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Provisional Peer Reviewed Toxicity Values for

o,p'-Dichlorodiphenyldichloroethane *(o,p'*-DDD)

(CASRN 53-19-0)

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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

PROVISIONAL TOXICITY VALUES FOR *o,p'*-DDD (CASRN 53-19-0)

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

o,p'-DDD [1,1-dichloro-2,2-bis(2,4'-dichlorophenyl)ethane, *o,p'*-dichlorodiphenyl-dichloroethane, *o,p'*-TDE, or mitotane] was not listed on IRIS (U.S. EPA, 2007), the HEAST (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2000). The CARA list (U.S. EPA 1991, 1994) included a carcinogenicity assessment document for DDT and related compounds (U.S. EPA, 1986), but this document contained no information regarding the *o,p'* isomer of DDD. OPP did not have an oral slope factor (OSF) for *o,p*'-DDD. The ATSDR Toxicological Profile for DDT and related compounds (ATSDR, 2000) included little information relevant to carcinogenicity of *o,p*'-DDD: one equivocal epidemiological study and a few *in vitro* tests showed very weak estrogenic potential or no androgenic potential. The NTP (2007) status report listed a 2-year carcinogenicity assay by intraperitoneal (i.p.) injection and cited negative results for *in vitro* genotoxicity tests (mutagenicity in *Salmonella,* chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells). An Environmental Health Criteria document on DDT and related compounds (WHO, 1979) contained no information related to carcinogenicity of *o,p'*-DDD; the document did discuss its therapeutic use, under the name mitotane, for chemical adrenalectomy in treatment of adrenal cortical carcinoma or bilateral adrenal hyperplasia.

IARC (1991) also discussed use of *o,p'*-DDD in treatment of adrenal cortical carcinoma, but did not classify *o,p'*-DDD with regard to carcinogenicity. IARC (1974, 1991) noted the existence of a study in which testicular tumors developed in rats exposed to *o,p'*-DDD in food (Lacassagne and Hurst, 1965), but did not consider it further, probably because only three rats were permitted to survive long enough for tumors to develop. IARC (1991) concluded from the few available *in vitro* assays that there was no evidence that *o,p'*-DDD induced genetic effects. *o,p'*-DDD did not induce mutation in *Salmonella typhimurium* or induce transformation in mouse

embryos cells. An unspecified isomer of DDD did not induce unscheduled DNA synthesis in primary hepatocyte cultures from rat, mouse, or Syrian hamster. Equivocal results were reported for induction of chromosomal aberrations in cultured rodent cells. Potentially relevant mechanistic data cited in IARC (1991) included the finding that *o,p'*-DDD bound irreversibly in the alveolar and bronchiolar areas of rabbit and mouse lung.

Literature searches were conducted from 1998 to June 2000 and 2000 to 2007 for studies relevant to *o,p'*-DDD. The databases searched were TOXLINE, MEDLINE, CANCERLIT, RTECS, GENETOX, HSDB, CCRIS, TSCATS, EMIC/EMICBACK, and DART/ETICBACK.

This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

REVIEW OF PERTINENT LITERATURE

Human Studies

Reviews by U.S. EPA (1986), WHO (1979), and IARC (1974, 1991) listed no data regarding carcinogenicity of *o,p'*-DDD to humans by any route of exposure. The ATSDR toxicological profile for DDT and related compounds (ATSDR, 2000) cited one small epidemiological study. In this study, Wassermann et al. (1976) calculated that the mean concentration of *o,p'*-DDD in cancerous breast tissue was higher than in noncancerous breast tissue in the same small group of women (n=9); however, the difference was not statistically different and the ranges of concentrations were nearly identical in the two kinds of tissue. The literature search identified no new studies regarding carcinogenicity of *o,p'*-DDD to humans following oral exposure.

Several case reports described the use of *o,p'*-DDD, as mitotane, in the treatment of adrenocortical cancer (Baudin et al., 2001; Bergenstal et al., 1960; Decker et al., 1991; Hogan et al., 1978; Iino et al., 2000; Terzolo et al., 2000; Wooten and King, 1993). In general, patients were given mitotane orally, delivering between 1 and 10 grams of *o,p'*-DDD daily (14-143 mg/kg-day) in divided doses for up to 54 months. In all cases, patients were given steroid replacement therapy to counteract side effects commonly associated with the suppression of adrenal hormone production caused by *o,p'*-DDD. The main side effects were gastrointestinal (nausea, vomiting, diarrhea) and neurological (lethargy, somnolence, ataxia, confusion, dysarthria, vertigo). These studies were not suitable for derivation of an RfD because of pre-existing cancer and concurrent administration of other medications (steroid hormones and chemotherapeutic agents).

Animal Studies

A 30-day study by Cueto and Brown (1958) identified an FEL of 4 mg/kg-day for *o,p'*-DDD in dogs based on adrenal necrosis leading to death. Cueto and Brown (1958) fractionated

technical grade DDD and tested the fractions and isolates for adrenocorticolytic activity. They fed 4 mg/kg-day of purified *o,p'*-DDD in gelatin capsules to two male dogs for 30 days; one control dog was left untreated for 100 days. The endpoints examined included general appearance, periodic tests of adrenal activity, and after necropsy, examination of adrenal histopathology. After four days of treatment, adrenal function, as measured by responses to an injection of ACTH, was severely impaired; the expected increase in urinary excretion of 17-hydroxycorticoids was abolished, and the expected decrease in eosinophil counts was reduced by 88%. Treatment with *o,p'*-DDD caused massive necrosis and atrophy of the adrenals. Treated dogs became anorexic and weak, leading to hair loss and death. The dose of 4 mg/kg-day was a FEL in dogs because of adrenal necrosis leading to death. This study identified *o,p'*-DDD as the adrenocorticolytic fraction in technical grade DDD, but was not a suitable basis for derivation of an RfD because the applied dose was a FEL.

Other subchronic studies in dogs supported the adrenocorticolytic action of *o,p'*-DDD administered as mitotane. In both healthy dogs and dogs with Cushing's disease (hyperadrenocorticism), oral administration of *o,p'*-DDD at doses of 50 mg/kg-day or higher caused a state of hypoadrenocorticism in some animals (den Hertog et al., 1999; Kirk and Jensen, 1975; Schechter et al., 1973; Vilar and Tullner, 1959; Lorenz et al., 1973). Typically, the adrenal cortex became necrotic and dogs developed weakness, in some cases with blindness, anisocoria, and convulsions leading to death. Thus, 50 mg/kg-day was a FEL in dogs for severe adrenal effects leading to death in some animals.

An incompletely described 5-week study by Hamid et al. (1974) reported adrenal atrophy and a 12% reduction in the weight of adrenals, but no effect on plasma corticosteroid concentration, in male Sprague-Dawley rats treated with 121 mg/kg-day of *o,p'*-DDD. Reduced body weight and impaired immune function (reduced organ weights of spleen and thymus, reduced cellular immune responses to injected sheep red blood cells) also were reported. Gellert and Heinrichs (1975) observed delayed onset of puberty and reduced adrenal weights relative to body weights in female offspring of pregnant Sprague-Dawley rats gavaged with 29 mg/kg-day of *o,p'*-DDD on gestational days 15-19. Fregly et al. (1968) found no significant effect on adrenal weight (relative to body weight) or adrenal function but identified significant thyroid effects (increased relative organ weight, hypothyroidism) in male Holtzman rats fed diets containing 0.1 or 0.3% *o,p'*-DDD (68 or 162 mg/kg-day) for six weeks. The results of these studies suggested that the adrenals of rats were less sensitive to *o,p'*-DDD than those of humans or dogs.

Other Studies

In the study cited in the NTP (2007) status report, Weisburger (1977) administered 0, 125, or 250 mg/kg-day of *o,p'*-DDD (vehicle not specified) by i.p. injection to groups of Sprague-Dawley rats and Swiss mice (25 per gender per group) 3 days a week for 6 months and monitored tumor development for 1 year following the last injection. Treatment with *o,p'*-DDD had no effect on survival of male and female rats, but apparently increased the tumor incidence (primarily breast tumors in females and parathyroid tumors in males) 1.5- to 2-fold over controls (tumor incidence and survival data were not reported for the doses individually). Tumor

incidence in treated male mice was not significantly different from controls, possibly because of significantly reduced survival. The tumor incidence in treated female mice was 1.5- to 2-fold higher than controls and primarily involved the lung.

Lund et al. (1990) reported increased cell proliferation (increased thymidine incorporation and mitotic number), in the lungs of female C57B1 mice that were injected once intraperitoneally with 100 mg/kg of *o,p'*-DDD. In another experiment, groups of three mice were gavaged with 0, 10 or 50 mg/kg of *o,p'*-DDD in corn oil twice a week for 6 weeks; 3 days after the last dose, mice were injected intravenously with ^{14}C-*o,p'*-DDD and sacrificed 24 hours later. The amount of label covalently bound to lung protein (but not liver protein) was significantly reduced in a dose-dependent manner. According to the authors, these results demonstrated the specific bioactivation of *o,p'*-DDD in the lung, which would result in localized binding to cellular macromolecules.

Other studies have investigated the estrogenic or androgenic activities of DDT and related compounds, since these properties might contribute to their carcinogenic potential. Using an *in vitro* yeast reporter gene system, Gaido et al. (1997) found that *o,p'*-DDD was very ineffective with regard to activation of expression of the estrogen receptor gene. The calculated effective concentration for 50% response (EC_{50}) for *o,p'*-DDD was 3.32 E-03, representing a potency $15x10^7$ times less than estradiol. This experiment suggested that *o,p'*-DDD was not estrogenic. Using an *in vitro* human hepatoma cell reporter gene system, Maness et al. (1998) found that *o,p'*-DDD and related compounds did not stimulate expression of the human androgen receptor (hAR) gene. However, the DDT isomers, including *o,p'*-DDD, were able to inhibit androgen-dependent expression of the hAR gene. The concentration of the most potent isomer, *p,p'*-DDE, required to inhibit androgen receptor activity by 50% was 1.86 µmol; an inspection of the dose-response curve indicated that the inhibitory concentration for 50% inhibition (IC_{50}) for *o,p'*-DDD (not reported numerically) would be higher. These experiments suggested that *o,p'*-DDD has weak antiandrogenic activity.

No additional supporting information was located in the literature search.

The toxicity of *o,p'*-DDD has been associated with the biotransforming activity of adrenocortical mitochondria (Cai et al., 1995a,b). *o,p'*-DDD undergoes β-hydroxylation, then spontaneous dehydrohalogenation, leading to the formation of the reactive intermediate acyl halide, which can convert to *o,p'*-dichlorodiphenylacetic acid or bind covalently to protein or plasma membrane (but not DNA). In comparative in vitro studies of adrenal mitochondrial extracts, Martz and Straw (1980) found the dog to have the highest production of *o,p'*-DDD metabolites. Compared to the dog (set as 100%), the values were 41% in rabbit, 24% in human, 13% in rat, and 5% in guinea pig. The covalent binding of *o,p'*-DDD to human adrenal mitochondrial protein was confirmed by Jönsson and Lund (1994) using tumor-free tissue derived from adrenalectomies.

FEASIBILITY OF DERIVING A PROVISIONAL RfD FOR *o,p'*-DDD

The data were inadequate to derive a provisional RfD for *o,p'*-DDD. The available clinical studies reported the use of dose levels, 14-143 mg/kg-day, that adversely affected the adrenal cortex in humans (Bautin et al., 2001; Bergenstal et al., 1960; Decker et al., 1991; Hogan et al., 1978; Terzolo et al., 2000; Wooten and King, 1993). Dogs and humans were similar in that the adrenal cortex was the critical target of *o,p'*-DDD (Kirk and Jensen, 1975; Schechter et al., 1973; Vilar and Tullner, 1959; Lorenz et al., 1973; den Hertog et al., 1999). However, the lowest dose level reported in a subchronic dog study, 4 mg/kg-day, was a FEL because of severe adrenal atrophy leading to death (Cueto and Brown, 1958). Rat studies (Hamid et al., 1974; Fregly et al., 1968) reported more severe effects on the function of the thyroid or the immune system than on the adrenals. These results suggested that the adrenal cortex is not the primary target of *o,p'*-DDD in the rat, and that this species was not an appropriate model for *o,p'*-DDD effects in humans. This is supported by mechanistic studies indicating that humans are less sensitive than dogs, but more sensitive than rats to *o,p'*-DDD (Martz and Straw, 1980). Thus, the database lacks a study that could serve as a suitable basis for derivation of an RfD for *o,p'*-DDD. However, the data make clear that exposure to *o,p'*-DDD poses significant toxic risks to the adrenal cortex.

FEASIBILITY OF DERIVING A PROVISIONAL RfC FOR *o,p'*-DDD

No inhalation toxicity data in humans or animals was identified, so no p-RfC could be derived for *o,p'*-DDD.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR *o,p'*-DDD

Because the only available data were in rats and mice treated i.p., under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), this review classified *o,p'*-DDD as having "*Inadequate Information to Assess Carcinogenic Potential*".

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR OR INHALATION UNIT RISK FOR *o,p'*-DDD

Neither a provisional oral slope factor nor a provisional inhalation unit risk could be derived for *o,p'*-DDD because of the lack of suitable human and animal oral or inhalation data.

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