10-31-2003

Provisional Peer Reviewed Toxicity Values for

Endosulfan sulfate

(CASRN 1031-07-8)

Derivation of a Chronic Oral RfD

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

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
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
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
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
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

10-31-2003

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ENDOSULFAN SULFATE (CASRN 1031-07-8)
Derivation of a Chronic Oral RfD

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may 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), or OSRTI.

INTRODUCTION

An RfD for endosulfan sulfate is not available on IRIS (U.S. EPA, 2002), the Drinking Water Standards and Health Advisories list (U.S. EPA, 2000a), or the HEAST (U.S. EPA, 1997). Existing regulations for endosulfan sulfate have been based on data for endosulfan. Endosulfan is composed of two isomers: α-endosulfan (70%) and β-endosulfan (30%). Technical endosulfan is at least 94% endosulfan isomers, but also contains a small amount of endosulfan sulfate, which occurs as a result of oxidation, biotransformation, or photolysis of endosulfan isomers (ATSDR, 2000). For endosulfan sulfate, the national recommended water quality criteria human health values for consumption of "water + organism" and "organism only" are 110 and 240 μg/L, respectively (U.S. EPA, 1999a), derived from the RfD for endosulfan (U.S. EPA, 2002). WHO (1982) derived a temporary acceptable daily intake for man of 0 - 0.008 mg/kg body weight for α-endosulfan, β-endosulfan and endosulfan sulfate combined, based on unpublished endosulfan

feeding studies in dogs and rats; NOAEL values were 0.75 and 1.5 mg/kg, respectively (Hazleton Laboratories, 1959a,b). The CARA list (U.S. EPA, 1991a, 1994) includes an Ambient Water Quality Criteria Document (U.S. EPA, 1980) and a Health Effects Assessment for α- and β-endosulfan (U.S. EPA, 1987). A Health and Environmental Effects Document for Endosulfan was also identified (U.S. EPA, 1991b). Other EPA documents (1999b, 2000b, 2001a,b,c), a Toxicological Profile for endosulfan (ATSDR, 2000), the NTP (2002) status report, and IARC (1998) and WHO documents (1982, 1984, 1988, 1989) were consulted for relevant information. Literature searches were conducted from 1998 to December 2001 for studies relevant to the derivation of an RfD for endosulfan sulfate. The databases searched were: TOXLINE, MEDLINE, CANCERLIT, RTECS, GENETOX, HSDB, CCRIS, TSCATS, EMIC/EMICBACK and DART/ETICBACK.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No studies were identified that investigated the effects of repeated-dose oral exposure of humans to endosulfan sulfate.

Animal Studies

No animals studies were identified that investigated the effects of repeated-dose oral exposure to endosulfan sulfate.

Other Studies

Endosulfan sulfate is the primary metabolite of both α- and β-endosulfan, and has been detected in serum and tissue samples of orally-exposed animals (Braun and Lobb, 1976; Cole and Casida, 1986; Das and Garg, 1981; Deema at al., 1966; Gorbach et al., 1968; Schuphan et al., 1968) and people following acute ingestion of endosulfan (Boereboom et al., 1998; Coutselinis et al., 1978; Demeter et al., 1977; Demeter and Heyndrickx, 1978). Risk assessments and reviews for endosulfan (U.S. EPA, 2001a,b,c; ATSDR, 2000; IARC, 1998; WHO, 1984, 1988) have concluded that α-endosulfan, β-endosulfan, and endosulfan sulfate are approximately equal in toxicity; however, limited toxicity data support this conclusion.

Dorough et al. (1978) reported the results of acute lethality testing in female albino rats (27-30 g) using the method of Deichmann and LeBlanc (1943) for α-endosulfan, β-endosulfan, endosulfan sulfate and four other endosulfan metabolites. Compounds were administered orally in a 1:1 mixture of water:Tween 80. The LD_{50} approximation for endosulfan sulfate was 8

mg/kg. Lethal doses of this compound caused convulsions and death within 1 hour of treatment, but survivors showed "almost no symptoms of poisoning."

In vitro assays showed that endosulfan sulfate and endosulfan affected similar endpoints, and that the sulfate was less toxic. Endosulfan sulfate did not induce mutations in *Salmonella typhimurium* (Dorough et al., 1978). Dubey et al. (1984) observed that the toxicity of endosulfan sulfate was approximately half the toxicity of endosulfan in measurements of rat liver mitochondrial respiration and enzyme activities. Ruch et al. (1990) also observed that endosulfan sulfate was approximately half as effective as endosulfan in the inhibition of gap junctional intercellular communication in primary cultured F344 rat and B6C3F1 mouse hepatocytes. Flodstrom et al. (1988) reported that very similar toxicities were observed for endosulfan sulfate, α-endosulfan, β-endosulfan, technical endosulfan and analytical endosulfan in cytotoxicity assays and intercellular communication assays in WB rat liver cells and wild type and mutant Chinese hamster V79 lung fibroblast cells. Endosulfan sulfate and α-endosulfan exhibited similar activities in a cell free assay using extracts from adult rat prostate tissue (Brieske et al., 1997); both slightly reduced binding of the androgen [^{3}H]-methyltrienolone to androgen receptor protein.

FEASIBILITY OF DERIVING A PROVISIONAL RfD FOR ENDOSULFAN SULFATE

Derivation of a provisional reference dose for endosulfan sulfate is precluded by the lack of adequate human or animal studies.

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7-31-2003

Provisional Peer Reviewed Toxicity Values for

Endosulfan sulfate

(CASRN 1031-07-8)

Derivation of a Carcinogenicity Assessment

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

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VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ENDOSULFAN SULFATE (CASRN 1031-07-8)
Derivation of a Carcinogenicity Assessment

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

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INTRODUCTION

An assessment of the carcinogenicity of endosulfan sulfate is not available on IRIS (U.S. EPA, 2002), or in the HEAST (U.S. EPA, 1997) or Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). The CARA list (U.S. EPA, 1991a, 1994) includes a Health Effects Assessment for α- and β-endosulfan (U.S. EPA, 1987) that included no cancer data for endosulfan sulfate. Subsequent U.S. EPA documents on endosulfan have also reported no cancer data for endosulfan sulfate (U.S. EPA, 1991b, 1999). IARC (2002) has not evaluated endosulfan sulfate for carcinogenicity. Review endosulfan documents by ATSDR (2000), which included endosulfan sulfate, and WHO (1984), as well as the NTP (2002) status reports, were also consulted for relevant information. Literature searches were conducted from 1998 to December 2001 for studies relevant to the derivation of an oral slope factor for endosulfan sulfate. The databases searched were: TOXLINE, MEDLINE, CANCERLIT, RTECS, GENETOX, HSDB, CCRIS, TSCATS, EMIC/EMICBACK and DART/ETICBACK.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No studies were located regarding the carcinogenic effects of endosulfan sulfate in humans following exposure by any route.

Animal Studies

No studies were located regarding the carcinogenic effects of endosulfan sulfate in animals following exposure by any route.

Other Studies

Dorough et al. (1978) observed no evidence of mutagenicity with or without S-9 liver homogenate in *Salmonella typhimurium* strains TA1535 or TA1978 (up to 100 µg/plate), or TA98 or TA100 (up to 1000 µg/plate).

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR FOR ENDOSULFAN SULFATE

Derivation of a provisional oral slope factor for endosulfan sulfate is precluded by the lack of human or animal cancer data.

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