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Provisional Peer Reviewed Toxicity Values for

Endrin

(CASRN 72-20-8)

Derivation of an Oral Slope Factor

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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
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
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

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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

IRIS (U.S. EPA, 2001) classifies endrin in cancer weight-of-evidence Group D, not classifiable as to human carcinogenicity, based on inadequate human and animal data. This assessment, which was verified 10/19/88, is also found on the Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). OPP also lists endrin in Group D. No cancer assessment for endrin is contained in the HEAST (U.S. EPA, 1997). Relevant documents in the CARA list (U.S. EPA, 1991, 1994) include a Health Effects Assessment (U.S. EPA, 1987) and a Drinking Water Criteria Document (U.S. EPA, 1992). Neither of these documents derived an oral slope factor for endrin due to the absence of adequate data showing an increase in tumors in treated animals. IARC (1974, 1987) assigned endrin to Group 3, not classifiable as to its carcinogenicity to humans, based on lack of human data and inadequate animal data. Reviews by ATSDR (1996), WHO (1992), and Bus and Leber (2001), and the NTP (2001a,b) management status report and health and safety reports, were consulted for relevant information. Literature searches were conducted from 1986 to October 2001 for studies relevant to the derivation of an

oral slope factor for endrin. The databases searched were: TOXLINE, MEDLINE, CANCERLIT, RTECS, HSDB, GENETOX, CCRIS, TSCATS, EMIC/EMICBACK and, for the period August-October 2001, BIOSIS and NTIS.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

Cohort mortality studies of workers exposed to endrin and other organochlorine pesticides have found no evidence for an association between endrin and cancer in humans, but had low statistical power to detect an effect. One study, reviewed by U.S. EPA (1992, 2001), reported no increase in cancer deaths among workers exposed to endrin and other organochlorine pesticides, but was limited by short follow-up time (12 years), no exposure data, and few deaths. A study of workers in a Dutch endrin manufacturing plant, described by WHO (1992) and ATSDR (1996), found no evidence of increased cancer rates after 4-13 years of exposure and 15 years of follow-up, but the small size of the cohort gave the study low statistical power. No additional data regarding carcinogenicity of endrin in humans following oral exposure were located.

Animal Studies

The animal carcinogenicity data for endrin have previously been characterized as inadequate by U.S. EPA (1992, 2001). Negative results were reported for two strains of mice, but one study was confounded by high mortality among low-dose males because of accidental overdosing. Negative results in a dog study were considered inconclusive because of the relatively short study duration. Although NCI (1978) reported negative results for carcinogenicity in rats (because of inconsistencies in dose-relationships and statistical significance for the observed tumor increases), U.S. EPA (1992, 2001) considered the results suggestive; furthermore, the study was limited by a less-than-lifetime dosing regimen. One investigator independently reevaluated tumor data from the NCI (1978) study and concluded that results were positive; however, his criteria for classifying lesions appeared to differ from those of other investigators. No more recent animal carcinogenicity data for endrin were located.

Other Studies

Endrin yielded mostly negative results for genotoxicity in bacteria and mammalian cells *in vitro* (U.S. EPA, 1992, 2001; ATSDR, 1996). With or without metabolic activation, endrin did not produce reverse mutations in *Salmonella typhimurium* or *Escherichia coli*, but did yield positive results in an SOS test evaluating induction of reporter-gene activity in *E. coli* PQ37 (Venkat et al., 1995). Endrin was not mutagenic in mouse lymphoma cells, and did not induce DNA repair or unscheduled DNA synthesis in primary cultures of rat or hamster hepatocytes. Endrin did not increase the frequencies of sister chromatid exchanges in human lymphoid cells.

Rats and mice gavaged with single doses of endrin had significant increases in DNA single-strand breaks in liver and brain (Hassoun et al., 1993; Bagchi et al., 1992, 1993, 1995, 2000), and single-strand DNA breaks were also detected in fetal mouse livers following maternal oral administration of 4.5 mg/kg of endrin (Hassoun and Stohs, 1996); however, the same studies reported concomitant increases in lipid peroxidation in those tissues, suggesting that the observed DNA damage is due to endrin-induced oxidative damage, rather than a direct genotoxic effect of endrin.

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR FOR ENDRIN

A provisional oral slope factor for endrin cannot be derived because there are no adequate human or animal oral cancer data demonstrating carcinogenic activity.

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