UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
Bethesda, MD 20814

Memorandum

Date: October 30, 2010

TO : Michael A. Babich, Ph.D., Project Manager, Phthalates, Section 108 of CPSIA

THROUGH: Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Health Sciences
Lori E. Saltzman, M.S., Director, Division of Health Sciences

FROM : Kent R. Carlson, Ph.D., Toxicologist, Directorate for Health Sciences
Leslie E. Patton, Ph.D., Toxicologist, Directorate for Health Sciences

SUBJECT : Toxicity Review of **Dimethyl phthalate (DMP)**

The following memo provides the Versar Inc. and SRC, Inc. contractor's and U.S. Consumer Product Safety Commission's (CPSC's) Health Sciences staff assessment of the potential toxicity associated with **DMP**.

CPSC staff assesses a product's potential health effects to consumers under the Federal Hazardous Substances Act (FHSA). The FHSA is risk-based. To be considered a "hazardous substance" under the FHSA, a consumer product must satisfy a two-part definition. First, it must be "toxic" under the FHSA, or present one of the other hazards enumerated in the statute. Second, it must have the potential to cause "substantial illness or injury during or as a result of reasonably foreseeable handling or use." Therefore, exposure and risk must be considered in addition to toxicity when assessing potential hazards under the FHSA (CPSC, 1992; summarized at 16 CFR 1500.135)

The FHSA addresses both acute and chronic hazards. While the FHSA does not require manufacturers to perform any specific battery of toxicological tests to assess the potential risk of chronic health hazards, the manufacturer is required to label a product appropriately according to the requirements of the FHSA. The first step in the risk assessment process is hazard

* This report was prepared for the Commission pursuant to contract CPSC-D-06-0006. It has not been reviewed or approved by, and may not necessarily reflect the views of, the Commission

identification, that is, a review of the available toxicity data for the chemical under consideration and a determination of whether the chemical is considered “toxic”. Chronic toxicity data (including carcinogenicity, neurotoxicity, and reproductive and developmental toxicity) are assessed by the CPSC staff using guidelines issued by the Commission (CPSC, 1992). If it is concluded that a substance is “toxic” due to chronic toxicity, then a quantitative assessment of exposure and risk is performed to evaluate whether the chemical may be considered a “hazardous substance”. This memo represents the first step in the risk assessment process; that is, the hazard identification step.

FINAL

TOXICITY REVIEW FOR DIMETHYL PHTHALATE (DMP, CASRN 131-11-3)

Contract No. CPSC-D-06-0006
Task Order 012

Prepared by:

Versar Inc.
6850 Versar Center
Springfield, VA 22151

and

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

Prepared for:

Kent R. Carlson, Ph.D.
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

July 19, 2011

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LIST OF ABBREVIATIONS AND ACRONYMS

AGD	Anogenital distance
AGI	Anogenital index
ALP	Alkaline phosphatase
DBP	Dibutylphthalate
DEHP	Diethylhexyl phthalate
DMBA	7,12-dimethylbenzanthracene
DMP	Dimethyl phthalate
GD	Gestation day
GOT	Glutamate oxaloacetate transaminase
GPT	Glutamate pyruvate transaminase
i.p.	Intraperitoneal
LOAEL	Lowest-observed-adverse-effect level
LD_{50}	Median lethal dose
LMWPEs	Low molecular weight phthalate esters
MMP	Monomethyl phthalate
NOAEL	No-observed-adverse-effect level
NTP	National Toxicology Program
PND	Postnatal day
SD	Standard deviation
SE	Standard error
TPA	12-O-tetradecanoylphorbol-12-acetate

EXECUTIVE SUMMARY

DMP is a minor use plasticizer found in a variety of consumer products.

Oral exposure to DMP resulted in LD_{50} values of 8,200, 5,200, 2,900, 10,100, and 8,600 mg/kg for rats, rabbits, guinea pigs, chicks, and mice, respectively. One additional study in rats had LD50s of 5740 mg/kg (male), 4390 mg/kg (female), and 5420 mg/kg (combined). Two case reports of humans that died following ingestion of mixtures containing DMP were inadequate to use. Dermal LD_{50}s for DMP were reported to be > 11,000 mg/kg (rabbits), >4,800 mg/kg (guinea pigs), and 38,000 mg/kg (rats). In a poorly reported study, one out of two cats died when exposed to a 10.2 mg/L DMP "mist". In a large human study, reactions were qualified as irritant following dermal exposure. Two additional human studies qualified results as equivocal irritation or no irritation. Studies in mice, rabbits, and guinea pigs all reported no significant dermal irritation following dermal exposure. In rabbits, instillation of DMP into the eye caused very slight irritation. This study was poorly described however. Sensitization to DMP was described in a human case report, but not in an additional larger human study, or poorly described rabbit study.

Evidence supported the conclusion that DMP was a subchronic toxicant. Short- to intermediate-term exposure to DMP induced decrements in body weight gain, changes in hemoglobin, and increases in absolute and relative liver weight.

Acceptable daily intakes values (ADI's) are calculated when a given chemical is considered "toxic" and sufficient toxicity information is available. The ADI is the amount of a chemical that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers.

Overall, a lack of comprehensive studies pertaining to particular organ systems or exposure durations (i.e. acute, subchronic, or chronic) prohibited the calculation of an ADI for systemic, reproductive, or developmental effects. Even though NOAELs and LOAELs could be described for a particular study (i.e. bodyweight decrements, changes in hemoglobin, increases in liver weight), the lack of other supporting studies suggests that there was "inadequate evidence" for the technical designation of DMP as a "chronic hazard" when considering FHSA criteria (16 CFR §1500.135).

TOXICITY REVIEW FOR DIMETHYL PHTHALATE (DMP, CASRN 131-11-3)

1. INTRODUCTION

This report summarizes available data for the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure information on dimethyl phthalate (DMP). This assessment was prepared from a variety of review articles (NICNAS, 2008; EPA, 2010; HSDB, 2009; ECB, 2000) as well as supplemental independent studies retrieved from literature searching.

Historically, concerns regarding most phthalates have been associated particularly with their potential to induce adverse reproductive/developmental effects in humans (NICNAS, 2008). The structural and physicochemical properties of certain phthalates allow migration and leaching out of products, especially soft plastics, have also been a concern (NICNAS, 2008).

2. PHYSICO-CHEMICAL CHARACTERISTICS

This section highlights the identity and key physicochemical properties of DMP. DMP is comprised of a pair of 1-carbon esters linked to a benzene-dicarboxylic acid ring. The branched ester side chains are in an *ortho* configuration, in contrast to those found in isophthalates (*meta*) or terephthalates (*para*).

DMP is currently considered to belong to the Low Molecular Weight Phthalate Esters (LMWPE) group.

The identity and physicochemical properties of DMP can be seen in Tables 2.1 and 2.2 (NICNAS, 2008; HSDB, 2009; U.S. EPA, 2010).

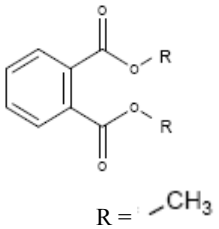
Table 2.1 Names, Structural Descriptors, and Molecular Formulas of DMP (NICNAS, 2008)	
CAS Number:	131-11-3
Chemical Name:	1,2-Benzenedicarboxylic acid, dimethyl ester
Common Name:	Dimethyl phthalate (DMP)
Molecular Formula:	C10H10O4
Structural Formula:	
Molecular Weight:	194.19
Synonyms:	Dimethyl-1,2-benzenedicarboxylate, Phthalic acid dimethyl ester, Dimethyl benzeneorthodicarboxylate, Dimethyl o-phthalate
Purity/Impurities/Additives:	None identified

Table 2.2 Physicochemical Properties of DMP	
Physical state	Colorless oily liquid (NICNAS, 2008)
Melting point	5.5 °C (NICNAS, 2008, HSDB, 2009; U.S. EPA, 2010)
Boiling point	284°C (NICNAS, 2008); 283.7°C (HSDB, 2009; U.S. EPA, 2010)
Density	1190 kg/m^3 (20°C) (NICNAS, 2008)
Vapor pressure	8.0 x 10^{-4} kPa (20°C) (NICNAS, 2008)
Water solubility	4.3 g/L (20°C) (NICNAS, 2008); 4.0 g/L (25°C) (HSDB, 2009); 2.8-4.3 g/L (25°C) (U.S. EPA, 2010)
Partition coefficient n-octanol/water (log Kow)	1.47-2.12 (NICNAS, 2008); 1.60 (HSDB, 2009); 1.46-1.90 (U.S. EPA, 2010)
Henry's law constant	1.9x10-^{7} atm-m^3/mole (U.S. EPA, 2010)
Flash point	146°C (closed cup; HSDB, 2009)

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

In general, DMP is manufactured commercially in a closed system by catalytically esterifying phthalic anhydride with methanol (HSDB 2009). As with other phthalates, the unreacted alcohols are recovered and reused, and the DMP mixture is purified by vacuum distillation or activated charcoal. The purity of DMP can achieve 99% or greater using current manufacturing processes (BASF, 2008). The remaining fraction of the DMP commercial mixture

can contain a maximum of 0.05-0.1% water (BASF, 2009; Unitex Chemical Corp, 2009). DMP is currently marketed by BASF (Palatinol®M), Eastman Chemical Company (DMP), and Unitex Chemical Corporation (Uniplex 110).

Supply

U.S. production of DMP has stayed the same since the implementation of chemical tracking in 1975 (3-6,000 metric tons). Recently, production has declined slightly from 4,000 metric tons (2005) to 3,600 metric tons (2008). DMP's proportion of the total phthalate production market has remained static at approximately 0.6-0.7% over the past 5 years (Bizzari, 2007, 2009).

In the past 20 years, U.S. consumption (in metric tons) of DMP has been within a metric ton or two less than production estimates, and currently, percentages of total phthalate consumption market are similar to production. This suggests that most DMP produced in the U.S. is utilized locally.

Use

The LMWPEs are used primarily as solvents or in cellulose acetate polymers rather than as plasticizers for PVC (ECB, 2006; Godwin, 2010). The non-confidential industrial processing and uses reported in the 2006 Inventory Update Rule submission for DMP included chemical, paint, and coating manufacturing (U.S. EPA, 2010). The non-confidential commercial and consumer use included paints, coatings, rubber, and plastic products (U.S. EPA, 2010). DMP has been used in automotive parts, encapsulation of electrical wiring, mining and construction, fabrication of fiberglass, paints, nitrocellulose, cellulose acetates, plasticizer in children's toys, and rubber (NICNAS, 2008). Other uses include solvent for cosmetics, plasticizer, creams, perfumes, candles, hair sprays, and shampoos, (Godwin 2010), and formerly as an insect repellent. Lower molecular weight phthalates are also reported to be used as solvents in fragrance bases for household cleaning products (NICNAS, 2008). According to the Cosmetic Ingredient Review (CIR) panel, the highest reported concentration of DMP in cosmetics was 2% (CIR, 2003).

4. TOXICOKINETICS

4.1. Absorption

No studies were located that provide quantitative information on the rate or extent of absorption of DMP in animals or humans following inhalation exposure.

DMP is readily and extensively absorbed by the gastrointestinal tract in rats. Phthalates detected in urine collected for 24 hours from adult male CD Charles River rats accounted for 44.6 mole percent of an orally administered gavage dose of 0.1 mL DMP (approximately 1 g) (Albro and Moore, 1974). Detected phthalates included free phthalic acid (14.4% of detected phthalates) and monomethyl phthalate (MMP, 77.5%), in addition to the parent DMP (8.1%). An in vitro study using an everted gut-sac preparation from the Sprague-Dawley rat small intestine provided supporting evidence that DMP is readily absorbed from the gastrointestinal system and further found that DMP is extensively hydrolyzed to the monoester MMP during absorption by esterases within the mucosal epithelium (White et al., 1980).

Quantitative data for dermal absorption of DMP in rats indicate that approximately 40% of an applied dose was absorbed over a 7-day period under aerated occluded conditions. Elisi et al. (1989) compared the dermal absorption of several phthalate diesters in rats. In this study, single doses of 30–40 mg/kg of various [^{14}C]-labeled phthalate diesters, including DMP, were applied in an ethanol solution to the clipped skin of male F344 rats (n=3); the authors reported that the dosing corresponded to approximately 5–8 mg/cm^2 skin (157 µmol/kg). The [^{14}C]-labeled compounds were uniformly labeled on the aromatic ring. After the ethanol evaporated, the treated skin was covered with a circular plastic cap that had been perforated for aeration. Every 24 hours for 7 days, urine and feces were collected for measurement of radioactivity. On the 7th day, the animals were sacrificed, and radioactivity in several organs including the skin was measured. The chemical nature of the radioactivity in the collected excreta and tissues was not characterized in this study. Elsisi et al. (1989) reported that as the length of the alkyl side chain increased, the amount excreted in urine decreased in the first 24 hours. The rate of excretion of DMP was essentially constant over the 7 day observation period at 6–7.5% of the applied dose. The 7-day cumulative dose excreted in urine and feces for DMP was approximately 39%. Upon sacrifice 7 days after dermal application, the brain, spinal cord, lung, liver, spleen, intestine, kidney, testis, fat, and muscle were removed for determination of radioactivity. The amounts of radioactivity in the selected organs, reported as percentages (± standard deviation [SD]) of the applied dose, were 0.3% ± 0.03 in adipose tissue, 0.6% ±

0.07 in muscle, and <0.5% for all other tissues (brain, spinal cord, and testis). Radioactivity recovered from the treated skin accounted for 19% ± 23 of the applied dose, while 0.4% ± 0.4 was recovered from untreated skin and 5.0% ± 0.3 was recovered in the plastic cap used to cover the exposed area. Including the excreted DMP (39% over 7 days), the total recovered amount was 66% ± 26. From these data, it is estimated that about 65% of the applied dose was absorbed by the skin over the 7-day period [(39.9% in urine, feces, and tissues) ÷ (66% recovered—5% detected in plastic cap)]. These results indicate that DMP is extensively absorbed by the skin under occluded conditions.

In vitro studies have reported dermal absorption rates of 2.5–4 μg/cm^2/hour through human epidermis, 40–50 μg/cm^2/hour through rat epidermis, and a peak rate of 3 μg/cm^2/hour through pig skin (Hilton et al., 1994; as cited in NICNAS 2008; Reifenrath et al., 1989; Scott et al., 1987). Dermal absorption appeared to be highly solvent dependent in rat skin and to a lesser extent in human skin (Hilton et al., 1994; as cited in NICNAS, 2008).

4.2. Distribution

No studies were located on the distribution of DMP in animals or humans following oral or inhalation exposure to DMP.

Elisi et al. (1989) reported that 0.6 and 0.3% of an applied single dermal dose of 157 μmol/kg [^{14}C]-DMP was found in muscle and adipose tissue, respectively, of rats following 7 days of dermal exposure. Less than 0.5% of the applied dose was detected in all other tissues examined (brain, spinal cord, and testis). These results indicate that absorbed DMP is distributed to non-portal-of-entry tissues and is rapidly cleared with limited accumulation.

4.3. Metabolism

Analysis of phthalates in 24-hour urine following oral administration of DMP to rats indicated that DMP was extensively metabolized, principally to MMP (which accounted for 77.5% of recovered phthalates in urine) and phthalic acid (which accounted for 14.4% of recovered phthalates) (Albro and Moore, 1974). Similarly, MMP accounted for >97% of phthalates detected in 24-hour urine collected from rats given single intraperitoneal (i.p.) injections of 2 g DMP/kg (Kozumbo and Rubin, 1991). In in vitro studies, rat liver homogenates hydrolyzed 97% of [^{14}C]-labeled DMP to MMP in 2 hours, whereas skin homogenates displayed relatively limited hydrolytic activity (Kozumbo and Rubin, 1991; Kozumbo et al., 1982;

Kaneshima et al., 1978). Other in vitro studies showed that DMP is hydrolyzed to MMP by liver homogenates and intestinal mucosal cell preparations from rats, baboons, and ferrets, as well as by intestinal mucosal cell preparations from humans (White et al., 1980; Lake et al., 1977). The results indicate that DMP can be rapidly metabolized to MMP and phthalic acid by the liver and intestinal mucosal cells and that metabolism in the skin is relatively slow.

4.4. Elimination

As described above (under Sections 4.2 and 4.3), the metabolite MMP, and to a lesser extent intact DMP, have been detected in urine from rats treated with DMP orally, dermally, and intraperitoneally (Kozumbo and Rubin, 1991; Elsisi et al., 1989; Albro and Moore, 1974). Although the majority of excreted radioactivity observed in dermally-exposed rats appeared in the urine after 24 hours, Elsisi et al. (1989) also detected a small amount of [^{14}C]-DMP in the feces. Demonstrating the importance of urinary excretion versus fecal excretion, about 6 and 0.1% of the administered dose of DMP in this study were excreted in the urine and feces, respectively, during the first 24-hour period of exposure.

4.5. Toxicokinetics Conclusions

Results from animal studies indicate that DMP is rapidly and extensively absorbed by the gastrointestinal tract and skin, distributed widely to tissues following absorption, and rapidly cleared and eliminated from the body, principally as metabolites in the urine (Kozumbo and Rubin, 1991; Elsisi et al., 1989; Albro and Moore, 1974). MMP and phthalic acid are the major and minor metabolites identified in urine, respectively. Results from in vitro studies indicate that DMP is hydrolyzed to MMP by liver homogenates and intestinal mucosal cell preparations from rats, baboons, and ferrets, as well as by intestinal mucosal cell preparations from humans (White et al., 1980; Lake et al., 1977), and that skin homogenates show markedly less hydrolytic activity than liver homogenates (Kozumbo and Rubin, 1991; Kozumbo et al., 1982; Kaneshima et al., 1978). No studies were located on the toxicokinetics of inhaled DMP.

5. HAZARD INFORMATION

This section contains brief hazard summaries of the adverse effects of DMP in a variety of animal and bacterial species. More detailed discussions of the studies can be viewed in the Appendices. When evaluating hazard study data, Consumer Product Safety Commission (CPSC) staff utilized the definitions for toxicity as presented in regulations (16 CFR §1500.3(c)(2)(ii)) and the chronic hazard guidelines (16 CFR §1500.135) in the Federal Hazardous Substances Act (FHSA; 15 U.S.C. 1261-1278). When considering the FHSA, substances that are "known" or "probable" toxicants are "toxic" and substances that are considered "possible" toxicants are "not toxic" (Table 5.1).

Table 5.1. Classification of Chronic Hazards (as per the FHSA)

Evidence	Human Studies	Animal Studies
Sufficient evidence	**Known**	**Probable**
Limited evidence	**Probable**	Possible
Inadequate evidence	Possible	—

Oral exposure to DMP resulted in LD_{50} values of 8,200, 5,200, 2,900, 10,100, and 8,600 mg/kg for rats, rabbits, guinea pigs, chicks, and mice, respectively. One additional study in rats had LD50s of 5740 mg/kg (male), 4390 mg/kg (female), and 5420 mg/kg (combined). Two case reports of humans that died following ingestion of mixtures containing DMP were inadequate to use. Dermal LD_{50}s for DMP were reported to be > 11,000 mg/kg (rabbits), >4,800 mg/kg (guinea pigs), and 38,000 mg/kg (rats). In a poorly reported study, one out of two cats died when exposed to a 10.2 mg/L DMP "mist". In a large human study, reactions were qualified as irritant following dermal exposure. Two additional human studies qualified results as equivocal irritation or no irritation. Studies in mice, rabbits, and guinea pigs all reported no significant dermal irritation following dermal exposure. In rabbits, instillation of DMP into the eye caused very slight irritation. This study was poorly described however. Sensitization to DMP was described in a human case report, but not in an additional larger human study, or poorly described rabbit study.

Evidence also supported the conclusion that DMP was a subchronic toxicant. Short- to intermediate-term exposure to DMP induced decrements in body weight gain, changes in hemoglobin, and increases in absolute and relative liver weight.

Acceptable daily intakes values (ADI's) are calculated when a given chemical is considered "toxic" and sufficient toxicity information is available. The ADI is the amount of a

chemical that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers. ADI's were not estimated for DMP relevant exposure durations for the general population or for other sensitive subpopulations because confirmatory data on toxicological endpoints and methodological clarifications were not available.

In the following discussions, hazard information was divided into sections thought to be of interest for regulatory matters (i.e., for labeling and other mitigation measures) as well as for biological and pathological consistency. More specifically, hazards were divided into whether the exposure was singular or repeated. Hazards associated with repeated exposures were further divided into groupings based on the affected organ system (i.e., hepatic, neurological, hematologic, etc.) and discussed in terms of the exposure duration if sufficient information existed to do so (***acute***, ≤14 days; ***intermediate-term*** or ***subchronic***, 15–364 days; ***long-term*** or ***chronic***, ≥365 days; and ***multigenerational***; ATSDR, 2007) where appropriate. Discrete study information can be reviewed in the Appendices.

ACUTE DOSE TOXICITY

5.1. Acute Oral Toxicity

The only acute oral data for DMP in humans are based on two case studies of men accidentally ingesting a plastic catalyst containing DMP. Deisher (1958) reported that a 34-year-old male longshoreman suffered chemical burns of the upper alimentary tract following the accidental ingestion of a plastic catalyst containing 60% methyl-ethyl-ketone peroxide and 40% diluent DMP, with 11% minimum of active oxygen. A 47-year-old man who accidentally ingested a similar solution died within 4 days from hepatic coma associated with blood coagulation disorders (Karhunen et al., 1990).

Results from acute oral toxicity studies in animals indicate that DMP has low lethality potency. Oral LD_{50} values of 8,200, 5,200, 2,900, 10,100, and 8,600 mg/kg were reported for rats, rabbits, guinea pigs, chicks, and mice, respectively, by Draize et al. (1948) based on exposures of 10 animals/species/dose at 4–12 graded doses per species (6-day observation period). Union Carbide Corp. (1987) reported peroral LD_{50} values of 5,740 (males), 4,390 (females) and 5,120 (combined) mg/kg for Sprague-Dawley albino rats following gavage treatment of five males and five females per dose at five graded dose levels with a mixture reported to contain 85% DMP (no other information on the constituents of this mixture were

provided). Treated rats in this study exhibited unsteady gait, sluggishness, lacrimation, kyphosis, red crust around the nose and eyes, wetness on the periurogenital fur, drooping eyelids, piloerection, an unkempt appearance, and a moribund appearance prior to death. Survivors recovered within 3–7 days (14-day observation period). Necropsy revealed mottled and red to pink lungs, glandular portion of stomachs white to red, red focal areas in some stomachs, a few gas-filled stomachs, and red intestines.

The human case studies provide limited evidence and relevance when considering the acute oral toxicity of DMP. Sufficient information is provided, however, in animal studies to conclude that the majority of DMP LD_{50}s are greater than the oral LD_{50} range (50–5,000 mg/kg) required by the FHSA to conclude that a chemical is acutely toxic.

The weight of evidence including probable animal data are sufficient, therefore, to support the conclusion that DMP does not fit the definition of "acutely toxic" via oral exposure under the FHSA (16 CFR §1500.3(c)(2)(i)(A)).

5.2. Acute Dermal Toxicity

Draize et al. (1948) reported a dermal LD_{50} value of >10 mL/kg in rabbits (>11,000 mg/kg using the reported density of 1190 kg/m^3 for DMP). The European Commission European Chemicals Bureau database for DMP (European Commision, 2000) lists dermal LD_{50} values ranging from >4,800 mg/kg in guinea pigs to 38,000 mg/kg in rats.

Sufficient information is provided in the referenced animal studies to show that all of LD_{50}s are greater than the dermal LD_{50} range (200–2,000 mg/kg) required by the FHSA to conclude that a chemical is acutely toxic. DMP, therefore, does not fit the definition of "acutely toxic" via dermal exposure under the FHSA (16 CFR §1500.3(c)(2)(i)(C)).

5.3. Acute Inhalation Toxicity

No mortality was reported among rats inhaling a saturated vapor of DMP for 6 hours/day, but additional details about this study are lacking (Levinskas, 1973; as cited in NICNAS, 2008). Review of the same report indicated 100% survival among cats inhaling a mist containing 2.0 mg DMP/L and 50% mortality (one of two cats died) among cats inhaling a mist containing 10.2 mg DMP/L (Levinskas, 1973; as cited in NICNAS, 2008).

The lack of additional acute inhalation toxicity and methodological data for DMP can be considered a data gap and supports the conclusion that there is "inadequate evidence" for the designation of DMP as "acutely toxic" via inhalation under the FHSA (16 CFR §1500.3(c)(2)(i)(B)).

5.4. Acute Toxicity – Other Routes

Published i.p. LD_{50} values for DMP include 3,375 mg/kg in rats (Singh et al., 1972) and 3,980 mg/kg in mice (Lawrence et al., 1975).

5.5. Primary Skin Irritation

Dermal irritation was not a prevalent response in studies of human subjects reviewed by NICNAS (2008). Three of 190 subjects exposed to 0.5% DMP in a cream base showed irritant responses and another 6 subjects showed equivocal irritant responses (Takenaka et al., 1970; as cited in NICNAS, 2008). No signs of irritation were observed in 10 subjects following application of a solution of 50% DMP in ethanol to facial skin (Frosch and Kligman, 1977; as cited in NICNAS, 2008).

In animal studies, the incidence of skin acanthosis, ulceration, exudates, or hyperkeratosis was not markedly elevated in male Swiss CD-1 mice following dermal application of undiluted DMP (0.1 mL) 5 times/week for 52 weeks, compared with controls exposed to acetone (NTP, 1995). For example, respective incidences for DMP-exposed and control mice were 11/49 versus 8/50 for acanthosis, and 4/49 versus 1/50 for hyperkeratosis (NTP, 1995). Repeated application (25 repeated doses) of 4 mL undiluted DMP/kg to the shaven abdomen of each of three rabbits under occluded conditions for a period of 33 days did not result in significant skin irritation (Dow Chemical Company, 1946). Similarly, no significant primary irritation of the skin was noted in rabbits with either intact or abraded skin (except in molting areas) following single dose and 90-day repeated exposures to DMP (Lehman, 1955; Draize et al., 1948) or in guinea pigs with intact or abraded skin following dermal applications of 0.05 mL DMP (E.I. Dupont, 1970).

Dermal irritation was noted in one of two human studies. Slightly increased incidence of acanthosis and hyperkeratosis were observed in an NTP animal study, while other animal studies reported no significant skin irritation.

The weight of evidence including sufficient human and animal data supported the conclusion that DMP did not fit the definition of "corrosive" as outlined in the FHSA (16 CFR §1500.3(c)(3)).

Insufficient methodological descriptions and contradictory human and animal evidence supported the conclusion that there is "inadequate evidence" for the designation of DMP as a "primary [dermal] irritant" when considering FHSA criteria (16 CFR §1500.3(c)(4)).

5.6. Primary Eye Irritation

Slight irritation of the eye has been noted following ocular application of undiluted DMP to rabbits (Lawrence et al., 1975; Carpenter and Smyth, 1946; Draize et al., 1944).

The lack of additional methodological information and toxicity data on the ocular properties of DMP can be considered a data gap and supports the conclusion that there is "inadequate evidence" for the designation of DMP as a "primary irritant" or "corrosive" under the FHSA (16 CFR §1500.3(c)(3) and 16 CFR §1500.3(c)(4)), respectively.

5.7. Sensitization

In a patch test study of a mixture of 2% DMP, 2% diethyl phthalate, and 2% dibutylphthalate (DBP) in petrolatum, 1 out of 1,532 subjects showed an allergic response (Schulsinger and Mollgaard, 1980). No allergic reactions to occluded dermal exposure to 5% DMP for 2 days were noted in another clinical study of 310 subjects (Kanerva et al., 1999), but a case report is available of a woman with contact dermatitis, who showed allergic reactions in patch tests with scrapings from her plastic eyeglass frames, as well as to 5% DMP, 5% diethyl phthalate, or 5% DBP (Oliwiecki et al., 1991).

In an animal study, sensitization was not reported in rabbits receiving daily dermal applications of DMP (Lehman, 1955). No further methodology or results were reported in this study.

The lack of additional methodological information, contradictory human study findings, and a lack of high-concentration DMP-alone exposure studies can be considered data gaps and

support the conclusion that there is “inadequate evidence” for the designation of DMP as a “strong sensitizer” as defined in the FHSA (16 CFR §1500.3(c)(5)).

REPEAT DOSE TOXICITY

As reviewed in Appendices A and B, data for repeated dose toxicity of DMP are limited to a poorly reported 2-year dietary exposure study of rats (Lehman, 1955), a few oral toxicity studies of rats exposed to DMP for 4 days to 4 weeks (Kwack et al., 2009; Foster et al., 1980; Oishi and Hiraga, 1980; Bell et al., 1978), and gestational exposure developmental/reproductive toxicity studies of pregnant Sprague-Dawley rats exposed to 0, 0.25, 1, or 5% DMP in the diet on gestation days (GDs) 6–15 (Field, 1993; NTP, 1989), 0 or 750 mg/kg-day by gavage on GD 14–postnatal day (PND) 3 (Gray et al., 2000), or pregnant CD-1 mice exposed by gavage to 0, 3,500, or 5,000 mg/kg-day on GDs 6–13 (Hardin et al., 1987; Plasterer et al., 1985). Appendix A provides a summary of the no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values for organ-specific endpoints for oral exposure to DMP. Appendix B provides descriptive summaries of the available studies.

5.8. General Effects (Clinical Signs, Food/Water Consumption, Body Weight)

Oral exposure to DMP doses ≥~3,600 mg/kg-day has been associated with decreased body weight in rats (see Table A.1 in Appendix A). Decreased body weight gain or growth was reported in female rats of unspecified strain exposed to 4 or 8% DMP, but not 2%, in the diet for 2 years (~3,668 or 7,336 mg/kg-day, but not 1,884 mg/kg-day) (Lehman, 1955) and pregnant Sprague-Dawley rats exposed to 5% DMP in the diet (~3,600 mg/kg-day), but not 1% (~800 mg/kg-day), on GDs 6–15 (Field, 1993; NTP, 1989). Decreased body weight gain, compared with control values, was not observed in pregnant CD-1 mice exposed to 3,500 or 5,000 mg/kg-day on GDs 6–13, although the higher of these doses produced mortality in 28% of the exposed dams during exposure (Hardin et al., 1987; Plasterer et al., 1985). Body weight was not affected in pregnant Sprague-Dawley rats exposed to 750 mg/kg-day on GD 14–PND 3 (Gray et al., 2000); young male Sprague-Dawley rats exposed to 500 mg/kg-day for 4 weeks (Kwack et al., 2009) or 1,400 mg/kg-day for 4 days (Foster et al., 1980); or young male JCL:Wistar rats exposed to 2% DMP in the diet (~1,862 mg/kg-day) for 1 week (Oishi and Hiraga, 1980).

5.9. Hematology

In the only available study examining hematological endpoints following oral exposure to DMP, hemoglobin was the only hematological endpoint affected by a 4-week exposure to 750 mg/kg-day in young, male Sprague-Dawley rats (Kwack et al., 2009). Hemoglobin

concentration was decreased by about 17 % in exposed rats, compared with control rats (see Table B.3 in Appendix B).

5.10. Hepatotoxicity

Increased liver weight has been associated with exposure to approximate DMP doses ≥~1,860 mg/kg-day, but available oral toxicity studies have not microscopically examined liver sections from exposed rats (see Table A.1 in Appendix A). Increased relative liver weights were observed in pregnant Sprague-Dawley rats exposed to 5% DMP in the diet (~3,600 mg/kg-day), but not 1% (~800 mg/kg-day), on GDs 6–15 (Field, 1993; NTP, 1989) and in young male JCL:Wistar rats exposed to 2% DMP in the diet (~1,862 mg/kg-day) for 1 week (Oishi and Hiraga, 1980). Absolute liver weights were also significantly increased in the treated rats in the Oishi and Hiraga study (1980). In another study, relative liver weights were not significantly different from control values in male Sprague-Dawley rats exposed to 0.5% DMP in the diet (~107 mg/kg-day) for 21 days (Bell et al., 1978). Relative liver weights were not changed, compared with controls, in young male Sprague-Dawley rats exposed to 500 mg/kg-day for 4 weeks; serum activities of alkaline phosphatase (ALP), but not glutamate oxaloacetate transaminase (GOT) or glutamate pyruvate transaminase (GPT), were increased in exposed rats in this study (Kwack et al., 2009). Other biochemical parameters were also affected by DMP. Hepatic total lipid levels and cholesterol were significantly reduced in male Sprague Dawley rats by subchronic dietary exposure to 0.5% DMP (~107 mg/kg-day) (Bell et al., 1978).

The weight of evidence from the above studies supported the conclusion that there was "sufficient animal evidence" for the designation of DMP as a "hepato-toxicant".

5.11. Renal Toxicity

Chronic nephritis was reported to occur in female rats of an unspecified strain exposed to 8% DMP, but not 4%, in the diet (~7,336 and 3,668 mg/kg-day, respectively), but the report of this study did not specify the incidence or severity of this effect (Lehman, 1995). No exposure-related effects on kidney weights were observed in young male Sprague-Dawley rats exposed to 500 mg/kg-day for 4 weeks (Kwack et al., 2009), young male JCL:Wistar rats exposed to 2% DMP in the diet (~1,862 mg/kg-day) for 1 week (Oishi and Hiraga, 1980), or pregnant Sprague-Dawley rats exposed to up to 5% DMP in the diet (~3,600 mg/kg-day) on GDs 6–15 (Field, 1993; NTP, 1989). These studies did not, however, histologically examine kidney sections from exposed rats.

5.12. Reproductive Toxicity

No single- or multiple-generation reproductive toxicity studies of animals exposed to DMP were located. Results from oral exposure studies of animals exposed during gestation or before attaining sexual maturity (see Section 5.13) have found evidence that DMP is not as potent a male rat reproductive toxicant as certain other phthalate esters, such as diethylhexyl phthalate (DEHP), DBP, or butylbenzyl phthalate (see Foster, 2006 for review of reproductive development following DEHP, DBP, and BBP exposure).

The weight of evidence from the above studies supported the conclusion that there was "insufficient animal or human evidence" for the designation of DMP as a "reproductive toxicant".

5.13. Prenatal, Perinatal and Post-natal Toxicity

No evidence for developmental toxicity was found in a study of standard developmental endpoints in pregnant Sprague-Dawley rats exposed to up 5% DMP in the diet (~3,600 mg/kg-day) on GDs 6–15 (Field, 1993; NTP, 1989) or in a study of reproductive tract endpoints in male offspring of Sprague-Dawley rat dams exposed by gavage to 750 mg/kg-day on GD 14–PND 3 (Gray et al., 2000). Endpoints in the first study included number of resorptions, number of live fetuses per litter, fetal body weight, and incidences of litters or fetuses with gross, visceral, or skeletal malformations or variations (Field, 1993; NTP, 1989; see Appendices A and B for more details). Endpoints in male offspring in the second study included body weight on PNDs 1 and 21, and at 3–5 months of age, anogenital distance (AGD) on PND 2, age at puberty, testicular histology at PND 2, presence of nipples/areolas at PND 13, and weights of liver and reproductive tract tissues at 3–5 months of age (Gray et al., 2000; see Appendices A and B for more details). Studies of pregnant CD-1 mice exposed to 3,500 or 5,000 mg/kg-day on GDs 6–13 found no effects on pup survival or body weight (i.e., numbers of live pups per litter, pup weight at birth or PND 3) or on incidence of fetuses with gross abnormalities; the higher of these doses produced mortality in 28% of the exposed dams during exposure. Examinations for visceral or skeletal malformations or variations and weight corrections for gravid uteri were not conducted in these studies (Hardin et al., 1987; Plasterer et al., 1985; see Appendices A and B for more details).

Following exposure to DMP by other routes, no evidence for exposure-related developmental effects was found in pregnant rats exposed to dermal doses up to ~2,380 mg/kg-

day on GDs 6–15 or 1–20 (Hansen and Meyer, 1989), but i.p. injection of doses ≥400 mg/kg-day into pregnant Sprague-Dawley rats on GDs 5, 10, and 15 resulted in decreased fetal body weight, increased resorptions, and increased percentage of fetuses with skeletal malformations (Singh et al., 1972).

No clear exposure-related effects on reproductive tract endpoints have been found in studies of young, sexually immature rats including Sprague-Dawley rats exposed to 500 mg/kg-day doses for 4 weeks (Kwack et al., 2009) or 1,400 mg/kg-day for 4 days (Foster et al., 1980) and JCL:Wistar rats exposed to 2% DMP in the diet (~1,862 mg/kg-day) for 1 week (Oishi and Hiraga, 1980). Endpoints in the first and second studies included weights of reproductive tract tissues and sperm counts and motility (Kwack et al., 2009; see Appendices A and B for more details) and testes weight and histology (Foster et al., 1980; see Appendices A and B for more details). Endpoints in the third study included testes weight and histology and testosterone concentrations in serum and testes (Oishi and Hiraga, 1980; see Appendices A and B for more details). Testosterone concentrations in testes were decreased by about 50% in exposed JCL:Wistar rats, compared with controls (Oishi and Hiraga, 1980). The adversity of this effect is uncertain, because other phthalates, which induced testicular toxicity in this study (e.g., DBP, diisobutyl phthalate, and DEHP), caused increased testosterone concentration at the same time point (Oishi and Hiraga, 1980).

The weight of evidence from the above studies supported the conclusion that there was "limited animal evidence" for the designation of DMP as a "developmental toxicant".

5.14. Carcinogenicity

Genotoxicity

In *in vitro* genotoxicity tests, DMP induced mutations in *Salmonella typhimurium* strains TA100 or TA1535 in the absence, but not the presence, of metabolic activation in some tests (Agarwal et al., 1985; Kozumbo et al., 1982; Seed et al., 1982; see Table 5.1), but not in others (Kubo et al., 2002; NTP, 1995; see Table 5.1). DMP did not induce mutations in *S. typhimurium* strains TA98, TA1537, or TA2637 with or without metabolic activation (Kubo et al., 2002; NTP, 1995; Agarwal et al., 1985; Kozumbo et al., 1982), but did induce mutations in mouse L5178Y lymphoma cells (Barber et al., 2000; see Table 5.2). DMP induced sister chromatid exchanges, but not chromosome aberrations, in Chinese hamster ovary cells (NTP, 1995), but reportedly did not induce chromatid aberrations in human leukocyte cultures (Tsuchiya and Hattori, 1976). In

in vivo tests, DMP did not clearly induce hepatic chromosome aberrations in rats following dermal exposure for 1 month, chromatid exchanges in bone marrow in mice following single i.p. injections of 1.4 mg/kg, or dominant lethal mutations in mice following i.p. or dermal administration (Yurchenko, 1977; as cited in NICNAS, 2008; see Table 5.2).

Table 5.2. Genotoxicity Test Results for DMP

Test System	Endpoint	Test Substance Concentration	Results		Reference
			With Activation	Without Activation	
In Vitro Tests					
S. typhimurium TA98, TA100, TA1535, TA1537	Reverse mutation	33–6,666 µg/plate	Negative	Negative	NTP, 1995
S. typhimurium TA98, TA100	Reverse mutation	500–4,000 µg/plate	Negative in TA98 Negative in TA100	Negative in TA98 Positive in TA100	Kozumbo et al., 1982
S. typhimurium TA98, TA100, TA1535, TA1537, TA2637	Reverse mutation	up to 2,000 µg/plate	Negative in TA1535 Negative in other strains	Positive in TA1535 Negative in other strains	Agarwal et al., 1985
S. typhimurium TA100	Reverse mutation	5–10 mM	Negative in TA100	Positive in TA100	Seed et al., 1982
S. typhimurium TA98, TA100	Reverse mutation	Up to 100 nM per plate	Negative	Negative	Kubo et al., 2002
Mouse L5178Y lymphoma cells	Mutation	Up to 0.6 µL/mL	Positive	Negative	Barber et al., 2000
Chinese hamster ovary cells	Sister chromatid exchange	Up to 2,960 µg/mL	Positive	Negative	NTP, 1995
Chinese hamster ovary cells	Chromosome aberrations	Up to 5,100 µg/mL	Negative	Negative	NTP, 1995
Human leukocyte cultures	Chromatid aberrations	Up to 250 µg/mL	Not tested	Negative	Tsuchiya and Hattori, 1976
In Vivo Tests					
Rat	Chromosome aberrations in liver	1.25 g/kg-day dermal for 1 month	Equivocal		Yurchenko, 1977; as cited in NICNAS, 2008
Mouse	Chromatid exchanges in bone marrow	1.4 g/kg, i.p. injection	Negative		Yurchenko, 1977; as cited in NICNAS, 2008
Mouse	Dominant lethal mutation	1,250 mg/kg, single i.p. injection or dermally 5 days/week for 2 months	Negative		Yurchenko, 1977; as cited in NICNAS, 2008

Initiation and Promotion

The National Toxicology Program (NTP) (1995) conducted a study of the tumor initiation and promotion activity of dermally applied undiluted DMP in male Swiss CD-1 mice. In the initiation study, mice (n=49–50 per group) were dosed dermally once during week 1 with 0.1 mL undiluted DMP, followed by application of 0.005 mg of 12-*O*-tetradecanoylphorbol-12-acetate (TPA) dissolved in acetone, 3 times/week for 8 weeks, then 0.0025 mg TPA 2 times/week for 44 weeks (52 weeks of promotion). In the promoter study, mice (n=49–50 per group) were dosed once in week 1 with 0.05 mg 7,12-dimethylbenzanthracene (DMBA) dissolved in acetone, followed by application of 0.1 mL undiluted DMP, 5 times/week for 52 weeks. Comparative control groups included vehicle control (acetone/acetone), initiation/promotion positive control (DMBA/TPA), promotion control (DMBA/acetone), and initiation control (acetone/TPA). Based on the incidence of skin neoplasms, DMP did not exhibit activity as an initiator or promoter for skin carcinogenesis (see Table 5.3).

Table 5.3. Incidences of Skin Neoplasms in Male Swiss CD-1 Mice Dermally Exposed to DMP in a 1-Year Tumor Initiation/Promotion Study

Treatment	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Carcinoma
Vehicle control			
acetone/acetone	0/50	0/50	0/50
Initiation control			
acetone/DMP	0/49	0/49	0/49
Promotion Control			
DMP/acetone	0/50	0/50	0/50
DMP initiation			
acetone/TPA	5/50[a]	0/50	5/50[a]
DMP/TPA	3/49[a]	1/49	4/49[a]
DMP promotion			
DMBA/acetone	1/50	2/50	3/50
DMBA/DMP	1/50	0/50	1/50
Initiation/promotion positive control			
DMBA/TPA	23/49[a,b,c]	7/49[a,b,c]	25/49[a,b,c]

[a]Significantly different ($p \leq 0.05$) from vehicle control (acetone/acetone) by logistic regression.
[b]Significantly different ($p \leq 0.05$) from promotion control (DMBA/acetone) by logistic regression.
[c]Significantly different ($p \leq 0.05$) from initiation control (acetone/TPA) by logistic regression.

Source: NTP (1995).

Carcinogenicity Studies

No adequate lifetime-exposure carcinogenicity studies are available for DMP.

The weight of evidence from the above studies supported the conclusion that there was "insufficient animal evidence" for the designation of DMP as a "carcinogen".

6. EXPOSURE

HSDB (2009) has reported that occupational exposure to DMP may occur through inhalation of aerosols and dermal contact with this compound at workplaces where it is produced or used. The available monitoring data indicate that the general population may be exposed to DMP via inhalation of ambient air, ingestion of drinking water, and dermal contact with products containing DMP (HSDB, 2009). Exposure data specific to DMP were not found.

7. DISCUSSION

Studies examining possible associations between indices of exposure to DMP (and other phthalates) and health outcomes in humans are inadequate to identify potential health hazards from exposure to DMP (see Appendix B for a summary of these studies). Results from studies of animals exposed repeatedly to DMP (mostly by the oral route) provide evidence, however, that DMP has less potential to induce health hazards than some other phthalates, such as DEHP and butylbenzyl phthalate.

Data for noncancer toxicity of DMP from repeated oral exposure of animals are limited to a poorly reported 2-year dietary exposure study of rats (Lehman, 1955), a few oral toxicity studies of rats exposed to DMP for 4 days to 4 weeks (Kwack et al., 2009; Foster et al., 1980; Oishi and Hiraga, 1980, and Bell et al., 1978), and gestational exposure developmental/ reproductive toxicity studies of pregnant Sprague-Dawley rats exposed to 0, 0.25, 1, or 5% DMP in the diet on GDs 6–15 (Field, 1993; NTP, 1989) or 0 or 750 mg/kg-day by gavage on GD 14–PND 3 (Gray et al., 2000) or pregnant CD-1 mice exposed by gavage to 0, 3,500, or 5,000 mg/kg-day on GDs 6–13 (Hardin et al., 1987; Plasterer et al., 1985) (see Appendices A and B). No single or multiple-generation reproductive toxicity studies of animals exposed to DMP are available.

No evidence for developmental toxicity was found in a study of standard developmental endpoints in pregnant Sprague-Dawley rats exposed to up 5% DMP in the diet (~3,600 mg/kg-day) on GDs 6–15 (Field, 1993; NTP, 1989) or in a study of reproductive tract endpoints in male offspring of Sprague-Dawley rats dams exposed by gavage to 750 mg/kg-day on GDs 14–PND 3 (Gray et al., 2000). Exposure of pregnant CD-1 mice to 3,500 or 5,000 mg/kg-day on GDs 6–13 resulted in no effects on offspring survival or body weight or the incidence of offspring with gross abnormalities, but these studies did not examine offspring for visceral or skeletal malformations or variations (Hardin et al., 1987; Plasterer et al., 1985). Exposure-related developmental effects were not found in pregnant rats exposed to dermal doses up to ~2,380 mg/kg-day of GDs 6–15 or 1–20 (Hansen and Meyer, 1989), but i.p. injection of doses ≥400 mg/kg-day into pregnant Sprague-Dawley rats on GDs 5, 10, and 15 resulted in decreased fetal body weight, increased resorptions, and increased percentage of fetuses with skeletal malformations (Singh et al., 1972).

Oral exposure to DMP doses ≥~3,600 mg/kg-day has been associated with decreased body weight in rats (see Table A.1 in Appendix A). Decreased body weight gain or growth was reported in female rats of unspecified strain exposed to 4 or 8% DMP, but not 2%, in the diet for 2 years (~3,668 or 7,336 mg/kg-day, but not 1,884 mg/kg-day) (Lehman, 1955) and pregnant Sprague-Dawley rats exposed to 5% DMP in the diet (~3,600 mg/kg-day), but not 1% (~800 mg/kg-day), on GDs 6–15 (Field, 1993; NTP, 1989). Decreased body weight gain was not observed in pregnant CD-1 mice exposed to 3,500 or 5,000 mg/kg-day on GDs 6–13, although the higher of these doses produced mortality in 28% of the exposed dams during exposure (Hardin et al., 1987; Plasterer et al., 1985). Body weight was not affected in pregnant Sprague-Dawley rats exposed to 750 mg/kg-day on GD 14–PND 3 (Gray et al., 2000); young male Sprague-Dawley rats exposed to 500 mg/kg-day for 4 weeks (Kwack et al., 2009) or 1,400 mg/kg-day for 4 days (Foster et al., 1980); or young male JCL:Wistar rats exposed to 2% DMP in the diet (~1,862 mg/kg-day) for 1 week (Oishi and Hiraga, 1980).

Limited data suggest that DMP is not a potent hematotoxic agent. Oral exposure to 750 mg/kg-day DMP for 4 weeks decreased hemoglobin concentrations by about 17% in young, male Sprague-Dawley rats, but did not affect other hematological endpoints (Kwack et al., 2009; see Table A.1 in Appendix A).

Increased liver weight has been associated with exposure to approximate DMP doses ≥~1,860 mg/kg-day, but available oral toxicity studies did not histologically examine liver sections from exposed rats (see Table A.1 in Appendix A). Increased absolute or relative liver

weights were observed in pregnant Sprague-Dawley rats exposed to 5% DMP in the diet (~3,600 mg/kg-day) on GDs 6–15 (Field, 1993; NTP, 1989) and in young male JCL:Wistar rats exposed to 2% DMP in the diet (~1,862 mg/kg-day) for 1 week (Oishi and Hiraga, 1980). Relative liver weights were not changed in young male Sprague-Dawley rats exposed to 500 mg/kg-day for 4 weeks; however, serum activities of ALP, but not GOT or GPT, were increased (Kwack et al., 2009). In another study, relative liver weights were not significantly different from control values in male Sprague-Dawley rats exposed to 0.5% DMP in the diet (~107 mg/kg-day) for 21 days (Bell et al., 1978).

No exposure-related effects on kidney weights were observed in studies of rats exposed to doses as high as ~3,600 mg/kg-day, but these studies did not histologically examine kidney sections (Kwack et al., 2009; Field, 1993; NTP, 1989; Oishi and Hiraga, 1980). Chronic nephritis was reported to occur in female rats exposed to 8% DMP, but not 4%, in the diet (~7,336 and 3,668 mg/kg-day, respectively), but the report of this study did not specify the incidence or severity of this apparent effect (Lehman, 1995).

No adequate lifetime-exposure carcinogenicity studies are available for DMP. DMP did not exhibit activity as an initiator or promoter for skin carcinogenesis in male Swiss CD-1 mice (NTP, 1995). As reviewed in Section 5.14, results from in vitro and in vivo genotoxicity tests are mixed, and suggest that DMP may be genotoxic under some circumstances, but not others.

Overall Uncertainty

The hazard database for DMP consisted primarily of a few "subchronic" and "developmental" studies. Additional studies satisfactorily described acute effects of single DMP exposures.

Toxicity data associated with DMP exposure are limited. Only a few reliable no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) values for developmental or repeated-dose systemic toxicity were identified. These have been listed in Appendix A.

Overall Acceptable Daily Intakes

Acceptable daily intakes values (ADI's) are calculated when a given chemical is considered "toxic" and sufficient toxicity information is available. The ADI is the amount of a

chemical that one may be exposed to on a daily basis without posing a significant risk of health effects to consumers. ADI's were not estimated for DMP relevant exposure durations for the general population or for other sensitive subpopulations because confirmatory data on toxicological endpoints and methodological clarifications were not available.

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Appendix A. Summary of Endpoints by Organ System

Table A.1. Summary of Oral Exposure NOAELs/LOAELs Identified for DMP by Organ Systems

Species (Gender)	Exposure Route	Dose (mg/kg-day) (Number of Animals per Dose Group)	Dose Duration	Effect Category	Toxicological Endpoint (mg/kg-day)	Toxicological Basis	Citation
Acute or Repeated Dose Toxicity Studies							
Unspecified strain rat (age not specified) (F)	Oral, 0, 2, 4, or 8% in diet	0, 1,834, 3,668, or 7,336 mg/kg-day assuming U.S. EPA reference values for body weight (0.229 kg) and food intake (0.021 kg/day) for Fischer 344 rats 10 females per group	2 years	General	NOAEL=1,834 LOAEL=3,668	Growth rate was affected in 4 and 8% groups, but report did not specify magnitude of the effect.	Lehman, 1955
				Liver	NOAEL=Not determined LOAEL=Not determined	Reporting was inadequate to determine a NOAEL or LOAEL. No liver effects were mentioned.	
				Kidney	NOAEL=Not determined LOAEL=Not determined	Reporting was inadequate to determine NOAEL or LOAEL. "Chronic nephritis" was reported in the 8% group, but neither incidence nor severity were not reported.	
				Testes	NOAEL=Not determined LOAEL=Not determined	Reporting was inadequate to determine NOAEL or LOAEL. No testicular effects were mentioned.	
Sprague-Dawley rat (3–4 weeks old) (M)	Oral, gavage	0 or 1,400 (7.2 mmol/kg) 12 rats per group	4 days	General	NOAEL=1,400 LOAEL=None	No difference in body weight between exposed and control groups.	Foster et al., 1980
				Testes	NOAEL=1,400 LOAEL=None	No effects on testes weight or histology. Same dose of di-n-pentyl phthalate or di-n-hexyl phthalate produced decreased testes weight and atrophy of seminiferous tubules.	

Table A.1. Summary of Oral Exposure NOAELs/LOAELs Identified for DMP by Organ Systems							
Species (Gender)	**Exposure Route**	**Dose (mg/kg-day) (Number of Animals per Dose Group)**	**Dose Duration**	**Effect Category**	**Toxicological Endpoint (mg/kg-day)**	**Toxicological Basis**	**Citation**
Sprague-Dawley rat (age not specified; 200–225 g body weight) (M)	Oral, diet	0 or 0.5% in diet (5,000 ppm) Estimated dose is 107 mg/kg-day, using U.S. EPA reference values for body weight (0.267 kg) and food intake (0.0057 kg/day) in male Sprague-Dawley rats 8 exposed, 6 control rats	21 days	General	NOAEL=107 LOAEL=Not determined	DMP did not influence body weight gain during exposure [65.7 g (SE 6.0, n=8) versus 68.0 g (SE 8.8, n=6)] or relative liver weight [4.1 (SE 0.2, n=8) versus 4.0 (SE 0.1, n=9)]. Exposure to DEHP or DBP increased relative liver weight and inhibited lipid biosynthetic activities in liver "minces "compared with liver minces from control rats. Lipid biosynthetic activities in liver minces from DMP-exposed rats were not significantly different from control values. For example, mean incorporation of [^{14}C]-labeled mevalonic acid into cholesterol or squalene were not significantly different from control means [722 (SE 133) versus 632 (SE 297) units for cholesterol, 1,175 (SE 231) versus 1,532 (SE 510) units for squalene]. No histology was performed in this study.	Bell et al., 1978
				Liver	NOAEL=107 LOAEL=Not determined		
				Kidney	NOAEL=Not assessed LOAEL=Not assessed		
				Testes	NOAEL=Not assessed LOAEL=Not assessed		
Sprague-Dawley rat (5weeks old) (M)	Oral, gavage	DMP: 0 or 500 MMP: 0 or 250 (monomethyl phthalate) 10 and 20 rats per exposed groups and control groups, respectively	4 weeks	General	NOAEL=500 DMP; 250 MMP LOAEL=None DMP or MMP	No differences in body weight between exposed and control groups.	Kwack et al., 2009
				Liver	NOAEL=None DMP; 250 MMP LOAEL=500 DMP; None MMP	Increased serum ALP in DMP-exposed, but no changes from control in serum GOT or GPT, or relative liver weight. Histology not conducted. No effects on liver endpoints in MMP-exposed group.	
				Kidney	NOAEL=500 DMP; 250 MMP LOAEL=None DMP or MMP	No effects on kidney weight. No histology was conducted	

Table A.1. Summary of Oral Exposure NOAELs/LOAELs Identified for DMP by Organ Systems							
Species (Gender)	**Exposure Route**	**Dose (mg/kg-day) (Number of Animals per Dose Group)**	**Dose Duration**	**Effect Category**	**Toxicological Endpoint (mg/kg-day)**	**Toxicological Basis**	**Citation**
				Testes	NOAEL=500 DMP; 250 DMP LOAEL=None DMP or MMP	No exposure-related effects on weight of testes or left epididymis, or sperm count or motility. Histology was not conducted.	
JCL:Wistar rat (5 weeks old) (M)	Oral, 2% in diet	0 or 1,862 Calculated using reported average BW (0.169 kg) and U.S. EPA allometric equation to estimate food intake (0.0157 kg/day). 10 treated rats, 20 control rats	1 week	General	NOAEL=1,862 LOAEL=None	No effects on body weight gain during exposure.	Oishi and Hiraga, 1980
				Liver	NOAEL=None LOAEL=1,862	Increased liver weight and decreased liver zinc levels. Liver apparently was not examined microscopically.	
				Kidney	NOAEL=1,862 LOAEL=None	No significant changes in kidney weight or kidney zinc levels. Kidney apparently was not examined microscopically.	
				Testes	NOAEL=1,862 LOAEL=None	Decreased concentrations of testosterone in serum and testes are of uncertain adversity, since no change in absolute or relative testes weight were seen, and microscopic histology detected no inhibition of spermatogenesis or desquamation of testes.	

Table A.1. Summary of Oral Exposure NOAELs/LOAELs Identified for DMP by Organ Systems							
Species (Gender)	**Exposure Route**	**Dose (mg/kg-day) (Number of Animals per Dose Group)**	**Dose Duration**	**Effect Category**	**Toxicological Endpoint (mg/kg-day)**	**Toxicological Basis**	**Citation**
Gestational Exposure Studies							
Sprague-Dawley rat (pregnant) (F)	Oral, 0, 0.25, 1.0, or 5% in diet	0, 200, 800, or 3,600, approximate doses estimated by NTP (1989). 29–30 dams per group; uterine contents assessed at GD 20	GDs 6–15	Maternal General	NOAEL=800 LOAEL=3,600	Decreased body weight gain and food consumption during treatment period in 5% dams.	Field et al., 1993; NTP, 1989
				Maternal Liver	NOAEL=800 LOAEL=3,600	Increased relative liver weight in 5% dams. No histology was conducted.	
				Maternal Kidney	NOAEL=3,600 LOAEL=None	No effects on absolute or relative kidney weight. No histology was conducted.	
				Developmental	NOAEL=3,600 LOAEL=None	No exposure-related effects on resorption number, live or dead fetuses per litter, fetal body weight, or incidences of litters or fetuses with gross, visceral, or skeletal malformations or variations.	
CD-1 mouse (pregnant) (F)	Oral, gavage	0, 3,500, or 5,000 43–50 dams per group, dams delivered and offspring assessed on PNDs 1 and 3	GDs 6–13	Maternal General	NOAEL=3,500 LOAEL=5,000	28% of 5,000-mg/kg dams died. No exposure-related effects on maternal weight gain or the number of viable litters.	Hardin et al., 1987; Plasterer et al., 1985
				Developmental	NOAEL=5,000 LOAEL=None	No exposure-related effects on numbers of liveborn per litter, average pup weight at birth or PND 3, or offspring survival to PND 3. No efforts made to assess malformations in offspring.	

Table A.1. Summary of Oral Exposure NOAELs/LOAELs Identified for DMP by Organ Systems							
Species (Gender)	**Exposure Route**	**Dose (mg/kg-day) (Number of Animals per Dose Group)**	**Dose Duration**	**Effect Category**	**Toxicological Endpoint (mg/kg-day)**	**Toxicological Basis**	**Citation**
Sprague-Dawley rat (pregnant) (F)	Oral, gavage	0, 750 19 control, 5 exposed dams, male offspring evaluated for endpoints up to 3–5 months of age	GD 14–PND 3	Maternal General	NOAEL=750 LOAEL=None	1/5 exposed dams died. Survivors showed no difference in body weight gain versus control.	Gray et al., 2000
				Developmental	NOAEL=750 LOAEL=None	Male offspring showed no significant ($p > 0.05$) effects on body weight at PND 1 or 21 or at 3–5 months of age. Other endpoints not different from control: AGD on PND 2, age at puberty, testicular histology at PND 2; presence of nipples/areolas at PND 13; or weights of liver or reproductive tract tissues at 3–5 months of age.	

F=female; M=male; SE = standard error

Appendix B. Critical Study Reviews

Human Studies

Several studies have looked for associations between levels of phthalate diesters or their metabolites, including DMP and MMP, and reproductive endpoints in humans, but the results do not provide adequate evidence that any specific phthalate, or DMP in particular, is a reproductive toxicant in humans.

Reduced fertility was reported in a group of women occupationally exposed to phthalates (including DMP), compared with a control group, but the results are inconclusive due to the lack of information on the selection of control group and on possible exposures to other substances (Aldyreva et al., 1975; as cited in NICNAS, 2007).

In vitro exposure of sperm cultures from putatively non-exposed men to various phthalates, including DMP, resulted in decreased sperm velocity and straight-line motion (Fredicsson et al., 1993; as cited in NICNAS, 2007).

No association was found between MMP levels in breast milk samples and the occurrence of cryptorchidism in a study of Danish-Finnish mothers and their offspring (Main et al., 2006)

Possible associations were examined between levels of phthalate monoesters, including MMP in urine of mothers and genital variables in their offspring, such as anogenital index (AGI [AGD normalized for body weight]) and testicular descent, but no significant associations were found with levels of MMP (Swan et al., 2005).

In a study of men attending an andrology clinic, no associations were found between urinary levels of MMP and variables of sperm, semen, and sperm DNA damage (Duty et al., 2003a, b).

Levels of DMP, and other phthalates including diethyl phthalate, DBP, and DEHP, in semen of a group of proven fertile men (i.e., who had offspring within 1 year of the study) were lower than levels in a group of infertile men (who had regular unprotected intercourse within 1 year without their partners achieving pregnancy) (Pant et al., 2008). In this study, increasing levels of DMP in semen were not correlated with decreasing sperm concentrations, motility, or

abnormal sperm, but significant correlations were found between increasing semen levels of diethyl phthalate, DBP, or DEHP and decreasing sperm concentration or motility, or increasing abnormal sperm.

Repeated Dose Oral Toxicity Studies in Animals

Lehman, 1955

The effect of chronic dietary exposure to DMP was investigated by Lehman (1955). However, due to poor reporting of methods and results, reliable NOAEL or LOAEL values for adverse effects are not identifiable with the exception of effects on growth. According to the study report, groups of 10 female rats (strain not reported) were fed diets containing 0, 2, 4, or 8% DMP for 2 years. Mortality rates in the DMP treatment groups did not differ from the control group. Growth rate in the 4 and 8% groups was slightly, but statistically, different (magnitude of change was not reported) from controls, although methods used to assess growth rate were not reported. "Chronic nephritis" was observed in female rats treated with 8% 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.

Bell et al., 1978

Bell et al. (1978) exposed male Sprague-Dawley rats (n=6 or 8; see Table A.1) of unspecified age weighing 200–225 g to 0 or 0.5% DMP in the diet for 21 days and measured body weight gain, liver weights, and lipid biosynthetic activities of liver minces. No histology was performed in this study, and only body weight and liver endpoints were evaluated. DMP did not influence body weight gain during exposure (see Table A.1). In contrast, exposure to DEHP or DBP increased relative liver weight and inhibited lipid biosynthetic activities in liver "minces" compared with liver minces from control rats. Lipid biosynthetic activities in liver minces from DMP-exposed rats were not significantly different from control values. For example, mean incorporation of [^{14}C]-labeled mevalonic acid into cholesterol or squalene were not significantly different from control means (see Table A.1).

Additional chronic or subchonic oral exposure toxicity studies of DMP in laboratory animals were not located, with the exception of a 4-week oral exposure study of organ weights,

hematology, and serum chemistry endpoints in sexually immature Sprague-Dawley rats (Kwack et al., 2009). This study is described in the next subsection in this Appendix.

Developmental/Reproductive Toxicity Studies in Animals

No one- or multiple-generation studies of reproductive performance in DMP-exposed animals were located.

Descriptions of gestational exposure and acute and repeated oral postnatal exposure developmental studies follow; the latter studies focus on effects in sexually immature animals. Also described are i.p. injection (Singh et al., 1972) and dermal exposure (Hansen and Meyer, 1989) developmental toxicity studies.

Gestational exposure studies in animals

Field et al., 1993; NTP, 1989

NTP (1989) assessed the developmental effects of dietary exposure to DMP in pregnant 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 eight 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 GDs 6–15. 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 GDs 6–9. 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, and 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, and 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 approximate daily dose of DMP to be 0, 200, 800, and 3,600 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 (GDs 6–15; see Table B.1), 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 GDs 6–9 (28% decrease) and GDs 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 with control (Table B.1). 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 endpoints, including number of implantation sites, number of resorptions, fetal viability, live and dead fetuses per litter, fetal body weight, or fetal growth. The incidences of external, visceral, and skeletal malformations were similar in the DMP treatment groups compared with control (Table B.1). 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% (3,600 mg/kg-day), respectively, for decreased body weight gain and increased relative liver weight. For fetal effects, a NOAEL of 5% (3,600 mg/kg-day) was reported; a LOAEL was not identified.

Table B.1. Selected Maternal and Fetal Endpoints in Sprague-Dawley CD Rats Exposed to DMP in the Diet on GDs 6–15

Endpoint	Percentage DMP in Diet			
	0	**0.25**	**1.0**	**5.0**
Approximate daily dose (mg/kg-day)	0	200	800	3,600
Number of dams Total treated	30	30	29	30
Number removed	1	2	0	0
Number (%) pregnant	26 (90)	25 (89)	26 (90)	28 (93)
Maternal body weight gain during exposure, unadjusted (g)	52.3 ± 1.4[a]	53.2 ± 2.0	50.9 ± 1.7	37.7 ± 2.3[b]
Maternal relative liver weight (% of body weight)	4.34 ± 0.06	4.40 ± 0.06	4.39 ± 0.06	4.59 ± 0.06[b]
Number of implantation sites/litter	14.9 ± 0.5	14.7 ± 0.4	14.6 ± 0.7	14.0 ± 0.6
% litters with resorptions	34.6	28.0	30.8	25.0
Number of dams with live litters	26	25	25	27
Number of live fetuses/litter	14.4 ± 0.6	14.4 ± 0.4	14.6 ± 0.4	14.2 ± 0.4
Fetal body weight (g)/litter	3.4 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	3.6 ± 0.1
Litters with any malformations/total litters	5/26	3/25	5/25	4/27
Number of litters with external malformations	0	0	1	2
Number of litters with visceral malformations	4	3	2	2
Number of litters with skeletal malformations	1	1	2	1
Litters with any variations/total litters	14/26	20/25	17/25	23/27

[a]Mean ± SE.
[b]Significantly ($p \leq 0.05$) different from control.

Source: Field et al. (1993); NTP (1989).

Hardin et al., 1987; Plasterer et al., 1985

No effects were observed in a gestational exposure developmental toxicity study in mice (Hardin et al., 1987; Plasterer et al., 1985). The developmental effects of DMP were evaluated in two tests. In one test, pregnant mice were administered corn oil vehicle (n=50) or 3,500 mg/kg-day DMP (n=49); in the second test, pregnant mice were administered corn oil vehicle (n=43) or 5,000 mg/kg-day DMP (n=43). Dosing was performed on GDs 6–13. Mice were examined daily for signs of toxicity and body weights were recorded on GDs 6 and 17. Following completion of delivery (PND 1), the number of live and dead pups and pup weight were recorded and pups. On 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 5,000 mg/kg-day DMP group died during the treatment period (the cause of death was not reported); no mortality was observed in mice treated with 3,500 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 offspring survival to PND 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/developmental parameters, even at a dose (5,000 mg/kg-day) overtly toxic to the dams.

Gray et al., 2000

No effects on male reproductive tract development were observed following gestational exposure of rats to DMP on GD 14–PND 3 (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 AGD (on PND 2); examination of the inguinal region for hemorrhagic testes (on PNDs 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 litter 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 was 21 in the DMP group and in the control group was 80. For all parameters assessed, DMP-exposed animals did not significantly ($p < 0.05$) differ from controls (see Table B.2 for data for selected endpoints).

Table B.2. Selected Maternal and Offspring Endpoints in Sprague-Dawley CD Rats Exposed to DMP by Gavage on GD 14–PND 3

Endpoint	Dose (mg/kg-day)	
	0	750
Number of dams	19	5
Number of dams with live pups at PND 2 and weaning	19	4
Maternal weight gain to GD 21 (g)[a]	104 ± 3.7	102 ± 5.6
Offspring endpoints		
Number of live pups/litter, PND 1[a]	13.5 ± 0.4	13.5 ± 09
Mean pup weight at birth (g)[a]	6.84 ± 0.06	6.59 ± 0.24
Mean male pup weight at weaning (g)[a]	83.2 ± 1.4	80.7 ± 2.1
Male offspring body weight at 3–5 months (g)[a]	613 ± 17	547 ± 15
Male offspring liver weight at 3–5 months (g)[a]	20.1 ± 0.8	19.9 ± 0.8
Number of nipples per male at 3–5 months[a]	0	0
Serum testosterone at 3–5 months (ng/mL)[a]	1.15 ± 0.13	1.40 ± 0.20
Male reproductive tissue weights at 3–5 months (mg)[a]		
Testes	3,508 ± 53	3,523 ± 86
Levator ani bulbocavernous muscle	1,275 ± 22	1,234 ± 39
Seminal vesicles	1,857 ± 45	1,798 ± 101
Ventral prostate	685 ± 21	677 ± 15
Paired epididymis	1,293 ± 18	1,251 ± 26

[a]Litter means ± SE; none of the means for the exposed group were significantly ($p > 0.05$) different from respective control means.

Source: Gray et al. (2000).

Liu et al., 2005

Oral exposure of pregnant Sprague-Dawley rats (on GDs 12–19) to phthalate esters (500 mg/mg-day in corn oil by gavage) with known effects on male reproductive organ development (DBP, DEHP, dipentyl phthalate, and benzyl butyl phthalate) produced significant alterations in expression of 391 of 30,000 genes examined in a microarray analysis of fetal testes (Liu et al., 2005). Pathways affected by exposure included those involved in cholesterol transport and steroidogenesis, in Sertoli cell development, and in communication between Sertoli cells and gonocytes. However, no significant changes in the expression of these genes were observed in fetal testes following oral administration of DMP (500 mg/kg-day) in corn oil to pregnant dams on GDs 12–19 (Liu et al., 2005). The results provide supportive evidence that gestational exposure to dimethyl phthalate is not a potent male rat reproductive tract toxicant like other phthalate esters, such as DBP and DEHP.

Hansen and Meyer, 1989

Groups of 24–25 pregnant Wistar rats (Mol:Wist) were dermally exposed under occluded conditions for 2 hours to 0.5, 1, or 2 mL/kg (~595, 1,190, or 2,380 mg DMP/kg, assuming a density of approximately 1.19) on GDs 6–15, or 2 ml/kg on GDs 1–20 (Hansen and Meyer, 1989). Control groups contained 23 (GDs 6–15) or 15 (GDs 1–20) rat dams. Rats were weighed and sacrificed on GD 21, and uterine contents were examined. Endpoints included weight of fetuses and numbers of corpora lutea, implantations, and live and dead fetuses (mean number per litter). Fetuses were examined for gross abnormalities; half were examined for skeletal malformations and the remaining half were examined for visceral malformations. No statistically significant exposure-related effects on any endpoint were found.

Singh et al., 1972

Pregnant Sprague-Dawley rats (n=5/group) were administered i.p. doses of 0 (untreated and vehicle controls were included), 0.338, 0.675, or 1.125 mL/kg on GDs 5, 10, and 15 (approximately 0, 400, 800, or 1,340 mg/kg) (Singh et al., 1972). Rats were weighed and sacrificed on GD 20, and uterine contents were examined. Endpoints included total numbers of corpora lutea, resorptions, live and dead fetuses, weight of fetuses, gross abnormalities in all fetuses (live and dead), and skeletal malformations in 30–50% of fetuses in each group. Mean weights of fetuses in all exposure groups were significantly ($p < 0.05$) lower than controls (see Table B.3). In the low- and high-dose groups, but not the mid-dose group, increased resorptions and decreased numbers of live fetuses were observed compared with control groups (see Table B.3). There were also apparent increased percentages of fetuses with malformations in all exposure groups (see Table B.3). No statistical analyses of the incidence data were performed in this study. The results indicate that i.p. injection into pregnant Sprague-Dawley rats of doses ≥400 mg/kg-day on GDs 5, 10, and 15 resulted in decreased fetal body weight, increased resorptions, and increased percentage of fetuses with skeletal malformations.

Table B.3. Effects in Fetuses of Pregnant Sprague-Dawley Rats Administered Dimethyl Phthalate on GDs 5, 10, and 15 by i.p. Injection

	Control Groups				DMP Dose (mg/kg-day)		
Endpoint[a]	**Untreated**	**Water**	**Saline**	**Cottonseed Oil**	**400**	**800**	**1,340**
Number of:							
Corpora lutea	60	59	62	59	65	55	55
Resorptions[b]	0 (0%)	4 (6.8%)	7 (11.5%)	4 (6.8%)	21 (33.3%)	0 (0%)	17 (32.1%)
Dead fetuses[b]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	5 (9.4%)
Live fetuses[b]	59 (100%)	55 (93.2%)	54 (88.5%)	55 (93.2%)	42 (66.7%)	52 (98.1%)	31 (58.5%)
Gross abnormalities[c]	0 (0%)	0 (0%)	1 (01.9%)	1 (1.8%)	4 (9.5%)	4 (7.5%)	4 (11.1%)
Skeletal abnormalities[d]	0 (0%)	0 (0%)	4 (14.3%)	3 (10.7%)	4 (25.0%)	6 (35.3%)	9 (75.0%)
Mean weight of fetuses[e]	4.83 (0.01)	4.40 (0.33)	4.10 (0.13)	4.45 (0.17)	2.38 (0.13)	2.60 (0.01)	2.20 (0.18)

[a]Each group contained five pregnant rats.
[b]Numbers in parentheses are percentages based on total number of implantations.
[c]Numbers in parentheses are percentages based on total number of fetuses.
[d]Numbers in parentheses are percentages based on total number of stained fetuses.
[e]Mean weight (g) with SE noted in parentheses and n=number of live fetuses per group.

Source: Singh et al. (1972).

Oral exposure studies in sexually immature animals

Kwack et al., 2009

Sexually immature (5-week-old) male Sprague-Dawley rats (n=5–6/group) were exposed to 0 or 500 mg/kg-day DMP, or 250 mg/kg-day MMP, by gavage in corn oil for 4 weeks and assessed for effects on body and organ weights, hematological and serum biochemical variables, and sperm counts and motility (Kwack et al., 2009). Mean terminal body weights in DMP- or MMP-exposed rats were not significantly ($p > 0.05$) different from the control mean. Mean relative organ weights in the DMP- and MMP-exposed groups were not significantly changed, compared with control means for thymus, heart, liver, spleen, kidney, adrenal, testis, or epididymis. No significant exposure-related changes were observed in hematological variables

(with exception of decreased hemoglobin; see Table B.4) or serum biochemical variables except for increased ALP activities (see Table B.4). Sperm counts and percent motility in DMP- and MMP-exposed groups were not significantly ($p > 0.05$) different from control means. Similar exposure to other phthalate diesters at 500 mg/kg-day in this study induced increased relative liver weight (DEHP, DBP, and diisononyl phthalate), decreased relative testes weight (DEHP, DBP), and decreased sperm count and/or motility (e.g., DEHP, DBP, butylbenzyl phthalate, and diisononyl phthalate).

Table B.4. Selected Organ Weights, Serum Chemistry, and Sperm Endpoints in 5-Week-Old Male Sprague-Dawley Rats Exposed to DMP or MMP by Gavage for 4 Weeks

Endpoint	Dose (mg/kg-day)		
	0 Control	500 DMP	250 MMP
Relative organ weight[a]			
Liver	2.45 ± 0.13	2.83 ± 0.29	2.63 ± 0.29
Paired testes	0.771 ± 0.046	0.766 ± 0.067	0.747 ± 0.061
Left epididymis	0.161 ± 0.011	0.173 ± 0.028	0.167 ± 0.010
Hematological or serum endpoints[a]			
Hemoglobin (g/dL)	16.80 ± 0.62	13.88 ± 4.64[b]	16.62 ± 0.82
GOT (IU/L)	75.67 ± 7.81	89.4 ± 11.97	77.83 ± 10.38
GPT (IU/L)	41.7 ± 7.03	47.6 ± 14.50	38.0 ± 9.38
ALP (IU/L)	347.0 ± 49.78	764.0 ± 122.48[b]	439.67 ± 183.57
Sperm endpoints			
Sperm count (10^6/g)	2,568.00 ± 154.90	2,348.00 ± 101.02	No data
Sperm motility (%)	74.67 ± 4.51	69.33 ± 2.89	

[a]Values are mean ± SD; n=6.
[b]Significantly ($p \leq 0.05$) different from respective control means.

Source: Kwack et al. (2009).

Oishi and Hiraga, 1980

Young (5 weeks old) sexually immature JCL:Wistar rats were fed diets containing 0 (n=20) or 2% (n=10) DMP for 1 week. Using reported average body weight (0.169 kg) and a U.S. EPA (1988) allometric equation to estimate food consumption, the daily dose of DMP was estimated to be 1,862 mg/kg-day. 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 with control means (see Table B.5). 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 compared with control values. Other phthalates, which induced testicular atrophy in this study (e.g., DBP, diisobutyl phthalate, and DEHP), caused increased testosterone concentrations in testes. The decreased levels of testosterone induced by DMP (which did not cause testicular atrophy), therefore, is of uncertain adversity.

Table B.5. Body and Organ Weights and Zinc Concentrations in 5-Week-Old Male JCL:Wistar Rats Exposed to DMP in the Diet for 1 Week[a]

Endpoint	DMP Dose (mg/kg-day)	
	0	1,862
Final body weight (g)	165.7 ± 10.5	168.7 ± 10.0
Absolute organ weights (g)		
Testes	1.45 ± 0.31	1.51 ± 0.28
Liver	7.88 ± 0.58	9.24 ± 0.81[b]
Kidney	1.71 ± 0.14	1.76 ± 0.13
Relative organ weights[c]		
Testes	0.87 ± 0.16	0.89 ± 0.14
Liver	4.76 ± 0.26	5.47 ± 0.30[b]
Kidney	1.03 ± 0.05	1.04 ± 0.05
Zinc concentration[d]		
Testes	19.9 ± 2.48	20.0 ± 1.87
Liver	29.0 ± 5.02	26.0 ± 3.89
Kidney	19.7 ± 1.91	19.7 ± 1.03
Serum	1.21 ± 0.91	1.21 ± 0.10

[a]Mean ± SD for 10 DMP exposed or 20 control rats.
[b]Significantly different from controls, $p < 0.05$.
[c]Values are expressed as g per 100 g of body weight.
[d]Values for DMP are expressed as µg/g of wet tissue or µg/mL of serum.

Source: Oishi and Hiraga (1980).

Foster et al., 1980

An examination of testicular endpoints following oral exposure of sexually immature Sprague-Dawley rats to about 1,400 mg/kg DMP for 4 days found no treatment-related effects (Gangolli, 1982; Foster et al., 1980). Groups of 12 young Sprague Dawley rats (weighing 70–90 g) were administered 0 or 7.2 mmol/kg-day (equivalent to 1,400 mg/kg-day) by gavage for 4 days. Although the age of the rats was not reported by Foster et al. (1980), an earlier report from the same institution indicated that young male Sprague-Dawley rats with a similar body

weight range (70–100 g) were 3–4 weeks of age (Cater et al., 1977). 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. Mean (SE, n=12) relative testes weights were 111 (2.9) for exposed and 100 (2.1) for controls. Histopathological assessment of testes from DMP-treated rats showed no lesions or evidence of atrophy. In contrast to DMP, exposure to 7.2 mmol/kg doses of di-n-pentyl phthalate or di-n-hexyl phthalate produced decreased testicular weight and moderate or severe atrophy of seminiferous tubules with loss of spermatocytes and spermatids in this study (Foster et al., 1980).