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Provisional Peer Reviewed Toxicity Values for

o,p'-DDT
(CASRN 789-02-6)

Derivation of a Carcinogenicity Assessment

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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
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
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 PEER REVIEWED TOXICITY VALUES FOR *o,p'*-DDT (CASRN 789-02-6) Derivation of a Carcinogenicity Assessment

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 science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. 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) does not list *o,p'*-DDT [*o,p'*-dichlorodiphenyltrichloroethane; 2-(2-chlorophenyl)-2-(4-chlorophenyl)-1,1,1-trichloroethane] and no oral slope factor is listed in the HEAST (U.S. EPA, 1997) or in the Drinking Water Standards or Health Advisories List (U.S. EPA, 2000). The CARA lists (U.S. EPA, 1991, 1994) include two health effects assessment documents (U.S. EPA, 1984, 1988) and a carcinogenicity assessment document for DDT and related compounds (U.S. EPA, 1986). None of these documents contained specific information regarding carcinogenicity of *o,p'*-DDT, although all discussed carcinogenicity assays testing technical grade DDT, which contains *o,p'*-DDT as a minor nearly inactive component (<22%). A NIOSH Special Occupational Hazard Review (NIOSH, 1978), an Environmental Health Criteria document (WHO, 1979), and IARC (1974, 1991) monographs on DDT and related compounds contain no information regarding carcinogenicity of *o,p'*-DDT. IARC (1991) assigned "DDT" to Group 2B, possibly carcinogenic to humans, based on inadequate evidence in humans and sufficient evidence in animals. It is not clear whether IARC intended that evaluation

to apply to *o,p'*-DDT, since most of the available cancer studies involved *p,p'*-DDT or technical grade DDT. The ATSDR Toxicological Profile for DDT and related compounds (ATSDR, 2000) discusses a few studies regarding cancer epidemiology and the weak estrogenic properties of *o,p'*-DDT. The NTP status report (NTP, 2001) does not list *o,p'*-DDT. Literature searches were conducted from 1998 to January 2001 for studies relevant to the derivation of an oral slope factor for *o,p'*-DDT. The databases searched were TOXLINE, MEDLINE, CANCERLIT, RTECS, GENETOX, HSDB, CCRIS, TSCATS, EMIC/EMICBACK, and DART/ETICBACK.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

Reviews by U.S. EPA (1988), WHO (1979), and IARC (1974, 1991) listed no data regarding carcinogenicity of *o,p'*-DDT, aside from studies on technical grade DDT of which *o,p'*-DDT is a minor nearly inactive component (<22 %). The ATSDR toxicological profile for DDT and related compounds (ATSDR, 2000) cited several epidemiological studies, none of which reported an association between *o,p'*-DDT exposure and cancer (Wasserman et al., 1976; Sturgeon et al., 1998; Dorgan et al., 1999). In these epidemiological studies *o,p'*-DDT was identified in the serum of participants. No additional studies regarding carcinogenicity of *o,p'*-DDT in humans were located in the literature search.

Animal Studies

No studies were located regarding chronic oral exposure of animals to *o,p'*-DDT.

Other Studies

o,p'-DDT treatment induced chromosomal breakage in cultured cells of the rat kangaroo Palmer et al. (1972). No additional genotoxicity studies for *o,p'*-DDT were located in the literature search.

Weak estrogenic activity of *o,p'*-DDT has been demonstrated in acute injection studies in rats (Bitman et al., 1968; Bitman and Cecil, 1970). *In vitro* assays have shown that *o,p'*-DDT binds weakly to the estrogen receptor (Kelce et al., 1995; Danzo, 1997; Shelby et al., 1996) and that it is a weak activator of the estrogen receptor gene (Gaido et al., 1997; Sohoni and Sumpter, 1998). *o,p'*-DDT does not activate the androgen receptor gene, but inhibits testosterone binding to its receptor (Danzo, 1997; Kelce et al., 1995; Maness et al., 1998). These results indicate that *o,p'*-DDT is a weak antiandrogen that has weak estrogenic activity and provide limited evidence for its carcinogenic potential.

The MCF-7 human breast cancer cell line has been used to evaluate the transforming potential of *o,p'*-DDT. *o,p'*-DDT significantly increased the phosphorylation of c-Neu, a

tyrosine kinase that is also activated as a result of estrogen binding to the estrogen receptor (Enan and Matsumura, 1998). However, the activity of *o,p'*-DDT in these assays was independent of the estrogen receptor. In another study, *o,p'*-DDT significantly increased foci formation in MCF-7 cells, although less effectively than estradiol (Hatakeyama and Matsumura, 1999). Induction of foci was associated with the activity of the c-Neu tyrosine kinase. The authors suggest that the apparent causal relationship between c-Neu tyrosine kinase and foci formation may provide a mechanism for the induction of breast cancer by organochlorine compounds such as *o,p'*DDT. In support of this hypothesis, they cite a study by Berger et al. (1988), which found a high correlation of Neu activation with an increased incidence of breast cancer.

FEASIBILITY OF DERIVING A PROVISIONAL ORAL SLOPE FACTOR FOR *o,p'*-DDT

A provisional oral slope factor for *o,p'*-DDT cannot be derived due to the lack of suitable data.

REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 2000. Toxicological Profile for 4,4'-DDT, 4,4'-DDE, 4,4'-DDD. Update. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

Berger, M.S., G.W. Locher, S. Saurer et al. 1988. Correlation of c-*erb*B-2 gene amplification and protein expression in human breast carcinoma with nodal status and nuclear grading. Cancer Res. 48: 1238-1243. (Cited in Hatakeyama and Matsumura, 1999)

Bitman, J. and H.C. Cecil. 1970. Estrogenic activity of DDT analogs and polychlorinated biphenyls. J. Agric. Food Chem. 18: 1108-1112.

Bitman, J., H.C. Cecil, S.J. Harris and G.F. Fries. 1968. Estrogenic activity of o,p'-DDT in the mammalian uterus and avian oviduct. Science. 162: 371-372.

Danzo, B.J. 1997. Environmental xenobiotics may disrupt normal endocrine function by interfering with the binding of physiological ligands to steroid receptors and binding proteins. Environ. Health Perspect. 105: 294-301.

Dorgan, J., J. Brock, N. Rothman et al. 1999. Serum organochlorine pesticides and PCBs and breast cancer risk: Results from a prospective analysis (USA). Cancer Causes Control. 10: 1-11.

Enan, E. and F. Matsumura. 1998. Activation of c-Neu tyrosine kinase by o,p'-DDT and β-HCH in cell-free and intact cell preparations from MCF-7 human breast cancer cells. J. Biochem. Molec. Toxicol. 12: 83-92.

Gaido, K.W., L.S. Leonard, S. Lovell et al. 1997. Evaluation of chemicals with endocrine modulating activity in a yeast-based steroid hormone receptor gene transcription assay. Toxicol. Appl. Pharmacol. 143: 205-212.

Hatakeyama, M. and F. Matsumura. 1999. Correlation between the activation of Neu tyrosine kinase and promotion of foci formation induced by selected organochlorine compounds in the MCF-7 model system. J. Biochem. Molec. Toxicol. 13: 296-302.

IARC (International Agency for Research on Cancer). 1974. DDT and associated substances. In: Some Organochlorine Pesticides. Lyon, France. Vol. 5, p. 83-124.

IARC (International Agency for Research on Cancer). 1991. DDT and associated compounds. In: Occupational Exposures in Insecticide Application, and Some Pesticides. Lyon, France. Vol. 53, p. 179-249.

Kelce, W.R., C.R. Stone, S.C. Laws et al. 1995. Persistent DDT metabolite *p,p'*-DDE is a potent androgen receptor antagonist. Nature. 375: 581-585.

Maness, S.C., D.P. McDonnell and K.W. Gaido. 1998. Inhibition of androgen receptor-dependent transcriptional activity by DDT isomers and methoxychlor in HEPG2 human hepatoma cells. Toxicol. Appl. Pharmacol. 151: 135-142.

NIOSH (National Institute for Occupational Safety and Health). 1978. Special Occupational Hazard Review for DDT. U.S. DHEW, PHS, CDC, Division of Criteria Documentation and Standards Development, Rockville, MD. September 1978. DHEW (NIOSH) Publ. No. 78-200.

NTP (National Toxicology Program). 2001. Management Status Report. Examined March 2001. Online.
http://ntp-server.niehs.nih.gov/htdocs/Results_Status/MSR/MSRTOC.html

Palmer, K., S. Green and M. Legator. 1972. Cytogenetic effects of DDT and derivatives of DDT in a cultured mammalian cell line. Toxicol. Appl. Pharmacol.
22: 355-364.

Shelby, M.D., R.R. Newbold, D.B. Tully et al. 1996. Assessing environmental chemicals for estrogenicity using a combination of *in vitro* and *in vivo* assays. Environ. Health Perspect. 104: 1296-1300.

Sohoni, P. and J. Sumpter. 1998. Several environmental oestrogens are also anti-androgens. J. Endocrinol. 158: 327-339.

Sturgeon, S.R., J.W. Brock, N. Potischman et al. 1998. Serum concentrations of organochlorine compounds and endometrial cancer risk (United States). Cancer Causes Control. 9: 417-424.

U.S. EPA. 1984. Health Effects Assessment for DDT. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. September.

U.S. EPA. 1986. The Assessment of the Carcinogenicity of Dicofol (kelthane™), DDT, DDE, and DDD (TDE). Office of Health and Environmental Assessment, Washington, DC. February. EPA/600/6-86/001.

U.S. EPA. 1988. Updated Health Effects Assessment for DDT. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. November. Final Draft.

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. July 1997. EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA. 2000. Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. Summer 2000. EPA 822-B-00-001. Examined March 2001. Online. http://www.epa.gov/ost/drinking/standards/dwstandards.pdf

U.S. EPA. 2001. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Examined March 2001. Online. http://www.epa.gov/iris/

Wasserman, M., D.P. Nogueira, L. Tomatis et al. 1976. Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. Bull. Environ. Contam. Toxicol. 15: 478-484.

WHO (World Health Organization). 1979. DDT and its Derivatives. Environ. Health Criteria 9. Geneva, Switzerland.