9-25-2007

Provisional Peer Reviewed Toxicity Values for

Dimethyl phthalate
(CASRN 131-11-3)

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

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR DIMETHYL PHTHALATE (CASRN 131-11-3)

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 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

Dimethyl phthalate (DMP) is a phthalate ester used in the manufacture of a variety of products such as vinyl swimming pools and seats, safety glass, toothbrushes, toys and clothing; it is also used as an ingredient of numerous nonplasticized products (NTP, 1995). DMP has the empirical formula $C_{10}H_{10}O_4$ (Figure 1).

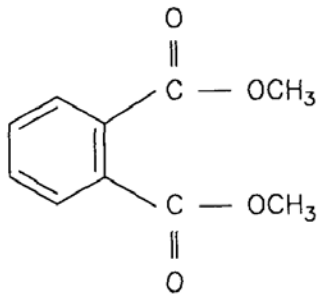

Figure 1. Dimethyl Phthalate Structure

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) (U.S. EPA, 2007) does not list a chronic oral reference dose (RfD), chronic inhalation reference concentration (RfC), or derive an oral slope factor or inhalation unit risk for cancer,

citing inadequate data. The IRIS weight of evidence assessment classifies DMP as a class D carcinogen (not classifiable) (U.S. EPA, 2007).

Subchronic or chronic RfDs for DMP are not listed in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The Chemical Assessment and Related Activities (CARA) list (U.S. EPA, 1991, 1994) includes a Health and Environmental Effects Profile (HEEP) (U.S. EPA,1987a), Drinking Water Criteria Document (DWCD) (U.S. EPA, 1987b), and Health Effects Assessment (HEA) (U.S. EPA, 1987c) for phthalic acid esters, but RfDs, RfCs, or cancer potency factors for DMP were not derived due to insufficient data. The American Conference of Governmental Industrial Hygienists (ACGIH) (2006), the National Institute for Occupational Safety and Health (NIOSH) (2006) and the Occupational Safety and Health Administration (OSHA) (2006) all list an 8-hour time weighted average (TWA) occupational exposure limit of 5 mg/m^3, set to control excess mist, not to protect against toxic or irritant effects. The Agency for Toxic Substances Disease and Registry (ATSDR) (2006), International Agency for Research on Cancer (IARC) (2006) and World Health Organization (WHO) (2006) have not produced documents regarding DMP or phthalic acid esters. Safety assessments of phthalate esters conducted by the Cosmetic Ingredient Review Expert Panel (CIREP) (CIREP, 1985, 2003) were consulted for relevant information.

Literature searches for studies relevant to the derivation of provisional toxicity values for DMP (CASRN 131-11-3) were conducted from 1965 to August 2007 in TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, TSCATS, RTECS, CCRIS, DART, EMIC/EMICBACK, HSDB, GENETOX and CANCERLIT and Current Contents.

REVIEW OF PERTINENT LITERATURE

Human Studies

No studies investigating the effects of subchronic or chronic oral or inhalation exposure to DMP in humans were identified.

Animal Studies

Oral Exposure

Chronic Toxicity – The effect of chronic dietary exposure to DMP was investigated by Lehman (1955). However, due to poor reporting of methods and results, data from this study cannot be used to identify NOAEL or LOAEL values for adverse effects of chronic oral exposure to DMP. According to the study report, groups of 10 female rats (strain not reported) were fed diets containing 0, 2.0, 4.0 or 8.0% DMP for 2 years. Mortality rates in the DMP treatment groups did not differ from the control group. Growth rate in the 4.0 and 8.0% groups was slightly, but statistically, different (direction and magnitude of change not reported) from controls, although methods used to assess growth rate were not reported. "Chronic nephritis" was observed in rats treated with 8.0% DMP, but not in the other DMP treatment groups. No

other effects of DMP treatment were noted. Comprehensive toxicity endpoints, such as histopathology or standard biochemical and hematological endpoints, were not assessed in this study. Additional chronic oral exposure studies of DMP to laboratory animals were not identified.

Subchronic/Developmental/Reproductive Toxicity – Subchronic oral toxicity studies evaluating comprehensive toxicological endpoints were not identified, although several studies assessing developmental effects of gestational exposure to DMP have been conducted (Gray et al., 2000; Field et al., 1993; NTP, 1989; Hardin et al., 1987; Plasterer et al., 1985; Booth et al., 1983). Although gestational exposure studies also include preliminary, short-term dose-ranging studies designed to identify test doses for evaluation of developmental effects, comprehensive toxicological endpoints were not examined. Studies investigating the testicular toxicity of DMP exposure have also been conducted (Gray et al., 2000; Foster et al., 1980; Oishi and Hiraga, 1980).

The developmental effects of exposure to dietary DMP were assessed in Sprague Dawley (CD) rats (NTP, 1989). The study consisted of a preliminary dose-ranging study and a "full developmental" study. Results of the developmental study were also reported in a peer-reviewed publication by Field et al. (1993). For the dose-ranging study, groups of 8 pregnant rats were exposed to dietary DMP at concentrations of 0, 0.25, 0.5, 1.0, 2.5 or 5.0% (equivalent to 200, 400, 800, 2,000 or 4,000 mg/kg-day, based on a projected average body weight of 275 g and an anticipated average daily food intake 22 g food/day) on gestational days (GD) 6 through 15. Throughout the treatment period, rats were examined twice daily for signs of toxicity. On GD 20, all animals were sacrificed and uteri were examined for implantation sites. Maternal body weight and selected organ weights (kidneys, liver) were assessed at the end of the treatment period. Fetal body weight was measured and dead and live fetuses were examined for external malformations. No maternal mortalities or clinical signs of toxicity were observed in any treatment group. Based on decreased maternal food consumption and weight gain, maternal toxicity was observed in the 5% DMP group. Food consumption in the 5% DMP group was significantly decreased compared to control during GD 6 through 9. Maternal weight gain over the entire treatment period was reduced by 33% ($p<0.01$) in the 5.0% DMP group, compared to controls, but not in the other DMP groups. Relative left kidney weight was significantly increased by 15, 20, 19, 14 and 21% in the 0.25, 0.5, 1.0, 2.5, or 5.0% DMP groups, respectively; absolute left kidney weight was significantly increased by 24, 19, 13 and 19% in the 0.5, 1.0, 2.5, or 5.0% DMP groups, respectively. No consistent changes in absolute or relative right kidney weight were observed. The biological significance of increased relative left kidney weight in DMP treatment groups was not established. Pregnancy rates in DMP groups were similar to control. No effect of DMP on fetal development was observed, based on fetal viability, body weight and the incidence of external malformations or variations.

Based on results of the dose-ranging study showing limited toxicity in dams at the highest exposure level, dietary concentrations of 0, 0.25, 1.0 and 5.0% were selected for the full developmental study (Field et al., 1993; NTP, 1989). The full developmental study followed the same protocol as the dose-ranging study, except with 29-30 animals per treatment group and additional assessments for fetal visceral and skeletal malformations. Based on weight and food consumption measured during the exposure period, the study authors calculated the daily dose of

DMP to be 0, 200, 800 and 3600 mg/kg-day in the 0, 0.25, 1.0 and 5.0% groups, respectively. No maternal mortalities or treatment-related signs of toxicity were observed during the study in any DMP groups. In the 5% group, maternal body weight gain was reduced by 28% ($p<0.01$) compared to control over the treatment period (GD 6-15), but did not differ significantly from control over the full gestation period (with or without correction for gravid uterine weights). Maternal weight gain was similar to control in the 0.25 and 1.0% groups. Correspondingly, significant decreases in food consumption were seen in the 5.0% group on GD 6-9 (28% decrease) and GD 9-12 (14% decrease), but not later, and the difference from control over the full gestation period was not statistically significant. Food consumption was similar to control in the 0.25 and 1.0% groups. Relative liver weight was increased by 5.8% ($p<0.01$) in the 5% DMP group, but not the 0.25 or 1% DMP groups, compared to control (NTP, 1989). Histopathological evaluation of the liver was not conducted. No effects were observed on absolute liver weight or absolute or relative left and right kidney weight in any DMP group. Pregnancy weights were similar in DMP groups compared to control. Treatment with DMP had no effect on any reproductive or developmental parameter, including number of implantation sites, number of resorptions, fetal viability, live and dead fetuses per litter, fetal body weight or fetal growth. The incidence of external, visceral and skeletal malformations was similar in the DMP treatment groups compared to control. Based on results of the full developmental study, the authors identified NOAEL and LOAEL values for maternal toxicity of 1.0% (800 mg/kg-day) and 5.0% (3600 mg/kg-day), respectively, for decreased body weight gain and increased relative liver weight. For fetal effects, a NOAEL of 5% (3600 mg/kg-day) was reported; a LOAEL was not identified.

Plasterer et al. (1985) assessed the effects of gestational exposure to the maximum tolerated dose (MTD) of DMP on the development of CD-1 mice. Results were also reported in an unpublished study (Booth et al., 1983). Initially, to identify the MTD (defined as the dose "at or just below the threshold for adult lethality"), an 8-day screening study was performed in non-pregnant female mice (67-71 days old). Groups of 10 mice were administered daily oral doses of 0, 875, 1750, 3500, 7000 or 11,890 mg/kg DMP in corn oil. No mortalities were observed in the control, 875 or 1750 mg/kg-day groups. Percent mortality in the 3500, 7000, and 11,890 mg/kg groups was 10, 50 and 100%, respectively. The average weight of surviving mice in DMP treatment groups was not different relative to control. No additional information on effects of DMP exposure was reported. The MTD was identified as 3500 mg/kg-day. Pregnant CD-1 mice (n=36) were administered 3500 mg/kg DMP in corn oil by gavage on GD 7 through 15; the control group of 40 mice was treated with corn oil. Gestational day 1 was defined as the day on which a seminal plug was identified. No treatment-related mortalities were observed in the DMP group. Maternal survival, weight gain and the number of rats delivering litters in the DMP group did not differ from control. No effect of DMP treatment was observed on the number of live and dead young per litter or on average pup weight. No gross congenital abnormalities were observed in the control or DMP groups.

No effects were observed in a gestational exposure study in mice (Hardin et al., 1987). A preliminary, 8-day, oral (gavage) dose-ranging study in non-pregnant female CD-1 mice was conducted to determine the LD_{10} value for DMP (5000 mg/kg-day), the exposure level selected for evaluation of developmental effects. Parameters assessed in the dose-ranging study were body weight, signs of toxicity and mortality. No additional information on methods or results of

the dose-ranging study was reported. The developmental effects of DMP were evaluated in two tests. In one test, pregnant mice were administered corn oil vehicle (n=50) or 3500 mg/kg-day DMP (n=49); in the second test, pregnant mice were administered corn oil vehicle (n=43) or 5000 mg/kg-day DMP (n=43). Mice were examined daily for signs of toxicity and body weights were recorded on GD 6 and 17. Following completion of delivery (postnatal day 1), the number of live and dead pups and pup weight were recorded and pups. On postnatal day (PND) 3, maternal and live pup weights were recorded. No systematic effort was made to examine either live or dead pups for malformations. Twelve dams (28%) in the 5000 mg/kg-day DMP group died during the treatment period (cause of death not reported); no mortality was observed in mice treated with 3500 mg/kg-day DMP or in controls. Maternal weight gain and the number of viable litters were similar between the DMP groups and matched controls. The number of liveborn per litter, percentage survival to postnatal day 3, birth weight and postnatal weight gain in the treated groups and matched controls were similar. Although not specifically assessed, no external malformations were noted in the DMP groups. This study found no effects on the measured reproductive parameters, even at a dose (5000 mg/kg-day) overtly toxic to the dams.

No effects on male sexual differentiation were observed following gestational exposure of rats to DMP (Gray et al., 2000). Pregnant Sprague Dawley rats were administered 0 or 750 mg/kg-day DMP in corn oil from GD 14 to PND 3. There were 19 control litters and 4 treated litters with live pups. Male offspring were assessed during the postnatal period through the onset of puberty. For all males, evaluations included: body weights and anogenital distance (AG) (on PND 2); examination of the inguinal region for hemorrhagic testes (on PND 9-10); examination for the presence of areolas/nipples (on PND 13); and examination for the onset of puberty, as indicated by preputial separation (daily after weaning). On PND 2, one male was randomly selected from each liter for necropsy, including paired testes weights and testicular histology. At 3-5 months of age, surviving males were sacrificed for blood collection (for measurement of serum testosterone) and necropsy (measurement of organ weights, examination for external and internal abnormalities of reproductive tissues). The number of males examined for malformations in the DMP group was 21 and in the control group was 80. For all parameters assessed, DMP-exposed animals did not differ from controls.

Serum testosterone levels were decreased in male rats exposed to dietary DMP for 1 week (Oishi and Hiraga, 1980). Young (5-weeks old) JCL:Wistar rats were fed diets containing 0 (n=20) or 2% (n=10) DMP for 1 week. Using average body weight and average daily food consumption for a weanling rat (U.S. EPA, 1988), the daily dose of DMP was calculated as 302 mg/kg-day. Body weight and food consumption were measured daily. At sacrifice after 1 week of treatment, blood samples were analyzed for serum zinc and testosterone and selected organs (testes, liver and kidneys) were analyzed for weight and zinc content. Body weight and food consumption between the groups was similar during the treatment period. Absolute and relative liver weights were increased by 17% ($p<0.05$) and 15% ($p<0.05$), respectively, compared to control. No treatment-related effects on absolute and relative weights of testes and kidneys were observed. Concentrations of testosterone in serum and testes and dihydrotestosterone in serum were significantly ($p<0.05$) reduced compared to control. Since data were presented graphically with poor resolution, the magnitude of change can only be approximated as a reduction of about 50%. Zinc content of serum, testes, liver and kidneys was unchanged compare to control.

A study on testicular effects of oral DMP exposure in young rats found no treatment-related effects (Foster et al., 1980). Groups of 12 young Sprague Dawley rats (weighing 70-90 g, age not reported) were administered 0 or 7.2 mmol/kg-day (equivalent to 1400 mg/kg-day) by gavage for 4 days. Body weight and food consumption were assessed throughout the exposure period. One day after administration of the final dose, testicular weight was measured and testes were examined for histopathological changes. No significant differences were observed in food intake, body weight gain or weight of the testes between the control and DMP groups. Histopathological assessment of testes from DMP-treated rats showed no lesions or evidence of atrophy.

Inhalation Exposure

Subchronic or chronic inhalation toxicity studies of DMP in animals were not identified.

Supporting Studies

Dermal Tumor Initiation/Promotion Studies – Studies assessing the carcinogenicity of oral or inhaled DMP were not identified. However, the NTP (1995) conducted a study on the dermal exposure to DMP in a 1-year initiation/promotion study in mice. In the initiation study, mice were dosed dermally with DMP to evaluate its activity as a skin tumor initiator, with and without the known skin tumor promoter 12-*O*-tetradecanoylphorbol-12-acetate (TPA). In the promoter study, mice were dosed dermally to evaluate the activity of DMP as a skin tumor promoter with and without the known skin tumor initiator 7,12-dimethylbenzanthracene (DMBA). Groups of 50 male Swiss (CD-1) mice were dermally administered various initiation/promotion treatments. Comparative control groups included vehicle control (acetone/acetone), initiation/promotion control (DMBA/TPA), initiator control (DMBA/acetone), and promoter control (acetone/TPA). Treatment groups included DMP initiation (DMP/TPA) and DMP promotion (DMBA/DMP). DMP (0.12 g) was applied 1 time per week in the initiation study and 5 times per week in the promoter study. Based on the incidence of skin neoplasms, DMP did not exhibit activity as an initiator or promoter for skin carcinogenesis.

Genotoxicity Studies – Results of *in vitro* assays of mutagenicity of DMP are summarized in Table 1. In bacterial (NTP, 1995; Kozumbo et al., 1982; Kozumbo and Rubin, 1991; Agarwal et al., 1985; Zeigler et al., 1985, 1982) and mammalian cells (Barber et al., 2000; Hazleton Biotechnologies, 1986a,b), negative results were observed for gene mutation without the addition of exogenous metabolic activation. Conflicting results were observed in gene mutation studies in bacterial cells with metabolic activation, with positive results observed in reports by Kozumbo et al. (1982), Kozumbo and Rubin (1991) and Agarwal et al. (1985). Results of gene mutation studies in mouse lymphoma cell lines were positive with metabolic activation (Hazleton Biotechnologies, 1986a,b). Positive results were obtained for effects of DMP on sister chromatid exchange with, but not without, metabolic activation (NTP, 1995; Loveday et al., 1990). DMP tested negative with and without metabolic activation for chromosomal aberrations in Chinese hamster ovary cells (NTP, 1995; Loveday et al., 1990) and

Table 1. Genotoxicity of Dimethyl Phthalate *In Vitro*

Test System	Endpoint	Results[a]		Reference
		With Activation	Without Activation	
Salmonella typhimurium (reverse mutation)	Gene mutation	–	–	NTP, 1995
S. typhimurium (reverse mutation)	Gene mutation	+	–	Kozumbo et al., 1982; Kozumbo and Rubin, 1991
S. typhimurium (reverse mutation)	Gene mutation	+	–	Agarwal et al., 1985
S. typhimurium (reverse mutation)	Gene mutation	–	–	Zeigler et al., 1982, 1985
Mouse lymphoma cells	Gene mutation	+	–	Barber et al., 2000
Mouse lymphoma cells	Gene mutation	+	–	Hazleton Biotechnologies, 1986a
Mouse lymphoma cells	Gene mutation	+	–	Hazleton Biotechnologies, 1986b
Chinese hamster ovary cells	Sister chromatid exchange	+	–	NTP, 1995
Chinese hamster ovary cells	Sister chromatid exchange	+	–	Loveday et al., 1990
Chinese hamster ovary cells	Chromosomal aberrations	–	–	NTP, 1995
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Loveday et al., 1990
Balb/3T3 cells	Cell transformation	–	X	Barber et al., 2000
Balb/C-3T3	Cell transformation	–	X	Litton Bionetics, Inc., 1986
Balb/C-3T3	Cell transformation	–	X	Litton Bionetics, Inc., 1985

[a] – = negative; + = positive
X: Test with exogenous metabolic activation was not conducted

for cell transformation in Balb/3T3 cells (Barber et al., 2000; Litton Bionetics, Inc., 1985, 1986). Additional studies assessing the genotoxic effects of DMP *in vivo* were not identified.

Mechanism of Action Studies – Testicular toxicity, including underdeveloped or absent reproductive organs, hypospadias, cryptorchidism, decreased anogenital distance, and decreased sperm production have been observed following gestational exposure of rats to some phthalate esters (dibutyl phthalate, diethylhexyl phthalate) (Liu et al. 2005), although no evidence of developmental toxicity to the male reproductive system has been observed following gestational exposure of rats to dimethyl phthalate (Gray et al., 2000). Results of a toxicogenomics study by Liu et al. (2005) suggest that phthalate ester-induced toxicity to the male reproductive system may be mediated through altered expression of testicular genes. Oral exposure of pregnant Sprague-Dawley rats (on GD12-19) to phthalate esters (500 mg/mg-day in corn oil by gavage) with known effects on male reproductive organ development (dibutyl phthalate, diethylhexyl phthalate, dipentyl phthalate, and benzyl butyl phthalate) produced significant alterations in

expression of 391 of 30,000 genes in fetal testes (Liu et al., 2005). Gene pathways affected by exposure included those involved in Sertoli cell development and in communication between Sertoli cells and gonocytes. However, no significant changes in gene expression were observed in fetal testes following oral administration of DMP (500 mg/kg-day) in corn oil to pregnant dams on GD 12-19 (Liu et al., 2005). Results of the study by Lui et al., (2005) provide supportive evidence that gestational exposures to dimethyl phthalate may not be toxic to developing male reproductive organs.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR DIMETHYL PHTHALATE

Studies investigating the effects of subchronic or chronic oral exposure in humans to DMP were not identified. Oral exposure studies in animals are limited to a poorly reported chronic study in rats (Lehman, 1955), several gestational exposure studies in rats and mice (Gray et al., 2000; Field et al., 1993; NTP, 1989; Hardin et al., 1987; Plasterer et al., 1985; Booth et al., 1983) and short-term (e.g., 1 week or less) studies investigating the potential effects of DMP on the male reproductive system in rats (Gray et al., 2000; Foster et al., 1980; Oishi and Hiraga, 1980). Results of gestational exposure studies indicate that DMP does not produce adverse effects on reproductive outcome or fetal development, even at doses producing maternal toxicity. However, assessments of maternal toxicity in both dose-ranging and developmental portions of gestational exposure studies were based on only a few parameters (signs of toxicity, body weight gain and weights of selected organs). Since comprehensive toxicological endpoints were not assessed, the available studies are not suitable for use in derivation of subchronic and chronic p-RfDs for DMP. However, a "screening" level value for oral DMP exposure is provided in the Appendix.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR DIMETHYL PHTHALATE

No studies investigating the effects of subchronic or chronic inhalation exposure to DMP in humans or animals were identified. The lack of suitable data precludes derivation of subchronic and chronic p-RfCs for DMP.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR DIMETHYL PHTHALATE

Weight-of-Evidence Descriptor

Studies evaluating the carcinogenic potential of oral or inhalation exposure to DMP in humans were not identified in the available literature. Cancer bioassays for DMP have not been conducted in animals for either oral or inhalation exposure. DMP did not exhibit activity as an initiator or promoter for skin carcinogenesis in a 1-year dermal initiation/promotion study in mice conducted by NTP (1995). The available studies on the mutagenic potential of DMP are

equivocal. The current IRIS assessment (9/07/1988) indicates that the human carcinogenic potential is not classifiable (classification of D) under the 1986 Guidelines for Carcinogen Risk Assessment (U.S.EPA, 1986). Under the 2005 Guidelines for Carcinogen Risk Assessment(U.S. EPA, 2005), inadequate information is available to assess the carcinogenic potential of DMP.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for DMP is precluded by the lack of suitable data.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2006. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH.

Agarwal, D.K., W.H. Lawrence, L.J. Nunez et al. 1985. Mutagenicity evaluation of phthalic acid esters and metabolites. J. Toxicol. Environ. Health. 16:61-69.

ATSDR (Agency for Toxic Substances and Disease Registry). 2006. Toxicological Profile Information Sheet. Available at http://www.atsdr.cdc.gov/toxpro2.html

Barber, E.D., M. Cifone, J. Rundell et al. 2000. Results of the L5178 mouse lymphoma assay and the Balb/3T3 *in vitro* transformation assay for eight phthalate esters. J. Appl. Toxicol. 20:69-80.

Booth, G.M., W.S. Bradshaw and M.W. Carter. 1983. Screening of priority chemicals for potential reproductive hazard. Prepared by MESA Corp, Orem, UT. Prepared for National Institute for Occupational Safety and Health, Cincinnati, OH.

CIREP (Cosmetic Ingredient Review Expert Panel). 1985. Final report on the safety assessment if dibutyl phthalate, dimethyl phthalate, and diethyl phthalate. J. Amer. College Toxicol. 4(3)267-303.

CIREP (Cosmetic Ingredient Review Expert Panel). 2003. Dibutyl phthalate, dimethyl phthalate, and diethyl phthalate re-review summary. Available at: http://www.cir-safety.org/staff_files/phthalates_summary.pdf

Field, E.A., C.J. Price, R.B. Sleet et al. 1993. Developmental toxicity evaluation of diethyl and dimethyl phthalate in rats. Teratology. 48:33-44.

Foster, P.M.D., L.V. Thomas, M.W. Cook et al. 1980. Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. Toxicol. Appl. Pharmacol. 54:392-398.

Gray, L.E., J. Ostby, M. Price et al. 2000. Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicol. Sci. 58:350-365.

Hardin, B.D., R.L. Schuler, J.R. Burg et al. 1987. Evaluation of 60 chemicals in a preliminary development toxicity test. Teratogen. Carcinogen. Mutagen. 7:29-48.

Hazleton Biotechnologies. 1986a. Mutagenicity of dimethylphthalate in a mouse lymphoma mutation assay. Unpublished study. Fiche Number OTS0510741. Document Number 40-8626244.

Hazleton Biotechnologies. 1986b. Mutagenicity of dimethylphthalate in a mouse lymphoma mutation assay. Unpublished study. Fiche Number OTS0510527. Document Number 40-8626225.

IARC (International Agency for Research on Cancer). 2006. Search IARC Monographs. Available at http://monographs.iarc.fr/

Liu, K., K.P. Lehmann, M. Sar, S.S. Young and K.W. Gaido. 2005. Gene expression profiling following in utero exposure to phthalate esters reveals new gene targets in the etiology of testicular dysgenesis. Biol. Repro. 73:180-192.

Kozumbo, W.J., R. Kroll and R.J. Rubin. 1982. Assessment of the mutagenicity of phthalate esters. Environ. Health Perspect. 45:103-109.

Kozumbo, W.J. and R.J. Rubin. 1991. Mutagenicity and metabolism of dimethylphthalate and its binding to epidermal and hepatic macromolecules. J. Toxicol. Environ. Health. 33:29-46.

Lehman, A.J. 1955. Insect repellents. Q. Bull. Assoc. Food Drug Off. 19:87-99.

Litton Bionetics, Inc. 1985. Evaluation of dimethylphthalate in the *in vitro* transformation of Balb/C-3T3 cells – final report. Unpublished study. U.S. EPA/OPTS Public Files. Fiche # OTS050508501. Document Number 40-8526196.

Litton Bionetics, Inc. 1986. Evaluation of 1A dimethylphthalate in the in vitro transformation of Balb/C-3T3 cells – final report. Unpublished study. U.S. EPA/OPTS Public Files. Fiche # OTS050508504. Document Number 40-8526194.

Loveday, K.S., B.E. Anderson, M.A. Resnick et al. 1990. Chromosome aberration and sister chromatic exchange tests in Chinese hamster ovary cells *in vitro*: results with 46 chemicals. Environ. Mol. Mutagen. 16:272-303.

NIOSH (National Institute for Occupational Safety and Health). 2006. NIOSH Pocket Guide to Chemical Hazards. Available at http://www.cdc.gov/niosh/npg/npgd0000.html#F

NTP (National Toxicology Program). 1989. Developmental toxicity evaluation of dimethyl phthalate (CAS No. 131-11-3) administered to CD rats on gestational days 6 through 15. Prepared by Research Triangle Institute, Research Triangle Park, NC for National Toxicology Program, Research Triangle Park, NC.

NTP (National Toxicology Program). 1995. Toxicology and Carcinogenesis Studies of Diethyltphthalate (Cas No. 84-66-2) in F344/N Rats and B6C3F_1 Mice (Dermal Studies) with Dermal Initiation/Promotion Study of Diethylphthalte and Dimethylphthalate (Cas No. 131-11-3) in Male Swiss (CD-1) Mice. National Institutes of Health, Research Triangle Park, NC.

Oishi, S. and K. Hiraga. 1980. Testicular atrophy induced by phthalic acid esters: effect on testosterone and zinc concentrations. Toxicol. Appl. Pharmacol. 53:35-41.

OSHA (Occupational Safety and Health Administration). 2006. OSHA Standard 1910.1000 TableZ-1. Part Z, Toxic and Hazardous Substances. Available at http://www.osha-slc.gov/OshStd_data/1910_1000_TABLE_Z-1.html

Plasterer, M.R., W.S. Bradshaw, G.M. Booth et al. 1985. Developmental toxicity of nine selected compounds following prenatal exposure in the mouse: naphthalene, p- nitrophenol, sodium selenite, dimethyl phthalate, ethylenethiourea, and four glycol ether derivatives. J. Toxicol. Environ. Health. 15:25-38.

U.S. EPA. 1987a. Health and Environmental Effects Profile for Phthalic Acid Alkyl, Aryl and Alkyl/Aryl Esters. 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.

U.S. EPA. 1987b. Drinking Water Criteria Document for Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

U.S. EPA. 1987c. Health Effects Assessment for Selected Phthalic Acid Esters. 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.

U.S. EPA. 1988. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Prepared by Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/600/6-87/008. PB88-179874.

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

U.S. EPA. 1994. Chemical Assessments and Related Activities. 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 PB 97-921199.

U.S. EPA. 2005. Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001F. Federal Register 70(66):17765-17817. Available online at http://www.epa.gov/raf

U.S. EPA. 2006. 2006 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. Summer, 2006. EPA 822-R-06-013. Available at http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

U.S. EPA. 2007. Integrated Risk Information System (IRIS). Online. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. http://www.epa.gov/iris/

WHO (World Health Organization). 2006. Online Catalogs for the Environmental Criteria Series. Available at http://www.who.int/dsa/cat98/zehc.htm

Zeigler, E., S. Haworth, K. Mortelmans et al. 1985. Mutagenicity testing of di(2-ethylhexyl)phthalate and related chemicals in *Salmonella*. Environ. Mut. 7:213-232.

Zeigler, E., S. Haworth, W. Speck et al. 1982. Phthalate ester testing in the National Toxicology Program's Environmental Mutagenesis Test Development Program. Environ. Health Perspect. 45:99-101.

APPENDIX

Derivation of a Screening Value for Dimethyl Phthalate (CASRN 131-11-3)

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for dimethyl phthalate (DMP). However, information is available for this chemical which, although insufficient to support derivation of a provisional oral reference dose (p-RfD), under current guidelines, may be of use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "Screening Value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. In some cases, as for DMP, a screening vale was developed and included in an Appendix as a result of comments received during external review. Thus, the information in this appendix has not undergone external peer review but is a result of recommendations made by reviewers regarding the limited dataset available for DMP. In the OSRTI hierarchy, Screening Values are considered to be *below* Tier 3, "Other (Peer-Reviewed) Toxicity Values."

Screening Values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available. Screening Values may be used, for example, to rank relative risks of individual chemicals present at a site to determine if the risk developed from the associated exposure at the specific site is likely to be a significant concern in the overall cleanup decision. Screening Values are not defensible as the primary drivers in making cleanup decisions because they are based on limited information. Questions or concerns about the appropriate use of Screening Values should be directed to the Superfund Health Risk Technical Support Center.

The available toxicity database reveals a paucity of reliable data for DMP. Studies investigating the effects of subchronic or chronic exposure to DMP in humans were not identified. Oral exposure studies in animals were limited to a poorly reported chronic duration study in rats (Lehman, 1955), and several short-term studies (10 days or less), to include gestational exposures, in mice or rats. Results of the gestational and short-term studies indicate that DMP does not produce adverse effects on reproductive outcome or fetal development in rodents. There are maternal effects (e.g. decreased body weight gain, increased relative liver weight) reported in pregnant rat dams exposed orally to DMP at high doses. However, such findings should be considered with caution as there was a palatability issue, with an associated decrease in body weight, observed in animals exposed to high doses of DMP (e.g. NTP, 1989; Field et al., 1993). Although DMP did not appear to be fetotoxic or teratogenic (NTP, 1989; Field et al., 1993; Plasterer et al., 1985; Hardin et al. 1987; Gray et al., 2000), or display evidence of gene alterations in fetal testes (Liu et al., 2005), changes indicative of exposure to some phthalate esters were observed in male weanling rats (5 weeks of age) exposed to oral DMP for one week at a dose of 302 mg/kg-day (Oishi and Hiraga, 1980). These effects included a significant increase in absolute and relative liver weight, and a statistically significant decrease in serum and testicular testosterone levels (approximately 50% compared to controls). It should be noted that the available chronic study (Lehman, 1955), did not evaluate downstream effects that could arise as a result of decreased testosterone levels. In addition, the short duration and exposure to only one dose in the Oishi and Hiraga (1980) study, does not inform the dose-

response or persistence of the effects. Thus, this study is considered inappropriate for derivation of a p-RfD in the primary portion of this PPRTV document. An oral subchronic reference screening level value of **1.0E-1 mg/kg-day DMP**, based on a free-standing LOAEL for increased absolute and relative liver weight and decreased serum and testicular testosterone in male rats, is derived as follows:

Male Rat LOAEL = 302 mg/kg-day

DMP oral subchronic reference screening value = 302 mg/kg-day / 3000

= 0.1 mg/kg-day or 1.0E-1 mg/kg-day

The aggregate uncertainty of 3000 consists of a factor of 10 each for human interindividual variability (UF_H), interspecies variability (UF_A), and extrapolation from a LOAEL to NOAEL (UF_L). A factor of three is included to account for deficiencies in the database which includes developmental toxicity studies but does not include standard subchronic bioassays of toxicity, studies of potential reproductive effects from exposure to DMP in male rats and mice, or two-generation reproductive toxicity studies. Exposure to multiple phthalate esters in the environment should be taken into consideration when conducting a risk assessment for DMP. Studies have shown that several phthalate esters may have a common endpoint of toxicity related to developmental and reproductive effects.