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Provisional Peer Reviewed Toxicity Values for

Dinoseb

(CASRN 88-85-7)

Derivation of an Oral Slope Factor

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
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

Dinoseb is classified on IRIS in cancer weight-of-evidence Group D - not classifiable as to human carcinogenicity (U.S. EPA, 2001). The assessment, verified on 5/3/89, was based on lack of human and inadequate animal carcinogenicity data, comprising two studies in mice (Innes et al., 1969; Dow Chemical Co., 1981) and one in rats (Dow Chemical Co., 1977). Dinoseb is also listed in Group D on the Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). A cancer assessment for dinoseb is not included in the HEAST (U.S. EPA, 1997). The CARA list (U.S. EPA, 1991, 1994) includes a Health and Environmental Effects Profile (HEEP) for Dinoseb (U.S. EPA, 1984) that found no evidence for carcinogenicity of this chemical. IARC (2001) has not reviewed the carcinogenicity of dinoseb. ATSDR (2001) has not produced a Toxicological Profile for dinoseb and no Environmental Health Criteria Document is available (WHO, 2001). NTP (2001) has not studied the carcinogenic potential of dinoseb. Updated literature searches for cancer data were conducted from 1983 to 2001. The databases searched

were: TOXLINE, MEDLINE, CANCERLIT, CCRIS, TSCATS, HSDB, RTECS, GENETOX, DART/ETICBACK, and EMIC/EMICBACK.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

Case-control studies in Swedish cancer patients, described in U.S. EPA (1984), found no evidence of increased risk of malignant lymphomas or malignant mesenchymal soft tissue tumors associated with dinoseb exposure (Eriksson et al., 1979; Hardell et al., 1981).

Animal Studies

Long-term studies of dinoseb exposure in mice (Innes et al., 1969; Dow Chemical Co., 1981) and rats (Dow Chemical Co., 1977) did not show an increase in tumors and/or were inadequate studies of carcinogenicity (U.S. EPA, 1984, 2001). No additional studies subsequent to the 1989 IRIS review were located.

Other Studies

Genotoxicity assays of dinoseb have generally shown no mutagenic activity, but have demonstrated an ability to interact with DNA and RNA (U.S. EPA, 1984, 2001). In bacteria, dinoseb was not mutagenic in multiple assays in *Salmonella typhimurium* and *Escherichia coli*, but produced positive results in differential toxicity tests comparing growth of repair-/recombination-deficient and proficient strains of *S. typhimurium*, *E. coli* and *Bacillus subtilis*. Assays for mitotic gene conversion in the yeast *Saccharomyces cerevisiae* produced mixed results. A sex-linked recessive lethality assay in *Drosophila* was negative. Results were also negative for unscheduled DNA synthesis in cultured human lung fibroblasts. Sperm morphology studies showed an increase in the occurrence of abnormal sperm in treated rats, but no effect in mice.

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR FOR DINOSEB

A provisional oral slope factor for dinoseb cannot be derived due to lack of human and inadequate animal cancer data.

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