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Provisional Peer Reviewed Toxicity Values for

o-Phthalic acid
(CASRN 88-99-3)

Superfund Health Risk Technical Support Center
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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

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PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR *o*-PHTHALIC ACID (CASRN 88-99-3)

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 HQ 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

The HEAST (U.S. EPA, 1997) reports that data are inadequate for quantitative risk assessment of *o*-phthalic acid. There is no listing for *o*-phthalic acid on IRIS (U.S. EPA, 2005a) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). The CARA lists (U.S. EPA, 1991, 1994) report a HEEP for Phthalic Acids (U.S. EPA, 1986). ATSDR (2003) has not published a Toxicological Profile for *o*-phthalic acid, and no Environmental Health Criteria Document is available (WHO, 2003). ACGIH (2003), NIOSH (2003), and OSHA (2003) have not developed occupational exposure limits for *o*-phthalic acid. Neither IARC (2003) nor NTP (2003) have evaluated the carcinogenicity of *o*-phthalic acid. Literature searches were conducted from 1985 through August, 2003 for studies relevant to the derivation of provisional toxicity values for *o*-phthalic acid. Databases searched included: TOXLINE (supplemented with NTIS and BIOSIS updates), MEDLINE, CANCERLIT, TSCATS, RTECS,

CCRIS, DART/ETICBACK, EMIC/EMICBACK, HSDB, and GENETOX. Additional literature searches from August 2003 through October 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

No studies of the toxicity of *o*-phthalic acid in humans were located in the available literature.

Animal Studies

Murakami et al. (1986) fed groups of 5 male Wistar rats diets containing 0, 0.5%, or 5% of *o*-phthalic acid for 34-36 days (estimated doses of 0, 500, or 5000 mg/kg-day assuming a growing rat consumes 10% of its body weight per day in a subchronic study). Body weight was monitored throughout the study. At termination, serum chemistry, liver mitochondrial enzyme activity, organ weights (liver, kidney, spleen, testes), and histopathology (liver, kidney, testes) were evaluated. Body weights in both treated groups were similar to controls throughout the study. Serum chemistry and liver enzyme analyses showed no effects. Organ weights in treated rats did not differ from controls, and no lesions were found by light microscopic examination. The high dose of 5000 mg/kg-day was a NOAEL in this study.

Ema et al. (1997) exposed groups of 11 pregnant female Wistar rats to 0, 1.25, 2.5, or 5% of *o*-phthalic acid in the diet (0, 1021, 1763, or 2981 mg/kg-day, respectively, as estimated by the study authors) from gestation days 7 through 16. Rats were observed daily for signs of clinical toxicity, and body weights, food consumption, and water consumption were recorded daily. On sacrifice at gestation day 20, the numbers of live and dead fetuses and uterine weights were determined. Fetuses were sexed and evaluated for external malformations; 2/3 of the fetuses from each litter were evaluated for skeletal malformations, while the others were evaluated for internal malformations. No deaths or clinical signs of toxicity were observed in pregnant rats. Body weight gain was lowered on gestation days 7-16 (when treatment occurred) in the 2.5 and 5% groups. Following cessation of treatment, body weight gains returned to normal or increased above controls; food consumption data during these periods suggest that changes in body weight were related to decreased food consumption. No differences between control and treated animals were seen in numbers of corpora lutea per litter, implantations per litter, resorptions and dead fetuses per litter, live fetuses per litter, postimplantation loss per litter, or sex ratio of live fetuses. The weight of high-dose male fetuses, but not female fetuses, was decreased relative to controls ($\approx$4%). No fetuses with external, skeletal, or internal malformations were found in any exposure group. Isolated skeletal variations occurred, but not at incidences significantly different from

controls. The degree of vertebral ossification was slightly lower in the high-dose group than in controls. This study found evidence of mild fetotoxicity (slightly reduced vertebral ossification and body weight of male fetuses) at the high-dose of 2981 mg/kg-day. Maternal body weight during gestation was reduced in the 1763 and 2981 mg/kg-day groups, apparently due to reduced food intake.

In other developmental toxicity studies, *o*-phthalic acid was not teratogenic or fetotoxic to the offspring of rabbit dams treated orally at 149.5 mg/kg-day (Smith et al., 1965) or mouse dams injected intraperitoneally with up to 400 mg/kg during gestation (Köhler et al., 1971).

Studies of male reproductive toxicity had mixed results. No testicular effects were observed in male rats treated by gavage with a single dose of 2300 mg/kg of *o*-phthalic acid (Cater et al., 1977). Oishi and Hiraga (1980) reported no changes in testes weight or the levels of testosterone or dihydrotestosterone in the serum or testes of rats exposed to diets containing 2% (≈2000 mg/kg-day) of *o*-phthalic acid for one week. Body, liver, and kidney weights were also unaffected. There was a slight, significant increase in the level of zinc in the kidneys, but the toxicological significance of this change is not clear.

Jha et al. (1998) exposed groups of male Swiss mice to daily intraperitoneal injections of 0, 40, or 80 mg/kg of *o*-phthalic acid for 5 days, and then evaluated the animals for the presence of dominant lethal mutations over the following 28 days. Treatment resulted in a significant increase in dominant lethal mutations in meiotic as well as postmeiotic stages of spermatogenesis; the most dramatic changes were seen from days 15-21 and 22-28 post-treatment. In a parallel study reported in the same manuscript, treatment of male mice with a single dose of 300 mg/kg of *o*-phthalic acid resulted in a dose-related increase in the number of abnormal sperm heads, which was most pronounced at 3 weeks post-treatment.

Other Studies

o-Phthalic acid was negative for mutagenicity at concentrations up to 2-10 mg/plate in *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA104, and TA1535, either with or without S9 mixture (Agarwal et al., 1985; Sayato et al., 1987). Results were also negative for induction of chromosomal aberrations and sister-chromatid exchange in CHO cells (Phillips et al., 1982). *o*-Phthalic acid produced dominant lethal mutations in male mice treated *in vivo* (Jha et al., 1998).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR *o*-PHTHALIC ACID

Data on the oral toxicity of *o*-phthalic acid in humans are not available. Murakami et al. (1986) conducted a 5-week dietary study of *o*-phthalic acid in rats that failed to identify any compound-related effects at doses up to 5000 mg/kg-day. Ema et al. (1997) found only mild fetotoxicity in rats exposed *in utero* to 2981 mg/kg-day. The effects may have been related to decreased maternal body weight during gestation in this group, which apparently resulted from reduced food intake. Other studies of gestational exposure found no effects produced by *o*-phthalic acid. Studies of effects on the male reproductive system by oral exposure were negative, although a study conducted by intraperitoneal injection reported production of abnormal sperm and dominant lethal mutations. In the absence of suitable oral studies of the subchronic or chronic toxicity of *o*-phthalic acid, derivation of subchronic or chronic oral p-RfD values is precluded.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR *o*-PHTHALIC ACID

In the absence of subchronic or chronic data on the inhalation toxicity of *o*-phthalic acid in humans or animals, derivation of subchronic or chronic p-RfC values is precluded.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR *o*-PHTHALIC ACID

Data on the potential carcinogenic effects of *o*-phthalic acid in humans or animals are not available. Mutagenicity studies in bacteria were negative, but *o*-phthalic acid produced dominant lethal mutations in male mice treated *in vivo*. Under the new Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005b), the data are inadequate for an assessment of human carcinogenic potential for *o*-phthalic acid.

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