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Provisional Peer Reviewed Toxicity Values for

Disulfoton

(CASRN 298-04-4)

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

An assessment of the carcinogenicity of disulfoton is not available on IRIS (U.S. EPA 2002) or in the HEAST (U.S. EPA, 1997). The Drinking Water Standards and Health Advisories list (U.S. EPA, 2000a) shows disulfoton in cancer-weight-of-evidence Group E - evidence of noncarcinogenicity for humans. The origin of this assessment was a 1988 Drinking Water Health Advisory (U.S. EPA, 1988) that reported no human data and several two-year studies in rodents that found no evidence of carcinogenicity. The CARA list (U.S. EPA, 1991, 1994) includes a Health and Environmental Effects Document (U.S. EPA, 1990) that assigned disulfoton to Group D, not classifiable as to human carcinogenicity, based on these same data. Also based on these data, the Office of Pesticide Programs classified disulfoton in Group E (U.S. EPA, 2000b,c). IARC (2001) has not evaluated the carcinogenicity of disulfoton. A Toxicological Profile for disulfoton (ATSDR, 1995), a recent review article (Storm, 2001), the NTP (2001) status report, and the WHO (2001) were also consulted for relevant information. Literature searches were conducted from 1989 to November 2001 for studies relevant to the derivation of an oral slope

factor for disulfoton. 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 cancer in humans exposed to disulfoton.

Animal Studies

The available carcinogenicity studies for disulfoton have been reviewed previously (U.S. EPA, 1988, 1990, 2000b,c; ATSDR, 1995). There was no evidence of carcinogenicity in male and female Sprague-Dawley rats fed up to 2 ppm (0.1 mg/kg-day) in the diet for 2 years (Carpy et al., 1975), male and female F344 rats fed up to 13 ppm (0.65 mg/kg-day) in the diet for 2 years (Hayes, 1985) or male and female CD-1 mice fed up to 16 ppm (2.4 mg/kg-day) in the diet for 2 years (Hayes, 1983). One- and two-year studies in dogs, described in the available reviews, also failed to find evidence of carcinogenicity, but used small numbers of animals, featured short exposure duration relative to lifetime and were not designed as cancer bioassays. No new carcinogenicity studies were located in the literature search.

The genotoxicity of disulfoton has been reviewed (U.S. EPA, 1988, 1990, 2000b,c; ATSDR 1995; Storm, 2001; Woo et al., 1996). Results were primarily negative in numerous tests for reverse mutation and differential toxicity in bacteria, with or without activation. Assays for mutation, gene conversion, mitotic crossing over, and DNA damage in the yeast *Saccharomyces cerevisiae* were uniformly negative with or without activation, while assays for genetic recombinants and chromosomal aberrations in barley seeds were all positive without activation. In mammalian cells, the test results were mixed. Results were positive for mutation in mouse lymphoma cells without, but not with, activation. With or without activation, results were negative for mutation in Chinese hamster ovary cells. Some positive and some negative results were reported for sister chromatid exchange in Chinese hamster ovary cells. There was no evidence of chromosomal aberrations in various human cell lines. Unscheduled DNA synthesis was observed in human lung fibroblasts when tested without, but not with, activation. *In vivo* studies found no effects on induction of micronuclei or dominant lethal mutations in mice, or sex-linked recessive lethal mutations in *Drosophila*. An epidemiological study in Morelos State, Mexico, observed evidence of genotoxicity in a group of 22 female and 8 male floriculturists that reportedly used disulfoton occupationally (in addition to organochlorines, carbamates, other organophosphates, and other chemicals). In comparison to unexposed controls, the floriculturists had statistically significant increases in peripheral blood lymphocyte sister chromatid exchange, cell proliferation kinetics and mitotic index (Gomez-Arroyo et al., 2000). However, it is not clear that the findings in this study can be attributed to disulfoton exposure. Overall, the data suggest that disulfoton has little genotoxic potency.

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR FOR DISULFOTON

A provisional oral slope factor for disulfoton cannot be derived because human oral cancer data are lacking and the available animal data provide no evidence of carcinogenicity.

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