphology, and testicular marker enzyme levels (LDH, SDH, GGT, G6PDH) analyzed	0, 1.8, 3.6, or 7.1[d] (purity 95.32%)	Decreased sperm count (epididymis), decreased spermatid count (testis), and increased percentage of sperm morphological abnormalities at ≥1.8 mg/kg-d; increased LDH, GGT, and G6PDH activity and decreased SDH activity at ≥1.8 mg/kg-d Developmental LOAEL: decreased sperm and spermatid counts; increased morphological abnormalities in sperm; increased LDH, GGT, and G6PDH activity; decreased SDH activity	Developmental: NDr	NDr	Developmental: 1.8	Sinha et al. (1997)

Table 5. Summary of Developmental Studies for Endosulfan (CASRN 115-29-7)

Study Type, Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry (mg/kg-d),[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	BMDL	LOAEL[a,b]	Reference
Developmental, 0/25, CD S-D rat, gavage, dams dosed GDs 6−19; 10 additional animals were added to the high-dose group due to mortality, 5 additional animals were added to the control group; maternal BWs recorded on GDs 0 and 20 (additional intervals not reported); gravid uterine weight, corrected BW, corrected BW gain, percentage live fetuses, number of resorptions per litter, percentage resorbed fetuses, and mean fetal weight and length assessed; fetuses examined for developmental abnormalities (full range of abnormalities not reported)	0, 0.66, 2.0, or 6.0[e] (purity 97.3%)	Maternal: mortality (7/25) and clinical signs of toxicity (face rubbing [20/35], brown exudates [4/35], rough coat [5/35], flaccidity [8/35], hyperactivity [11/35]) observed at 6.0 mg/kg-d; face rubbing (6/25) observed at 2.0 mg/kg-d; reduced maternal BW (GD 20) at 6.0 mg/kg-d Developmental: decreased mean fetal BW and crown-rump length at 6.0 mg/kg-d; reduction in percentage of live fetuses and an increase in the number of resorbed fetuses at 2.0 mg/kg-d only; increase in misaligned sternebrae at ≥0.66 mg/kg-d; increased incidence of litters with extra ribs and poorly ossified and unossified sternebrae at 6.0 mg/kg-d Maternal and offspring LOAEL: precluded due to replacement of animals during or after the study, which made interpretation difficult	Maternal: NDr Developmental: NDr	NDr	Maternal: NDr Developmental: NDr	FMC (1980), as summarized in Cal/EPA (2008), U.S. EPA (1994a), ATSDR (2000) and McGregor (1998)

Table 5. Summary of Developmental Studies for Endosulfan (CASRN 115-29-7)

Study Type, Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry (mg/kg-d),[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	BMDL	LOAEL[a,b]	Reference
Developmental, 0/6, CD S-D rat, gavage, dams dosed GDs 6−19; maternal BWs and clinical signs of toxicity recorded (intervals not reported); details of offspring parameters not reported	0, 1.25, 2.5, 5.0, 10, 20, or 40[e] (purity not reported)	Maternal: mortality observed at ≥10 mg/kg-d; clinical signs (salivation, piloerection, hyperactivity, head-rubbing, hostility, spasticity, tremors, and convulsions) observed at ≥2.5 mg/kg-d; decreased BW gain at ≥1.25 mg/kg-d (data not reported) Developmental: results not reported Maternal LOAEL: decreased BW gain	Maternal: NDr Developmental: NDr	NDr	Maternal: 1.25 Developmental: NDr	Fung (1980), as summarized in Cal/EPA (2008)
Developmental, 0/18−21, albino rat, gavage, dams dosed GDs 6−14; maternal BWs recorded GD 0, daily during dosing, and before and after c-section; c-section and sacrifice on GD 21; maternal viscera and uteri examined for gross pathology and resorptions; fetuses weighed and examined for external abnormalities; half of fetuses examined for skeletal abnormalities/variations, other half examined for soft-tissue abnormalities	0, 5.0, or 10.0[c] (purity not reported)	Mortality observed at ≥5.0 mg/kg-d (1/20, 5/21); increased percentage of litters with resorptions, percentage of fetuses with skeletal abnormalities, and incidence of 5th absent sternebrae at ≥5.0 mg/kg-d; increased incidence of fetuses with incomplete calcification and percentage of litters with skeletal or soft-tissue abnormalities at 5.0 mg/kg-d only Maternal LOAEL: mortality and increased resorptions sites Developmental LOAEL: not determinable due to effects seen only in the presence of mortality	Maternal: NDr Developmental: NDr	NDr	Maternal: 5.0 (FEL) Developmental: NDr	Gupta (1978)

Table 5. Summary of Developmental Studies for Endosulfan (CASRN 115-29-7)

Study Type, Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry (mg/kg-d),[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	BMDL	LOAEL[a,b]	Reference
Rabbit						
Developmental, 0/20−26, New Zealand white rabbit, gavage, dams dosed on GDs 6−28; maternal BWs and clinical observations recorded during gestation (frequency not reported); number of implantations, litter size, sex ratio, mean fetal weight and length, and numbers of live and resorbed fetuses were analyzed; offspring examined for external, soft-tissue, and skeletal abnormalities/variations	0, 0.3, 0.7, or 1.8[e] (purity 97.3%)	Mortality observed at 1.8 mg/kg-d (4/26); increased incidence of clinical signs of toxicity (convulsions/thrashing, noisy/rapid breathing, hyperactivity, salivation, and nasal discharge) at 1.8 mg/kg-d; decreased maternal BW gain during GDs 19−29, and BW gain corrected for gravid uterine weight at sacrifice at 1.8 mg/kg-d (data not reported) Maternal LOAEL: increased mortality and clinical signs of toxicity; decreased BW gain Developmental: no developmental effects observed	Maternal: 0.7 Offspring: 1.8	NDr	Maternal: 1.8 (FEL) Offspring: NDr	Nye (1981), as summarized in Cal/EPA (2008), U.S. EPA (1994a) and McGregor (1998)
Developmental, 0/unreported number of females, New Zealand White rabbit, gavage, dams dosed on GDs 6−18; range-finding study; dams observed for clinical signs and mortality	0, 0.5, 0.625, 1.0, 1.25, 2.0, 2.5, 5.0, 10, 20, 40, or 80[e] (purity not reported)	Mortality observed in dams at 2.0 mg/kg-d (2/6) and at ≥5.0 mg/kg-d (all animals died); clinical signs of neurotoxicity in dams (hyperactivity, opisthotonos, convulsions, and paralysis) observed at ≥1.25 mg/kg-d (data not reported) Maternal LOAEL: mortality and clinical signs of neurotoxicity Developmental LOAEL: no results reported	Maternal: 1.0 Developmental: NDr	NDr	Maternal: 1.25 Developmental: NDr	Fung (1981a), as summarized in Cal/EPA (2008)

Table 5. Summary of Developmental Studies for Endosulfan (CASRN 115-29-7)

Study Type, Number of Male/Female, Strain, Species, Route of Administration, Study Duration, Methods	Dosimetry (mg/kg-d),[a] Purity of Test Compound	Critical Effects	NOAEL[a,b]	BMDL	LOAEL[a,b]	Reference
Developmental, 0/3−10, New Zealand White rabbit, gavage, dams dosed on GDs 6−28; range-finding study; dams observed for clinical signs and mortality	0, 1, 2, 4, 8, or 12[e] (purity not reported)	Mortality observed in dams at ≥4 mg/kg-d (4/8 at 4 mg/kg-d, all animals died at higher doses); clinical signs of neurotoxicity in dams (hyperactivity, opisthotonos, convulsions, and paralysis) observed at ≥2 mg/kg-d (data not reported) Maternal LOAEL: mortality and clinical signs of neurotoxicity Developmental LOAEL: no results reported	Maternal: 1 Developmental: NDr	NDr	Maternal: 2 (FEL) Developmental: NDr	Fung (1981b), as summarized in Cal/EPA (2008)

[a]Reproductive studies are presented as duration-adjusted doses (from 5−6 d/wk to continuous 7 d/wk). Doses for oral developmental studies are not adjusted beyond continuous daily dose as dosing is typically every day throughout the developmental period.
[b]DU = data unsuitable; NA = not applicable; NV = not available; ND = no data; NDr = not determinable; NI = not identified; NP = not provided; NR = not reported; NR/Dr = not reported but determined from data; NS = not selected.
[c]Daily doses provided by the study author(s).
[d]Doses provided by the study author(s) were adjusted for continuous exposure using the following equation: $Dose_{adj}$ = dose (mg/kg) × (Days Dosed ÷ Total Days).
[e]Daily doses as reported in the secondary source(s).

BW = body weight; S-D = Sprague-Dawley.

Inhalation Exposures

The effects of inhalation exposure of animals to endosulfan have been evaluated in one short-term study (Hoechst Aktiengesellschaft, 1984b, as summarized in U.S. EPA, 2010).

Short-term Studies

Hoechst Aktiengesellschaft (1984b) evaluated the effects of endosulfan in a 21-day inhalation study in rats. The original study contained CBI and was not available for review. However, the study was summarized by U.S. EPA (2010) and is, therefore, considered peer reviewed. According to U.S. EPA (2010), male and female rats were exposed to 0, 0.0005, 0.0010, or 0.0020 mg/L (calculated to be equivalent to 0, 0.5, 1, or 2 mg/m^3) endosulfan (97.2% purity) by nose-only inhalation for 6 hours/day for 21 exposures over 29 days. Estimated human equivalent concentrations (HECs) based on default body-weight data (U.S. EPA, 1988) are 0, 0.09, 0.18, and 0.36 mg/m^3. However, because the vapor pressure of endosulfan is very low (2.7×10^{-7} Pa at 25°C; HSDB, 2009, 2010), the exposure system could be generating particles and not vapor. According to U.S. EPA protocol (U.S. EPA, 1994c), the dosage must be calculated based on particulate characteristics, which are not provided, thus precluding an accurate interpretation of the study's exposure atmosphere and accurate dosimetry (i.e., calculation of HECs).

(Hoechst Aktiengesellschaft, 1984b, as reported in U.S. EPA, 2010) The concentration and endpoint for risk assessment are based on a systemic NOAEL of 0.0010 mg/L [$NOAEL_{HEC}$ of 0.18 mg/m^3], and a LOAEL of 0.0020 mg/L [$LOAEL_{HEC}$ of 0.36 mg/m^3], based on decreased body weight in males, decreased leukocyte counts in males, and increased creatinine values in females. It should be noted that decreased body weight in adult males was more sensitive than body weight loss in adult females in the inhalation study. The protection of adult male body weight loss via the inhalation route therefore protects adult females and the young.

Subchronic-duration Studies

No studies were identified.

Chronic-duration Studies

No studies were identified.

Developmental Studies

No studies were identified.

Reproductive Studies

No studies were identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Appendix B provides other data for endosulfan and endosulfan sulfate.

DERIVATION OF PROVISIONAL VALUES

Tables 6 and 7 present summaries of noncancer and cancer reference values, respectively. IRIS data are indicated in the tables, if available. As explained above, these values are based on effects from exposure to the parent compound, endosulfan, and are considered to be appropriate for endosulfan sulfate, its principal metabolite in mammalian systems.

Table 6. Summary of Reference Values for Endosulfan Sulfate (CASRN 1031-07-8)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Rat/F pups	Endosulfan exposure resulted in a litter-based decrease in pup BW	3×10^{-3}	$BMDL_{05}$	0.29[a]	100	Gilmore et al. (2006)
Chronic RfD for endosulfan (mg/kg-d) IRIS (U.S. EPA, 1994a)	Rat/M Dog/F	Endosulfan exposure resulted in decreased BW gain, increased incidence of marked progressive glomerulonephrosis, and blood vessel aneurysms Neurological findings	6×10^{-3} (IRIS)[b]	NOAEL/ LOAEL	0.6	100	Hoechst Celanese Corporation (1989a,b)
Subchronic p-RfC (mg/m^3)	NDr						Hoechst Aktiengesellschaft (1984b) was determined to be inadequate for development of a p-RfC
Chronic p-RfC (mg/m^3)	NDr						

[a]Because the POD is based on a study evaluating the effects of endosulfan, a molecular weight conversion for endosulfan to endosulfan sulfate was applied to the POD during the determination of the screening subchronic p-RfD.
[b]A molecular weight conversion for endosulfan to endosulfan sulfate was applied to the IRIS RfD. However, after rounding, the value remained unchanged.

BW = body weight; NDr = not determined.

Table 7. Summary of Cancer Values for Endosulfan Sulfate (CASRN 1031-07-8)

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

NDr = not determined.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

Gilmore et al. (2006) is selected as the principal study for derivation of the subchronic p-RfD. Although this study was accepted by an agency of the United States government, it was not subjected to external review by independent scientists, which is a requirement for utilization of a study for development of provisional values. However, the study provides information that appears to be reasonably complete and reputable. Therefore, according to the PPRTV protocol, a screening level provisional RfD is presented in Appendix A. Please refer to this appendix for the screening p-RfD.

Derivation of Chronic RfD (Chronic RfD)

A chronic RfD of 0.006 mg/kg-day is available in IRIS (U.S. EPA, 1994a) for endosulfan based on a 2-year study in rats (Hoechst Celanese Corporation, 1989a) and a 1-year feeding study in dogs (Hoechst Celanese Corporation, 1989b). A UF of 100 was applied by IRIS (10 for intraspecies variability and 10 for interspecies extrapolation).

Because the principal study focused on the exposure of the parent compound, endosulfan, an MW conversion for consideration of endosulfan sulfate is applied to the IRIS chronic RfD (note the value does not change for endosulfan sulfate after rounding to one significant figure).

$$\begin{aligned} \textbf{Chronic RfD}_{\textbf{endosulfan sulfate}} &= MW_{metabolite} \div MW_{parent} \times RfD_{parent} \\ &= 422.95 \div 406.93 \times 0.006 \text{ mg/kg-day} \\ &= \mathbf{6 \times 10^{-3} \text{ mg/kg-day}} \end{aligned}$$

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

No repeat-dose studies investigating toxicological effects following inhalation exposure of endosulfan sulfate are available. Additionally, no studies investigating the effects of inhalation exposure to endosulfan in humans are considered appropriate for derivation of a subchronic p-RfC. Available endosulfan human inhalation studies are limited by poor exposure characterization and coexposures with other chemicals. The database of inhalation studies on endosulfan in animals is limited to a single, unpublished 21-day study in rats (Hoechst Aktiengesellschaft, 1984b). This study contains CBI and was unobtainable at the time of this assessment. The study is summarized in an assessment conducted by U.S. EPA (2010). However, no detailed information regarding the exposure delivery system is given. Because the vapor pressure of this compound is very low, the delivery system could provide particles and not vapor. Particle size information is not provided, which is necessary to calculate HECs. Without this dosimetry information, a reliable p-RfC cannot be developed.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

As indicated above, no value can be derived.

CANCER WOE DESCRIPTOR

Table 8 identifies the cancer WOE descriptor for endosulfan sulfate.

Table 8. Cancer WOE Descriptor for Endosulfan Sulfate			
Possible WOE Descriptor	**Designation**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	NA
"Likely to Be Carcinogenic to Humans"	NS	NA	NA
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	NA
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Inhalation and Oral**	**No data were available concerning the carcinogenic potential of endosulfan or endosulfan sulfate via the inhalation route. U.S. EPA (2010) evaluated data on the oral carcinogenicity of endosulfan and concluded that it is "*Not Likely to be Carcinogenic to Humans*". Because endosulfan is metabolized to endosulfan sulfate following absorption, the same conclusion is drawn for the metabolite. However, on further review, based on the paucity of data, "inadequate" is a more appropriate descriptor.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	NA

NA = not applicable; NS = not selected.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

U.S. EPA (2010) evaluated data on the oral carcinogenicity of endosulfan and concluded that it is "*Not Likely to be Carcinogenic to Humans*." No treatment-related neoplasms were observed in any of the combined chronic/carcinogenicity feeding studies on rats and mice. No further information was found indicating carcinogenic effects following oral exposure to endosulfan. Therefore, derivation of the p-OSF for endosulfan sulfate is precluded.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

The lack of data on the carcinogenicity of endosulfan precludes the derivation of quantitative estimates for inhalation (p-IUR) exposure.

APPENDIX A. PROVISIONAL SCREENING VALUES

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

Gilmore et al. (2006) is selected as the principal study for derivation of the screening subchronic p-RfD. The critical effect is decreased body weight in female pups. Details are provided in the "Review of Potentially Relevant Data" section. Based on the information provided in the Introduction section of this report, it is considered to be a reasonable assumption that studies performed using endosulfan are predictive of the toxicological effects that would occur following exposure to endosulfan sulfate. Tables 4 and 5 summarize the available databases of subchronic and developmental studies, respectively. The effects in fetal animals are seen at relatively lower doses when compared with adult animals. Table D.1 lists the BMD output models for all endpoints considered for derivation of the screening subchronic p-RfD with curve and BMD output text provided for the selected model in Appendix D (see Figure D.1 and the text output that follows the figure). Among the studies considered for derivation of the screening subchronic p-RfD, the Gilmore et al. (2006) data for decreased body weight in female pups on PND 11 provide the most sensitive POD ($BMDL_{05}$ = 0.29 mg/kg-day). Other reported developmental effects provide supporting evidence for the POD include delayed sexual development, decreased sperm production and spermatogenesis, and changes in reproductive organ weights (see Table 5). In addition, both neurological and immunological effects were reported at similar doses (0.9−2 mg/kg-day). In this regard, selecting the $BMDL_{05}$ of 0.29 mg/kg-day for decreased body weight in female pups as the POD will protect against these other identified effects. The Gilmore et al. (2006) rat data for decreased body weight on PND 11 gives a $BMDL_{05}$ of 0.29 mg/kg-day and provides evidence of the most sensitive indicator of toxicity among the available studies. Other potential endpoints from this study occurred at higher doses. Possible endpoints from other studies were considered, including the NOAEL of 0.5 mg/kg-day from Banerjee and Hussain (1986), but not selected because of lack of a clear toxicity threshold for these effects and the fact that the $BMDL_{05}$ of 0.29 for Gilmore et al. (2006) would be protective for the potential immunotoxicity endpoint. The use of the benchmark response (BMR) of 5% is appropriate for effects on early life periods. Data on a per-litter basis for this study are not available. Instead, the results were reported as litter-based means. Thus, the use of nested models provided by BMD software (BMDS) is not possible (U.S. EPA, 2012). Instead, continuous BMD models are used to determine the POD. The continuous data models in the U.S. EPA BMDS (version 2.1.2) were fit to litter-based means for pup body weights on PND 11 following exposure of maternal rats to endosulfan by diet from GD 6−PND 21 (see Table A.1). The Hill constant variance model provides the best model fit (see Table A.2).

Table A.1. Litter-based Body Weights (PND 11) of Female Pups from Female Wistar Rats Exposed to Endosulfan from GD 6−PND 21—Used for BMD Analysis[a]

Dose (mg/kg-d)	Number of Litters	Mean	Standard Deviation
0	23	23.6	1.726
3.74	23	21.7*	2.206
10.8	23	20.9*	2.590
29.8	21	20.4*	2.200

[a]Gilmore et al. (2006).
*Significantly different from control at $p < 0.01$; statistical test run was not reported.

Table A.2. Model Predictions for Female Pup Bodt Weight (PND 11)[a]

Model	Homogeneity Variance *p*-value	Goodness-of-Fit *p*-value[b]	AIC for Fitted Model	BMD_{05} (mg/kg-d)	$BMDL_{05}$ (mg/kg-d)
Hill (constant variance)	**0.298**	**0.960**	**235.99**	**1.63**	**0.29**
Exponential (M4) (constant variance)	0.298	0.653	236.19	2.07	0.77
Exponential (M5) (constant variance)	0.298	0.653	236.19	2.07	0.77
Exponential (M2) (constant variance)	0.298	0.010	243.28	12.28	8.68
Exponential (M3) (constant variance)	0.298	0.010	243.28	12.28	8.68
Linear (constant variance)	0.298	0.008	243.62	13.01	9.41
Polynomial (constant variance)	0.298	0.008	243.62	13.01	9.41
Power (constant variance)	0.298	0.008	243.62	13.01	9.41

[a]Gilmore et al. (2006).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

The screening subchronic p-RfD for endosulfan sulfate is based on the $BMDL_{05}$ of 0.29 mg/kg-day based on decreased female pup body weight in rats (Gilmore et al., 2006).

Dosimetry

Molecular Weight (MW) Correction:

Because the principal study was performed with endosulfan, an MW conversion is necessary to convert the $BMDL_{05}$ for endosulfan sulfate as follows.

$$\begin{aligned} BMDL_{05(MW\ adj)} &= MW_{metabolite} \div MW_{parent} \times BMDL_{05\ parent} \\ &= 422.95 \div 406.93 \times 0.29 \text{ mg/kg-day} \\ &= 0.30 \text{ mg/kg-day} \end{aligned}$$

HED Conversion is not appropriate for a developmental endpoint:

EPA endorses body-weight scaling to the ¾ power to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions. The use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite but not for portal-of-entry effects or developmental endpoints. In this case (a developmental endpoint: pup weights), the adjustment is not recommended or applied since exposure to the chemical occurred through a sequential combination of in utero, lactational, and direct exposure to neonatal and juvenile animals post-weaning.

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= POD \div UF_C \\ &= 0.30 \text{ mg/kg-day} \div 100 \\ &= \mathbf{3 \times 10^{-3}\ mg/kg\text{-}day} \end{aligned}$$

Table A.3 summarizes the uncertainty factors (UFs) for the screening subchronic p-RfD for endosulfan sulfate.

Table A.3. UFs for Screening Subchronic p-RfD for Endosulfan Sulfate			
UF	**Value**	**Justification**	**Notes**
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. No dosimetric adjustment factor was utilized because a developmental endpoint was used for derivation.	No information is available regarding extrapolation from extrapolation from animals to humans.
UF_D	1	A UF_D of 1 is selected because there is an acceptable two-generation reproduction study in rats (Hoechst Aktiengesellschaft, 1984a) and multiple acceptable developmental studies via the oral route (see Table 5) for the endosulfan surrogate used in this assessment.	Developmental/Reproductive studies are available to evaluate these endpoints.
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially-susceptible individuals in the absence of information on the variability of response to humans.	No information is for human variability for exposure to this compound.
UF_L	1	A UF_L of 1 is applied because the POD is developed using a BMDL.	The use of benchmark dose analysis at a justifiable response level of a 5% BW decrement supports the value of 1 for the UF_L.
UF_S	1	A UF_S of 1 is applied because further adjustment for exposure duration is not warranted when developmental toxicity data are used to develop a POD.	None.
UF_C	100		

BW = body weight.

The confidence descriptors for the screening subchronic p-RfD for endosulfan sulfate are explained in Table A.4 below.

Table A.4. Confidence Descriptors for Screening Subchronic p-RfD for Endosulfan Sulfate

Confidence Categories	Designation[a]	Discussion
Confidence in study	H	Confidence in the principal study is high. The study of Gilmore et al. (2006), although on endosulfan rather than endosulfan sulfate, was adequate in design for a developmental neurotoxicity study in rats. While the original study is not available due to the inclusion of CBI, both a DER and a review of the data by U.S. EPA (2010) provide sufficient review of the data. The study is GLP compliant. Several studies report effects at doses similar to those seen in the principal study providing supporting evidence.
Confidence in database	H	The database (based on endosulfan) includes multiple subchronic-duration studies in rats and mice (see Table 4), multiple developmental studies in rats and rabbits (see Table 5), and a two-generation reproductive study in the rat (Hoechst Aktiengesellschaft, 1984a).
Confidence in screening subchronic p-RfD[b]	H	The overall confidence in the screening subchronic p-RfD is high.

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

APPENDIX B. ADDITIONAL INFORMATION

ATSDR (2000) reported the following information regarding the biodegradation of endosulfan in soil:

> *Endosulfan released to soil is most likely subjected to photolysis (on soil surfaces), hydrolysis (under alkaline conditions), or biodegradation. Endosulfan has been shown to be biodegraded by a wide variety of soil microorganisms in numerous studies. Sixteen of 28 species of fungi, 15 of 49 species of soil bacteria, and 3 of 10 species of actinomycetes metabolized radiolabeled endosulfan in a laboratory study under aerobic conditions (Martens 1976). Endosulfan sulfate was the major product of the fungal metabolism, whereas the bacterial transformation produced endosulfan diol. Degradation of endosulfan by soil fungi and bacteria has also been reported (El Beit et al. 1981b). Biotransformation occurs under both aerobic and anaerobic conditions. Aerobic incubation of soil with endosulfan yielded mainly endosulfan sulfate (30−60%), some endosulfan diol (2.6%), and endosulfan lactone (1.2%) (Martens 1977). Flooded (anaerobic) incubation produced mainly endosulfan diol (2−18%), endosulfan sulfate (3−8%), and endosulfan hydroxyether (2−4%). In aqueous nutrient media (20EC) containing a mixed culture of microorganisms isolated from a sandy loam soil, endosulfan was reported to be transformed to endosulfan diol with half-lives of about 1.1 and 2.2 weeks for the α- and β-isomers, respectively (Miles and Moy 1979).*
>
> *A two-membered bacterial coculture was found to aerobically degrade α- and β-endosulfan efficiently without accumulating any of its metabolites. However, the degradation of soil-bound endosulfan was slower by 4-fold than in culture media; only 50% of the material (initially at 50 ppm) was degraded in 4 weeks (Awasthi et al. 1997). A field study report stated that endosulfan was transformed to endosulfan sulfate following incorporation of 6.7 kg/hectare of the pesticide into sandy loam soil (Stewart and Cairns 1974). The half-lives for the α- and β-isomers were reported to be 60 and 800 days, respectively. Pseudomonad microbes have been reported to isomerize β-endosulfan to α-endosulfan and biodegrade both isomers to endosulfan alcohol and endosulfan ether (U.S. Department of Interior 1978). In a field study conducted from 1989−1990 in northern India, dissipation of endosulfan in sandy loam soil was examined (Kathpal et al. 1997). It was found that α-endosulfan could be detected up to 14 and 28 days in two different soil plots, while β-endosulfan could be detected up to 70 and 238 days. An overall half-life for endosulfan degradation ranged from 39.5 to 42.1 days. Endosulfan residues dissipated to an extent of 92−97% in the first 4-week period of application and by about 99% in 238 days. A residue half-life of 15 days for endosulfan (unspecified isomer) has been reported in Australian black soil when incubated at 30 EC at field capacity moisture level (Kathpal et al. 1997). Fate and movement of endosulfan isomers and endosulfan sulfate under field application conditions have been studied (Antonious and Byers 1997). New modes of cultivation showed reduced runoff water and sediment loss and reduced endosulfan movement from the site of application to the surface*

water runoff. Results indicated vertical movement of the pesticide through the vadose zone at a concentration of 0.63 µg/L. Soil core data shows endosulfan leaches from 23 to 46 cm into the soil (Antonious and Byers 1997).

On plant surfaces, as in soils, numerous studies have demonstrated that endosulfan is oxidized to endosulfan sulfate. Initial residues of endosulfan on treated vegetables generally range from 1 to 100 mg/kg. However, residue levels typically decrease to less than 20% of initial levels within 1 week after treatment (NRCC 1975). Residues of endosulfan isomers are generally negligible after 2−3 weeks; the α-isomer is much less persistent than the β-isomer. In most plant residue studies, endosulfan sulfate residue levels tend to increase relative to the parent isomers and other metabolites and appear to be very persistent (Coleman and Dolinger 1982).

HUMAN STUDIES

Oral Exposures

Acute

Bernardelli and Gennari (1987)

Bernardelli and Gennari (1987, as summarized in ATSDR, 2000) described the case of a 55-year-old woman who died after taking endosulfan orally (amount unspecified) in a colorless liquid containing 55% xylene. No gross anatomical or histological abnormalities were found. The authors indicated that a malignant melanoma and the coexposure of xylene may have contributed to her death.

Blanco-Coronado et al. (1992)

Blanco-Coronado et al. (1992, as summarized in ATSDR, 2000) reported a case of poisoning in a woman who ingested an unknown amount of endosulfan in food. The woman experienced tonic-clonic convulsions, nausea, vomiting, headache, and dizziness 1−4 hours after eating the endosulfan-contaminated food. When admitted to the hospital, the endosulfan concentrations (both isomers) in the stomach, blood, and urine were 55.4, 2.4, and 3 mg/L, respectively. The patient suffered from renal failure, disseminated intravascular coagulation, thrombi in the pulmonary arteries and aorta, and cardiogenic shock; she died 8 days later from these complications. Postmortem examination revealed bilateral pleural effusions, congested and edematous lungs, hyaline membranes, microatelectasia, polymorphonuclear lymphocytes, red cells in the alveoli, and interstitial fibrosis.

Lo et al. (1995)

Lo et al. (1995, as summarized in ATSDR, 2000) presented the case of a man who ingested an unknown amount of endosulfan and died 10 days later. The man suffered from muscle fasciculations and episodes of convulsions. The authors indicated that the cause of death was cardio-respiratory arrest/heart failure and pulmonary edema. The patient had an elevated white blood cell count. Mucosal inflammation of the stomach and proximal small intestine, centrilobular congestion of the liver, slight prominence of the bile canaliculi, and extensive tubular necrosis of the kidney were noted in postmortem examinations.

Shemesh et al. (1988)

Shemesh et al. (1988, summarized in ATSDR, 2000) described a case in which a 20-year-old man attempted suicide through the ingestion of 200 mL of Thionax (30% endosulfan). He presented with respiratory effects including hypoxia due to alveolar hypoventilation and pulmonary edema. Within the first 16 hours, he also experienced episodes of tachycardia and hypertension followed by cardiogenic shock. These respiratory and cardiovascular symptoms occurred even though his stomach was pumped and he was given activated charcoal during the first 16 hours after exposure. During the 2 subsequent weeks, the man experienced recurrent aspiration pneumonia and consistently required mechanical ventilation. The patient also experienced recurrent convulsions during this period. A year after the exposure, his mental activity (presumably his psychomotor activity) was still impaired, and he took medicine to control his seizures. The authors stated that the respiratory effects were likely secondary to the direct effects of endosulfan on the central nervous system (CNS) rather than a direct action of the substance on the lungs. The authors were unsure whether the endosulfan was directly responsible for the cardiovascular effects. It was unclear if other ingredients in Thionax may have contributed to the man's symptoms.

Pradhan et al. (1997)

Pradhan et al. (1997, summarized in ATSDR, 2000) reported on a patient who ingested around 75 mL of liquid endosulfan (35% w/v). The patient suffered from nausea, gagging, vomiting, and diarrhea. The patient also had tonic-clonic seizures and myoclonic jerks, psychosis, cortical blindness, and limb rigidity. Reversible lesions of the basal ganglia and occipital cortex were apparent on magnetic resonance images.

Inhalation Exposures

Acute

Chugh et al. (1998)

In an occupational study, Chugh et al. (1998, summarized in ATSDR, 2000) reported on 18 cases of endosulfan poisoning between October 1995 and September 1997 in agricultural workers in India who applied endosulfan to crops but did not use protective equipment to limit dermal or inhalation exposure to the chemical. Exposed workers experienced gastrointestinal symptoms including discomfort after meals, nausea, and vomiting. Neurological symptoms included dizziness, confusion, irritability, muscle twitching, tonic-clonic convulsions, and conduction defects. Respiratory effects included an increase in dyspnea and respiratory rate. The authors also reported cardiovascular effects including tachycardia and bradycardia.

Singh et al. (1992)

Singh et al. (1992, summarized in ATSDR, 2000) reported on 22 workers who applied endosulfan to cotton and rice fields and experienced gastrointestinal effects. The workers suffered from nausea, vomiting, abdominal pain, and diarrhea. The authors reported that the effects were most likely the result of dermal exposure to endosulfan because workers who suffered cuts on the legs from the plants had more severe symptoms. Three of the 22 workers exhibited tremors, and 11/22 experienced convulsions although all patients recovered from these conditions.

Aleksandrowicz (1979)

Aleksandrowicz (1979, as summarized in ATSDR, 2000) described a case of long-term (possibly permanent) brain damage in an industrial worker occupationally exposed to endosulfan while cleaning vats containing residues. Acute effects included repeated convulsions and impaired consciousness; afterward, he was disoriented and agitated. The man showed cognitive and emotional deterioration, impaired memory, and impaired visual-motor coordination 2 years after the exposure. The authors noted that the man consumed 1 L of wine per week, which may have contributed to the impairment and decreased endosulfan metabolism in the liver.

Short-term Studies

No studies were identified.

Long-term Studies

García-Rodríguez et al. (1996)

In an epidemiologic study, García-Rodríguez et al. (1996, summarized in ATSDR, 2000) examined the association between the geographic use of pesticides in relation to the homes of children and incidence of cryptorchidism (undescended testes) in Granada, Spain. Cryptorchidism incidence was ascertained from records of surgical correction for the disorder. Exposure levels were not available in this study although ATSDR (2000) reported that other studies indicated there was significant endosulfan exposure in the region. However, the authors did not find any clear association between local pesticide use and incidence of cryptorchidism.

Roberts et al. (2007)

Using a retrospective case-control study design, Roberts et al. (2007) investigated the association between maternal ambient pesticide exposure near agricultural fields and autism spectrum disorders (ASDs) among children in the Central Valley of California. The study population included 269,746 singleton births between January, 1, 1996, and December 31, 1998, to mothers that lived in one of the 19 counties of the Sacramento River Valley and San Joaquin River Valley (also known as the Central Valley).

Authors specifically investigated the risk of ASDs among children that were not born prematurely (i.e., not born <37 weeks gestation or weighing <2,500 g). ASD cases were ascertained using the California Department of Developmental Services (DDS); cases included all children reported by DDS as receiving services for autism or who have an ASD diagnostic code from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. DDS ran regional centers (RCs) that provided voluntary services for people with autism, mental retardation, and other developmental disabilities. DDS services were used by people of many racial/ethnic groups and socioeconomic levels; however, there was some possibility of disparity and lack of case identification. For example, children with milder forms of developmental disabilities, such as Asperger's Syndrome, may not be eligible for services at the centers.

Staff of the California Center for Autism and Developmental Disabilities Research and Epidemiology collected demographic information for the cases identified through DDS live birth vital records (e.g., first name, last name, date of birth, sex). The control:case ratio was 15:1, with control births randomly selected from the study population of full-term singleton births described above. The DDS RC was used as a covariate; 6 centers served the 19 counties identified in the study population. For controls, RCs were simulated based on the assumption that migration during the first years of life would be the same for cases and controls.

Pesticide data were obtained from the California Department of Pesticide Regulation (DPR), which included agricultural pesticide applications from January 1995 to January 1999 (total number of applications: 6,710,727). Data are reported to DPR by county agriculture commissioners and referenced to public land survey sections. The authors refined these data through land-use survey field polygons data provided by the California Department of Water Resources. Exposure determination was based on both spatial and temporal data. Residence address at time of birth and last maternal menstrual cycle (to estimate gestation time) were compared with temporal and spatial proximity to the pesticide applications reported to DPR. The authors estimated the pounds of pesticides applied during temporal windows (Days 7−49 [CNS development], Days 4−24 [neural tube development], and Day 14−date of birth [gestation]) within a specified radius of the mother's residence. The pesticide use was divided into quartiles based on the estimated pounds of exposure. The authors selected pesticides for inclusion based on plausibility of biological connection to autism, physical characteristics (e.g., a widely used pesticide), and community concerns expressed through a series of meetings with local governmental and nongovernmental organizations. A total of 249 combinations of compounds, buffer radii, and temporal periods met the requirement of five exposed cases and controls that were initially identified.

Authors used a conditional logistic regression model for analysis, controlling for maternal race/ethnicity, education, and RC of diagnosis. Final analysis indicated that 465 ASD cases and 6,975 matched controls were retained in the final study population; 85.2% of cases were male versus 51.4% of cases in controls. Results indicated that the fourth (highest) quartile of pesticide exposure was statistically significantly associated with applications occurring during the CNS development period (odds ratio [OR] = 4.2; 95% confidence interval [CI]: 1.7−10.9; $p \leq 0.05$). All other neural tube, CNS, and gestation periods/exposure levels did not yield significant ORs. The authors reported that organochlorine pesticides were associated with ASD regardless of the size of the buffer radius between application site and residence; however, the effects were smaller as the buffer radius increased (with the OR finally becoming nonsignificant with a buffer around 1,750 m [data not reported]). The authors also reported that there was a significant OR of 7.6 (95% C.I.: 3.1−18.6; $p \leq 0.05$) for 26−81 days postfertilization in the fourth quartile of pesticide application. The authors concluded that these 8 weeks represent the maximum embryonic susceptibility to organochlorine pesticides.

In the study area, dicofol and endosulfan accounted for more than 98% of the organochlorine pesticides applied. During the a posteriori time period (26−81 days postfertilization), 88 subjects (cases and controls) lived within 500 m of a dicofol application, and 27 lived within 500 m of an endosulfan application. Due to a small sample size, however, authors could not calculate ORs specific to endosulfan. The authors indicated that the magnitudes of association were slightly higher for endosulfan compared with dicofol (data not reported).

An important strength of this study was its ability to estimate both space and timing of pesticide application with relatively high confidence. The authors were also able to assess the biological plausibility of certain compounds' ability to interfere with neurological development. The DDS diagnosis system has also been used in prior studies and has proven to be a good measure of autism. In some exposure categories, however, the number of cases was small (e.g., the fourth quartile of exposure had only 29 subjects, 8 of which had ASD). Misclassification of exposure may have occurred because an estimated 1 in 3 mothers changed addresses during

pregnancy. It was also not possible to separate the effects of individual pesticides, so no definitive conclusions can be reached for the relationship between endosulfan exposure and ASDs. Furthermore, authors were not able to address all confounders such as use of prenatal vitamins, alcohol consumption, smoking, and familial history of cognitive disorders.

Saiyed et al. (2003)

Saiyed et al. (2003) conducted a study to analyze the relationship between endosulfan exposure and reproductive development in male children and adolescents (10−19 years old). Subjects included 117 male schoolchildren in a village near cashew plantations where endosulfan had been aerially sprayed for more than 20 years and 90 comparable controls from another village 20 km away without a history of endosulfan exposure.

The study collected clinical history and included a physical examination, assessment of sexual maturity rating (SMR) according to Tanner's classification, serum levels of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and endosulfan residues. Serum samples were drawn at approximately the same time on examination day, centrifuged, separated, stored, and analyzed with a gas chromatography-electron capture detector (GC-ECD) to quantify endosulfan residues. Hormones were estimated by radioimmunoassay.

Descriptive statistics were measured for subjects and controls. Multiple regression analysis was performed using age and aerial endosulfan exposure (AEE; AEE subjects = 1; controls = 0) to endosulfan as independent variables while SMR and serum hormone levels served as dependent variables. The multiple regression equation below was used to analyze variance in dependent variables attributable to independent variables. SPSS (version 6.1.4) was used for statistical analysis.

$$\text{SMR score} = b_0 + b_1(\text{age}) + b_2\ (\text{AEE})$$

Where:

b_0 = regression constant
b_1 = regression coefficient of age
b_2 = regression coefficient of exposure

The regression coefficients of age and exposure were fitted for SMR scores for pubic hair, testes, and penis. Other multiple regression equations were fitted to testosterone, LH, and FSH serum levels. Another multiple regression analysis was conducted to analyze the relationship of serum testosterone versus age, AEE, and serum LH levels.

There were no significant differences in the descriptive statistics (age, height, weight, Basal Metabolic Index [BMI], skin fold thickness) of participating subjects and controls and nonparticipating subjects and controls (Saiyed et al., 2003). Six cases (5.1%; not statistically significant) of congenital malformations were observed in the study group, including undescended testis (2), congenital hydrocele (3), and congenital inguinal hernia (1). Table C.1 summarizes results of multiple regression analysis. The R^2 (coefficient of determination) values corresponding to SMR of pubic hair, testes, and penis were 0.48, 0.43, and 0.43, respectively ($p < 0.01$). These values indicated that a significant proportion of variance in SMR scores could be attributed to age and positive endosulfan exposure. The exposure (AEE) coefficient (b_2) was negative in all equations, indicating delayed sexual maturity associated with positive exposure to

endosulfan. Positive age coefficients (b_1) were also observed as age was expected to increase with sexual maturity. Multiple regression analysis of serum testosterone levels resulted in an R^2 value of 0.61, indicating 61% of the variation of testosterone levels was expected to be attributed to age, AEE, and serum LH ($p < 0.001$). Regression of serum testosterone against age and serum LH produced positive coefficients for age and serum LH levels. This confirmed that age and serum LH increased, as expected, with serum testosterone levels. The negative AEE coefficient of −0.62 indicated that testosterone levels in exposed individuals were statistically lower than expected by age and LH levels. Endosulfan was detected in serum of 78% of the endosulfan-exposed study group and 29% of the control group participants. Table C.2 summarizes the mean serum endosulfan levels for exposed and control groups. A significant ($p < 0.001$) increase in serum endosulfan residues in endosulfan-exposed study males was observed when compared with the control group. The study authors concluded that endosulfan exposure may delay sexual maturity and affect hormone synthesis and that a larger sample study and a long-term follow up should be conducted to validate these findings.

While SMR study nonparticipation rates were high (57% for exposed, 33% for control), growth-related descriptive statistics for participants and nonparticipants were comparable (see Table C.3). The study authors stated that random variability in hormone levels would have increased exposure misclassification (testosterone levels) and decreased the power of the study by biasing the results towards the null. To minimize the effect of diurnal variation in hormone secretion and, thus, hormone serum levels, all blood samples were collected within the same 2-hour window, 1,000−1,200 hours.

A Critique noting deficiencies in the study design have been reported (Indulkar, 2004). According to the critiques, Saiyed et al. (2003) incorrectly stated that endosulfan was the only pesticide sprayed for decades when in fact other pesticides were also used in exposed and control study areas. In addition, it was noted that the SMR and hormone level data displayed a poor correlation with age, the sample size was too small, and normal biological SMR and hormone ranges were not reported in the study for reference.

Chronic-duration Studies

Aschengrau et al. (1998)

In a population-based case-control study, Aschengrau et al. (1998) studied the association between breast cancer incidence in females and exposure to suspected estrogenic chemicals, including endosulfan. Incident cases were Cape Cod, Massachusetts permanent residents from five towns who were diagnosed with breast cancer between 1983 and 1986 and registered in the Massachusetts Cancer Registry. Controls were also permanent residents of similar age and race from the same population. Random digit dialing, Medicare beneficiary lists, and death certificates were used to identify controls. Controls were gathered for a larger study of nine cancers. The controls for the breast cancer study were selected from this pool by stratification of breast cancer cases by age, gender, vital status, and, if applicable, year of death. Controls were then selected if they fell into a stratum with one or more cases.

Exposure was assessed for each case or control in a stepwise process (Aschengrau et al., 1998). Exposure for each job held by a study subject was determined using the National Institute for Occupational Safety and Health National Occupational Exposure Survey (NIOSH/NOES) database, chemical production and usage information, and the expert judgment of a certified industrial hygienist. Exposure was assessed for 18 substances showing estrogenic activity,

including α- and β- endosulfan, by cross-referencing job types held by women in the study with information from the NIOSH/NOES database. An extensive database and literature search on the production and usage of the 18 suspected xenoestrogens were used to identify jobs in which women were not likely to have been exposed. Occupational exposure estimates were assigned a level of confidence (probable or possible) by an industrial hygienist based on interview information on specific job duties.

Subjects were categorized as having one or more jobs with probable or possible exposure to suspected xenoestrogens overall as well as to specific chemicals such as endosulfan (Aschengrau et al., 1998). ORs for probable exposure were calculated to assess the relative risk of breast cancer by exposure categories. Crude OR 95% confidence intervals (CIs) were calculated (Miettinen's test, ≥5 exposed cases; Fisher's exact method, <5 exposed cases). Multivariate logistic regression models were used to calculate ORs adjusted for confounders, and 95% CIs were calculated using the maximum likelihood estimate of standard errors. The authors noted that the number of subjects evaluated was insufficient to examine by exposure duration.

Only a few subjects were occupationally exposed to endosulfan plus other xenoestrogens (3 cases, 7 controls), and no cases or controls were exposed to only endosulfan (Aschengrau et al., 1998). The crude OR for endosulfan plus other suspected xenoestrogens was 1.3 (95% CI: 0.2−1.2). The adjusted OR was 0.8 (95% CI: 0.2−3.2) after adjusting for core confounders (age at diagnosis or index year, vital status at interview, family history of breast cancer, age at first birth, personal history of breast cancer, benign breast disease) and education level. Given the small study size for endosulfan (3 exposed) and exposure to multiple compounds, it is difficult to draw any conclusions about endosulfan from the findings of this study.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

The genotoxicity of endosulfan has been studied in bacteria, yeast, mammalian cells in culture, and in laboratory animals (see Table B.1). Selected data on the acute toxicity, toxicokinetics, and mode of action of endosulfan are present. As shown in Table B.1, numerous genotoxicity studies have been conducted in bacteria, yeast, mammalian cells, and in laboratory animals. These data are inconclusive as both positive and negative results are seen. In addition, it is possible that some of these studies used formulations of endosulfan that may have contained epichlorohydrin, a known genotoxic compound, as a stabilizer (ATSDR, 2000). U.S. EPA (2010) noted that chronic animal bioassays in rats and mice provided no evidence that endosulfan is carcinogenic and concluded that endosulfan is neither mutagenic nor carcinogenic. The limited information available on endosulfan sulfate (Bajpayee et al., 2006) also indicates that this metabolite is neither mutagenic nor carcinogenic. Based on the WOE, it is concluded that endosulfan is not a genotoxic compound. Because of the similarities in structure and chemical characteristics between endosulfan and endosulfan sulfate, it is also concluded that endosulfan sulfate is not a genotoxic compound.

Short-term Studies

Dorough et al. (1978) conducted an acute toxicity test on female albino mice; however, the discussion of this experiment, including a description of the mice (such as weight gain), was limited, making the study methodology difficult to ascertain (see Table B.2). For endosulfan isomers and metabolites, authors reported dosing female mice with initial concentrations of 120 mg/kg, which were then adjusted throughout the study. Results indicated that the acute

toxicity of endosulfan sulfate (LD_{50} = 8 mg/kg) was similar to the toxicity of α-endosulfan (LD_{50} = 11 mg/kg).

Metabolism/Toxicokinetic Studies

Table B.2 reports data concerning the kinetics of endosulfan. Endosulfan was absorbed following exposure, with the highest levels of accumulation taking place in the liver and kidneys (Dorough et al., 1978). Endosulfan and endosulfan sulfate have also been detected in human placenta, umbilical cord serum, and breast milk, indicating the likelihood of the compounds to be passed from mother to fetus and/or child (Campoy et al., 2001; Cerillo et al., 2005). Figure B.1 shows the metabolic pathway for endosulfan. Endosulfan is readily metabolized to endosulfan sulfate and endosulfan diol and then further metabolized to endosulfan lactone either directly from the sulfate or indirectly via the corresponding ether and hydroxyether from endosulfan diol (ATSDR, 2000). Studies have demonstrated that elimination of endosulfan and its metabolites occurs via renal and biliary excretion (Dorough et al., 1978; Wilson and Leblanc, 1998; ATSDR, 2000). In addition, endosulfan is eliminated via breast milk in lactating women (Campoy et al., 2001; Cerillo et al., 2005).

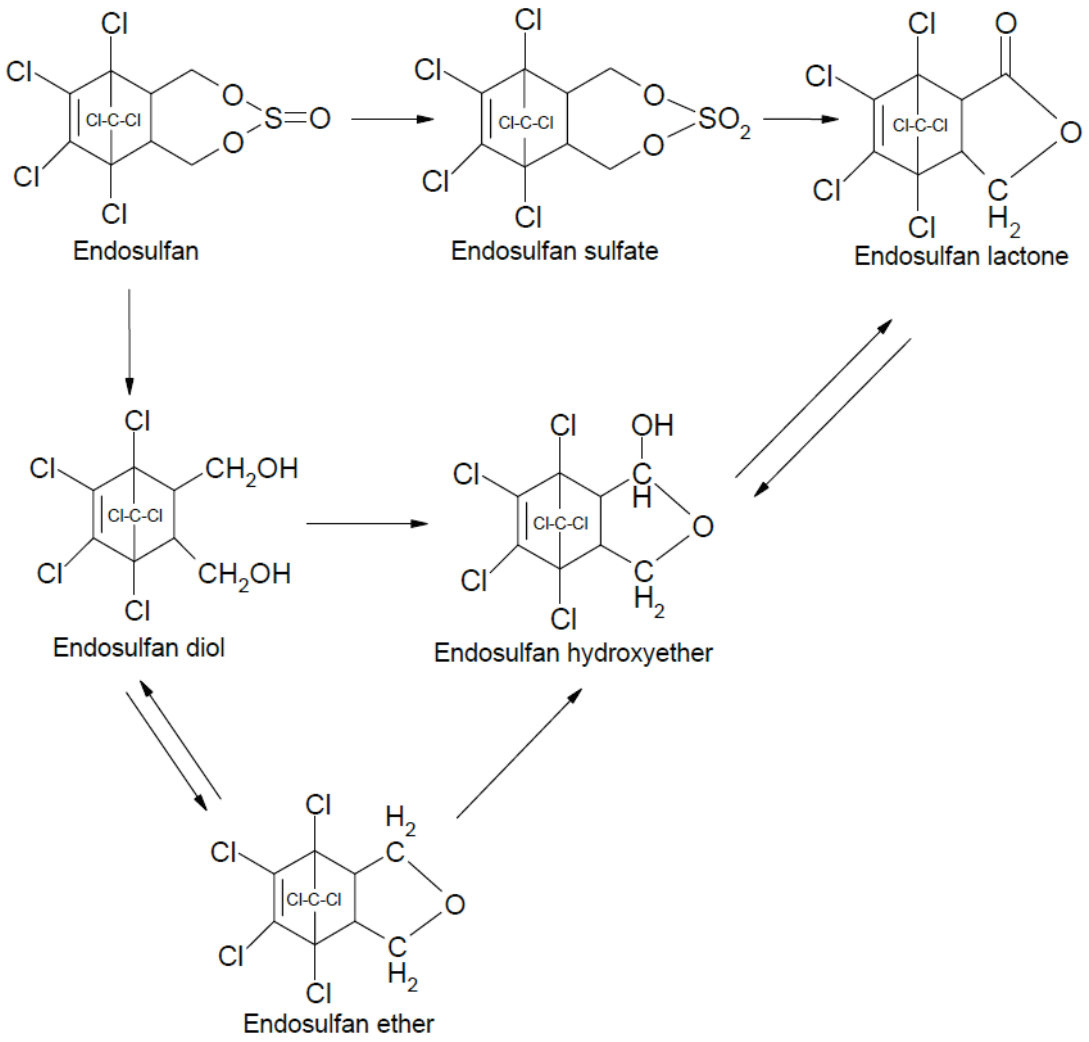

Figure B.1. Proposed Metabolic Pathway for Endosulfan
Source: ATSDR (2000)

Mode of Action/Mechanistic Studies

ATSDR (2000) summarizes the available evidence on the mode of action for endosulfan. Table B.2 also summarizes these studies, which indicate that the neurotoxicity induced by endosulfan involves a GABA-antagonism mechanism of toxicity via binding of endosulfan at multiple receptors in neurons and inhibiting the GABAergic function. While no data on the immunotoxic mode of action for endosulfan were identified, a close dynamic relationship exists between the neurological and immunological systems (Banerjee and Hussain, 1987). Therefore, it is possible that different modes of action exist for the neurotoxicity and immunotoxicity of endosulfan and that they are linked.

Limited data exist concerning the mode of action for the developmental effects caused by endosulfan. Wilson and LeBlanc (1998) reported an increased testosterone biotransformation in male and female mice fed endosulfan for 7 days. An in vitro study with human sperm indicated that at 1 nM, endosulfan inhibited the acrosome reaction (AR) initiated by progesterone

(ATSDR, 2000). Because chloride channels activated by GABA are involved in the AR (ATSDR, 2000), it is possible that the modes of action for the neurological, immunological, and reproductive effects of endosulfan are linked.

A full evaluation of these data is provided in ATSDR (2000).

Table B.1. Summary of Endosulfan Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium* strains TA97a, TA98, TA100, TA102, TA104, TA1535, TA1537, TA1538, and TA1978 with and without S9 activation	3,256 mg/L (Pednekar et al., 1987) 5,000 µg/plate (Shirasu et al., 1978; Moriya et al., 1983)	−	−	Endosulfan was not found to be mutagenic with or without metabolic activation; cell growth was inhibited by 90% at 1,650−3,256 mg/L among the different strains (Pednekar et al., 1987)	Pednekar et al. (1987), Moriya et al. (1983), Dorough et al. (1978), Shirasu et al. (1978), Quinto et al. (1981), Adams (1978), and Shirasu et al. (1982), as reported in Cal/EPA (2008)
	S. typhimurium strain TA98 with and without S9 activation; commercial endosulfan (7:3 α:β isomers), α-endosulfan, β-endosulfan, endosulfan diol, endosulfan ether, endosulfan hydroxyether, endosulfan lactone, and endosulfan sulfate were tested; *S. typhimurium* strains TA97a, TA100, TA102, and TA104 also were tested	1 µg/plate	+ (all compounds were tested excluding commercial endosulfan)	+ (all compounds were tested excluding commercial endosulfan)	Reverse mutations were increased in TA98 for all compounds except for the commercial endosulfan formulation (7:3 α:β isomers); more revertants were observed in TA98 than in any other strain tested; Bajpayee et al. (2006) suggested an interaction between the isomers could have inhibited the induction of a frame-shift mutation in TA98	Bajpayee et al. (2006)
	S. typhimurium strains TA97a, TA100, and TA102 with and without S9 activation; commercial endosulfan (7:3 α:β isomers), α-endosulfan, β-endosulfan, endosulfan diol, endosulfan ether, endosulfan hydroxyether, endosulfan lactone, and endosulfan sulfate were tested; *S. typhimurium* strains TA98 and TA104 also were tested	DU	±	±	Reverse mutations were increased in TA97a, TA100, and TA102 with and without S9 activation; the increases were not concentration-dependent and are, thus, equivocal	Bajpayee et al. (2006)

Table B.1. Summary of Endosulfan Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Reverse mutation	*S. typhimurium* strain TA104 with and without S9 activation; commercial endosulfan (7:3 α:β isomers), α-endosulfan, β-endosulfan, endosulfan diol, endosulfan either, endosulfan hydroxyether, endosulfan lactone, and endosulfan sulfate were tested; *S. typhimurium* strains TA97a, TA98, TA100, and TA102 also were tested	20 µg/plate	−	−	No increase in reverse mutations relative to controls in strain TA104 caused by treatment with any of the compounds tested	Bajpayee et al. (2006)
	Escherichia coli K12 strainAB1157 (repair proficient) was treated with various concentrations of endosulfan with and without ampicillin	10 µg/mL	+	NR	Mutation index increased with dose to a maximum of 14.4	Chaudhuri et al. (1999)
	E. coli (strain not specified)	NR	−	NR	Results reported by Cal/EPA (2008) in summary table only	Fahrig (1974), as reported in Cal/EPA (2008)
	E. coli WP2 *hcr*	NR	−	NR	Concentration-specific data have not been provided for endosulfan although Moriya et al. (1983) reported testing up to a maximum concentration of 500 µg/plate for all pesticides examined	Moriya et al. (1983)
SOS repair induction	*E. coli* WP2 prophage λ induction assay	150 µg/mL	+	NR	Endosulfan induced prophage λ with maximum induction of 3.5-fold higher than spontaneous induction	Chaudhuri et al. (1999)

Table B.1. Summary of Endosulfan Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
SOS repair induction	*S. typhimurium* TA1535/pSK 1002 induction of *umu*	150 µg/mL	+	NR	Endosulfan induced *umu* gene expression with maximum induction of 4.2-fold higher than spontaneous induction	Chaudhuri et al. (1999)
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	*Saccharomyces cerevisiae* strain D_7 without metabolic activation; cells treated with 1% endosulfan dissolved in acetone at exposure times of 10, 20, and 30 min; treated colonies compared with 10% (v/v) acetone controls	1% (w/v)	+	NR	Endosulfan induced reverse mutations; these effects increased with exposure time	Yadav et al. (1982)
	S. cerevisiae strain D4; gene conversion assay at the *Ade 2* and *Trp 5* loci, treated for 4 hr	5,000 µg/mL	−	−	Cal/EPA (2008) reported that there was no treatment-related increase in gene conversion when compared with controls; Cal/EPA (2008) stated the study was acceptable under Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Guidelines	Milone and Hirsch (1984), as summarized in Cal/EPA (2008)
	S. cerevisiae T1/PG-154, T2/PG-155	10 µg/mL	+	NR	Results were reported by Cal/EPA (2008) in summary table only; therefore, it is unknown at which doses a significant effect occurred; Cal/EPA (2008) stated the study was not acceptable under FIFRA Guidelines	L'vova (1984), as reported in Cal/EPA (2008)
	Schizosaccharomyces pombe haploid 4-hr exposure	500 µg/L	−	−	Results reported by Cal/EPA (2008) in summary table only; Cal/EPA (2008) stated the study was not acceptable under FIFRA Guidelines	Mellano (1984), as reported in Cal/EPA (2008)

Table B.1. Summary of Endosulfan Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Mutation	*Drosophila melanogaster* fed endosulfan dissolved in dimethyl sulfoxide (DMSO) and diluted with 5% sucrose solution; induction of sex-linked recessive lethals (SLRLs) measured in males exposed as larvae (at 50 or 100 ppm) and in adult male germ cells (3 broods) exposed for 48 hr (at 150 or 200 ppm)	100 ppm (larvae) 200 ppm (adult)	+	NR	Significant increases in SLRLs in larvae at 100 ppm and in the combined data for the 3 adult male broods at 200 ppm; data suggested a dose-response induction of SLRLs	Velázquez et al. (1984)
Recombination induction	*S. cerevisiae* strain D_7 without metabolic activation; cells treated with 1% endosulfan dissolved in acetone at exposure times of 10, 20, and 30 min; treated colonies compared with 10% (v/v) acetone controls	1% (w/v)	−	NR	Endosulfan did not induce mitotic cross-over	Yadav et al. (1982)
	S. cerevisiae strain D_7 without metabolic activation; cells treated with 1% endosulfan dissolved in acetone at exposure times of 10, 20, and 30 min; treated colonies compared with 10% (v/v) acetone controls	1% (w/v)	+	NR	Endosulfan induced mitotic gene conversion; effects increased with exposure time	Yadav et al. (1982)
Chromosomal aberration	*S. cerevisiae* strain D_7 without metabolic activation; cells treated with 1% endosulfan dissolved in acetone at exposure times of 10, 20, and 30 min; treated colonies compared with 10% (v/v) acetone controls	1% (w/v)	+	NR	Endosulfan increased the percentage of aberrant colonies that formed at the *ade 2* locus; effects increased with exposure time	Yadav et al. (1982)

Table B.1. Summary of Endosulfan Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Chromosomal malsegregation	ND	ND	ND	ND	NA	NA
Mitotic arrest	ND	ND	ND	ND	NA	NA
Sex chromosome loss	Induction of sex chromosome loss in germ cells (3 broods) of adult males exposed for 24 hr	50 ppm	+	NDr	Significant increases in frequency of sex chromosome loss resulted in exceptional offspring from the germ cells of the adult male broods when data from all three broods combined	Velázquez et al. (1984)
Genotoxicity studies in mammalian cells—in vitro						
Mutation	L5178Y tk^{+}/tk^{-} mouse lymphoma cell forward mutation assay; treated for 4 hr without rat S9 metabolic activation	25 µg/mL	+	NR	In the first test, the lowest observed effective dose was 18.6 µg/mL without metabolic activation; 25 µg/mL reduced the relative total growth to 5%, and there was a 21-fold increase in mutant fraction relative to controls; in the second test, there was moderate toxicity, and mutagenic responses were 2- and 4-fold above controls	McGregor (1988)
Chromosomal aberrations	ND	ND	ND	ND	NA	NA
Sister chromatid exchange (SCE)	Human lymphoid cells, LAZ-007 cell line, incubated with 10^{-6}–10^{-4} M endosulfan for 48 hr without rat S9 metabolic activation, and for 1 hr with or without metabolic activation	10^{-6} M (48 hr)	+	NR	Significant increase in SCE frequency in cells exposed to 10^{-6}–10^{-4} M endosulfan without metabolic activation for 48 hr; no significant difference was observed for cells exposed with or without metabolic activation for 1 hr	Sobti et al. (1983)
		10^{-4} M (1 hr)	–	–		

Table B.1. Summary of Endosulfan Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Sister chromatid exchange (SCE)	Human HepG2 cells were treated with 1×10^{-12}–1×10^{-5} M α-endosulfan or	1×10^{-5} M (α-endosulfan)	−	NR	Significant increase in SCE observed for β-endosulfan at 1×10^{-7}–1×10^{-5} M; a nonsignificant increase in SCE was observed for α-endosulfan	Lu et al. (2000)
	β-Endosulfan for 48 hr and examined for SCE using single-cell gel electrophoresis (SCG) assays	1×10^{-7} M (β-endosulfan)	+			
DNA damage	Human HepG2 cells treated with 2×10^{-5}–1×10^{-3} M α-endosulfan or β-endosulfan for 1 hr and examined for DNA strand breaks using SCG assays	2×10^{-4} M (α-endosulfan)	+	NR	Significant increase in DNA strand breaks observed for α-endosulfan at 2×10^{-4}–1×10^{-3} M and for β-endosulfan at 1×10^{-3} M	Lu et al. (2000)
		1×10^{-3} M (β-endosulfan)	+			
	Chinese Hamster ovary (CHO) cells using the alkaline Comet assay with endosulfan, α-or β-endosulfan, endosulfan diol, endosulfan ether, endosulfan hydroxyether, endosulfan lactone, or endosulfan sulfate, as well as positive and negative controls	0.25 μM	+	NR	Significant increase in olive tail movement (OTM; the product of the distance of DNA migration from the body of nuclear core and the total fraction of DNA in the tail) produced by all compounds tested at 0.25−10.0 μM, except for β-endosulfan and endosulfan parent compound, which were significant at ≥1.0 μM; all compounds tested had significant concentration-dependent increase in % tail DNA at 0.25−10 μM, except for endosulfan, which was significantly increased ≥1.0 μM; α-endosulfan and endosulfan lactone produced the greatest amount of damage, and the isomeric mixture (parent compound) produced the least	Bajpayee et al. (2006)

Table B.1. Summary of Endosulfan Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
DNA damage	Human lymphocyte cells (from single male donor) using the Comet assay	0.25 µM	+	NR	All test compounds produced significant concentration-dependent increase in OTM and % tail DNA at ≥0.25 µM, except for α-endosulfan, which was significantly increased at ≥1.0 µM	Bajpayee et al. (2006)
	Human lymphocytes	100 µg/mL	−	NR	Results reported by Cal/EPA (2008) in summary table only; therefore, it is unknown at which doses a significant effect occurred; Cal/EPA (2008) stated the study was not acceptable under FIFRA Guidelines	Shirasu et al. (1978), as reported in Cal/EPA (2008)
	NMRI mice (5/sex/dose); after 6 hr, bone marrow removed and assessed for induction of micronuclei	5.0 mg/kg	−	NR	Results reported by Cal/EPA (2008) in summary table only; therefore, it is unknown at which doses a significant effect occurred; Cal/EPA (2008) stated the study was not acceptable under FIFRA Guidelines	Cifone (1983), as reported in Cal/EPA (2008)
	Rat bone marrow and spermatogonia; rats administered treatment by gavage for 5 d	11 mg/kg	−	NR	Results reported by Cal/EPA (2008) in summary table only; only one dose tested; Cal/EPA (2008) stated the study was not acceptable under FIFRA Guidelines	Dikshith and Datta (1978), as reported in Cal/EPA (2008)
	F344 male rat primary hepatocytes, autoradiographic unscheduled DNA synthesis (UDS) assay; 3 cultures/dose and 50 cells/culture were analyzed	51.0 µg/mL	−	NR	Cal/EPA (2008) reported that there was no UDS observed at any concentration tested, but there was toxicity observed at 51.0 µg/mL; Cal/EPA (2008) stated the study was acceptable under FIFRA Guidelines	Hoechst Aktiengesellschaft (1984b), as reported in Cal/EPA (2008) and ATSDR (2000)

Table B.1. Summary of Endosulfan Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
DNA damage	Human lung carcinoma (A 549 cells) UDS assayed using liquid scintillation counting	NR	±	±	ATSDR (2000) concluded the study was inconclusive because the author did not present any evidence that DNA synthesis was inhibited, and there were high background levels of DNA synthesis	Hoechst Celanese Corporation (1988), as reported in ATSDR (2000)
DNA adducts	Cultured fetal rat liver, fetal quail liver, and human liver hepatoblastoma (Hep G2) cells incubated for 72 hr with 50 µM endosulfan prepared in DMSO (<0.1% v/v medium) and 10^{-6} M dexamethasone (to maintain cytochrome P450 expression and promote cell survival); DNA-adduct formation measured using the ^{32}P-postlabeling method; mRNA extracted and hybridized (Northern blot) to cDNA probes coding for human CYP1A1, CYP2E, and CYP3A4 and rat CYP1A1, CYP2B1, and CYP3A1 as well as human glyceraldehydes 3-phosphate dehydrogenase (GADPH); real-time PCR of Hep G2 cell mRNA for expression of human CYP3A7	50 µM	+	NR	DNA adducts formed in rat and human hepatic cells, likely by selectively inducing expression of CYP3A family enzymes (CYP3A1 mRNA in rat liver cells and CYP3A7 mRNA in Hep G2 human cells); no DNA adducts were observed in quail hepatocytes	Dubois et al. (1996)
Frequency of micronuclei	Human HepG2 cells treated with 1×10^{-7}–1×10^{-3} M α-endosulfan or β-endosulfan for 48 hr and examined for increased frequency of micronuclei using SCG assays	1×10^{-3} M (α-endosulfan)	−	NR	Significant increase in frequency of micronuclei observed for β-endosulfan at 5×10^{-5}–1×10^{-3} M; nonsignificant increase in frequency of micronuclei observed for α-endosulfan	Lu et al. (2000)
		5×10^{-5} M (β-endosulfan)	+			

Table B.1. Summary of Endosulfan Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in mammals—in vivo						
Chromosomal aberrations and DNA damage	0/6, Syrian hamsters, single intraperitoneal injection of a commercial insecticide containing 35% endosulfan at 8, 16, 40, or 80 mg/kg-BW; recorded number of chromosomal aberrations induced in bone marrow cells and compared with negative controls (no treatment) and positive controls (treated with 40 mg/kg-BW cyclophosphamide)	8 mg/kg-BW	+	NA	Significant increase in the number of aberrations observed at all doses tested	Dzwonkowska and Hübner (1986)
	Mouse bone marrow	0.2, 1.0, 5.0 mg/kg	+	NA	Results reported by Cal/EPA (2008) in summary table only; therefore, it is unknown at which doses a significant effect occurred	Kurinnyĭ et al. (1982), as reported in Cal/EPA (2008)
	Mouse bone marrow	1.75, 3.5, 5.25 mg/kg	+	NA	Results reported by Cal/EPA (2008) in summary table only; therefore, it is unknown at which doses a significant effect occurred	Sharma and Guatam (1991), as reported in Cal/EPA (2008)
	Mouse bone marrow	1.0, 10 mg/kg	+	NA	Results reported by Cal/EPA (2008) in summary table only; therefore, it is unknown at which doses a significant effect occurred	L'vova (1984), as reported in Cal/EPA (2008)
Chromosomal aberrations and DNA damage	Alkaline Comet assay of DNA damage following occupational application of pesticide mixture (including endosulfan) compared with DNA levels prior to application	NR	+	NA	DNA damage in mononuclear leukocytes increased in 2 of 4 workers (pesticide mixtures)	Lebailly et al. (1998), as reported in ATSDR (2000)

Table B.1. Summary of Endosulfan Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Chromosomal aberrations and DNA damage	Cytochalasin-B method of arresting cytokinesis assessment of the frequency of micronuclei in peripheral blood lymphocytes of Chilean pesticide sprayers	NR	−	NA	Endosulfan reportedly applied by workers only 3.7% of the time (pesticide mixtures)	Venegas et al. (1998), as reported in ATSDR (2000)
	5-bromodeoxyuridine DNA-labeling technique assessment of frequency of micronuclei in Italian greenhouse workers	NR	+	NA	Exposed to mixtures	Falck et al. (1999), as reported in ATSDR (2000)
	Cytochalasin-B method of arresting cytokinesis assessment of the frequency of micronuclei in peripheral blood lymphocytes assessment of occupational exposure	NR	−	NA	Exposed to mixtures	Scarpato et al. (1996a,b) and Scarpato et al. (1997), as reported in ATSDR (2000)
Sister chromatid exchange (SCE)	ND					
DNA adducts	ND					
Mouse biochemical or visible specific locus test	ND					
Dominant lethal	Swiss albino mice	9.8, 12.7, 16.6, 21.6 mg/kg	+	NA	Results reported by Cal/EPA (2008) in summary table only; therefore, it is unknown at which doses a significant effect occurred; Cal/EPA (2008) stated the study was acceptable under FIFRA Guidelines	Milone and Hirsch, (1986), as reported in Cal/EPA (2008)

Table B.1. Summary of Endosulfan Genotoxicity						
			Results[b]			
Endpoint	Test System	Dose Concentration[a]	Without Activation	With Activation	Comments	References
	Albino mice, intraperitoneal injection	5, 10 mg/kg	−	NA	Results reported by Cal/EPA (2008) in summary table only; Cal/EPA (2008) stated the study was not acceptable under FIFRA Guidelines	Arnold (1972), as reported in Cal/EPA (2008)
Genotoxicity studies in subcellular systems						
DNA binding	ND					

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

Table B.2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute	Female albino mice were dosed orally with α- or β- endosulfan isomers or endosulfan metabolites in a 1:1 mixture of Tween80 and water. An initial dose of 120 mg/kg was administered and then increased or decreased according to the up-and-down method.	LD_{50} (mg/kg) values were as follows: α-endosulfan = 11 β-endosulfan = 36 endosulfan sulfate = 8 endosulfan hydroxyl ether = 120 endosulfan lactone = 120 endosulfan ether = 270 endosulfan diol = >2,000	α-Endosulfan and endosulfan sulfate were the most acutely toxic.	Dorough et al. (1978)
Metabolism/ toxicokinetic	In an occupational exposure to endosulfan, a worker applied 300 L of 0.7 g/L endosulfan in a greenhouse. 10 urine samples were taken for 3 d following exposure, and urine extracts were analyzed using gas chromatography tandem mass spectrometry (GC-MS/MS) to identify α- and β-endosulfan and endosulfan metabolites.	The peak endosulfan concentration in the urine of 5,368 pg/mL was reached 0.2 d after exposure and concentration decreased to near-control levels after 1.5 d (2,239−2,535 pg/mL). The half lives of α-endosulfan and β-endosulfan were 1.35 and 1.67 d, respectively, by first-order kinetics.	α-Endosulfan was excreted more quickly than β-endosulfan. Both were excreted via first order kinetics.	Arrebola et al. (1999), as reported in Cal/EPA (2008)
	In an occupational exposure to endosulfan, workers applied endosulfan for 2−5 hr/d without protective equipment or clothing, during either the day or week prior to providing urine samples. Urine samples were analyzed for endosulfan and metabolites using GC-MS/MS (Vidal et al., 1997). The amounts of endosulfan applied were not reported.	In workers applying endosulfan during the week prior to providing urine samples, 4/5 of the workers' urine contained α-endosulfan (84−123 pg/mL), β-endosulfan (<18−169 pg/mL), endosulfan sulfate (amount not reported), and endosulfan lactone (amount not reported). In workers applying endosulfan during the day prior to providing urine samples, 4/4 of the workers' urine contained α-endosulfan (787−894 pg/mL), β-endosulfan (801−896 pg/mL), endosulfan sulfate (amount not reported), and endosulfan lactone (amount not reported).	Although the amounts applied were not reported, workers exposed to endosulfan in the previous day had greater amounts of endosulfan and endosulfan metabolites in their urine than those who were exposed 1 wk earlier.	Vidal et al. (1998), Vidal (1997), as reported in Cal/EPA (2008) and ATSDR (2000)
	3 fatal human poisoning cases; blood and tissues were analyzed for combined α- and β-endosulfan concentration using gas-chromatography-electron capture detection (GC-ECD). The amounts ingested were not reported.	Blood endosulfan concentrations ranged from 0.4−0.8 mg/100 mL blood. Liver, kidney, and brain concentrations ranged from 0.08−0.14, 0.24−0.32, and 0.025−0.03 mg/100 g tissue, respectively.	Highest levels of endosulfan were found in the kidney and blood. The amount ingested was not reported.	Coutselinis et al. (1978); Coutselinis et al. (1976), as reviewed in ATSDR (2000)

Table B.2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetic	Women environmentally exposed to contaminants in rural Kazakhstan; the levels of endosulfan in breast milk were measured.	Two out of 19 breast milk samples had detectable endosulfan, but the specific concentrations were not reported.	Endosulfan is detectable in human breast milk, indicating that infants of exposed mothers may be exposed through breast milk.	Lutter et al. (1998), as reported in ATSDR (2000)
	Male albino rats were administered 2.5 or 7.5 mg/kg/d of a 2:1 α-:β-endosulfan mixture orally for 60 d. α- and β-endosulfan concentrations were measured in the testis, epididymis, seminal vesicles, ventral prostate, liver, brain, kidney, spleen, lung, and heart using gas-liquid chromatography coupled with an electron capture detector.	α-Endosulfan was measured at the highest concentration in the kidneys (574 and 1,655 ng/g, respectively, in the 2.5- and 7.5-mg/kg-d groups). β-Endosulfan was measured at the highest concentration in the seminal vesicle (960 and 1,344 ng/g, respectively, in the 2.5- and 7.5-mg/kg-d groups). Combined α- and β-endosulfan was greatest in the seminal vesicle and kidney at 1,008 and 587 ng/g, respectively, in the 2.5 mg/kg-d group. The kidney had the greatest concentration of combined endosulfan isomers in the 7.5 mg/kg-d group with 1,676 ng/g, followed by the seminal vesicle at 1,434 ng/g. The concentration of β-endosulfan was higher than α-endosulfan in the seminal vesicle, epididymis, heart, and liver in both dose groups.	α- and β-endosulfan distributed to the greatest extent into the kidneys and seminal vesicle. There were some differences in the relative distribution of α- and β-endosulfan between the two dose levels, indicating a different pattern of distribution of the two isomers.	Ansari et al. (1984)

Table B.2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetic	Female albino rats (number not specified) administered a single gavage dose of approximately 2 mg/kg [^{14}C]-labeled endosulfan in corn oil, and then feces and urine were collected.	5 d after dosing, 88% and 87% of the [^{14}C]-labeled α- and β-endosulfan administered via gavage was eliminated in the urine (13−19%) and feces (68−75%). 5 d after dosing via gavage, kidney and liver tissues showed 0.35 and 1.66 ppm of [^{14}C]-endosulfan residue, respectively, after treatment with α-endosulfan, and 0.22 and 1.13 ppm, respectively, after treatment with β-endosulfan (both were equal to a combined 1.5% of the gavage dose). Animals receiving endosulfan in the diet had the greatest distribution of [^{14}C]-endosulfan residues in the kidney and liver, where endosulfan accumulated but had a half-life of about 7 d.	α- and β-endosulfan administered via gavage were mainly eliminated through the feces and urine.	Dorough et al. (1978)
	Male rats (number not specified) had a cannula surgically implanted in their bile ducts and then received a single oral dose of 1.2 mg/kg of [^{14}C]-labeled α- or β-endosulfan.	47% and 29% of [^{14}C]-labeled α- and β-endosulfan administered via gavage, respectively, was collected in the bile via the implanted cannula after 48 hr.	Collecting the bile decreased elimination in the feces but did not alter urinary excretion of α- and β- endosulfan, suggesting that metabolites were excreted from the liver into the intestine without allowing for resorption and elimination by the kidney.	Dorough et al. (1978)
	Female albino rats (number not specified) were fed 5 ppm of either α- or β-[^{14}C]endosulfan for up to 14 d, 25 ppm of α-[^{14}C]endosulfan for 14 d, or 25 ppm of 7:3 mixture of α-:β-[^{14}C]endosulfan for 14 d. Urine and feces were collected daily. The kidney, liver, visceral fat, subcutaneous fat, muscle, and brain were removed and analyzed for [^{14}C] residue content.	Animals receiving endosulfan in the diet eliminated 61−65% of the dose after 14 d of feeding (56−57% in the feces and 7−9% in the urine). Afterwards, the animals eliminated an additional 8% during the 14 d after stopping treatment. Kidney tissues had greatest [^{14}C] residues followed by the liver. [^{14}C] residues were detected in the kidney, liver, visceral fat, subcutaneous fat, muscle, and brain.	Animals receiving α- and β-[^{14}C]endosulfan in the diet over 14 d eliminated the majority of endosulfan in the feces. The kidneys and liver contained the greatest amount of noneliminated endosulfan residues.	Dorough et al. (1978)

Table B.2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetic	Female mice (number not specified) were fed endosulfan at a dose of 7.5 mg/kg-d for 7 d, and then for an additional 36 h after a Day-7 intraperitoneal injection with 125,000 dpm [^{14}C]testosterone in 100 µL corn oil. Feces and urine were collected 8, 24, 32, and 48 h after injection and assessed for elimination of [^{14}C]testosterone. Urine samples were brought up to equal volume using distilled water, and [^{14}C]testosterone was measured using scintillation counting in a 100 µL aliquot. Ground up dried feces were oxidized to release [^{14}C] into scintillation cocktail that was then quantified via liquid scintillation spectroscopy.	94% and 97% of [^{14}C] was eliminated after 48 hr in controls and treated animals, respectively. 70% and 30% of the total recovered radioactivity were eliminated in the feces and urine, respectively. The [^{14}C] clearance rate in the feces was not affected by endosulfan treatment, but the clearance rate in the urine was increased ~3.6-fold, and the total rate of elimination was increased 2.3-fold. There was no significant effect on serum testosterone or 17β-estradiol levels caused by endosulfan treatment.	While feces is the primary route of elimination of endosulfan in mice, endosulfan treatment increased the rate of clearance of [^{14}C] administered as [^{14}C]testosterone. However, these effects were not sufficient to alter hormone homeostasis in treated mice.	Wilson and Leblanc (1998)
	Male and female cats (n = 28) were administered a single i.v. injection of 3 mg/kg endosulfan dissolved in propylene glycol and sacrificed at 15 min, 30 min, or at 1, 2, 4, or 6 hr by air administered directly to the heart. Blood was drawn, and plasma was separated. Tissue samples were taken from the liver, spinal cord, cerebral cortex, cerebellum, and brain stem. Tissues and plasma were evaluated for identification of endosulfan and endosulfan sulfate.	Peak concentrations of endosulfan in the brain were found at the earliest time point examined (15 min after administration) and then decreased. Endosulfan sulfate levels peaked in the brain at 1 hr postadministration and in the liver within 15 min postadministration.	Endosulfan sulfate is a major metabolite of endosulfan, and the liver is a site of high metabolic activity for this conversion.	Khanna et al. (1979)

Table B.2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Metabolism/ toxicokinetic	Healthy, breast-feeding volunteers (17−35 yr) were randomly selected from two hospitals in Southern Spain. Milk samples were drawn 1−7 d postdelivery (colostrum), 6−12 d (transition), and 13−35 d postdelivery transition (mature) between 11 and 12 am. For each sample, 5−10 mL was collected from the first breast, the baby was fed for 5−10 min, and more milk was drawn, and this was repeated with the other breast and combined for analysis. A liquid-liquid extraction was conducted, purified, and analyzed via gas chromatography.	Results indicated that endosulfan and endosulfan sulfate were present in human breast milk in both agricultural and urban settings and in each type of milk, allowing it to be passed from mother to child during breastfeeding.	Results indicated that endosulfan and endosulfan sulfate can be passed from mother to child during breastfeeding.	Campoy et al. (2001)
	Women of reproductive age in Southern Spain: Adipose tissue analysis: 149 women undergoing various surgeries, samples (subcutaneous abdominal fat or mammary tissue) collected during surgery. Placenta and umbilical cord blood analysis: 200 women, sampled at term deliveries. Breast milk analysis: 23 breast feeding women volunteers selected randomly from placenta volunteers; mature milk drawn Days 13−35 postdelivery. Samples were extracted and eluted using HPLC, fractions containing pesticides were analyzed by gas chromatography and electron-capture detection and then by gas chromatography and mass spectrometry.	Adipose tissue: endosulfan ether most frequently detected (49.6%); endosulfan sulfate highest mean concentration (16.16 ± 92.56 ng/g fat; 12.8% of samples). Placenta: endosulfan sulfate most frequently detected (67.5%); endosulfan diol highest mean concentration (15.62 ± 19.23 ng/g placenta). Umbilical cord serum: endosulfan diol most frequently detected (81%), α-endosulfan (76.5%); endosulfan diol highest mean concentration (13.23 ± 11.34 ng/mL serum). Human milk: endosulfan ether (100%) and endosulfan lactone (91.3%) most frequently detected; β-endosulfan highest mean concentration (10.70 ± 8.71 ng/mL human milk). Highest combined endosulfan (α- and β-) was in adipose tissue and then human milk samples. Endosulfan sulfate was found to be the main metabolite, present in all analyzed tissues.	Endosulfan and its metabolites are present in adipose tissue, placenta, umbilical cord serum, and human milk in women of reproductive age in southern Spain.	Cerillo et al. (2005)

Table B.2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Mode of action/ mechanistic	Male S-D rats were partially hepatectomized and treated for 70 d according to the following protocol: Group 1 was administered a vehicle control; Group 2 was administered technical grade endosulfan (ENDOtech) at 1 mg/kg-d; Group 3 was administered ENDOtech at 5 mg/kg-d; Group 4 (control) was not partially hepatectomized but was administered with ENDOtech at 5 mg/kg/d; Groups 5−8 were partially hepactectomized and injected with 30 mg nitrosodiethylamine (NDEA) before being administered (2 mL/kg corn oil, 1 mg/kg, and 5 mg/kg, or 500 ppm of Phenobarbital, respectively). Treatment was carried out for 10 d, and discontinued for two prior to sacrifice.	No clinical signs of toxicity observed; no significant difference was observed between test Groups 2−4 and controls in terms of body-weight gain, relative liver weights, and plasma transaminase activities; treatment Groups 6 and 7 had significantly increased relative liver weights; all rats treated with endosulfan showed congestion of the peritoneum and inner organs. No significant differences were observed between Groups 6, 7 (treatments), and 5 (control) in terms of the number of γ-glutamyltranspeptidase (GGT)-positive enzyme altered foci per cm^3, and percentage liver tissue occupied by foci. Groups 6 and 7 showed significantly decreased mean focal volume compared with Group 5. Treatment Groups 1−4 (not treated with NDEA) showed low incidence of GGT-positive hepatocyte foci.	No dose-related increase in enzyme-altered foci incidence after induction with NDEA.	Flodström et al. (1988)

Table B.2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Mode of action/ mechanistic	Male S-D rats were partially hepatectomized and treated according to the following protocol: Group 1 served as a control and was fed a normal diet; Group 2 was the positive control and was fed a diet of 750 ppm DDT; Groups 3−5 were initiated by injection of 30 mg/kg NDEA and were fed diets of 30, 100, or 300 ppm α-endosulfan (Groups 3a−3c), β-endosulfan (Groups 4a−4c), or 73:27 (α:β)-endosulfan as an isomeric mixture (Groups 5a−5c) for 20 wk. Groups 1d, 3d, 4d, and 5d were not initiated and fed standard diet or 300 ppm α-endosulfan, β-endosulfan, or 73:27 (α:β)-endosulfan.	No clinical signs of toxicity were observed. A statistically significant decrease in body-weight gain was observed in all initiated groups exposed to β-endosulfan and 73:27 (α:β)-endosulfan (Groups 4a−4c and 5a−5c, respectively) during the promotion period and in the uninitiated β-endosulfan group (4d). Absolute and relative liver and kidney weights were increased in a dose-related manner by α-endosulfan, β-endosulfan, and 73:27 (α:β)-endosulfan. Relative liver weight was significantly increased in all high-dose groups (3c−d, 4c−d, 5c−d) regardless of initiation. Relative kidney weight was significantly increased in the mid-dose groups (3b−d, 4b−d, 5b-d). Blood plasma alanine aminotransferase (ALT) activity was significantly increased in the initiated, high-dose α-endosulfan group (3c), and aspartate aminotransferase (AST) activity was significantly decreased in the initiated, mid-dose α-endosulfan group (3b) and the initiated, low-dose 73:27 (α:β)-endosulfan group (5a). A significant increase in GGT activity was observed in blood plasma in the initiated, high-dose α-endosulfan group and in the initiated, mid-dose 73:27 (α:β)-endosulfan group. All test substances caused a marginal (2−3 × control) induction of both forms of hepatic cytochrome P450-dependent mono-oxygenases, induced a dose-dependent, nonfocal diffuse expression of GGT in hepatocytes, and enhanced development of altered hepatic foci (AHF) (initiated, high-dose α-endosulfan group only).	Endosulfan enhances clonal expansion of carcinogen-induced, phenotypically altered hepatocytes, indicating that endosulfan has tumor-promoting ability, but it requires initiation by other compounds.	Fransson-Steen (1992a)

Table B.2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Mode of action/ mechanistic	WBF344 rat liver epithelial cells and male S-D primary rat hepatocytes tested endosulfan isomers for the following: (1) the effect of α- and β-endosulfan on gap junction intercellular communication (GJIC); (2) the influence of dibuturyl cyclic AMP (dB-cAMP) on GJIC inhibition induced by α- and β-endosulfan; (3) the effect of 7:3 (α:β)-endosulfan, α-, or β-endosulfan on intracellular concentration of cyclic AMP ($[cAMP]_i$); (4) concentration-response and kinetics (recovery time) of 7:3 (α:β)-endosulfan, α-, or β-endosulfan, and endosulfan metabolites on GJIC in WBF344 rat liver cells (30 min treatment).	(1) In WBF344 liver cells, α- and β-endosulfan treatment resulted in a concentration-dependent decrease in GJIC, but there was no difference in inhibition between the two isomers. In primary hepatocytes, β-endosulfan was a more potent inhibitor of GJIC compared with α-endosulfan (40% inhibition with 10 μM β compared with 40% inhibition with 50 μM α). (2) In WBF344 liver cells, pretreatment with 0.1−0.5 mM dB-cAMP significantly enhanced GJIC by approximately 25%. dB-cAMP was unable to counteract the GJIC-inhibitory effect of α- or β-endosulfan at 5 μM. In primary rat hepatocytes, no increase in GJIC was observed with 0.1−0.5 mM dB-cAMP pretreatment. However, pretreatment with 0.25 and 0.5 mM dB-cAMP significantly prevented the inhibitory effect of GJIC by 75μM β-endosulfan but not 75μM α-endosulfan. (3) In WBF344 liver cells, significant increase of $[cAMP]_i$ was observed after exposure to 5 μM 7:3 (α:β)-endosulfan for 10 min; however, after 30 min of exposure, $[cAMP]_i$ returned to normal. (4) Endosulfan sulfate and 7:3 (α:β)-endosulfan strongly inhibited GJIC at ≥5−10 μM (complete inhibition at 25 μM); however, the effects were reversible and returned to control levels after 30 min. Endosulfan ether inhibited GJIC at ≥10 μM (complete inhibition at 100μM). Endosulfan lactone inhibited GJIC at ≥100 μM.	Differences in GJIC induced by α- and β-endosulfan in primary rat hepatocytes and rat liver epithelial cells suggest different mechanisms of inhibition in the two cell types. Endosulfan, its isomers, and metabolites are unlikely to inhibit GJIC by decreasing intracellular cAMP.	Fransson-Steen (1992b)

Table B.2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Mode of action/ mechanistic	5−10 male or female mice were fed endosulfan at doses of 0, 3.8, 7.5, or 15 mg/kg-d for approximately 7 d. Livers were removed, and microsomal and cytosolic cell fractions were isolated. Testosterone hydroxylase, 17 β-hydroxysteroid dehydrogenase, UDP-glucuronosyltransferase activities were assayed using microsomal protein and [^{14}C]testosterone. Sulfotransferase activity was assayed using cytosolic protein [^{14}C]testosterone. Thin-layer chromatography was used to isolate metabolites, and liquid scintillation spectroscopy and liquid scintillation counting were used to quantify the products of the various enzymatic reactions assayed.	BW was decreased in males at 15 mg/kg-d. Endosulfan treatment resulted in a significant dose-dependent increase in testosterone hydroxyl metabolite formation in female mice, with the most frequent hydroxylation occurring at the 16β-position. In males, treatment significantly reduced the rate of conversion of testosterone to androstenedione and increased hydroxylation at the 16β- position (significantly at only 15 mg/kg-d). Glucuronic acid and sulfate conjugation rates were unaffected. Serum testosterone and 17β-estradiol levels were slightly decreased although the difference was not statistically significant.	Endosulfan treatment resulted in increased testosterone biotransformation in male and female mice although the increased rate of elimination of testosterone compensated for these effects. There was no effect on serum testosterone levels.	Wilson and Leblanc (1998)
	^{3}H-dihydropicrotoxinin and GABA receptors were used. No other methodological details were provided.	The ability of endosulfan to induce convulsions was correlated with its potency as a noncompetitive GABA antagonist acting at the chloride channel within the GABA receptor. By inhibiting GABA-induced chloride flux into the neurons, the membranes become hyperpolarized, and cell firing is inhibited.	Endosulfan acts as a noncompetitive GABA antagonist at the chloride channel within the GABA receptor in brain synaptosomes.	Abalis et al. (1986); Cole and Casida (1986); Gant et al., (1987); and Ozoe and Matsumura (1986), as reported in ATSDR (2000)
	Primary cultures of cortical neurons from 15-d-old mice fetuses were used. No other methodological details were provided.	α-Endosulfan blocked the chloride uptake induced by GABA by interacting with the t-butylbicyclophosphorothionate binding site.	GABA-antagonism mechanism of toxicity via binding of endosulfan at multiple receptors in neurons and inhibiting GABAergic function.	Pomés et al. (1994), as reported in ATSDR (2000)

BW = body weight; DU = data unsuitable; NA = not applicable; NV = not available; ND = no data; NDr = not determinable; NR = not reported; NR/Dr = not reported by the study author but determined from data; NS = not selected.

APPENDIX C. DATA TABLES

Table C.1. Summary of Multiple Regression Analysis of SMR (Sexual Maturity Rating) Parameters Against Age and Endosulfan Aerial Spray Exposure[a]

SMR Parameter	R^2	Intercept (b_0)	Age		AEE (Aerial Endosulfan Exposure)	
			b_1	SE	b_2	SE
Pubic hair	0.48**	−2.54**	0.36**	0.03	−0.43**	0.11
Testes	0.43**	−2.07**	0.32**	0.03	−0.32*	0.11
Penis	0.43**	−2.00**	0.32**	0.03	−0.37*	0.12

[a]Sayied et al. (2003).

*Significantly different from controls at $p < 0.05$; multiple regression analyses performed by the study authors.
**Significantly different from controls at $p < 0.01$; multiple regression analyses performed by the study authors.

Table C.2. Serum Endosulfan Levels in Study and Control Subjects[a]

Parameter[b]	Controls (n = 45)	Study (n = 70)
α-Endosulfan (ppb)	0.87 ± 0.23	4.24 ± 0.74** (487)
β-Endosulfan (ppb)	0.40 ± 0.17	1.77 ± 0.36** (443)
Endosulfan sulfate (ppb)	0.10 ± 0.08	1.47 ± 0.33** (1,470)
Total endosulfan (ppb)	1.37 ± 0.40	7.47 ± 1.19** (545)

[a]Sayied et al. (2003).
[b]Mean ± SE (% of controls).

**Significantly different from controls at $p < 0.01$; multiple regression analyses performed by the study authors.

Table C.3. Growth-Related Parameters in Study and Control Subjects[a]

Parameter[b]	Controls (n = 90)	Study (n = 117)
Age (years)	13.10 ± 2.12	12.80 ± 2.07 (98)
Height (cm)	141 ± 10.60	139 ± 13.30 (99)
Weight (kg)	30.70 ± 7.44	29.50 ± 8.93 (96)
Body mass index	15.30 ± 1.98	15.00 ± 2.11 (98)
Skin-fold thickness (mm)	7.31 ± 2.15	7.40 ± 2.28 (101)

[a]Sayied et al. (2003).
[b]Mean ± SD (% of controls).

Table C.4. Albumin Versus Globulin Ratio of Serum in Tetanus Toxoid-Stimulated and Unstimulated Rats Exposed to Various Levels of Endosulfan for 8−22 Weeks[a,b]

Parameter		Exposure Group (mg/kg-d)			
		0	0.5	0.9	1.8
Stimulated					
Albumin: globulin ratio[c]	8 wk	1.00 ± 0.14	1.00 ± 0.20 (100)	1.10 ± 0.21 (110)	1.08 ± 0.14 (108)
	12 wk	0.94 ± 0.17	1.05 ± 0.10 (112)	1.05 ± 0.05 (112)	1.11 ± 0.12* (118)
	18 wk	0.96 ± 0.11	1.02 ± 0.10 (106)	1.00 ± 0.25 (104)	1.10 ± 0.15* (115)
	22 wk	0.85 ± 0.11	1.00 ± 0.14 (118)	1.14 ± 0.20* (134)	1.15 ± 0.10* (135)
Unstimulated					
Albumin: globulin ratio[c]	8 wk	1.26 ± 0.26	1.23 ± 0.11 (98)	1.17 ± 0.15 (93)	1.20 ± 0.12 (95)
	12 wk	1.25 ± 0.10	1.36 ± 0.21 (109)	1.21 ± 0.04 (97)	1.18 ± 0.14 (94)
	18 wk	1.15 ± 0.14	1.14 ± 0.17 (99)	1.22 ± 0.07 (106)	1.30 ± 0.05 (113)
	22 wk	1.25 ± 0.14	1.16 ± 0.21 (93)	1.14 ± 0.16 (91)	1.20 ± 0.15 (96)

[a]Banerjee and Hussain (1986).
[b]Stimulated rats were immunized with tetanus toxoid in Freund's complete adjuvant 20 d prior to termination of treatment. Unstimulated rats were treated in a manner similar to stimulated rats except for immunization.
[c]Albumin:globulin ratios were calculated from percentage of total protein content. Values are expressed as mean ± standard deviation (% relative to controls) of 10−12 rats per group.

*Significantly different from controls at $p < 0.05$; ANOVA performed by the study authors.

Table C.5. Serum Immunoglobulin Concentrations in Tetanus Toxoid-Stimulated and Unstimulated Rats Exposed to Various Levels of Endosulfan for 8−22 Weeks[a,b]

Parameter		Exposure Group (mg/kg-d)			
		0	0.5	0.9	1.8
Stimulated[c]					
Serum IgM (mg/mL)	8 wk	0.70 ± 0.12	0.66 ± 0.12 (94)	0.64 ± 0.15 (91)	0.63 ± 0.10 (90)
	12 wk	0.72 ± 0.11	0.64 ± 0.12 (89)	0.64 ± 0.10 (89)	0.60 ± 0.15 (83)
	18 wk	0.68 ± 0. 13	0.64 ± 0.10 (94)	0.60 ± 0.10 (88)	0.57 ± 0.14 (84)
	22 wk	0.70 ± 0.12	0.64 ± 0.15 (91)	0.58 ± 0.18 (83)	0.55 ± 0.10 (79)
Serum IgG (mg/mL)	8 wk	15.56 ± 1.50	14.88 ± 2.30 (96)	14.61 ± 2.22 (94)	14.05 ± 2.07 (90)
	12 wk	15.11 ± 1.20	14.00 ± 2.80 (93)	13.00 ± 2.08* (86)	12.75 ± 1.15* (84)
	18 wk	15.01 ± 2.62	14.08 ± 2.20 (94)	12.70 ± 1.60* (85)	12.15 ± 1.30* (81)
	22 wk	15.20 ± 1.20	14.00 ± 2.12 (92)	12.10 ± 2.10** (80)	12.56 ± 1.45** (83)
Unstimulated[c]					
Serum IgM (mg/mL)	8 wk	0.52 ± 0.10	0.49 ± 0.16 (94)	0.44 ± 0.12 (85)	0.45 ± 0.15 (87)
	12 wk	0.51 ± 0.13	0.50 ± 0.15 (98)	0.45 ± 0.06 (88)	0.44 ± 0.15 (86)
	18 wk	0.50 ± 0.10	0.49 ± 0.13 (98)	0.44 ± 0.20 (88)	0.45 ± 0.10 (90)
	22 wk	0.52 ± 0.15	0.48 ± 0.12 (92)	0.42 ± 0.16 (81)	0.42 ± 0.13 (81)
Serum IgG (mg/mL)	8 wk	12.50 ± 2.53	11.15 ± 1.03 (89)	12.19 ± 1.50 (98)	11.60 ± 1.30 (93)
	12 wk	12.40 ± 2.15	12.00 ± 2.00 (97)	12.17 ± 1.60 (98)	10.11 ± 2.50 (82)
	18 wk	11.24 ± 1.88	10.18 ± 1.81 (91)	10.18 ± 1.50 (91)	10.35 ± 1.66 (92)
	22 wk	11.50 ± 2.20	10.57 ± 2.50 (92)	10.43 ± 1.70 (91)	10.00 ± 1.30 (87)

[a]Banerjee and Hussain (1986).
[b]Stimulated rats were immunized with tetanus toxoid in Freund's complete adjuvant 20 d prior to termination of treatment. Unstimulated rats were treated in a manner similar to stimulated rats except for immunization.
[c]Values are expressed as mean ± standard deviation (% relative to controls) of 10−12 rats per group.

*Significantly different from controls at $p < 0.05$; ANOVA performed by the study authors.
**Significantly different from controls at $p < 0.01$; ANOVA performed by the study authors.

Table C.6. Antibody Response of Male Wistar Albino Rats to Tetanus Toxoid After 8−22 Weeks of Treatment to Endosulfan[a,b]

Parameter		Exposure Group (mg/kg-d)			
		0	**0.5**	**0.9**	**1.8**
No. of animals		10−12	10−12	10−12	10−12
$-Log_2$ antibody titer[c]	8 wk	14.53 ± 1.05	13.72 ± 2.17 (94)	12.72 ± 1.30* (88)	10.30 ± 1.73** (71)
	12 wk	14.80 ± 0.99	13.81 ± 1.55 (93)	12.32 ± 1.61* (83)	12.13 ± 1.67** (82)
	18 wk	14.90 ± 0.93	13.96 ± 1.92 (94)	10.99 ± 1.49** (74)	8.57 ± 1.36** (58)
	22 wk	14.80 ± 1.18	15.17 ± 0.74 (103)	9.66 ± 1.67** (65)	8.79 ± 1.11** (59)

[a]Banerjee and Hussain (1986).
[b]Data digitized for this review.
[c]Values are expressed as mean ± S.D (% relative to controls).

*Significantly different from controls at $p < 0.05$; ANOVA performed by the study authors.
**Significantly different from controls at $p < 0.01$; ANOVA performed by the study authors.

Table C.7. Leukocyte Migration Inhibition (LMI) Response of Male Wistar Albino Rats to Tetanus Toxoid After 8−22 Weeks of Treatment to Endosulfan[a,b]

Parameter		Exposure Group (mg/kg-d)			
		0	**0.5**	**0.9**	**1.8**
No. of animals		10−12	10−12	10−12	10−12
Leukocyte migration inhibition (%)[c]	8 wk	45.37 ± 3.08	40.23 ± 9.74 (89)	38.42 ± 7.44* (89)	34.31 ± 7.69** (76)
	12 wk	50.18 ± 6.15	49.91 ± 6.92 (99)	40.16 ± 8.21* (80)	32.97 ± 5.64** (66)
	18 wk	48.07 ± 5.38	43.70 ± 11.28 (91)	30.35 ± 6.92** (63)	24.70 ± 13.85** (51)
	22 wk	46.21 ± 4.87	40.30 ± 6.15 (87)	30.29 ± 5.13** (66)	30.54 ± 4.62** (66)

[a]Banerjee and Hussain (1986).
[b]Data digitized for this review.
[c]Values are expressed as mean ± S.D (% relative to controls).

*Significantly different from controls at $p < 0.05$; ANOVA performed by the study authors.
**Significantly different from controls at $p < 0.01$; ANOVA performed by the study authors.

Table C.8. Macrophage Migration Inhibition (MMI) Response of Male Wistar Albino Rats to Tetanus Toxoid After 8−22 Weeks of Treatment to Endosulfan[a,b]

Parameter		Exposure Group (ppm)			
		0	**0.5**	**0.9**	**1.8**
No. of animals		10−12	10−12	10−12	10−12
Macrophage migration inhibition (%)[c]	8 wk	35.36 ± 6.11	32.52 ± 5.86 (92)	27.91 ± 5.35* (79)	25.58 ± 5.09** (72)
	12 wk	31.87 ± 7.64	30.82 ± 5.61 (97)	23.40 ± 4.84** (73)	21.33 ± 4.84** (67)
	18 wk	31.18 ± 5.60	26.31 ± 5.09 (84)	16.60 ± 5.09** (53)	18.35 ± 4.84** (59)
	22 wk	35.84 ± 5.09	30.21 ± 8.92 (84)	14.89 ± 12.73** (42)	10.27 ± 9.68** (29)

[a]Banerjee and Hussain (1986).
[b]Data digitized for this review.
[c]Values are expressed as mean ± S.D (% relative to controls).

*Significantly different from controls at $p < 0.05$; ANOVA performed by the study authors.
**Significantly different from controls at $p < 0.01$; ANOVA performed by the study authors.

Table C.9. Maternal Body Weight and Food Consumption for Female F344 Rats After Oral Exposure to Endosulfan from GD 6−PND 21[a]

Observation/ Study Week[c]	Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]			
	0	50 (3.74)	150 (10.8)	400 (29.8)
Mean body weight (g)				
GD 0	202.5 ± 2.44	196.5 ± 2.71 (97)	198.7 ± 2.91 (98)	198.5 ± 2.16 (98)
GD 6	221.8 ± 3.99	213.9 ± 3.76 (96)	220.1 ± 3.16 (99)	220.0 ± 2.12 (99)
GD 13	250.7 ± 3.16	238.3 ± 3.11* (95)	226.6 ± 3.00* (90)	209.7 ± 2.60** (84)
GD 20	311.6 ± 4.25	293.6 ± 4.24* (94)	282.8 ± 4.11** (91)	268.2 ± 3.36** (86)
LD 0	241.1 ± 3.74	231.2 ± 3.55 (96)	219.1 ± 3.27** (91)	210.7 ± 3.64** (87)
LD 4	253.0 ± 3.61	241.4 ± 3.25 (95)	234.0 ± 4.00** (92)	226.0 ± 2.51** (89)
LD 7	262.0 ± 3.62	255.7 ± 2.79 (98)	245.3 ± 4.04* (94)	241.6 ± 3.53** (92)
Mean food consumption (g/animal/d)				
GDs 6−13[d]	19.8 ± 0.39	17.5 ± 0.54** (88)	12.8 ± 0.31** (65)	9.5 ± 0.32** (48)
GDs 13−20	21.2 ± 0.43	19.7 ± 0.55 (93)	18.1 ± 0.53** (85)	17.5 ± 0.53** (83)
LDs 0−7	34.2	32.1 (94)	31.4 (92)	32.2 (94)
LDs 7−14	50.6	49.1 (97)	48.3 (95)	48.8 (96)
LDs 14−21	61.7	58.5 (95)	60.7 (98)	60.5 (98)
LDs 0−21	146.5	139.7 (95)	140.4 (96)	141.5 (97)

[a]Gilmore et al. (2006).
[b]Doses reported in data evaluation record; unclear if converted by authors or reviewers.
[c]Values expressed as mean ± SD (% of control); % was calculated.
[d]No standard deviations provided in data evaluation record.

*Significantly different from control at $p < 0.05$; test was not reported.
**Significantly different from control at $p < 0.01$; test was not reported.

Table C.10. Litter-based Body Weights of Pups from Female F344 Rats Exposed to Endosulfan from GD 6−PND 21[a]

Observation/ Study Day[c]	Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]			
	0	**50 (3.74)**	**150 (10.8)**	**400 (29.8)**
No. of litters	23	23	23	21
Preweaning mean body weight (g)—male				
PND 0	5.8 ± 0.09	5.8 ± 0.11 (100)	5.9 ± 0.09 (102)	5.9 ± 0.12 (102)
PND 4[d]	9.2 ± 0.18	9.1 ± 0.21 (99)	8.7 ± 0.19 (95)	8.5 ± 0.25 (92)
PND 4[e]	9.3 ± 0.18	9.1 ± 0.21 (98)	8.8 ± 0.18 (95)	8.5 ± 0.26 (91)
PND 11	24.3 ± 0.42	22.3 ± 0.49** (92)	21.5 ± 0.50** (88)	21.1 ± 0.52** (87)
PND 17	37.6 ± 0.67	35.0 ± 0.82* (93)	34.3 ± 0.68** (91)	33.3 ± 0.61** (89)
PND 21	47.5 ± 0.78	44.5 ± 1.10 (94)	43.9 ± 0.81** (92)	42.5 ± 0.86** (89)
Preweaning mean body weight (g)—female				
PND 0	5.5 ± 0.08	5.5 ± 0.10 (100)	5.6 ± 0.08 (102)	5.6 ± 0.10 (102)
PND 4[d]	8.9 ± 0.17	8.8 ± 0.17 (99)	8.4 ± 0.17 (94)	8.2 ± 0.24* (92)
PND 4[e]	8.9 ± 0.17	8.7 ± 0.17 (98)	8.5 ± 0.18 (96)	8.2 ± 0.23 (92)
PND 11	23.6 ± 0.36	21.7 ± 0.46** (92)	20.9 ± 0.54** (89)	20.4 ± 0.48** (86)
PND 17	36.5 ± 0.63	34.1 ± 0.78 (93)	33.5 ± 0.70** (92)	32.5 ± 0.59** (89)
PND 21	45.9 ± 0.62	43.0 ± 0.97* (94)	42.7 ± 0.90 (93)	41.3 ± 0.83** (90)
Postweaning mean body weight (g)—male				
PND 28	77.0 ± 10.4	75.0 ± 7.6 (97)	71.5 ± 6.9 (93)	69.1 ± 7.8* (90)
PND 35	125.4 ± 13	117.7 ± 113.2 (94)	111.3 ± 10.5* (89)	110.1 ± 11.7* (88)
PND 42	171.6 ± 14.4	162.2 ± 15.7 (95)	154.7 ± 12.8* (90)	154.0 ± 14.6* (90)
PND 49	214 ± 15.6	203 ± 17.6 (95)	194.5 ± 14.2* (91)	193.2 ± 18.1* (90)
PND 56	257 ± 17.9	245.7 ± 20 (96)	236.9 ± 16.6* (92)	234.9 ± 21* (91)
PND 63	289.3 ± 19.3	277.8 ± 24 (96)	269.5 ± 17* (93)	267.2 ± 23.2* (92)
PND 70	317.6 ± 22.7	304.8 ± 26.7 (96)	297.0 ± 19.1* (94)	294.0 ± 25.1* (93)

Table C.10. Litter-based Body Weights of Pups from Female F344 Rats Exposed to Endosulfan from GD 6−PND 21[a]

Observation/ Study Day[c]	Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]			
	0	**50 (3.74)**	**150 (10.8)**	**400 (29.8)**
Postweaning mean body weight (g)—female				
PND 28	75.5 ± 10.3	73.3 ± 6.7 (97)	70.5 ± 6.6 (93)	67.5 ± 7.6* (89)
PND 35	111.7 ± 9.8	108.5 ± 8.3 (97)	105.7 ± 7.7 (95)	102.2 ± 9.0* (91)
PND 42	136.8 ± 9.4	134.6 ± 8.7 (98)	130.8 ± 7.2 (96)	126.6 ± 9.8* (93)
PND 49	152.1 ± 9.9	149.1 ± 9.7 (98)	146.0 ± 8.4 (96)	142.6 ± 11.2* (94)
PND 56	171.3 ± 11.6	167.2 ± 11.5 (98)	166.4 ± 8.9 (97)	161.9 ± 12.5 (95)
PND 63	181.8 ± 11.5	178.2 ±11.5 (98)	178.0 ± 9.4 (98)	172.9 ± 12.9 (95)
PND 70	191.0 ± 11.4	187.6 ± 11.4 (98)	188.2 ± 10.2 (99)	182.9 ± 13.7 (96)

[a]Gilmore et al. (2006).
[b]Doses reported in data evaluation record; unclear if converted by authors or reviewers.
[c]Values expressed as mean ± SE (% of control); % was calculated.
[d]Before standardization (culling).
[e]After standardization (culling).

*Significantly different from control at $p < 0.05$; test was not reported.
**Significantly different from control at $p < 0.01$; test was not reported.

Table C.11. Mean Age of Sexual Maturation in Offspring Female Wistar Rats After Oral Exposure to Endosulfan from GD 6−PND 21[a]

Observation/ Study Week[c]	Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]			
	0	**50 (3.74)**	**150 (10.8)**	**400 (29.8)**
Number of animals (M/F)	66/77	67/69	69/69	63/63
Day of preputial separation (males)	44.9 ± 0.40	44.8 ± 0.29 (100)	47.1 ± 0.49* (105)	46.8 ± 0.43* (104)
Day of vaginal opening (females)	33.0 ± 0.27	34.0 ± 0.30* (103)	34.2 ± 0.40* (104)	34.0 ± 0.40 (103)

[a]Gilmore et al. (2006).
[b]Doses reported in data evaluation record; unclear if converted by authors or reviewers.
[c]Values expressed as mean ± SD (% of control); % was calculated.

*Significantly different from control at $p < 0.05$; test was not reported.

APPENDIX D. BMD OUTPUTS

Table D.1. Summary of the Viable BMD Models for the Screening Subchronic p-RfD for Endosulfan Sulfate

Study and Year	Endpoint	Gender/ Species	Model Name	BMD	BMDL	Goodness of Fit *p*-Value	AIC	Scaled Residual of Interest
Gilmore et al. (2006)	**Pup BW PND 11**	**F**	**Hill (constant variance)**	**1.6**	**0.29**	**0.9598**	**235.99**	**0.003**
Gilmore et al. (2006)	Pup BW PND 11	M	Exponential (M4) (constant variance)	1.9	0.61	0.7264	243.14	−0.122
Dalsenter et al. (1999)	Daily Sperm Production	M	Linear (constant variance)	0.85	0.68	0.7639	345.39	−0.245
Dalsenter et al. (1999)	Relative Testicular Weight PND 65	M	Linear (constant variance)	1.17	0.91	0.1735	−286.66	1.100

BW = body weight.

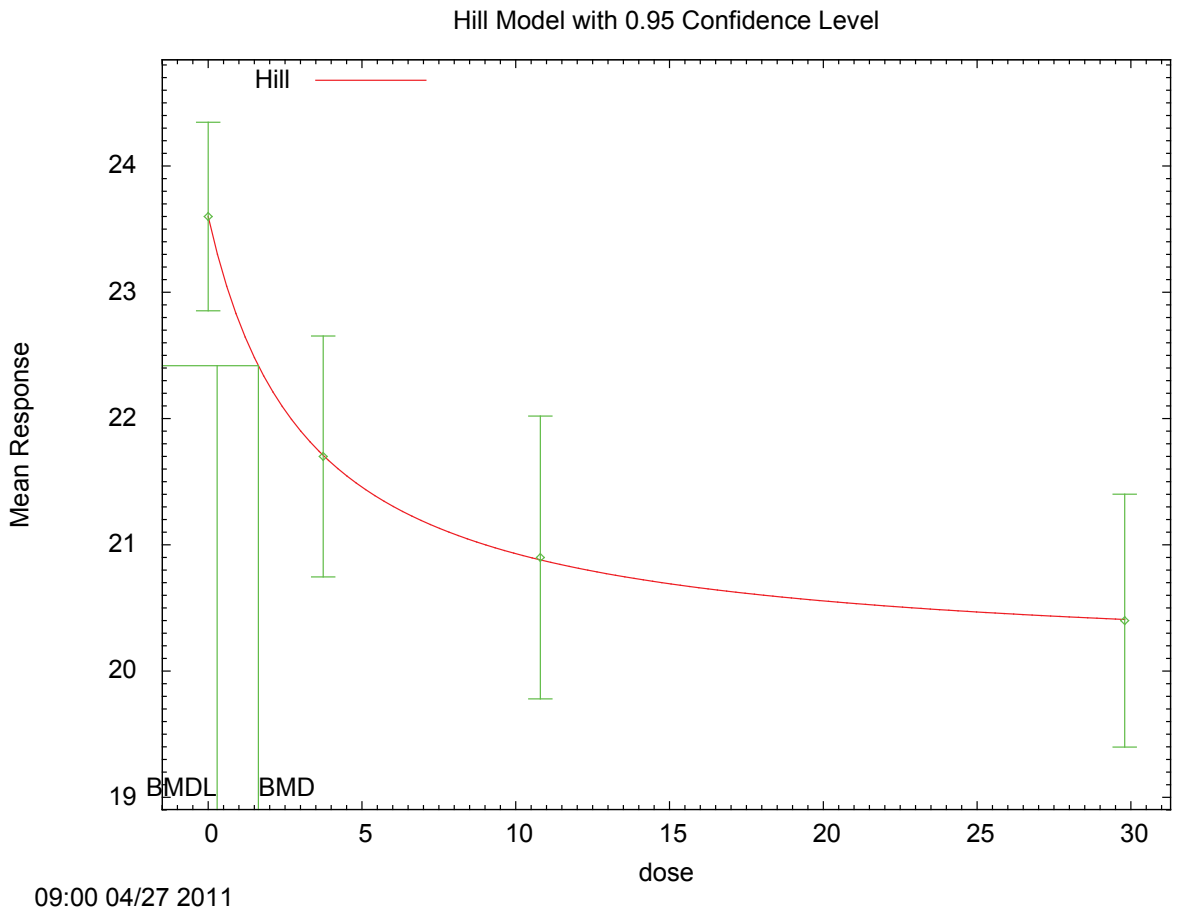

Figure D.1. Gilmore et al., 2006_Female Pup Body Weight PND 11_HillCV_RD10

```
 ================================================================================
        Hill Model. (Version: 2.15;  Date: 10/28/2009)
        Input Data File: C:/1/Gilmore et al 2006_Female Pup body weight PND
11_HillCV_RD10.(d)
        Gnuplot Plotting File:  C:/1/Gilmore et al 2006_Female Pup body
weight PND 11_HillCV_RD10.plt
                                          Wed Apr 27 09:00:26 2011
 ================================================================================

 add notes
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
```

A constant variance model is fit

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

Default Initial Parameter Values

alpha =	4.84843	
rho =	0	Specified
intercept =	23.6	
v =	-3.2	
n =	1.78837	
k =	3.14947	

Asymptotic Correlation Matrix of Parameter Estimates

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

	alpha	intercept	v	k
alpha	1	-4.4e-008	5.1e-008	-9.9e-009
intercept	-4.4e-008	1	-0.51	-0.33
v	5.1e-008	-0.51	1	-0.53
k	-9.9e-009	-0.33	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	4.63307	0.690658	3.27941	5.98674
intercept	23.5988	0.448458	22.7199	24.4778
v	-3.5371	0.777193	-5.06037	-2.01383
n	1	NA		
k	3.26121	2.61941	-1.87274	8.39516

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

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	23	23.6	23.6	1.73	2.15	0.00258
3.74	23	21.7	21.7	2.21	2.15	-0.0208
10.8	23	20.9	20.9	2.59	2.15	0.0399
29.8	21	20.4	20.4	2.2	2.15	-0.0227

Model Descriptions for likelihoods calculated

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

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

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

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

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-113.993646	5	237.987292
A2	-112.152379	8	240.304758
A3	-113.993646	5	237.987292
fitted	-113.994919	4	235.989837
R	-126.468005	2	256.936011

Explanation of Tests

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

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	28.6313	6	<.0001

Test 2	3.68253	3	0.2978
Test 3	3.68253	3	0.2978
Test 4	0.00254481	1	0.9598

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

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

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

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

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Relative risk

Confidence level = 0.95

BMD = 1.63249

BMDL = 0.290268

APPENDIX E. REFERENCES

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