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Provisional Peer-Reviewed Toxicity Values for

Endosulfan
(CASRN 115-29-7)

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

COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
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
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	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR ENDOSULFAN (CASRN 115-29-7)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) 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) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. 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 U.S. EPA's 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 U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. 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 5-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 documents 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 Resource Conservation and Recovery Act (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 document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. 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 U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Endosulfan (CASRN 115-29-7) is a mixture of two stereoisomers: approximately 70% endosulfan I (endosulfan α; CASRN 959-98-8) and 30% endosulfan II (endosulfan β; CASRN 33213-65-9). A chronic reference dose (RfD) of 6×10^{-3} mg/kg-day for endosulfan is available on IRIS (U.S. EPA, 1994b). The RfD is based on reduced body weight gain in females, and increased incidence of marked progressive glomerulonephrosis and blood vessel aneurysms in males, in a 2-year rat feeding study (Hoechst Celanese Corp., 1989a), as well as decreased weight gain in males and neurologic findings in both sexes in a 1-year dog feeding study (Hoechst Celanese Corp., 1989b). In both studies, a NOAEL of approximately 0.6 mg/kg-day was identified. Uncertainty factors of 10 each for interspecies extrapolation and protection of sensitive humans were applied to the NOAEL to derive the RfD. No source document other than the IRIS record is given. The *Drinking Water Standards and Health Advisories* list (U.S. EPA, 2006) does not include an RfD for endosulfan. The HEAST (U.S. EPA, 1997) reports a subchronic RfD of 0.006 mg/kg-day for endosulfan, adopting the chronic RfD from IRIS as the subchronic RfD. In a *Toxicological Profile for Endosulfan*, ATSDR (2000) derived intermediate- and chronic-duration oral Minimal Risk Levels (MRLs) for endosulfan based on immunological and hepatic effects, respectively. The intermediate-duration oral MRL is based on a 6-week immunotoxicity study in rats exposed via the diet (Banerjee and Hussain, 1986). Uncertainty factors of 10 each for interspecies and intraspecies variability were applied to the NOAEL of 0.45 mg/kg-day to derive the intermediate-duration oral MRL of 0.005 mg/kg-day. The chronic duration oral MRL is based on the same dog-feeding study as the IRIS RfD (Hoechst Celanese Corp., 1989b). However, ATSDR selected 0.6 mg/kg-day as a LOAEL and 0.18 mg/kg-day as a NOAEL based on increased serum alkaline phosphatase levels. Uncertainty factors of 10 each for interspecies and intraspecies variability were applied to the NOAEL of 0.18 mg/kg-day to derive the chronic-duration oral MRL of 0.002 mg/kg-day.

Neither IRIS (U.S. EPA, 2009) nor the HEAST (U.S. EPA, 1997) reports an RfC for endosulfan. ATSDR (2000) has not derived any inhalation MRLs for endosulfan. ACGIH (2007), NIOSH (2005), and OSHA (2009) have all adopted the same occupational exposure limit (time-weighted average) of 0.1 mg/m^3. ACGIH cites liver damage, CNS impairment, and kidney damage as potential effects in exposed workers (ACGIH, 2007).

An assessment of the carcinogenicity of endosulfan is not available on IRIS (U.S. EPA, 2009), in the HEAST (U.S. EPA, 1997), or in the *Drinking Water Standards and Health Advisories* list (U.S. EPA, 2006). The CARA list (U.S. EPA, 1991a, 1994a) includes a Health Effects Assessment for α- and β-endosulfan (U.S. EPA, 1987) that assigned endosulfan to cancer weight-of-evidence Group D (under U.S. EPA 1986 *Guidelines for Carcinogen Risk Assessment*), "*Not classifiable as to human carcinogenicity*," based on inconclusive animal data. A subsequent draft Health and Environmental Effects Document (U.S. EPA, 1991b) also assigned endosulfan to Group D. Based on more recent negative studies, the Office of Pesticide Programs has classified endosulfan in Group E: "*Evidence of noncarcinogenicity for humans*" (U.S. EPA, 1999). Endosulfan has not previously been evaluated under the U.S. EPA (2005) *Guidelines for Cancer Risk Assessment.* NCI (1968, 1978) has conducted carcinogenicity bioassays of endosulfan. Endosulfan is not included in the *11th Report on Carcinogens* (NTP, 2005). IARC (2009) has not evaluated endosulfan for potential carcinogenicity.

Review documents by ATSDR (2000), WHO (1984, 1989), and U.S. EPA (1999, 2000, 2001) were consulted for relevant information. To identify toxicological information published since the ATSDR (2000) Toxicological Profile for Endosulfan, update literature searches were conducted in December 2007 using the following databases: MEDLINE, TOXLINE, BIOSIS DART/ETIC (each searched from 1998−December 2007), TSCATS1/2, CCRIS, GENETOX, HSDB, RTECS (not date-limited), and Current Contents (searched from June 2007−December 2007). A final search of the published literature was conducted for endosulfan (December 2007−August 2009).

A Notice of Availability for the Reregistration Eligibility Decision (RED) for Endosulfan is being published in the *Federal Register*. To obtain a copy of the RED document, please contact the OPP Public Regulatory Docket (7502C), U.S. EPA, Ariel Rios Building, 1200 Pennsylvania Avenue NW, Washington, DC 20460, telephone (703) 305-5805. Electronic copies of the RED and all supporting documents are available on the Internet at http://www.epa.gov/pesticides/reregistration/status.htm.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

Case control studies of 261 patients with breast cancer (Ashengrau et al., 1998) and 30 patients with gall bladder carcinoma (Shukla et al., 2001) did not find associations between serum levels of endosulfan and cancer.

Animal Studies

The available carcinogenicity studies for endosulfan following oral exposure have been reviewed previously (see U.S. EPA, 1987, 1991b, 1999; ATSDR, 2000; WHO, 1984). There was no evidence of carcinogenicity in male or female NMRI mice fed endosulfan in the diet at concentrations up to 18 ppm (2.5 mg/kg-day) for 2 years (Hoechst Celanese Corporation, 1988; Hack et al., 1995), in male or female Sprague-Dawley rats fed up to 75 ppm (3.25 mg/kg-day) for 2 years (Hoechst Celanese Corporation, 1989a; Hack et al., 1995), or in male or female Wistar rats fed up to 100 ppm (8 mg/kg-day) for 2 years (Keller, 1959).

Oral exposure (gavage followed by diet) of male and female B6C3F1 and B6AKF1 mice to 1.0 or 2.15 mg/kg-day of endosulfan for 73−76 weeks produced some suggestive findings including statistically significant ($p < 0.05$) elevations in total tumor incidence and pulmonary adenomas in all treatment groups combined., These findings, however, are not considered biologically relevant because no significant differences were apparent for individual endosulfan treatment groups, and because no pulmonary carcinomas were diagnosed in endosulfan-treated animals (Innes et al., 1969; NCI, 1968). Low survival in all treated B6C3F1 mice and high-dose B6AKF1 mice complicates interpretation of this study.

The results of a subsequent NCI (1978) study do not support the assessment of carcinogenicity by endosulfan. No evidence of carcinogenicity was observed in male or female B6C3F1 mice fed up to 6.9 or 3.9 ppm (1.3 or 0.76 mg/kg-day), respectively, for 78 weeks, female Osborne-Mendel rats fed up to 445 ppm (39 mg/kg-day) for 71 weeks, or male Osborne-Mendel rats fed up to 952 ppm (75 mg/kg-day) for 72−82 weeks. The maximum tolerated dose was clearly exceeded, as evidenced by high mortality in male rats and mice and other serious nonneoplastic effects (weight loss, kidney, and testicular damage) in all treated rat groups. A reevaluation of the histology slides (Reuber, 1981) reported statistically significant ($p < 0.05$) increases in certain types of tumors grouped across tissues in female rats (total neoplasia, malignant tumors, sarcomas, lymphosarcomas, and reproductive system tumors) and male rats (endocrine organ tumors). The incidence of parathyroid adenomas in male rats was also reported to be increased. In mice, the reevaluation found a marginally significant increase in the incidence of liver carcinomas in low-dose females—but not in high-dose females or males. Reuber (1981) failed to report details regarding definitions of neoplasia used, tissue occurrence of neoplasia observed, and how his data compare with data from the original study (NCI, 1978). The conclusions of the reevaluation have not been independently confirmed.

Other Studies

Evidence of hepatic tumor-promoting activity was observed in one of two studies in male Sprague-Dawley rats initiated by partial hepatectomy and nitrosodiethylamine treatment. Flodstrom et al. (1988) did not observe an increase in hepatic foci positive for γ-glutamyltranspeptidase in rats exposed to α-endosulfan, β-endosulfan, or technical endosulfan for 10 weeks at doses up to 5 mg/kg-day. In contrast, Fransson-Steen et al. (1992) observed statistically significant increases in the number and volume of hepatic foci positive for γ-glutamyltranspeptidase in larger test groups of male rats fed α-endosulfan, β-endosulfan, or technical endosulfan for 20 weeks up to 15 mg/kg-day. Based on observations that endosulfan has exhibited activity as an endocrine disruptor (U.S. EPA, 1999) and induced proliferation in hormone-responsive human (endometrial and breast) cancer cell lines (Coumoul et al., 2001; Soto et al., 1994; Vonier et al., 1996; others), a hypothesis was suggested that endosulfan may promote cancer formation in humans through a mode-of-action involving endocrine disruption.

However, other studies have produced conflicting results (e.g., Arcaro et al., 1998; Newbold et al., 2001) and insufficient data are available to evaluate the hypothesis.

Reviews generally consider endosulfan to be genotoxic (U.S. EPA, 1991b, 1999; ATSDR, 2000; WHO, 1984). Extensive mutagenicity testing in *Salmonella typhimurium* and *Escherichia coli* strains reported both positive and negative results with and without metabolic activation. Conflicting positive and negative results have also been seen in assays for mutation, gene conversion, and chromosome aberrations in *Saccharomyces cerevisae*—although no mutations were seen in *Schizosaccharomyces pombe*. Similarly, both positive and negative tests for gene mutation have been observed in cultured mouse lymphoma cells with and without metabolic activation. Endosulfan did not induce unscheduled DNA synthesis in primary rat hepatocytes. Endosulfan induced micronuclei in cultured sheep lymphocytes and sister chromatid exchange in both preimplantation embryos of hybrid mice and human lymphoid cells in vitro. Endosulfan also induced chromosome aberrations in bone marrow cells of Syrian hamsters. Both positive and negative results were seen in assays measuring the formation of micronucleated polychromatic erythrocytes in mice. Endosulfan induced sex-linked recessive lethal mutations and sex-chromosome loss in *Drosophila*. Both positive and negative results have been observed in dominant lethal mutation studies in male mice. A cluster of four women living near endosulfan-contaminated areas in Florida produced five children born with global developmental delay, hypotonia, carnitine deficiency, and β-hydroxy butyrate anomalies suggestive of mitochondrial DNA damage (Thrasher, 2000). However, it is not clear that these effects can be attributed to endosulfan exposure.

Additional information, not summarized in this document, is available from the U.S. EPA, Office of Pesticide Programs (OPP). Because endosulfan is a currently registered pesticide, many potentially useful toxicity studies have been submitted to the OPP as confidential business information (CBI). This information is unpublished and is unavailable for use in this assessment. The OPP maintains its own program for developing health-based values (e.g. RfDs and RfCs) for pesticides. Consequently, no values are developed here.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL p-RfD VALUES FOR ENDOSULFAN

A provisional oral RfD for endosulfan is not derived because an RfD is available on IRIS.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR ENDOSULFAN

A provisional inhalation reference concentration (p-RfC) is not derived because endosulfan is a currently registered pesticide. Additional information can be obtained by contacting the U.S. EPA, Office of Pesticide Programs.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ENDOSULFAN

Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the lack of available evidence suggests that there is "*Inadequate Information* [to] *Assess the Carcinogenic Potential*" of endosulfan.

Quantitative Estimates of Carcinogenic Risk

Oral Exposure

A provisional oral slope factor (p-OSF) is not derived because endosulfan is a currently registered pesticide. Additional information can be obtained by contacting the U.S. EPA, Office of Pesticide Programs.

Inhalation Exposure

A provisional inhalation unit risk (p-IUR) is not derived because endosulfan is a currently registered pesticide. Additional information can be obtained by contacting the U.S. EPA, Office of Pesticide Programs.

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